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CLINICAL REVIEW

Efficacy of light therapy versus antidepressant drugs, and of the combination versus monotherapy, in major depressive episodes: A systematic review and meta-analysis

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SUMMARY

Although light therapy (LT) has been shown to be efficient in the treatment of seasonal and non-seasonal depression, it is underused in clinical settings and antidepressant drugs (AD) remain so far the usual first line treatment. The aim of this systematic review and weighted random effect meta-analysis is to examine the randomized controlled trials that compared directly light therapy and antidepressant drugs, as well as their combination (LT + AD). A total of 397 participants were included, with a moderate to severe major depressive episode, from seven independent populations. The median duration of intervention was 5 wks (range 2–8 wks). The superiority (lower depression score) of LT + Placebo compared to AD + Placebo was non-significant (SMD = 0.19 [−0.08–0.45]; p = 0.17). The combination LT + AD was superior to AD + Placebo (SMD = 0.56 [0.24–0.88]; p < 0.001). This superiority was confirmed in the subgroup of patients with non-seasonal depression (SMD = 0.55 [0.16–0.93]; p = 0.005). Meta-analyses showed no or small heterogeneity between studies (I^2 = 0%, 18.41%, and 39.23% respectively). No potential publication biases were observed by statistical tests and visual inspection of the funnel plots. No differences were observed between LT and AD, with a clear superiority of the combination, thus both LT monotherapy and combination may be proposed as a first line treatment in seasonal and non-seasonal depression.

Introduction

The use of light for its antidepressant properties dates back to the beginning of civilization [1], and a growing body of evidence has been generated regarding the efficacy of light therapy (LT, also formerly named phototherapy or heliotherapy) [1]. LT has been the cornerstone treatment of seasonal affective disorder (SAD) for more than three decades, with the first case series being published in 1984 [2]. Since this first documentation of light therapy in SAD, several meta-analyses of randomized trials have confirmed that LT is more efficient than placebo in subjects with seasonal unipolar depression [3], and seasonal bipolar depression [4]. Moreover, LT is also efficacious and well tolerated in the treatment of adults with moderate to severe non-seasonal unipolar depression, with effect sizes equivalent to those observed in trials using selective serotonin reuptake inhibitors (SSRIs) [3,5]. LT has the advantage of being also effective in improving both sleep and circadian rhythms, which may be altered in depression, contrary to antidepressant drugs (AD) that target mainly mood [6].

In parallel, LT implementation also evolved as an augmentation strategy to antidepressant drugs in non-seasonal depression, for both unipolar and bipolar disorders (MDD and BD) [1]. In up to 50–60% of patients who did not respond to AD alone [7], LT used as an augmentation increased the number of responders [8]. These studies raise the question of recommending AD and LT as a first-line combination treatment in order to maximize patients' response rates, rather than using LT as a second or third line augmentation strategy. Indeed, a shorter duration of untreated depression is

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Glossary of terms

AD	antidepressant drug
BD	bipolar disorder
MDD	major depressive disorder
LT	light therapy
SAD	seasonal affective disorder
SD	standard deviation
SMD	standardized mean difference

associated with more favorable outcomes, including depression-related disability [9].

Despite several meta-analyses and a good level of evidence for the efficacy of LT in SAD and non-seasonal depression, there is no current treatment consensus. Some authors consider that existing studies have methodological problems [10], while other consider that sufficient evidence-based high quality studies have been published, and that LT is an acceptable treatment to be used in seasonal and non-seasonal depression [11–13]. Therefore, most current therapeutic guidelines do not address LT in detail, with LT recommendations that are tentative and only focus on SAD [14,15]. One other possible reason for the limited use in clinical settings may be the assumption that LT is inferior to AD, or might be efficient only as an augmentation or add-on strategy. Indeed, no meta-analysis has examined the randomized controlled trials which directly compared LT and AD, nor those comparing the combination of LT and antidepressant as first line therapy versus monotherapies.

Therefore, we conducted a systematic review and meta-analysis of randomized controlled-trials, aiming to evaluate 1) the efficacy of AD versus LT in major depressive episode, and 2) the efficacy of the combination LT + AD versus both monotherapies.

Methods

Literature search strategy

A systematic review and meta-analysis was conducted following the recommendations of the Cochrane group [16] and PRISMA guidelines [17].

Eligibility

A priori, we determined the following inclusion criteria for the studies:

- Criterion A: has to be a controlled trial with intervention and control arms;
- Criterion B: must have enrolled only patients who have been diagnosed with a major depressive episode, unipolar or bipolar, according to DSM or ICD criteria, and assessed by standardized depression scales;
- Criterion C: must have light therapy (of any type such as bright white light, blue-enriched, dawn simulation) and an antidepressant medication as primary independent interventions (and not as an augmentation strategy);
- Criterion D: In studies assessing the efficacy of the combination of AD and LT, a valid placebo must be used as control (such as dim light or low-density negative air ions; placebo pill for antidepressant medication); no valid placebo is expected in the case of a direct comparison between light therapy and antidepressant medication;
- Criterion E: must have quantified the improvement in depression as an outcome variable by validated depression scales;
- Criterion F: if the trial administered LT and/or AD as adjunctive to another intervention (such as sleep deprivation therapy), it must be equally administered in both intervention and control arms to be able to rule out the effect of the adjunct treatment;
- Criterion G: must study adolescents or adults.

