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CLINICAL REVIEW

Sleep deprivation as a treatment for major depressive episodes: A systematic review and meta-analysis

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SUMMARY

Sleep deprivation, alone or in combination with pharmacological treatment and as part of a chronotherapy package, is of potential use for people with major depressive episodes, however the evidence base is still conflicting. The aim of this systematic review and meta-analysis is to assess the clinical effects of sleep deprivation in comparison to any other intervention for the acute and long-term treatment of mood disorders.

We searched electronic databases and trial registries (last update: 16th October 2021) for published and unpublished randomised controlled trials recruiting participants with a major depressive episode in unipolar or bipolar affective disorder.

The clinical outcomes of interest were the reduction in depressive symptoms at different timepoints and the number of participants experiencing at least one side effect.

Overall, 29 trials (1246 participants) were included. We did not find any difference in change in symptoms or all-cause discontinuation between interventions including SD compared to a control of the same intervention except without SD. In the included studies there were no available data for adverse events.

Using the most methodologically rigorous approach, we did not find evidence that the addition of sleep deprivation to treatment packages leads to enhanced depressive outcomes.

Introduction

Sleep deprivation (also known as "wake therapy") is defined as a period of imposed wakefulness (which can be total or partial with respect to exceeding a circadian cycle). Sleep deprivation (SD) has been accepted as a treatment for major depressive episodes (MDE) since the 1970s [1]. There have been many case studies and observational studies but few randomised control trials (RCTs) [2] and several recent systematic reviews of poor methodological quality. A widely cited review claimed a 50–80% response rate to SD in MDE using only uncontrolled within-subject data [2], thus these conclusions are likely to be biased because of the lack of a proper comparison group [3]. Increasingly SD is combined with sleep phase advance and bright light therapy (BLT) as a chronotherapy package based on the hypothesis that this will reset and stabilise circadian rhythmicity [4]. A recent meta-analysis of chronotherapy for the rapid treatment of depression found benefit for chronotherapy that included SD at 5–7 days [5] but demonstrated a smaller effect size in RCTs than in open label case series (33% rather than 62% of patients were reported to be responders) [5].

While mechanisms underlying the potential antidepressant effect of SD have received limited attention - and remain poorly understood – several putative pathways have been suggested [4]. It is known, for example, that extended wakefulness increases cortical excitability, glutamate release, and net synaptic strength [6]. In those with depression, SD may serve to shift the window of inducible

Abbreviations: BLT, Bright light therapy; BDNF, Brain derived nerve factor; RCT, Randomised control trial; SD, Sleep deprivation; SMD, Standardised mean difference; StD, Standard deviation; TMS, Transmagnetic stimulation; TSD, Total sleep deprivation.

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synaptic plasticity to a more optimal time, compensating for attenuated or deficient synaptic strength during typical wake periods, and subsequently driving acute improvement in mood [7,8]. Small studies have shown increased markers of neuroplasticity following SD in depression, including elevated serum levels of brain derived nerve factor (BDNF) [9] and altered inducibility of cortical associative plasticity using transmagnetic stimulation [10]. The focus on increased synaptic strength as a corrective mechanism suggests a potential role for selective disruption of slow wave activity during sleep in those with depression, to prevent overnight synaptic downscaling and decreased net synaptic strength.

In this review our aim was to assess the efficacy, acceptability and tolerability of SD in comparison to any other intervention for the acute and long-term treatment of major depressive episodes in unipolar or bipolar affective disorders. We examined all the available evidence to determine if SD is effective as a stand-alone treatment or if it can be determined that SD is an active component of a chronotherapy package.

Methods

We carried out a systematic review and meta-analysis of SD as a treatment for major depressive episodes. To reduce the risk of an overestimate of efficacy we chose to include only RCTs in this review and we attempted to quantify the specific effects of SD from that of chronotherapy packages that include SD. We considered for inclusion people of both sexes without age restriction with a current unipolar or bipolar major depressive episode according to any of the following standard operational criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM−III−R, DSM-IV, DSM-IV-TR, DSM-5, ICD-10. This review put no restriction on language and did not exclude on the basis of age or study setting in contrast to previous meta-analyses from 2017 [2] and 2020 [11].

We identified published and unpublished RCTs searching the following databases and registries: AMED, CINAHL, Cochrane Central Register of Controlled Trials, Embase, LILACS database, MEDLINE, PsycINFO, Clinicaltrials.gov, WHO International Clinical Trials Registry, China National Knowledge Infrastructure, Wanfang, and VIP (which includes the Chinese Scientific Journals Database). The search strategy used is detailed in S1 and the protocol is registered on PROSPERO: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019154243.

Primary outcomes

1. Reduction in depressive symptoms: Mean endpoint (or change) scores in depression severity from baseline to the time point in question.
2. Adverse events: Total number of participants experiencing at least one side effect

Secondary outcomes

1. Response rate: number of participants who responded to treatment (i.e., with a reduction of at least 50% compared to baseline) on the Hamilton rating scale for depression (HRSD), Montgomery-Åsberg depression rating scale (MADRS), or any other standardised rating scale.
2. Remission rate: Number of participants who achieved remission.
3. The number of drop-outs due to any cause (acceptability) and number of drop-outs due to side effects (tolerability).

