

Garbazza Corrado (Orcid ID: 0000-0002-8606-2944)
D'Agostino Armando (Orcid ID: 0000-0002-2126-799X)

Sustained remission from perinatal depression after bright light therapy: a pilot randomised, placebo-controlled trial

Corrado Garbazza^{1,2,3}, Fabio Cirignotta⁴, Armando D'Agostino⁵, Alessandro Cicolin⁶, Sandra Hackethal³, Anna Wirz-Justice^{1,2}, Christian Cajochen^{1,2*}, Mauro Manconi^{3,7,8*}
and the "Life-ON" study group

¹Centre for Chronobiology, University of Basel, Basel, Switzerland.

²Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland.

³Sleep Medicine Unit, Neurocenter of Southern Switzerland, Ospedale Civico, Lugano, Switzerland.

⁴University of Bologna, Bologna, Italy.

⁵Department of Mental Health and Addiction, ASST Santi Paolo e Carlo, Milan, Italy; Department of Health Sciences, Università degli Studi di Milano, Milan, Italy.

⁶Sleep Medicine Center, Department of Neuroscience, University of Turin, Turin, Italy.

⁷Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.

⁸Department of Neurology, University Hospital, Inselspital, Bern, Switzerland.

*These authors should be considered joint senior author

Corresponding author:

Corrado Garbazza, MD. Centre for Chronobiology, University of Basel, Basel, Switzerland. Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland. Wilhelm Klein-Strasse 27, CH-4002, Basel, Switzerland. Phone: +41 78 682 3915. E-mail: corrado.garbazza@upk.ch
CID: 0000-0002-8606-2944

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Conflict of interest disclosures

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Data availability statement

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

Ethics approval and patient consent statement

The “Life-ON” study has been approved by the respective ethics committee of the four participating centres in Italy and Switzerland. All participants gave written informed consent prior to study entry.

Abstract

Objective

Perinatal depression (PND) is a severe complication of pregnancy, affecting both mothers and newborns. Bright light therapy (BLT) has only been tested in a few studies for treating either antenatal or postnatal depression. We conducted a pilot trial to investigate the efficacy and safety of BLT for PND occurring at any time across the perinatal period.

Methods

A single-blind RCT was carried out in women with an EPDS >12 from the 2nd gestational trimester until 9 months postpartum. Participants received either 30-minutes morning BLT (10'000 lux) or dim red light (DRL, 19 lux) for 6 weeks.

Results

Twenty-two women were randomised to BLT (n=11) or DRL (n=11). Among those receiving BLT, 73% achieved remission (improvement \geq 50%, EPDS score \leq 12), in contrast to 27% in the DRL group ($p=0.04$). A significant influence of time on EPDS score and group-time interaction emerged, with a greater reduction in the BLT-group across the follow-up period. No women in either group reported major side effects.

Conclusion

Morning BLT induced a significant remission from PND as compared to DRL and this effect was maintained across the perinatal period. BLT showed an excellent safety profile and was well-tolerated, thus representing a valid therapeutic strategy in this vulnerable perinatal population.

Keywords: pregnancy, postpartum depression, light therapy

Significant Outcomes:

- In a randomized controlled trial with morning bright light therapy vs. low intensity dim red light, the active light intervention induced a rapid and significant remission from perinatal depression as compared to the placebo light
- The antidepressant effect of bright light therapy was maintained throughout the perinatal period, thus significantly modifying the course of the disease

- Given its efficacy, safety profile and acceptance by women with perinatal depression, BLT can be considered a valid therapeutic option in this vulnerable population, which may have difficulty accessing or be reluctant to other therapeutic interventions, such as psychotherapy or pharmacotherapy

Limitations:

- The population investigated was small, thus the study results should be interpreted carefully and considered preliminary to future larger RCTs
- The study was single-blind, meaning that the participants, but not the investigators, were blind to the two different light interventions tested