Search strategy

We searched the PubMed, PsychInfo, Cochrane Library (Trials), and ClinicalTrials.gov databases with no publication date restrictions and until the 12th of December 2018. The search in PubMed used the following keywords equation: ("light therapy" [All Fields] OR "light treatment" [All Fields] OR "phototherapy" [All Fields] OR "phototherapy" [MeSH Terms]) AND ("depression" [All Fields] OR "major depressive episode" [All Fields] OR "depressive disorder" [All Fields] OR "Bipolar Disorder" [All Fields] OR "seasonal affective disorder" [All Fields] OR "seasonal depression" [All Fields] OR "winter depression" [All Fields] OR "depressive disorder" [MeSH Terms]) AND ("antidepressant" [All Fields] OR "pharmacological treatment" [All Fields] OR "pharmacotherapy" [All Fields] OR "Antidepressive Drugs" [All Fields] OR "antidepressive agents" [All Fields] OR "Tricyclic" [All Fields] OR "Second-Generation Antidepressant" [All Fields] OR "Second-Generation Antidepressants" [All Fields] OR "antidepressive agents" [MeSH Terms]). The search in PsychInfo used the following keywords equation: Light therapy [tx] AND depression [tx] AND antidepressant [tx]. The search in the Cochrane Library used the following keywords equation: 'light therapy in Title Abstract Keyword AND depression in Title Abstract Keyword AND antidepressant in Title Abstract Keyword - (Word variations have been searched)'. Finally, the search on the ClinicalTrials.gov used the following keywords equation: Condition = depression, other terms = "light therapy".

Forward citation searching was conducted using the "cited by" function in PubMed. Backward citation searching was performed by reviewing the reference list in identified studies. Two reviewers (PAG, ER) independently screened the title, abstract, and keywords of each study identified by our search strategy and applied the inclusion criteria. Following this screen, the same procedure was applied to the full text of eligible studies. Authors were contacted to provide missing data. Discrepancies between reviewers were resolved by discussion with a third reviewer (PB). The literature search strategy is summarized in Fig. 1.

Data extraction

Two reviewers (PAG, ER) independently extracted the following data (N and prevalence, or means and standard deviations, SD) when present: 1) demographic data (sample size, age, gender), 2) clinical features (diagnosis, in−or out-patients, depression rating scale scores at baseline and at study post-intervention), 3) LT protocol (randomization groups, LT intervention [timing of administration, light intensity and duration of light exposure], placebo LT used, antidepressant intervention [molecule, dosage and timing of administration], intervention duration). Study outcome was based on the immediate post-intervention depressive symptom scores, as measured by a standardized and validated psychometric depressive symptoms scale. The large majority of studies did not report mean change scores or the standard deviation in change scores that would be required to use the average change in a depression score from baseline to trial end-point as the primary outcome. Therefore, post-intervention depression scores were used as in previous meta-analyses for LT versus placebo [18]. Any discrepancies in data extraction were corrected by re-examining the original publications and consensus agreement. When data were missing, researchers were contacted by PAG for further information.