As per protocol, we collected information about efficacy of treatment at different timepoints: 24 h (between 12 and 36 h); 72 h (between 37 and 96 h); 1 week (between four and 10 days); 2 weeks (11 days up to 3 weeks); 4 weeks (between three and 6 weeks) and 3 months (between 7 weeks and 6 months).

Three review authors (PM, KK, JX) independently screened titles for inclusion. We recorded the selection process in sufficient detail to complete a PRISMA [12] flow diagram. Risk of bias for each study was assessed independently by three reviewers using the Cochrane criteria [13]and the quality of the evidence for the primary outcomes was assessed using GRADE [13].

We calculated the mean difference (MD) or standardised mean difference (SMD) for continuous outcomes, and odds ratio (OR) for dichotomous outcomes (always with corresponding 95% CI). We calculated response and dropout rates out of the total number of randomised participants. We investigated heterogeneity between studies by visual inspection of the forest plots and then by calculating the I^2 statistic [14].

Analysis

Our main analysis was of change in symptoms for participants undergoing interventions including SD compared to controls having the same interventions except without SD (the only difference between the intervention group and the control group is whether they received SD, however both arms of the study may have been given interventions such as a pharmacological antidepressant or bright light therapy).

Sensitivity analysis

As we are aware that SD is often given as part of a chronotherapy package and this whole intervention is compared to a non-chronotherapy control, we decided to carry out a more inclusive sensitivity analysis of all the studies comparing SD with a control, whether or not the effect of SD could be isolated (for example the intervention group may have received an antidepressant, bright light therapy and SD but the control group only receive antidepressant) [15]. We also included data from a Chinese study excluded from the primary analysis, where the full randomisation methodology could not be confirmed due the Covid −19 pandemic [16], as the study authors were unable to clarify this specific issue. We used RevMan version 5 [17] and STATA 16.1 for statistical analysis and production of figures.

Results

From the initially identified 2164 citations, we retrieved 29 RCTs with 1246 participants (70% women), mean age was 42 (standard deviation 12·5 and age range from 15 to 72 years), and mean sample size was 43 (range 6−105), published between 1982 and 2021 (Fig. 1; PRISMA). Full clinical and demographic characteristics are reported in Table 1 (see also Table S2). There were a range of strategies for giving SD (see Table S1: Types of Sleep Deprivation Treatment).

Overall 743 participants were randomly assigned to some form of SD, and 503 to a non-Sleep Deprivation comparator and 225 participants were in studies that compared different schedules of SD. Median duration of treatment was 1 week (range one night to six months). Drop-out rates varied between 0% and 43·2% (Table S5). Participants were followed up after treatment completion for a mean duration of 5·3 weeks (ranging from 1 day to 29 weeks). Eight studies included unipolar depression only, 14 mixed unipolar and bipolar, and one study bipolar depression only. In the studies included in the meta-analysis four (14%) were rated as low risk [18−21], 19 (72%) unclear risk and four (14%) high risk of bias [22−25] (Fig. S1).