Introduction

Perinatal depression (PND) is a serious complication of pregnancy, affecting ca. 12% of women during the peripartum, with potentially dramatic consequences for mothers, newborns and their families¹. Since the identified risk factors fall into broad categories, and the safety profile of antidepressant drugs during pregnancy and breastfeeding is still debated, PND remains challenging to predict and treat, thus representing a major public mental health problem². Bright light therapy (BLT) is a non-pharmacological intervention based on circadian science, which has been consistently proven effective and safe for treating seasonal and non-seasonal affective disorders³. However, only a few studies have used BLT in either antenatal or postnatal depression, with overall promising but partly divergent findings^{4,5}. Five of them were randomised controlled trials (RCT) and two were open trials. Oren et al. and Corral et al. performed the first two open studies with BLT for women with antenatal depression (AND) (n=16, 10'000 lux, for 3-5 weeks, 60 min within 10 min of awakening) and postpartum depression (PPD) (n=2, 10'000 lux, for 4 weeks, 30 min between 7:00 am and 9:00), respectively^{6,7}. Both authors found a similar, substantial clinical improvement at the end of the treatment protocol, measured as a reduction of the baseline mean scores on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version (SIGH-SAD) and the 17-item Hamilton Depression Rating Scale (HDRS), respectively. Based on these encouraging findings, the same researchers conducted two different RCTs in the same populations. While Epperson et al. exposed 10 women

with AND to either BLT (7'000 lux, n=5) or dim red light (DRL) (500 lux, n=5) for 5 weeks, 60 min in the morning within 10 min of awakening⁸, Corral et al. performed a first RCT in 15 women with PPD using the same BLT protocol as in their previous case series, but introducing a DRL control group (600 lux, n=5)⁹. Interestingly, both trials showed no differences between treatment arms, with SIGH-SAD scores being similarly reduced by BLT and DRL. In this regard, the antidepressant effects of the higher-intensity placebo lights used in these studies remain unclear, considering that illuminance levels as low as 100 lux have been demonstrated to phase-shift human circadian rhythms¹⁰. In fact, in a recent RCT examining the effectiveness of BLT (9'000 lux, 5'000 K) vs. DRL (100 lux, 2'700 K) for 6 weeks, 30 min in the morning after awakening, in a larger sample of pregnant women with AND (n=67), Bais et al. did not find statistically significant differences between the two treatment groups, with a similar improvement in median depression scores on the SIGH-SAD, HDRS, and Edinburgh Postnatal Depression Scale (EPDS) at the end of the trial, 3 and 10 weeks after therapy, as well as 2 months postpartum⁵. By contrast, Wirz-Justice and colleagues using a similar protocol for BLT (7'000 lux, for 6 weeks, 60 min in the morning, n=16) as in Epperson et al. but a lower-intensity placebo light (70 lux, n=11), found that women with AND who received BLT had significantly greater scores improvement on the SIGH-ADS and HDRS than those in the DRL group¹¹. Moreover, the response rate (HDRS \geq 50% improvement) at week 5 was significantly greater for BLT (81.3%) as compared to DRL (45.5%) and clinical remission (HDRS \leq 8) was attained by 68.6% in the BLT group vs. 36.4% in the DRL group ($p < 0.05$)¹¹.

In general, all the above-mentioned studies focused on either AND or PPD, although this dichotomy no longer exists according to the current 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This, in fact, defines PND as the occurrence of a major depressive episode during pregnancy or within 4 weeks after delivery¹², while most experts even consider any depressive episode beginning up to the first year after childbirth as PND, regardless of the time of onset¹³. According to the DSM-V criteria, a RCT in 23 women with PND was recently published, in which participants were randomised to either BLT (10'000 lux) or placebo light (<500 lux) for 3 weeks, 45 min in the morning¹⁴. Surprisingly, despite the short protocol duration and the rather high illuminance level of the control light used, the authors found response rates after treatment, as assessed by the Montgomery-Åsberg Depression Rating Scale, of 75% in the BLT vs. 18.2% in the placebo group, and remission rates of 41.7% vs. 0%, respectively¹⁴.

1.1. Aims of the study

We here present the results of a pilot RCT aimed at testing the efficacy and safety of 6-week, morning BLT vs. a low-intensity DRL for the treatment of PND occurring at any time across the perinatal period, in which the participants have been followed-up for up to 1 year postpartum.