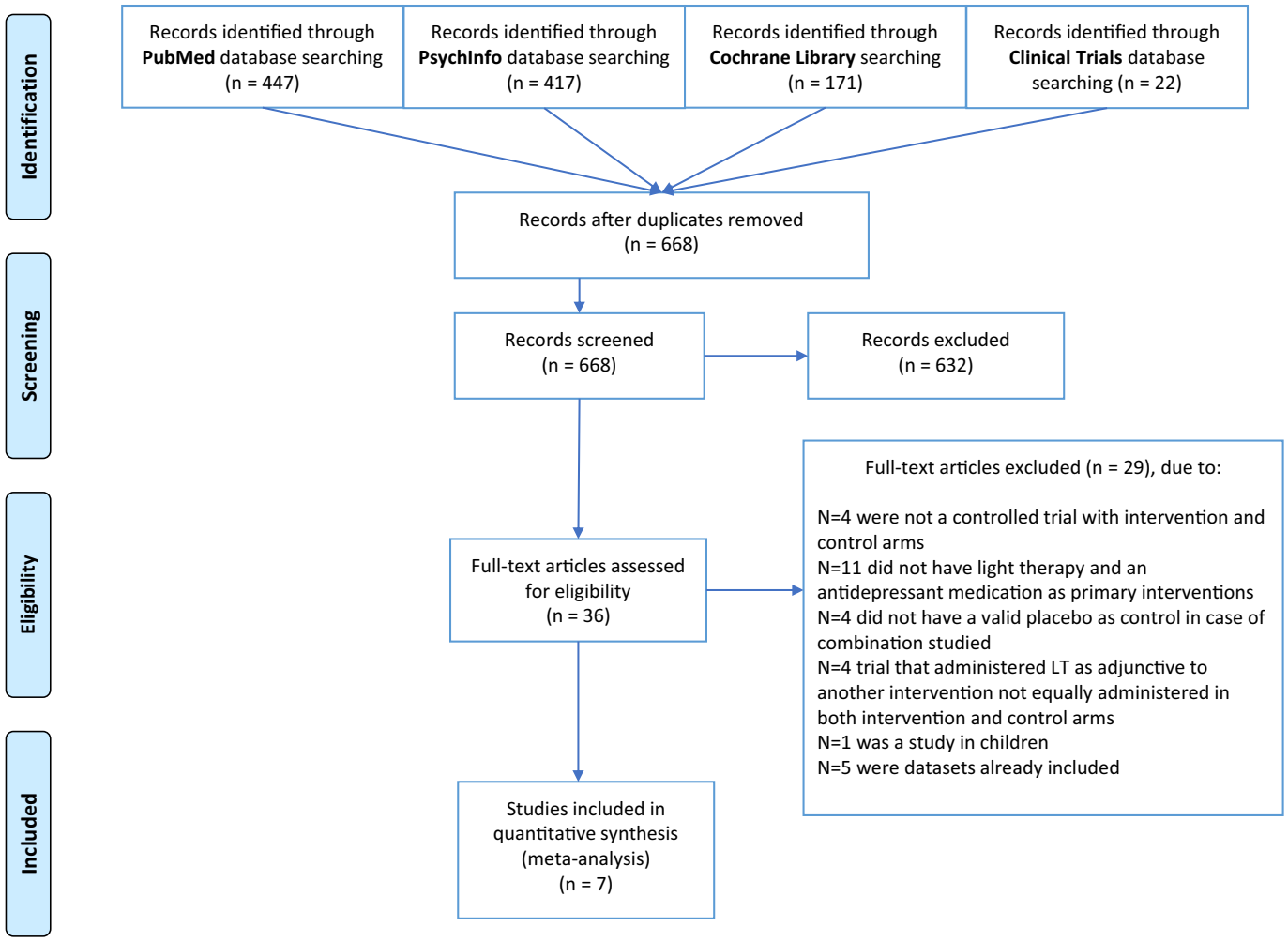


Fig. 1. Systematic review flow diagram of studies selection process.

Meta-analysis

We first conducted a meta-analysis to compare the monotherapeutic effect of AD and LT, by comparing the post-intervention mean depression score between a group receiving LT and placebo AD versus a group receiving AD and placebo LT. Secondly we conducted meta-analysis to compare the efficacy of the combination of AD + LT compared to AD + placebo LT. Lastly, we performed the LT + AD versus LT + placebo AD comparison, with no subgroups analyses possible because of too few studies. Mean depression scores, along with standard deviations (SD), were used in the calculation of the standardized mean difference (SMD) and 95% confidence interval (95% CI) for each study. Specifically, the SMD was defined as the post-intervention mean depression scores divided by the pooled SD of the measurements, which were weighted by sample size. The SMDs were interpreted in a manner similar to Cohen's d (0.20 = small ES; 0.50 = medium ES; 0.80 = large ES). To avoid the assumption that all studies are estimating a same treatment effect, a random effects meta-analysis was conducted [19]. The residual heterogeneity was assessed using the restricted maximum likelihood method [20]. Analyses were performed using METAFOR package in R (version 3.4.3) [21]. The I^2 statistic was used to quantify heterogeneity between studies, with the values of 25%, 50%, and 75% reflecting a small, medium, and large degree of heterogeneity, respectively [22].

To investigate whether the studies included in our meta-analysis are a representative sample of all published and unpublished studies that are conducted in the field, we checked for publication bias by funnel plot asymmetries (suggesting potential publication bias) investigated by visual inspection, and Egger's regression test for funnel plot asymmetry and the rank order correlation (Kendall's tau b) between the treatment effect and the standard error (significant correlation suggests that bias exists).

To assess the risk of biases for the retained studies, we used the Cochrane collaboration's tool for assessing risk of bias in randomized trials [23]. This risk of bias tool is a comprehensive approach to assess potential bias in randomized trials included in systematic reviews or meta-analyses, and proposes a clear and visual presentation of the study quality, evaluating both the design, the report of the results and other biases.

Finally, we tested the moderating role of the *a priori* selected factors: the duration of intervention, the dose of light, age, gender ratio, and baseline depression scores (*a priori* selected) using meta-regression models. Dose of light were scored as follows: 1 = less than traditionally recommended, 2 = adequate to recommendations, 3 = more than recommended (traditionally recommended: 10 000 Lux for 30 min, or 5000 Lux for 1 h, or 2500 Lux for 2 h) [24–26].

For all statistical analyses, the α level for significance was set to 0.05.

Results

Search results

As shown in Fig. 1, the initial search returned 668 records (after removal of duplicates). Following preliminary screening of the 668 titles and abstracts, 632 records were excluded, whilst 36 were reviewed in detail. We further excluded 29 studies upon full-text eligibility assessment. Amongst them four studies were not controlled trials, 11 did not have light therapy and an antidepressant medication as primary interventions, four were combination studies which did not have a valid placebo (as control), four had adjunctive treatment not equally administered in the intervention and control arm, and one was a study conducted in children. Additionally, five studies used the same population as one already included and were thus excluded [27–31]. Therefore, seven independent populations were included in the meta-analysis [11,32–37].

Study characteristics

Study designs

The seven studies included a total of 397 participants, including 110 patients treated with LT and an antidepressant drug, 109 treated with LT and a placebo drug, and 178 with an antidepressant drug and a placebo LT. The median sample sizes were, respectively for each group, 18 (range 4–48), 26 (range 9–48), and 20 (range 4–54). The majority of participants were outpatients except in the study of Benedetti el al. (2003) and Prasko et al. (2002), with seasonal or non-seasonal MDD and BD (see Table 1). Participants were all diagnosed according to DSM criteria: older studies used DSM-III-R and the most recent DSM-IV-TR. All studies included patients with moderate to severe major depressive episode. The methodologies varied considerably in terms of interventions (active LT, antidepressant, and placebos), and measurements including the scales used to assess depressive symptoms. The median duration of intervention was 5 wks (range 2–8 wks). Baseline and post-intervention scores of the primary depression measure are presented in Table 2.