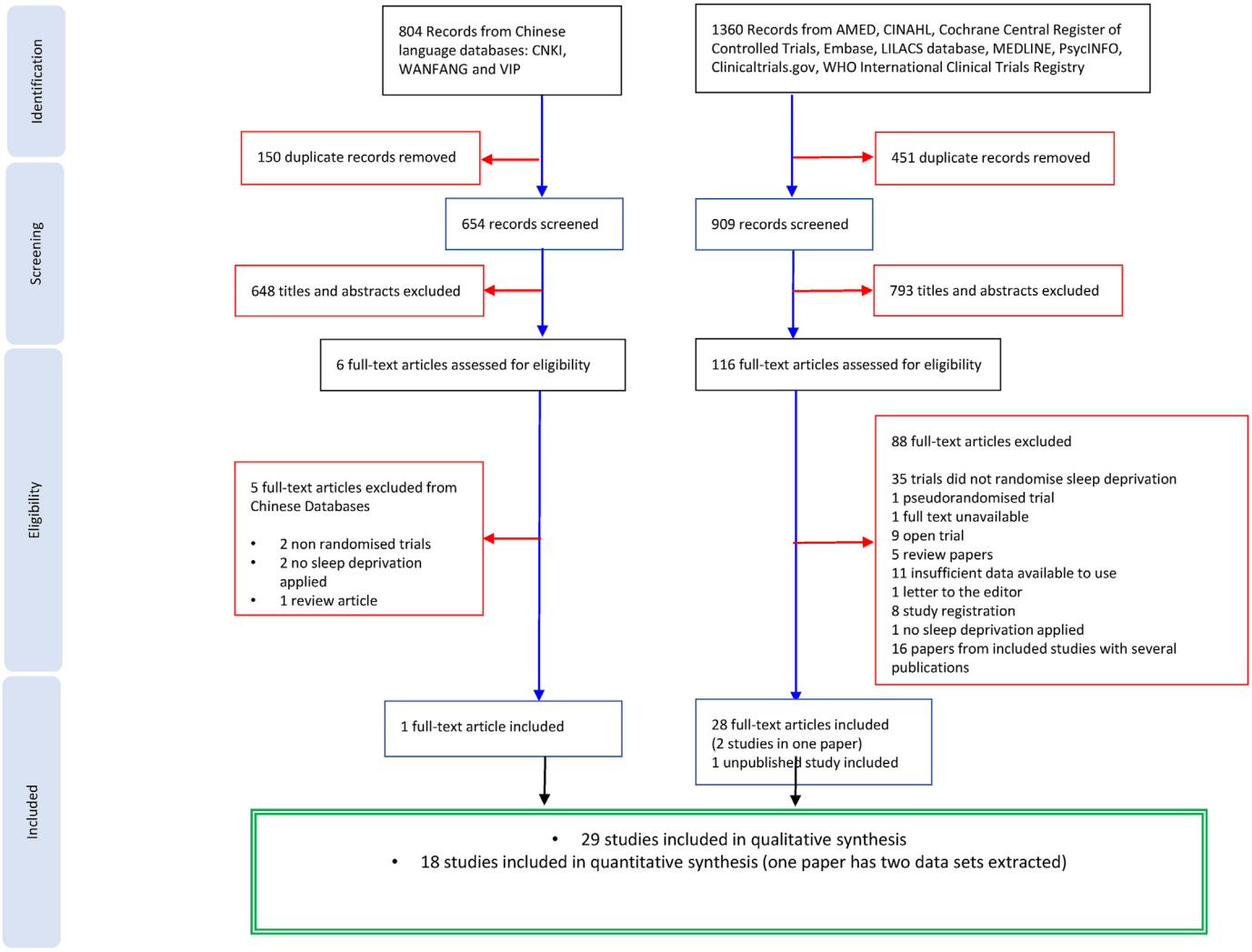

Fig. 1. PRISMA Flow chart. The flowchart shows the records identified through database searching (black boxes), the records screened (blue boxes), the records excluded (red boxes), and the studies included (green boxes). (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

There were 18 trials that we could include in the meta-analysis [16,18,20,21,24,26–40] and 11 studies that could not be analysed [19,22,23,25,41–47] (full details about each study reported in Tables S2- S5). The specific contribution of SD could not be separated from that of the whole chronotherapy package except in one study [26]. One small study looked at participants undergoing intense cognitive behavioural psychotherapy, and this did not show significant difference in outcome with or without SD as add-on [18].

Many studies did not describe adverse events (Table S5) [18–20,25,26,28,29,31,36,41–43,45,46]. In terms of severe adverse effects hypomania developed in four patients [21,32,38], two patients had an increase in psychotic symptoms [32,47], and suicidality increased in three patients [21,30,39] and there was possibly more severe suicidal ideation in the late sleep restricted patients of one study [23]. Feeling tired, headache, poor concentration and transient memory difficulties were described frequently in one study of total SD (TSD) given three times in one week [30] and this may be due to the intensity of TSD in this study as another study with only one TSD reported no adverse effects [37]. Twelve patients receiving SD discontinued treatment as a result of adverse effects from nine studies which reported this outcome [21,22,24,30,32,37–39,47] and nine people dropped out due to lack of efficacy of SD from six studies which reported this outcome [21,22,24,32,38,44].

Meta-analysis

We did not find any difference in change in symptoms for interventions including SD compared to a control of the same intervention except without SD at any time point (Fig. 2): at 1 week SMD was −0·12 (95%CI -0·37 to 0·61; I^2 = 0%); at 2 weeks SMD was −0·16 (95%CI -0·32 to 0·63; I^2 = 17%); at 4 weeks, 0.30 (95%CI -0·08 to 0·68; I^2 = 0%); at 3 months 0·22 (95%CI -0·68 to 1·12). The GRADE rating for this outcome was very low at each time point (Table S6). There were no available data for adverse events. Only one study had data for response and remission [28], and results were in line with the primary outcome (Table S4). In terms of discontinuation due to any cause SD was not different compared to those not allocated to SD: OR 0·67, 95%CI 0·12 to 3.62; two studies.

Sensitivity analysis

As a sensitivity analysis we included the all the studies comparing SD with a control (even when the effect of SD could not be separated from other components of a treatment package) and

Table 1
Table of included studies.