Methods

This study is part of the “Life-ON” project, a multicentre, prospective, cohort investigation on sleep and mood changes during the perinatal period¹⁵. Participants without a current or recent diagnosis of any psychiatric disorder (including unipolar or bipolar depression, or suicide attempt within the past 12 months) and who were not taking any psychopharmacological treatment or illicit drug, were enrolled during the first trimester of gestation and followed-up until 12 months postpartum. Women already suffering from a depressive episode at the baseline visit were excluded from participation, in accordance with the recruitment criteria and aims of the “Life-ON” project. The main focus of this study was to explore the relationship between changes in hormonal, biochemical and sleep-related factors occurring during the perinatal period and the onset of PND. So far, it is not completely understood which perinatal variables may play a role in causing PND and how the pathophysiology of PND may differ from that of unipolar depression. Ruling out women with predisposing conditions to and/or consequences of a major depression already present before pregnancy (e.g. disturbed sleep) was therefore necessary to better analyse those factors, emerging during the perinatal period, that may represent a specific risk for PND.

A single-blind RCT was conducted in a subsample of women with an Edinburgh Postnatal Depression Scale (EPDS) score >12 at any time point from the second trimester of pregnancy. Participants received either BLT (10'000 lux) or dim red light (DRL, 19 lux) for 6 weeks, 30 min in the morning, within 20 min after wake-up, and at a distance of 30 cm from the light box (Fig. 2). Between-group differences were calculated using the Kruskal-Wallis and Mann-Whitney U tests for ordinal/numeric data, while the Pearson's Chi-squared and Fisher's exact tests were used for categorical data. We constructed multilevel linear models to test for the influence of time and treatment group on EPDS values and log-linear models to test for socioeconomic factors influencing PND remission, such as marital status, educational level, working and housing conditions, smoking, perception of poverty (as assessed by the subjective question "overall, based on your current

economic situation, would you consider yourself poor?" yes/no), job loss or relocation in the previous six months, type of pregnancy (planned, unplanned, unwanted), number of children, family and personal history of depression, previous treatment for depression, other psychiatric disorders, current and past (pre-pregnancy) alcohol consumption. Definitive parameter selection was performed via exhaustive model testing based on Akaike information criteria. Only parameters significantly improving the model were included in the construction of the definitive regression models, fitted with the restricted maximum likelihood method. The study received approval from the local ethics committees. All participants gave written informed consent.

Results

A total of 47 women were approached to participate in the trial, of whom 25 accepted (53%), with three participants lost to follow-up. Twenty-two women were randomised to either an active light group (BLT, $n=11$, median age: 33yrs) or a placebo light group (DRL, $n=11$, median age: 32yrs). The remaining 22 women who developed PND during the main "Life-ON" study declined participation in the RCT. At the time of study inclusion, the BLT and DRL groups did not significantly differ in demographic and mood parameters, with, however, slightly lower median (IQR) EPDS of 5.5 (3.0|10.) points in the BLT group vs. 10.0 (8.5|12.0) points in the DRL group, respectively ($p=0.06$, $r=-0.4$). EPDS values at depression onset were comparable between the two groups, with a median (IQR) EPDS of 15.0 (13.5|16.5) points in BLT vs. 14.0 (13.5|16.5) points in DRL patients, respectively. After treatment, the EPDS scores dropped to 5.0 (2.5|12.0) points in the BLT group vs. 11.0 (8.0|13.5) points in the DRL group (Fig. 1a, $p=0.15$). Among women receiving active BLT, 73% achieved remission (improvement $\geq 50\%$, EPDS score ≤ 12) at the next follow-up visit, in contrast to 27% in the placebo DRL group ($p=0.04$) (Fig. 1b). The multilevel linear model revealed a significant influence of time on EPDS score and group-time interaction, with a greater, sustained reduction in the BLT-group across the whole follow-up period (Fig. 1c). Simple log-linear regression showed a significant effect of BLT on response to treatment ($\beta=1.96$, $z\text{-value}=2.05$, $p=0.04$). When controlling for other influencing factors, best model fit was achieved including EPDS at study entry ($\beta=-1.1$, $z\text{-value}=-1.8$, $p=0.07$), BLT ($\beta=0.6$, $z\text{-value}=0.2$, $p=0.8$), loss of work in the previous 6 months ($\beta=-2.5$, $z\text{-value}=-0.4$, $p=0.7$), unplanned pregnancy ($\beta=-3.97$, $z\text{-value}=-1.1$,

$p=0.3$) and positive history of depression ($\beta=2.7$, $z\text{-value}=0.95$, $p=0.3$) with Tjur's $R^2=0.75$. No women reported major side effects after either BLT or DRL, as assessed by the Systematic Assessment for Treatment Emergent Events at 3 and 6 weeks of treatment.