Risk bias assessment of included studies

Regarding the risk of bias assessment summarized in Table 3, four out of seven studies were judged to have 'high' or 'unclear' risk of bias for at least one essential methodological criterion. The three most recent studies were judged with a low risk of bias for all essential criteria. Approximately 70% of the randomized trials reported the method of randomized sequence generation. Nearly half failed to report the method of allocation concealment when randomizing participants. Most of included trials (6 out of 7) reported some form of masking of study participants, and also implemented masking of outcome assessors. The majority of included studies did not state whether a 'complete-case' or 'intention-to-treat' analysis was conducted, and the number of individuals approached for enrollment was rarely reported. Over 50% of the included studies were likely biased towards type II errors due to particularly small sample sizes of less than 20 people in each

Table 1
Study designs of included controlled trials.

Study	Diagnosis (criteria), in-/out-patients	Groups (total N; % female)	LT[a]	Placebo LT	AD	Outcome measure
Lam et al., 2016 [11]	Non-seasonal MDD (DSM-IV-TR) Out-patients	1) LT + AD (29; 51.7%) 2) Placebo LT + AD (31; 71.0%) 3) LT + placebo AD (32; 53.1%)	10 000 lux 30 min/d Morning	Inactive ion generator 30 min/d Morning	20 mg/d Fluoxetine	MADRS
Lam et al., 2006 [33]	Seasonal Winter MDD (DSM-IV) Out-patients	1) LT + placebo AD (48; 64.6%) 2) Placebo LT + AD (48; 68.8%)	10 000 lux 30 min/d Morning	100 lux placebo LT boxes used neutral density filters 30 min/d Morning	20 mg/d Fluoxetine	HRSD
Martiny 2004 [34]	Non-seasonal MDD (DSM-IV) Out-patients	1) LT + AD (48; 70.8%) 2) Placebo LT + AD (54; 66.7%)	10 000 lux 60 min/d Morning	50 lux Red light 30 min/d Morning	50 mg/d Sertraline	HRSD
Benedetti et al., 2003 [32]	Non-seasonal MDD and BD (without psychotic features) (DSM-IV) In-patients	1) LT + AD (18; 83.3%) 2) Placebo LT + AD (12; 75%)	400 lux (Green light) Morning	Deactivated negative ion generator Morning	40 mg/d Citalopram	HRSD
Prasko et al., 2002 [35]	Non-seasonal Recurrent MDD (DSM-III-R) In-patients	1) LT + AD (11; 72.7%) 2) LT + Placebo AD (9; 45.5%) 3) Placebo LT + AD (9; 54.5%)	5 000 lux 2 h/d Morning	500 lux Dim Red light 2 h/d Morning	150 mg/d Imipramine	HRSD
Thorell et al., 1999 [37]	SAD (DSM-III-R) Out-patients	1) LT + AD (4; 100%) 2) LT + Placebo AD (4; 100%)	350 candela/m^2 (≅4400 lux) 2 h/d Morning		40 mg Citalopram	CPRS-25
Ruhrmann et al., 1998 [36]	SAD (DSM-III-R) Out-patients	1) LT + Placebo AD (20; 70%) 2) AD + Placebo LT (20; 85%)	3 000 lux 2 h/d Chosen schedule: 2 h morning, 2 h evening or 1 h morning + 1 h evening.	100 lux Placebo light 2 h/d	20 mg/d Fluoxetine	HRSD

AD: Antidepressant; LT: Light Therapy; CPRS-25: Comprehensive Psychiatric Rating Scale- 25-item version for depression; DSM: Diagnostic and Statistical Manual of Mental Disorders; HRSD: Hamilton Rating Scale for Depression; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; BD: Bipolar Disorder; SAD: Seasonal Affective Disorder.

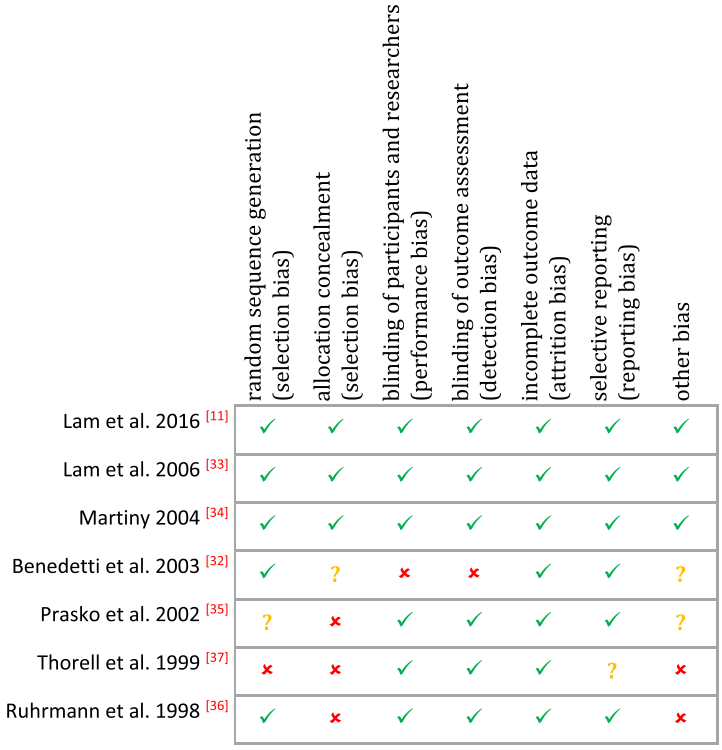
[a] Full spectrum white unless specified.

Table 2
Depression scale baseline and post-intervention scores, and moderators value by included controlled trials.