Study	Country	Interventions (N)	Setting	Study duration (weeks)	Frequency of Sleep deprivation	Age mean (StD)	Female ratio	Diagnosis	Depression rating scale	Baseline severity (StD)
Arnedt et al., 2016	USA	Partial Sleep Restriction + SSRI (49) vs SSRI (19)	Mixed	2	Once daily	26 (7.13) vs 26 (7.4)	0.55 vs 0.37	Unipolar	HDRS-17	18 (2.2) vs 18.2 (2.6)
Baxter et al., 1986	USA	Late Partial SD + Lithium (5) vs placebo (5) vs Lithium (5)	Inpatient	0.7	Twice in one week	39 (15.3) vs 44 (11) vs 43 (23.3)	0.5 vs 0.75 vs 0.5	Unipolar (7) Bipolar (5)	HDRS	35.4 (13.2) vs 30.2 (12.1) vs 33 (9.3)
Dopp et al., 2013	USA	Partial SD + SSRI (32) vs SSRI (15)	NR	8	NR	26 for whole study (7.2)	0.49 for whole study	NR	NA	NR
Elsenga et al., 1990	Netherlands	Partial SD as maintenance after Total SD + Clomipramine (20) vs once Total SD with Clomipramine (10)	Inpatient	1	Once or twice	49.1 vs 51.4 (9.4)	0.6 vs 0.7	Unipolar (23) Bipolar (6) Other (1)	NA	NR
Elsenga et al., 1982	Netherlands	Total SD with Clomipramine (12) vs placebo (11) vs Clomipramine (13)	Inpatient	2.1	4 times in two weeks	49 (15.7) vs 51 (14.7) vs 56 (13.2)	0.9 vs 0.9 vs 0.7	NR	Adapted shortened HDRS	17.83 (NR) vs 17.57 (NR) vs 15.47 (NR)
Gest et al., 2016	Germany	Once Total SD + Light Therapy (25) vs Light Therapy (37)	Inpatient	2	Once	16.1 (1.23) vs 15.7 (1.01)	0.88 vs 0.95	NR	BDI-II	34.63 (10.16) vs 35.86 (9.93)
Giedke et al., 2003	Germany	Once Total SD (17) vs Late Partial SD (22)	Inpatient	0.6	Once	49 for both arms combined (no SD)	0.54 for both arms combined	Unipolar (37) Bipolar (2)	HDRS-6	7.4 (2.1) vs 7.1 (2.5)
Giedke et al., 1992	Germany	Early Partial SD (14) vs Late Partial SD (16)	Inpatient	2	Once	48 for both arms combined (15)	0.6 for both arms combined	Unipolar (22) Bipolar (4) Schizoaffective (4) Other (3)	NA	NR
Giedke et al., 1990	Germany	Cross-over trial: Total SD cross over with Late Partial SD (16) vs undisturbed sleep crossover with Partial SD (17)	Inpatient	0.7−1.3	Once	42 (15) vs 48 (18)	0.63 vs 0.64	Unipolar (27) Other-(6)	MADRS	28 (5) vs 31 (9)
Grozinger et al., 2002	Germany	Selective REM Sleep Deprivation with trimipramine (19) vs NonREM selective Sleep Deprivation with trimipramine (18)	Inpatient	1.4	Once daily for 10 days	43.6 (11.6) vs 44.6 (10.2)	0.69 vs 0.71	Unipolar	HDRS-21	32.9 (4.2) vs 21.2 (2.5)
Hemmeter et al., 1995	Switzerland	Late Partial SD + trimipramine (9) vs trimipramine (9)	Inpatient	1	Three times per week	50 for both arms combined	0.33 for both arms combined	Unipolar (17) Bipolar (1)	HDRS-17	24 (33.7) vs 26 (5.5)
Holsboer-Trachsler et al., 1994	Germany and Switzerland	Late Partial SD + trimipramine (14) vs trimipramine (14) vs trimipramine + Light therapy (14)	Inpatient	6	Three times for one week and then weekly for three subsequent weeks	50 (7.3) vs 50 (8.5) vs 55 (10.65)	0.43 vs 0.36 vs 0.64	Unipolar (35) Bipolar (6) Other (1)	HDRS-17	22.98 (3.72) vs 26.02 (6.37) vs 22.69 (5.25)
Ioannou et al., 2021	Sweden	Total SD + Light Therapy (16) vs Sleep advice	Inpatient	1	Once	31.3 (13.1) vs 29.0 (8.6)	0.75 vs 0.82	Unipolar (10) Bipolar (2) Other (4) vs Unipolar (13) Bipolar (2) Other (2)	MADRS-S	35.50 (9.79) vs 37.97 (8.05)