Conclusions

Morning BLT induced a significant remission from PND as compared to morning DRL. Remarkably, this effect was also maintained across the perinatal period, with sustained mood improvement in the months following treatment. Psychosocial stressors indicative of a more fragile living condition at baseline reduced the overall likelihood of a positive response to treatment. BLT also showed an excellent safety profile and was well-tolerated by perinatal women, thus representing a valid therapeutic strategy in this vulnerable population. One of the strengths of our study is to have followed-up the participants for up to 12 months after delivery. None of the previous investigations included a sufficiently extended observation period to assess the long-term effects of BLT on mood, perhaps assuming that these would vanish once the BLT protocol was terminated. Moreover, in contrast to previous studies, which used placebo lights in a range between 70 and 600 lux^{4,5,14}, we adopted a low-intensity control light, likely further differentiating the neurobiological effects of the experimental light interventions. There is, in fact, growing evidence showing that humans are, on average, highly sensitive to lower illuminance levels than previously thought (dependent on their prior light exposure history, and individually variable) and that a 50% suppression of melatonin can occur even at <30 lux¹⁶. Therefore, although it is still debated which illuminance levels can enhance mood, when planning a RCT to test the efficacy of BLT for depression it seems appropriate to choose a rather low-intensity, and thus likely biologically inactive, placebo light.

This study has, however, also some limitations. The sample size is small, thus entailing that the study results should be interpreted with caution and replicated in larger RCTs, in order to gain further scientific evidence before generalising their clinical implications. The reduced number of participants was mainly due to the common difficulties in recruiting women for interventional trials during the perinatal period, and to the limited treatment compliance related to objective logistic problems (working commitments during pregnancy

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and care of the newborn after delivery). As a comparison, with the exception of the trial by Bais et al.⁵, none of the previous studies on BLT for depression during pregnancy and/or the postpartum succeeded to provide final data from >27 patients^{4,14}. In this regard, based on our experience, there was no a priori distrust or rejection of BLT as a therapeutic tool per se, which was instead well accepted and tolerated by women, but rather an issue of time compatibility, given that the treatment protocol required participants to sit for half an hour in the morning and for 6 weeks in front of a light box. New possibilities are emerging from portable light therapy devices (visors), that could allow women to have a greater mobility during the treatment sessions. However, there is still no solid evidence that these devices are as effective as the traditional BLT lamps, as only few of them have been accurately tested and validated for clinical use so far. Another limitation of the study is the single-blind design, in which researchers who regularly evaluated women's mood changes were not blind to the treatment group the participants were allocated to. Although a double-blind protocol would have been more rigorous from a methodological point of view, this was not applicable in the practice, as the investigators responsible for the interview and psychiatric assessment of the study participants were also in charge of the logistical aspects related to the management, operation control, and distribution of the lamps for BLT.

In conclusion, on the one hand our findings provide new evidence that BLT may be an effective therapeutic strategy in patients suffering from PND, irrespective of the time of onset, who may prefer a chronotherapeutic approach to a pharmacological or psychotherapeutic treatment. On the other hand, given the small population investigated, the study results should be considered preliminary and non-definitive, but they may open the way to larger RCTs, with even longer observation periods, which may elucidate the short- and long-term effects of BLT for perinatal mood disorders. Further research should also investigate the mechanisms underlying the therapeutic action of BLT for PND and the feasibility of mixed modality treatments (e.g., integrated chronotherapy¹⁷, combination of CBT-I and light/dark therapy¹⁸), which should be adequately tested in comparative effectiveness trials.