Study	LT + AD		LT + Placebo AD		AD + Placebo LT		Moderators				
	Baseline score (SD)	Endpoint score (SD)	Baseline score (SD)	Endpoint score (SD)	Baseline score (SD)	Endpoint score (SD)	Light dose[b]	Baseline score (mean)	Intervention duration in weeks (mean)	Age in years (mean)	Female (%)
Lam et al., 2016 [11]	26.9 (4.1)	10.0 (8.1)[a]	27.0 (5.8)	13.9 (11.1)[a]	26.6 (4.7)	17.9 (10.0)[a]	2	26.6	8	38.8	62.3
Lam et al., 2006 [33]	–	–	30.2 (5.5)	11.6 (9.9)	29.6 (5.3)	11.6 (9.5)	2	29.9	8	43.5	66.7
Martiny 2004 [34]	22.4 (4.4)	9.0 (4.4)	–	–	22.1 (3.5)	11.6 (4.3)	3	22.2	5	44.6	68.6
Benedetti et al., 2003 [32]	23.7 (6.9)	7.39 (7.7)	–	–	22.6 (4.9)	13.1 (8.3)	1	23.3	4	54.3	80.0
Prasko et al., 2002 [35]	23.0 (6.4)	17.0 (11.2)	23.1 (3.6)	8.7 (5.8)	24.7 (3.8)	13.0 (7.9)	3	23.6	3	42.6	65.5
Thorell et al., 1999 [37]	–	0.4 (0.3)	–	0.6 (0.2)	–	–	3	–	2	48.8	100.0
Ruhrmann et al., 1998 [36]	–	–	34.6 (5.4)	14.0 (10.5)	34.4 (6.5)	15.6 (8.2)	2	34.5	5	41.1	78.6

AD: Antidepressant; LT: Light Therapy.
[a] Calculated from change from baseline mean (SD).
[b] Dose of light were scored as follows: 1 = less than traditionally recommended, 2 = adequate to recommendations, 3 = more than recommended (traditionally recommended: 10 000 Lux for 30 min, or 5000 Lux for 1 h, or 2500 Lux for 2 h).

Table 3
Risk of bias table.



legend: red cross: high risk of bias, orange question mark: unclear, green mark: low risk of bias

arm. Finally, other reasons for 'high' risk of bias included: reporting only total sample demographics as opposed to demographics specific to each trial arm and failing to present a power calculation.

Meta-analysis

Separate weighted random-effects meta-analyses were undertaken for each of the comparisons that were eligible for analysis: the comparison LT + placebo AD versus AD + placebo LT (k = 4 studies), the combination LT + AD versus AD + placebo LT (k = 5), and the combination LT + AD versus LT + placebo AD (k = 2).

LT + placebo AD versus AD + placebo LT

Depressive scores were not significantly different between LT + placebo AD and AD + placebo LT, with a non-significant SMD in favor of LT + placebo AD of 0.19 $CI_{95\%}$ [−0.08–0.45] (z = 1.37, p = 0.17). Meta-analysis showed no heterogeneity between studies (I^2 = 0.00%). See Fig. 2.

LT + AD versus AD + placebo LT

Depressive scores were lower in the combination LT + AD versus AD + placebo LT, with a significant SMD in favor of LT + AD of 0.56 $CI_{95\%}$ [0.24–0.88] (z = 3.42, p < 0.001), accounting for a medium effect size. Meta-analysis showed a small heterogeneity between studies (I^2 = 18.41%). See Fig. 3.

In post-hoc analysis, we repeated this comparison in the subgroup of patients suffering only from non-seasonal depression and confirmed the better efficacy of LT + AD versus AD + placebo LT, with a significant SMD in favor of LT + AD of 0.55 $CI_{95\%}$ [0.16–0.93]

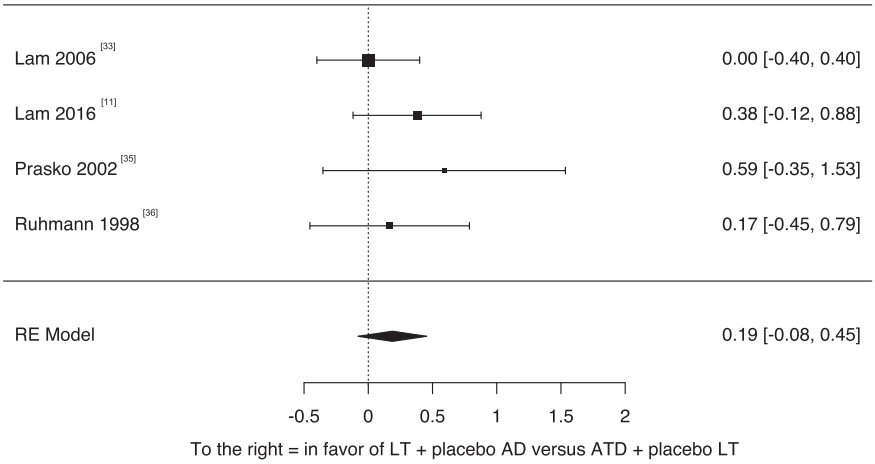


Fig. 2. Meta-analysis' forest plot of depressive scores comparison between light therapy and antidepressant drug monotherapies.