Kragh et al., 2017	Denmark	Total SD + Light therapy (32) vs medications (32)	Mixed	9	Three times in one week	38 (12) vs 40 (11.5)	0.50 vs 0.38	Unipolar (56) Bipolar (8)	HDRS-17	22.9 (5.03) vs 22.5 (5.09)
Kuhs et al., 1998	Germany	Twice weekly Late Partial SD + amitriptyline (20) vs once weekly Late Partial SD + amitriptyline (24)	Inpatient	2	Twice or once weekly	39 (13.7) vs 48 (13)	0.6 vs 0.67	Unipolar (40) Bipolar (4)	HDRS-21	27.2 (5.1) vs 24.9 (5.0)
Kuhs et al., 1996	Germany	Late Partial SD + amitriptyline (27) vs amitriptyline (24)	Inpatient	4	4–5 day intervals (in total six Late Partial SD)	43 (13.6) vs 46 (11.3)	0.59 vs 0.58	Unipolar (32) Bipolar (9) Other (10)	HDRS-21	26 (5.1) vs 27.4 (7.0)
Kundermann et al., 2008	Germany	Total SD + CBT (10) vs CBT (10)	Inpatient	3	two total SD per week and CBT 5 times a week	37 (8.1) vs 37 (8.22)	0.55 vs 0.30	Unipolar	HDRS-17	26.2 (5.7) vs 25.8 (2.53)
Martiny et al., 2012	Denmark	Total SD + Light therapy + duloxetine (37) vs exercise + duloxetine (38)	Mixed	8	three times in one week	47 (12.6) vs 48 (11.2)	0.65 vs 0.53	Unipolar (63) Bipolar (12)	HDRS-6, HDRS -17	23.9 (4.32) vs 22.3 (3.82)
Parry et al., 2000	USA	Late Partial SD (7) vs Early Partial SD (2)	Mixed	1	Once	NR	1.00	Peri-natal and unipolar depressive disorder	NA	NR
Putilov et al., 2005	Russia	Total SD + exercise or Light therapy (48) vs Medication free (21) vs Light therapy (18) vs exercise (18)	Inpatient	1	Once	NR	1.0	Unipolar	NA	NR
Reynolds et al., 2005	USA	Total SD + SSRI (27) vs placebo (27) vs SSRI (26)	Outpatient	2	Once	71 (6.7) vs 71 (8) vs 70 (6.8)	0.7 vs 0.7 vs 0.65	Unipolar	HDRS-17	21 (3.1) vs 20.8 (3.7) vs 18.9 (2.5)
Sack et al., 1988	USA	Late Partial SD (9) vs Early Partial SD (9)	Inpatient	2.4	2 in each cross	NR	0.78 for whole study	Unipolar (8) Bipolar (10)	NR	NR
Sharkey et al., 2019	USA	Partial Sleep Restriction + Light therapy (20) vs medications (20)	Outpatient	Variable	daily after week of baseline between weeks 24–28 of pregnancy)	NR	1.00	Perinatal Major Depressive episode or Anxiety disorder	HDRS-17	14.0 (3.3) vs 12.5 (3.6)
Szuba et al. a (Desi) 1994	USA	Late Partial SD + desipramine (3) vs Early Partial SD + desipramine (3)	Mixed	4.3	Once	29 (9.9) vs 36 (4.4)	1.00 vs 0.67	Unipolar	Bunney-Hamburg Global Assessment Scale	26.0 (5.0) vs 25.7 (3.5)
Szuba et al. b (Li) 1994	USA	Late Partial SD + Lithium (6) vs Early Partial SD + Lithium (3)	Mixed	4.3	Once	29 (10.1) vs 26 (3.4)	0.83 vs 1.00	Unipolar (4) and Bipolar (6)	Bunney-Hamburg Global Assessment Scale	26.2 (4.2) vs 27.3 (3.4)
Tang et al., 2010	China	Late Partial SD + SSRI (25) vs SSRI (24)	Inpatient	6	Twice weekly	29 (4.3) vs 28 (3.9)	1.00 vs 1.00	Post-natal depression	HDRS-17	22.6 (2.6) vs 23.4 (2.9)
Wu et al., 2009	USA	Total SD + Light therapy + Sleep phase advance + SSRI (32) vs SSRI (17)	Mixed	7	Once	39 (13.3) vs 40 (14.1)	0.31 vs 0.59	Bipolar	HDRS-19	19 (6.7) vs 18.5 (7.1)
Yuen et al., 2021	USA	Total SD + Light therapy + Sleep phase advance (22) vs Set sleep times + blue-filtered Light therapy (22)	Outpatient	6	Once or Twice	38 (14.3) vs 39 (16.4)	0.55 vs 0.55	Unipolar	SIGH-ADS	24.9 (6.5) vs 22.7 (6.7)

BDI= Beck depression inventory; CBT= Cognitive behavioural therapy; HDRS= Hamilton depression rating scale; MADRS = Montgomery Asberg depression rating scale; MADRS-S= Montgomery Asberg depression rating scale-Self Assessment; NA: Not assessed; NR = not reported; SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; SD = sleep deprivation; StD = standard deviation; SSRI= Selective Serotonin Reuptake Inhibitor.