Figures

Figure 1: Remission and non-response among the different light conditions and influence of time and intervention group on EPDS values across the follow-up period. a) Raincloud-plot with density plot, boxplot and individual EPDS values per patient pre- and post-treatment intervention. b) Percentage of remission and non-response to treatment stratified for the groups exposed to the experimental light conditions. c) EPDS values across the follow-up period relative to the beginning of therapy (yellow vertical bar) stratified for experimental light conditions. Mean time-intervals between the different follow-up visits were 55 days (min. 6 days, max. 132 days). The red dotted vertical line represents the cut-off value of EPDS=12. Right hand side: Results of the multilevel linear regression model predicting EPDS values by intervention group, time (not shown), and group-time interaction. BLT: bright light therapy. Std. Error: Standard error. Pr(>|z|): p-value. * $P<0.05$. ** $P<0.01$. *** $P<0.001$ (group-time interaction).

Figure 2: Experimental light conditions in the “Life-ON” RCT. Left: bright light (10’000 Lux). Right: red dim light (19 lux).

Acknowledgment Section

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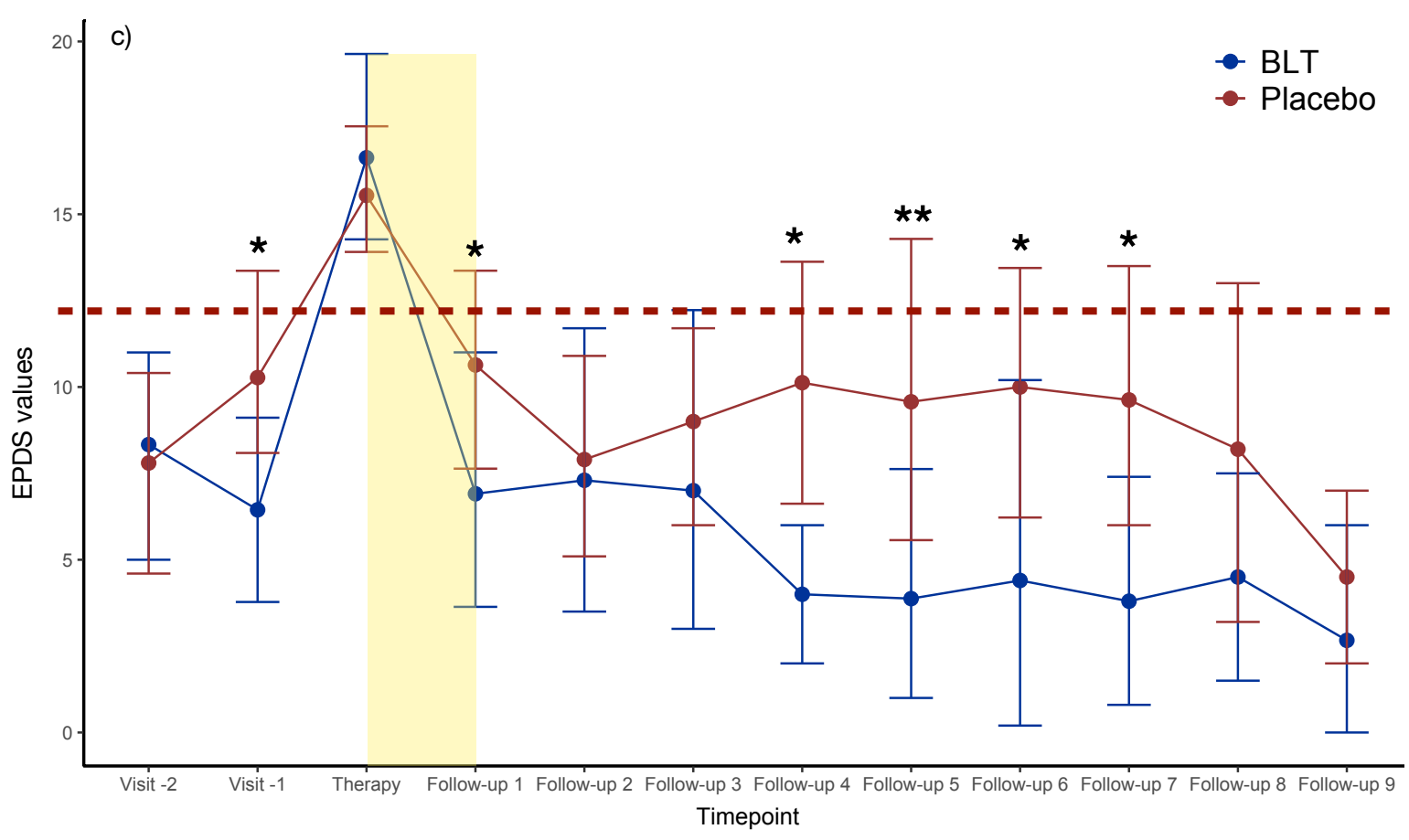
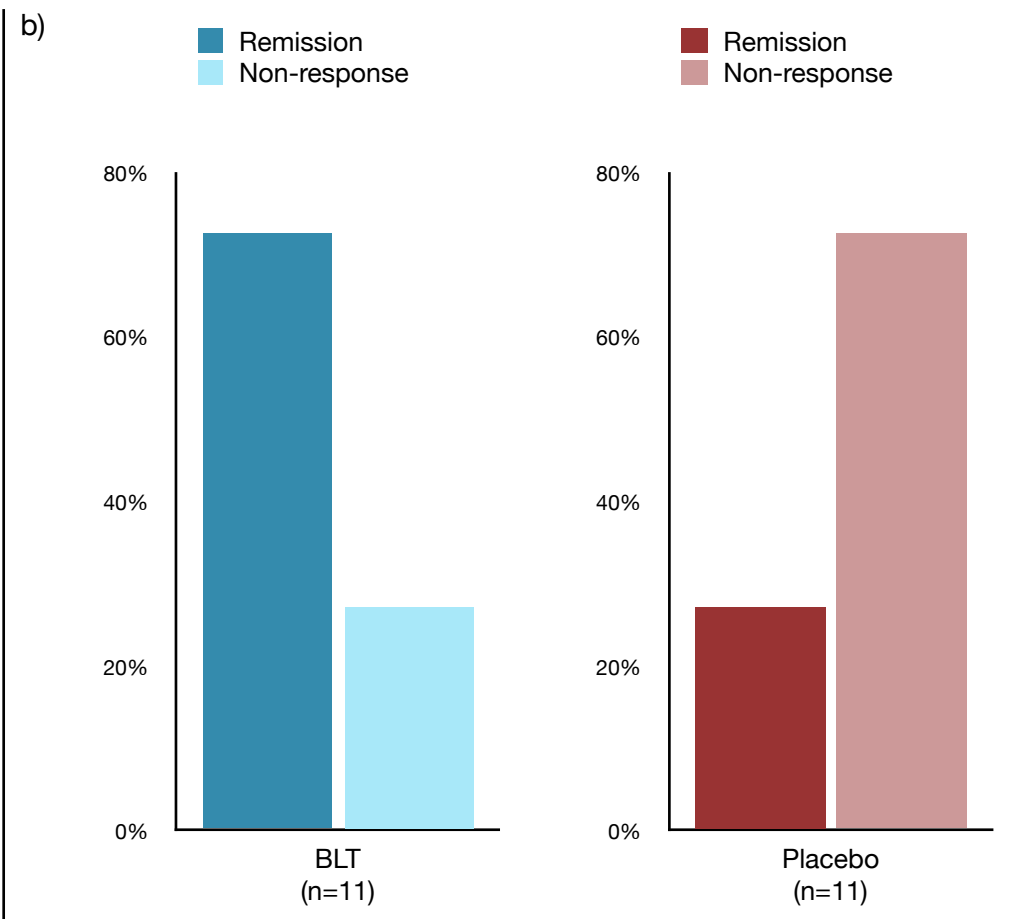