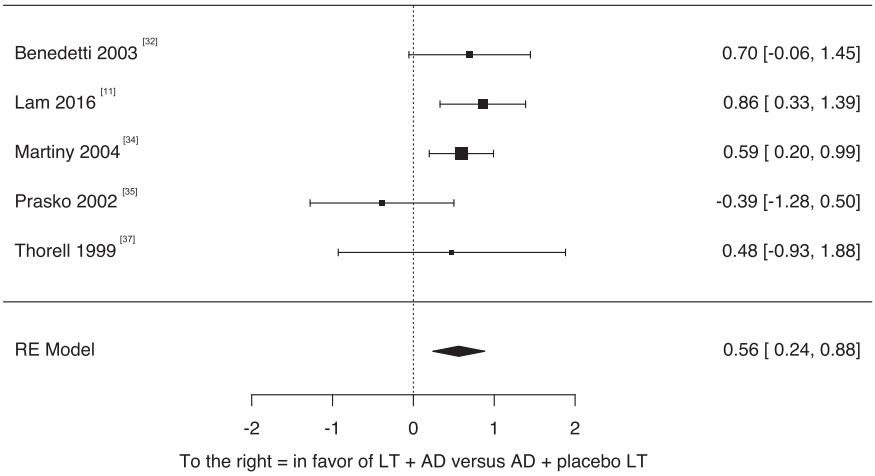


Fig. 3. Meta-analysis' forest plot of depressive scores comparison between the combination of light therapy and antidepressant drug versus antidepressant drug monotherapy.

(z = 2.80, p = 0.005). Meta-analysis showed a small heterogeneity between studies (I^2 = 39.23%) (Fig. 4).

LT + AD versus LT + placebo AD

We did not observe any difference in depressive scores between the LT + AD and the LT + placebo AD, with a SMD of 0.19 CI95% [-1.1 - 1.4] (z = 0.30, p = 0.77). Of note, only two studies were eligible for this meta-analyses [11,35] and results yielded great heterogeneity (I^2 = 82.72%), thus the interpretation of this result is very limited. See Fig. 5.

Publication bias

Visual examination of funnel plots suggested no publication biases for the comparisons LT + placebo AD versus AD + placebo LT (Fig. S1), and the combination LT + AD versus AD + placebo LT (Fig. S2). The Egger's regression test for funnel plot asymmetry confirmed the absence of asymmetry (p = 0.28, p = 0.34; respectively). Rank correlation tests for funnel plot asymmetry also confirmed the suggested absence of publication biases (Kendall's Tau = 0.33, p = 0.75; and Kendall's Tau = −0.40, p = 0.48; respectively).

Evaluation of moderators

For all *a priori* selected moderators, we did not find significant effects in the random effect model of the comparison LT + AD versus AD + placebo LT. Indeed, the main effects in the random effect model were not significant for the duration of intervention (Estimate = 0.129 [−0.026–0.28]; Z = 1.63; p = 0.10), dose of light (Estimate = −0.25 [-0.76–0.27]; Z = −0.93; p = 0.35), age (Estimate = 0.0048 [−0.081–0.091]; Z = 0.11; p = 0.91), gender ratio (Estimate = 0.0054 [-0.063–0.073]; p = 0.88), and baseline depression scores (Estimate = 0.018 [−0.11–0.14]; p = 0.78).

Discussion

Main results

This is the first meta-analysis in patients with moderate to severe major depressive episode to compare monotherapies LT and AD and to investigate the efficacy of the combination of both treatments. This brings the necessary complementary knowledge, in addition to the existing meta-analyses comparing LT with placebo, to change clinical practice and use LT as a first-line strategy or

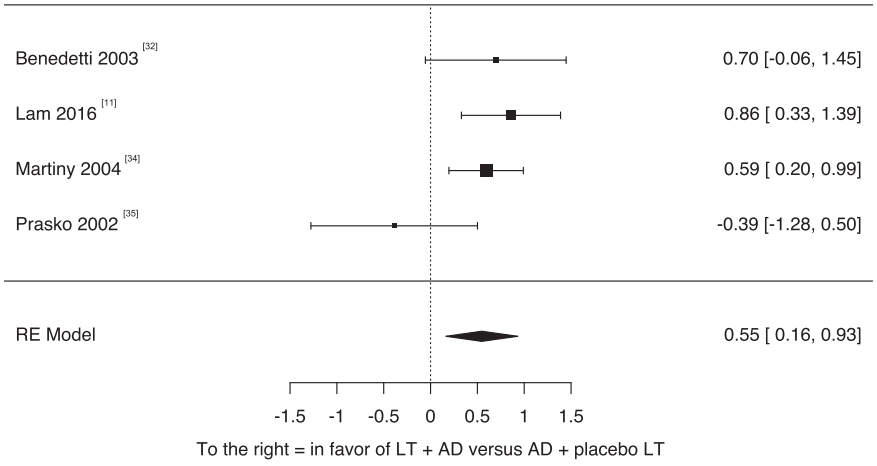


Fig. 4. Meta-analysis' forest plot of depressive scores comparison in non-seasonal depression between the combination of light therapy and antidepressant drug versus antidepressant drug monotherapy.

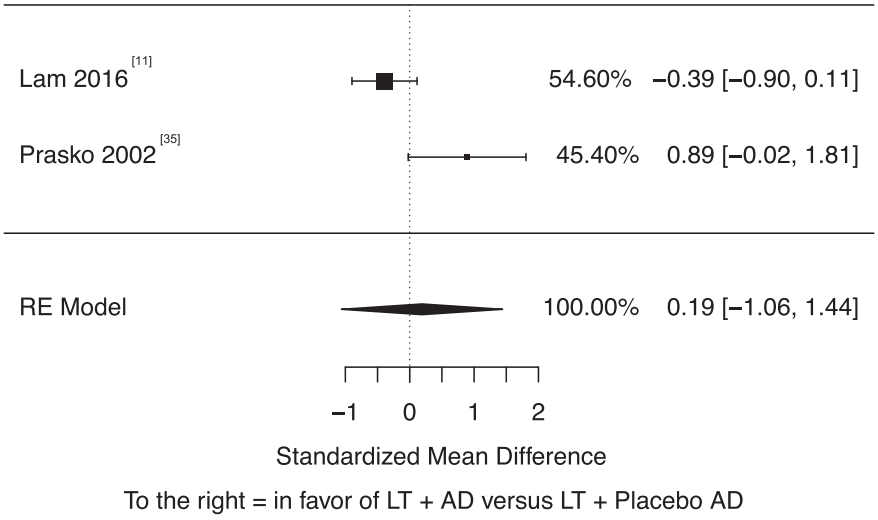


Fig. 5. Meta-analysis' forest plot of depressive scores comparison between the combination of light therapy and antidepressant drug versus light therapy alone.