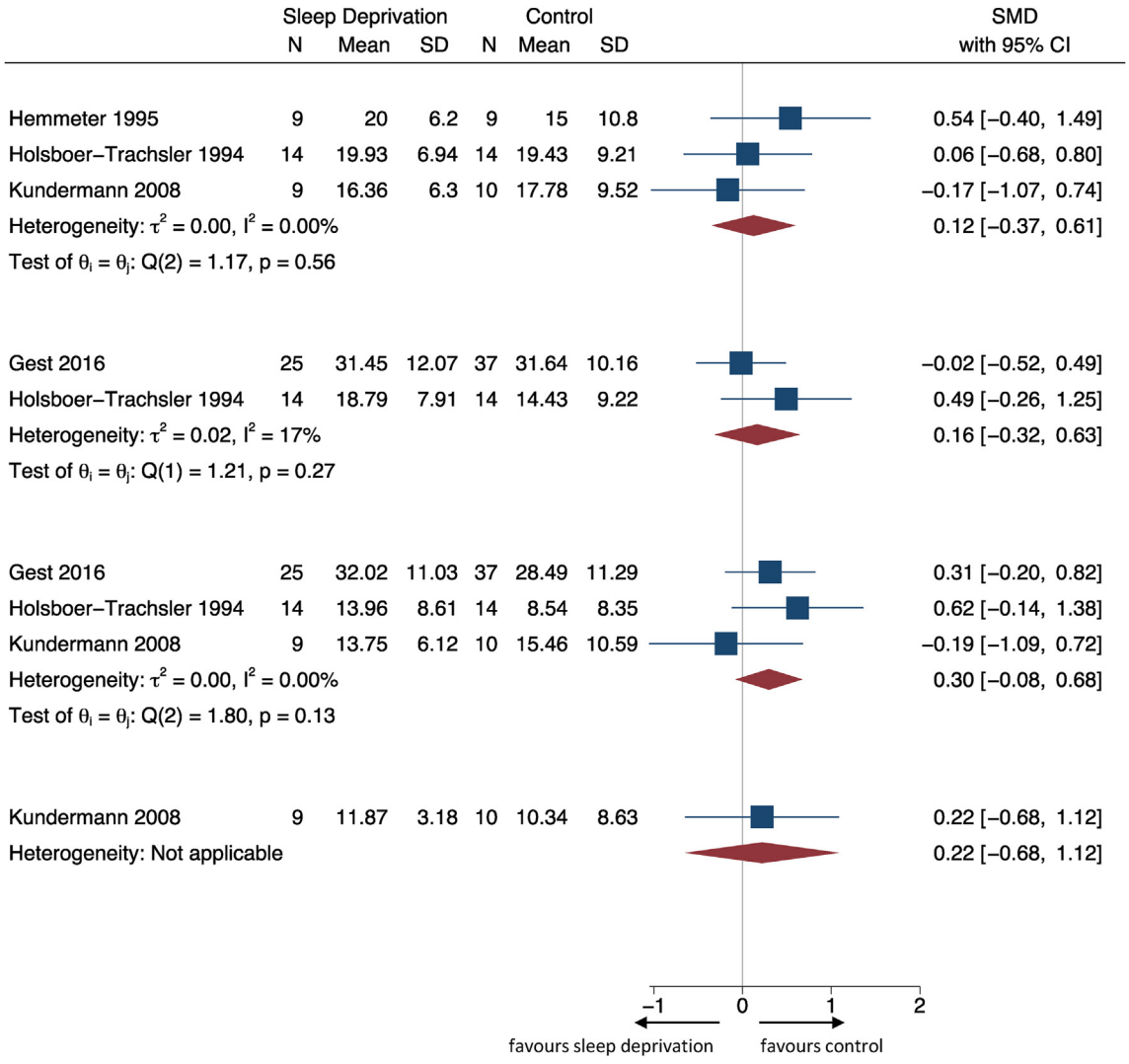

Fig. 2. Forest plot of the primary analysis. Meta-analysis of depressive symptoms in patients with depression for interventions including sleep deprivation compared to a control of the same intervention except without sleep deprivation, at 1 week, 2 weeks, 4 weeks and 3 months.

results were in favour of SD (Fig. 3): at 1 week SMD was −0·46 (95% CI -0·70 to −0·21; $I^2 = 35\%$) and at 3 months SMD was −0·55 (95% CI -1·01 to −0·09; $I^2 = 67\%$). At other time points the findings did not show any material difference: SMD at 24 h was −0·10 (95%CI -0·46 to 0·26; $I^2 = 0\%$); at 72 h SMD was −0·55 (95%CI -1·15 to 0·06); at 2 weeks SMD was −0·35 (95%CI -0·90 to 0·20; $I^2 = 83\%$); and at 4 weeks SMD was −0·28 (95%CI -0·87 to 0.31; $I^2 = 85\%$). There were a higher number experiencing adverse events in the participants undergoing SD compared those not undergoing SD but this did not reach significance (Fig. S2): OR 1·38 (95% CI 0·62 to 3.07; $I^2 = 0\%$). Similar results were found for dropout rates (Fig. S3): OR 1·33 (95%CI 0·75 to 2·37; $I^2 = 28\%$). No information was available for tolerability.

Discussion

Our meta-analysis could not demonstrate evidence of benefit for SD in MDE when using strict criteria for study inclusion and could not establish whether or not there was an immediate mood enhancing effect of SD although this has been reported previously in the literature [2,48]. Our sensitivity analysis demonstrated the risk of using studies that did not separate the effect of SD and assuming that this is evidence of the effectiveness of SD. The suggestion of benefit favouring chronotherapy packages cannot necessarily be attributed to the inclusion of SD. Therefore we do not believe that this can justify blind acceptance of SD as a therapeutic tool. There may be an unfounded assumption that SD is effective when in fact the effects seen in sensitivity analysis could well be driven by factors not related to sleep deprivation.