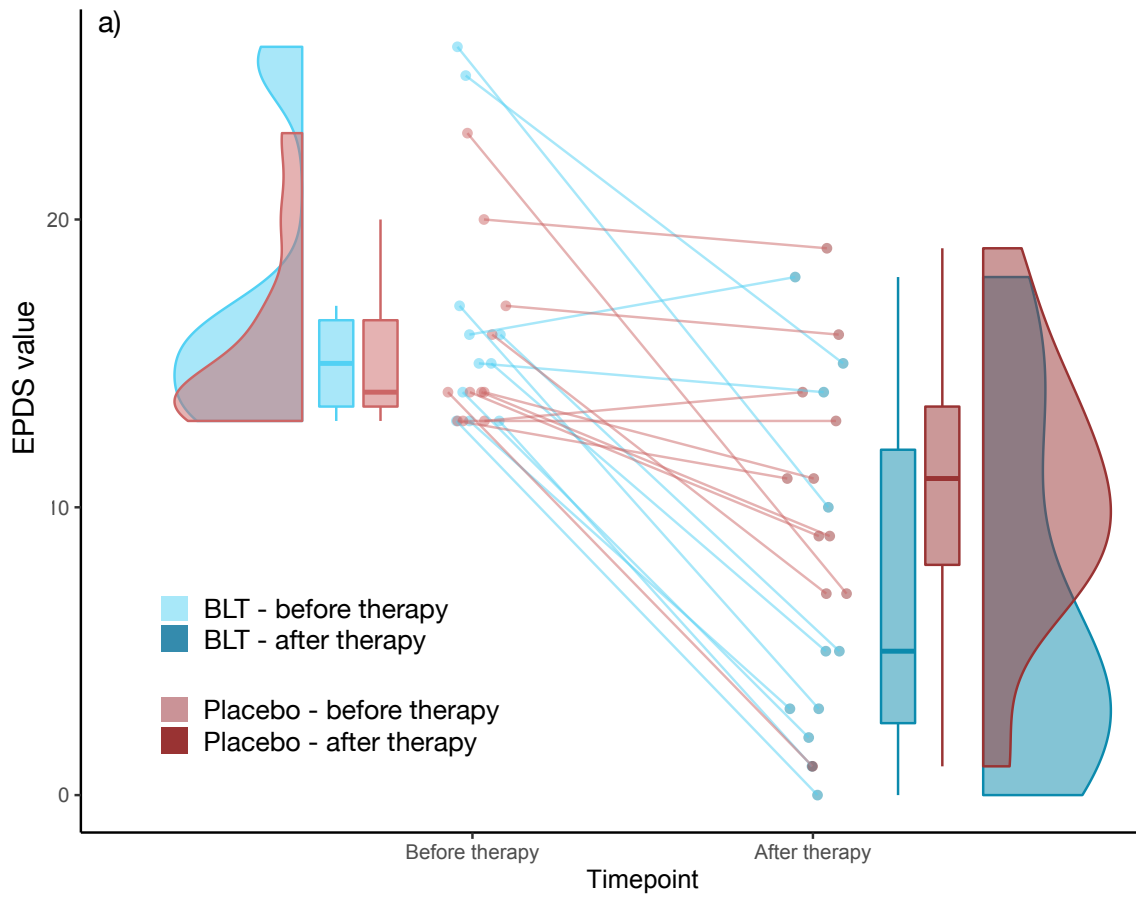
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	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	2.69	0.17	16.27	< 2e-16 ***
BLT	0.05	0.23	0.24	0.813
Visit-2 : BLT	-0.16	0.37	-0.44	0.658
Visit-1 : BLT	-0.62	0.30	-2.09	0.03681 *
Follow-up 1 : BLT	-0.58	0.28	-2.06	0.03933 *
Follow-up 2 : BLT	-0.25	0.30	-0.82	0.415
Follow-up 3 : BLT	-0.43	0.31	-1.39	0.165
Follow-up 4 : BLT	-0.96	0.33	-2.87	0.00407 **
Follow-up 5 : BLT	-1.09	0.40	-2.73	0.00629 **
Follow-up 6 : BLT	-1.04	0.48	-2.16	0.03055 *
Follow-up 7 : BLT	-1.16	0.50	-2.32	0.02018 *
Follow-up 8 : BLT	-0.82	0.51	-1.62	0.105
Follow-up 9 : BLT	-0.89	0.75	-1.19	0.234