the combination of the two. The latter comparison is also of great relevance since LT is, to date, mainly used to augment AD efficacy in the case of residual depressive symptoms or resistant depression [8]. Here we observe that LT and AD show no superiority of one treatment compared to the other in major depressive episode. This may plead for the possibility to use LT with the same expectations of efficacy as AD when used as a first-line antidepressant strategy, and this should be confirmed by non-inferiority studies. Moreover, it appears that the combination of LT and AD shows a greater efficacy with a clinically relevant medium effect size compared to AD monotherapy. The meta-analysis regarding comparison of the combination versus LT monotherapy shows similar efficacy of both strategies, but must be interpreted with extreme caution, since only two studies associated with important heterogeneity were included, thus awaiting further studies.

Strengths and limitations

The existing literature has several flaws that limit interpretation of the results. The main one is the small number of randomized trials which reduces statistical power and does neither allow further assessments of moderators nor to analyze all subgroups of patients. Most studies had also a small sample size which may have resulted in their individual point estimates being underpowered and prone to type II errors.

Among these shortcomings, we were not able to fully address issues about the light administration protocol, which is a major avenue to better implement LT in the clinical setting. All included randomized studies used LT daily and mostly during the morning, which appear to be two important factors, along with an estimated dose of light that did not seem to have a large influence on the results. Also, most studies used an intensity of light deemed an "efficient dose" [38]; thus a threshold effect could explain the fact we did not find a dose-effect response of light-intensity. Indeed, it is recommended that LT use in SAD may begin with a light intensity of 10 000 lux at an exposition duration of 30 min, or 5000 Lux for 1 h/d, or 2500 Lux for 2 h/d [24–26]. In addition, it has been observed that low-intensity blue-enriched light (750 lux) has a therapeutic effect comparable to standard bright light (10 000 lux) in treating SAD [39], thus the low intensity green light used in Benedetti et al. (2003) may also show these properties [32]. Early morning administration offers greater chances for remission [24–26]. In non-seasonal depression, the same daily early morning exposures to 2500 Lux for 2 h [40], 5000 Lux for 1 h [41], or 10000

Lux for 30 min [11] appear efficient in reducing depressive symptoms. Some differences may exist between subgroups of patients, and because of the few studies with comparable LT interventions, it was impossible to compare different protocols within depression subtypes such as unipolar or bipolar, and with or without seasonal pattern. In addition, there is a clear need to test different escalation dose protocols in different subgroups of depressed patients [38]. The real-life antidepressant practice of LT is to increase dose (duration and/or light intensity) in case of insufficient or partial response, leading to more responders [42]. Of note, the same dose-dependent response effect is observed with AD, and thus this argument should not be used to conclude, at this point, of a higher efficacy of LT versus AD. These results point to the need for future studies to compare different escalation dose protocols of LT to be able to identify the most efficient one.

The type of antidepressant which should be used in combination with LT also warrants closer examination. This meta-analysis included studies that mostly assessed SSRIs (6/7), with only one assessing tricyclics [35]. Post-hoc meta-analysis excluding the Prasko et al. study that used tricyclics increased the effect size of the combination LT + AD versus AD + placebo LT, with a significant SMD in favor of LT + AD of 0.68 $CI_{95\%}$ [0.39−0.97] ($p < 0.001$), with no heterogeneity between studies ($I^2 = 0\%$). Of note, the comparison of both monotherapies, LT versus SSRIs, remained non-significant ($p = 0.28$), with no heterogeneity between studies ($I^2 = 0\%$). So this meta-analysis mainly highlights antidepressant effects with SSRIs, and shows that LT versus SSRIs monotherapies show comparable efficacy, with a clear synergistic effect when combined [11,32−34,36,37].

The blinding of light treatment may be questionable and has been subject to several different placebos, including the use of a deactivated negative ion generator, red light and different light intensities [11,34]. Whereas the blinding of the investigators is possible, patients benefit from recognizably different treatments that can produce different expectations, no matter how the blinding of the patient is done. Indeed, it is understandable that participants cannot be masked to light therapy or placebo light to the same degree that is possible with a drug trial and a placebo pill, nevertheless investigators have often blinded participants to their study hypothesis.

Taken as a whole, methodological flaws, small sample sizes, and heterogeneity of published studies have resulted in a moderate strength of evidence. The quality of current evidence supports a recommendation for LT as a first line monotherapy, and combination therapy with AD. This first combination meta-analysis adds to the recommendations reached by previous meta-analyses regarding LT as an effective antidepressant treatment in seasonal and non-seasonal depressions, emphasizing that LT should be added to the armamentarium of available antidepressant strategies [3−5,8,18,43,44], even in older patients [45]. Not yet discussed though clinically highly relevant, compared with traditional AD, LT produces faster antidepressant benefits usually within a week, and also acts to stabilize and resynchronize circadian rhythm disturbances, and to improve associated sleep-wake disorders [6,46]. These latter chronobiological effects add to the synergistic antidepressant effect when combined with AD, and emphasize the usefulness of the combination as a first line strategy. Of note, combination with non-pharmacological chronotherapeutics, such as sleep deprivation and sleep phase advance, also show interesting efficacy and should be considered in future therapeutic guidelines [47].