When given as part of a chronotherapy package also including sleep stabilisation [21,30], chronic sleep restriction [33] or sleep phase advance strategies [19,37,38,40] and bright light therapy [21,26,30,37–40,46], it is important to consider to what extent is the therapeutic effect determined by SD rather than other components or a synergistic effect of the whole package. Of note a study in which all participants were given BLT, the addition of SD may have led to a less favourable outcome [26]. Interestingly a meta-analysis of BLT [49] in MDE showed a positive effect with 2–5 weeks of BLT. In reviewed trials the length of daily BLT therapy varied considerably ranging from 3 days [38], 1 week [39,40], 2 weeks [26],2 months [21,30] and 6 months [37]. This variation may mitigate against the conclusion that BLT alone caused the additional benefit to mood at 3 months and there is a need to further examine this research question. It has been suggested that

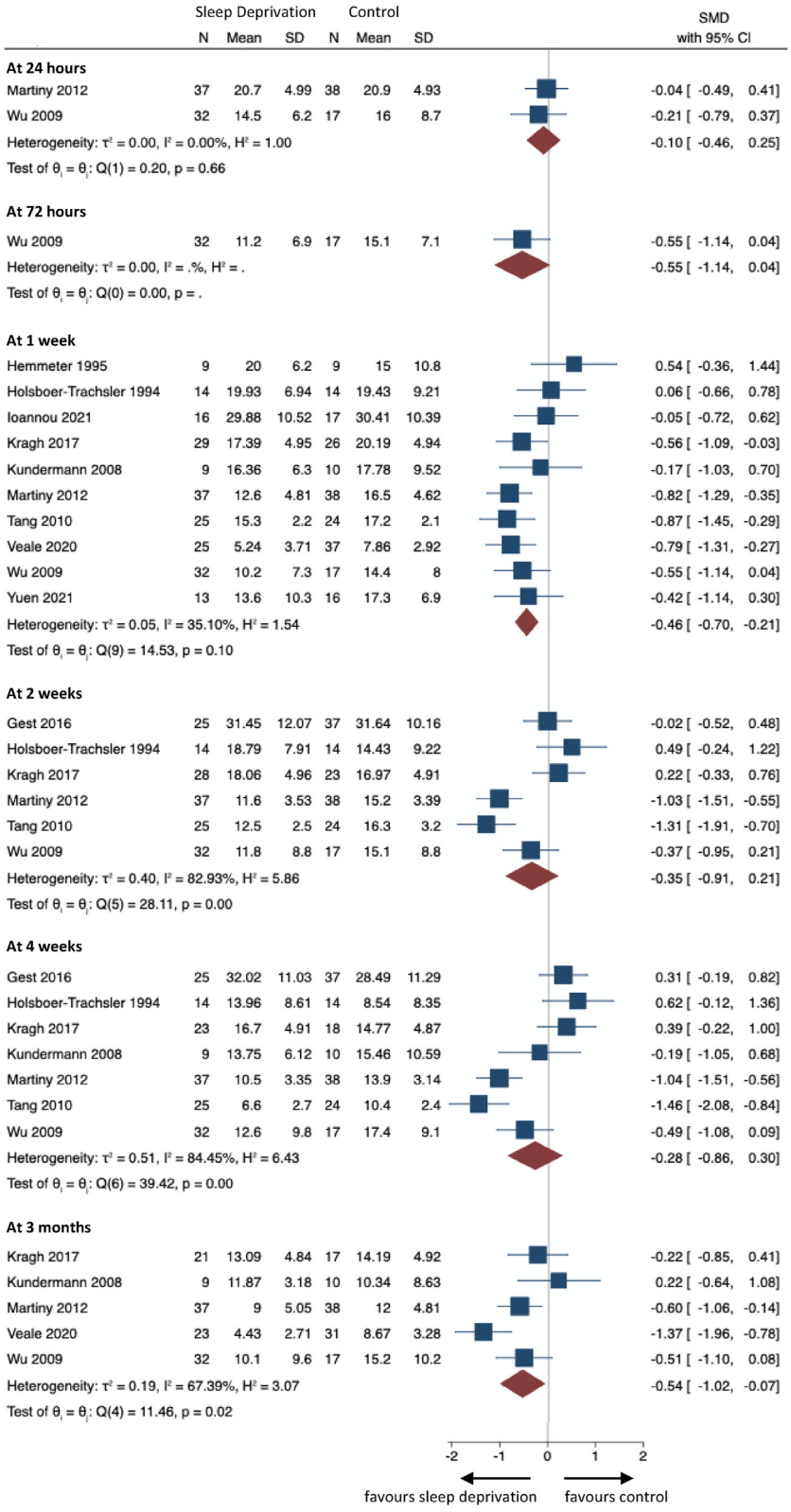

Fig. 3. Forest plot of the sensitivity analysis. Meta-analysis of depressive symptoms in patients with depression including all the studies comparing sleep deprivation with a control, even when the effect of sleep deprivation could not be separated from other components of a treatment package, at 1 week, 2 weeks, 4 weeks and 3 months.

combinations of non-pharmacological chronotherapies may be encouraging but none has a strong evidence base and large controlled studies are needed [50].

Age may be a factor impacting on efficacy of SD but it is hard to draw conclusions from such small studies. One study of adolescents did not show an advantage for SD [26]. Another study focused on older adults and this did not find significant benefit for SD either [20]. Even if SD could rapidly relieve low mood, it is expensive and time intensive if carried out in an inpatient unit over several days. Looking for cheaper interventions several chronotherapy studies were predominantly outpatient-based [21,30,37,38,40]. Our study could not confirm a role for SD in reducing suicidality as previously reported in non-randomised studies [51,52].