Tolerance and safety

Whereas methodologies varied considerably in terms of LT interventions, LT appeared to be well tolerated, with the most common adverse effects being headache, eyestrain, nausea and agitation, which were usually transient and mild [24−26,48]. This work focused on LT efficacy and did not examine specifically safety. Nevertheless, the available data in the included studies show that both AD and LT monotherapies are well tolerated with similar drop-out rates. Nevertheless, one study observed significant differences in treatment-emergent adverse events (TEAEs) in fluoxetine treated patients versus LT: agitation (12.5% versus 0%), sleep disturbance (29.2% versus 2.1%), palpitations (10.4% versus 0%), pointing to a more advantageous benefit-risk profile for LT [33]. The most recent randomized trial found that combination treatment did not show higher rates in any TEAE, suggesting that the combination may mitigate some of the adverse effects of fluoxetine and LT monotherapies, especially regarding sleepiness [11], although it is possible that the sample sizes were simply too low to observe significant differences in TEAE with only 30 patients per group. No randomized trials have reported data on long-term side effects or toxicity of LT, and there is a need for additional long-term follow-up studies.

Regarding manic switches in included randomized trials, only one patient with SAD treated with LT monotherapy presented an hypomania conversion [36]. Of note, few studies have used standardized scales for (hypo)mania, and agitation might be observed. Nevertheless, it is important to remember that these antidepressant strategies, LT and AD, must be initiated in patients with bipolar disorders only when treated with mood-stabilizers preventing manic switches [49]. In bipolar disorders, rates of manic switch after LT appear to be low [48,50], but particular attention should be paid with rapid cycling patients and in some cases, morning exposures [51]. Benedetti et al. performed a systematic review of the literature studies reporting the effect of LT in BD and concluded that the rate of switch into mania after morning LT was small and close to the 4.2% expected during the placebo treatment of BD, whereas the rate of switch into mania after antidepressant drug treatment ranged from 15 to 40% [48].

Regarding suicidal ideations, a case-report from 1997 of three cases (two individuals with seasonal bipolar depression et one with a seasonal unipolar depression) observed suicidal ideations emergence during the first week of LT in monotherapy for two of these individuals [52]. On the contrary, more recent studies have examined specifically this issue of suicidality and LT in patients with SAD and observed a protective effect. Indeed, half of the 191 individuals presented with a decrease of suicidal ideation, and only six of these individuals worsened their suicidal ideation [53]. This 'anti-suicidal' protective effect has also been confirmed in two studies combining LT with other therapeutic strategies in unipolar [54] and bipolar disorders [55]. To conclude, LT may worsen suicidal thoughts very sporadically, and shows rather preventive efficacy in the majority of patients.

It is commonly considered that the main relative contraindications for LT are ophthalmologic disorders (cataract, macular degeneration, glaucoma, retinitis pigmentosa) and disorders affecting the retina (retinopathy, diabetes, herpes, etc.); overall, patients at potential risk should have pretreatment ophthalmological examinations [26]. However, these are mostly theoretical and preventive recommendations since, to the best of our knowledge, no reports have been published to date of possible retinal toxicity of LT, which has been confirmed by a 5-year follow-up study that observed no adverse ocular effects [56].

Conclusion

No differences were observed between LT and AD efficacy when introduced as a first line treatment in major depressive episode with and without seasonal pattern. LT produces faster

antidepressant benefits than AD and also acts on circadian rhythm alterations. In addition, this meta-analysis shows a clear superiority of the combination of the two compared with AD alone, with a synergistic effect, thus supporting its use as an excellent first line antidepressant strategy. Finally, the good tolerance and safety profile, even regarding retinal toxicity, strengthen the recommendation to use this treatment option in major depressive episode with and without seasonal pattern.

Practice points

The systematic and meta-analytic comparison of light therapy (LT) and antidepressant drug (AD) monotherapies as well as their combination in moderate to severe depressive episodes demonstrates that:

1. LT and AD show no superiority of one treatment compared to the other - so both may be used as first-line treatments if monotherapies are preferred
2. The combination LT plus AD is more effective than AD alone, suggesting that the combination may be preferred as a first line treatment to boost and to accelerate response rate
3. The superiority of LT plus AD versus AD alone is also confirmed in non-seasonal depressive episodes

Research agenda

Further knowledge could be acquired in the future by investigating:

1. The most efficient lighting parameters to use (intensity, duration, color spectrum, time of day of administration)
2. The potential differences in LT effects in accordance to 1) clinical features (seasonal or non-seasonal, unipolar or bipolar disorders, etc); 2) biological rhythms; and 3) sleep and alertness (sleep homeostasis)
3. Whether LT can be used as a maintenance treatment
4. Predictive biomarkers of response and tolerability

Conflicts of interest

PAG has received consulting fees from Menarini, and received funding to attend national and international conferences from AstraZeneca, Lundbeck, and Otsuka. CMS was the chief investigator for a multi-center study for Neurim Pharmaceuticals, was investigator for Neurim Pharmaceuticals and Servier, and received financial compensations from Neurim, Biocodex, Janssen, Shire et UCB Pharma. ER has no conflicts of interest. PB has received funding to attend national and international conferences from Adiral, Assistance, LVL medical, Pharma Dom, ADS Alsace, and Bioproject pharma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.101213.

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