Many studies did not report on adverse events and the true extent of these are unknown. TSD may be better tolerated as a once only treatment [37] rather than trice weekly [30]. In severely unwell inpatients there may be more risk of serious side effects such as hypomania and worsening of psychotic symptoms. In this review there were no accounts of seizures but epilepsy was an exclusion criterion for recent chronotherapy studies [30,37,38] . That there were significant numbers of dropouts, often before treatment was given, need to be considered when designing future trials and raises questions about acceptability which may change depending on the other components of a treatment package. For future outpatient trials a concern would be the risk of participants driving when sleep deprived.

There has been some work in healthy controls examining commonalities between sleep deprivation and sleep restriction [53]. Three studies [19,23,41] restricted sleep in the hope of treating low mood and anxiety and this was presumably considered as a theoretical extrapolation from the sleep deprivation research but effects could relate to sleep consolidation, enhanced slow wave activity and circadian rhythm stabilisation [54]. As there was only a very limited change in hours of sleep these studies have not been included in the meta-analysis as they may be looking at a different mechanism of action.

Despite the uncertainties regarding the effectiveness of SD from the evidence available there is a reasonable theoretical framework to expect that SD may enhance a chronotherapeutic effect, which strengthens the argument for more research in the area to resolve this question. It has been suggested that SD may act via circadian mechanisms through direct enhancement of clock gene expression [55]. In support of this a recent transcriptome-wide study of 78 patients undergoing SD found that several circadian-related genes (including *PER1*) demonstrated increased expression in responders compared with non-responders [56]. The combination of SD with BLT and sleep phase advancement (triple chronotherapy) may also help to correct circadian misalignment and sleep disruption, serving to sustain therapeutic effects. That is, potentiation of sleep pressure through SD may provide conditions that are propitious for the advancement of sleep timing (and circadian physiology), which can then be reinforced through adjunctive morning light therapy and behavioural scheduling. Correcting the timing of sleep (particularly in those with evening chronotype [15]), and improving the regularity and consolidation of the sleep–wake cycle would be expected to deliver benefits to sleep quality, mood and daytime function. More attention to the relative contribution of chronotherapy components (and their interaction) is needed, as well as appropriate measurement of sleep and circadian rhythm disruption at baseline and post-intervention to determine potential moderation and mediation of depression treatment effects.

There are important limitations to this review. The small number and the low quality of the included studies are the main concerns. To address this problem, we carried out a comprehensive search of all available literature (for instance, we included two unpublished trials [19,37], other unpublished data [30] and a Chinese study [16], none of which have previously been included in reviews) and we attempted to contact authors as needed. None of the studies had large numbers of participants and some were very small with less than 10 participants [36,45]. In some studies the experimental and control groups were imbalanced in terms of non-specific factors such as timing, frequency and duration of treatments and the level of personal attention given to participants. These biases always favoured SD in the studies included. We excluded the only Chinese language paper [16] from the primary analysis as this did not fully describe the method of randomisation, and this paper was an outlier in terms of markedly favouring SD. The older studies generally had limited extractable information and often could not be used for the meta-analysis. None of the studies in our review are free of the risk of bias. It is inherently difficult to blind participants having sleep deprivation and not all of the studies blinded outcome assessors and attrition bias was an issue with many studies having high drop-out rates. To avoid overestimating the benefits of SD, we used intention-to-treat analysis for the primary outcome and used conservative statistical estimates when calculating adverse event ratios. There was significant heterogeneity in terms of the interventions. Some studies had ongoing repeated SDs over several timepoints whereas others will have had just one-off treatment and this 'dosing' may have impacted on efficacy and made comparing efficacy at different time points problematic.

In conclusion, from the current evidence we cannot firmly say that there is a role for SD in the treatment of depression. The need for a safe, non-pharmacological strategy for MDE is a strong argument for further RCTs in this field but from the current evidence we disagree with the proposed addition of SD to current guidelines for bipolar depression [57] and do not believe SD can be justifiably added to treatment guidelines for MDE at present.

Interpretation

Using the most conservative test we did not find evidence that the addition of SD to treatment packages leads to enhanced depressive outcomes. Studies designed to compare chronotherapy packages inclusive and exclusive of SD would be the next logical step needed to clarify if there is a future role for SD in the treatment of MDEs in mood disorders.

Practice Points

From the current evidence:

- It cannot be firmly said that there is a role for SD in the treatment of depression
- There is no evidence base for the proposed addition of SD to current guidelines for bipolar depression [57].
- There is no evidence base to justify adding SD to treatment guidelines for MDE at present.

Research Agenda

- Large well-structured single blinded RCTs are needed to establish if there is a role for SD in the treatment of depression, investigating further the impact of adding SD to chronotherapy packages and determining if using partial or total SD is preferable and at what frequency and duration of treatment.
- It is not possible to blind SD but blinding of the outcome assessors is imperative to avoid bias and it would be essential to carefully match the research contact time and attention given in the intervention and control groups.
- To facilitate the success of well powered, larger studies it may be more cost effective and acceptable to use an outpatient setting with actigraphy and smartphone technology to aid compliance with any treatment plan.

Conflicts of interest

Andrea Cipriani has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work.

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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.2022.101647.

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