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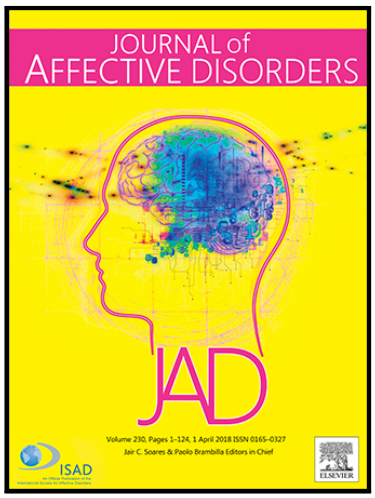


# Efficacy of Triple Chronotherapy in Unipolar and Bipolar Depression: a systematic review of the available evidence

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Highlights

- Stabilization of circadian rhythm abnormalities might improve depressive symptoms
- Available studies on the efficacy of Triple Chronotherapy is reviewed
- Fifty to 84% response rates were reported and 58–61% in three follow–up studies
- Side effects were negligible across studies
- Triple chronotherapy is a safe and effective add–on treatment for depression

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# Efficacy of Triple Chronotherapy in Unipolar and Bipolar Depression: a systematic review of the available evidence

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**ABSTRACT**

**Background:** Given the strong relationship between circadian rhythm disruption and mood regulation, combined chronotherapeutic approaches have been proposed for mood disorders. However, a comprehensive review of the available evidence on the efficacy of such interventions for depression is lacking.

**Aim:** To systematically review available literature on Triple Chronotherapy (Sleep Deprivation – Sleep Phase Advance – Bright Light Therapy) for depressive symptoms in Major Depression and Bipolar Depression**.**

**Methods:** We followed the PRISMA statement for systematic reviews to conduct a web-based search on PubMed, Scopus and Embase using a list of selected keywords relevant to depression and chronotherapy.

**Results:** After title and abstract screening of the 321 records retrieved, 25 potentially eligible studies were assessed at full-text screening. Nineteen studies were excluded for failure to match inclusion criteria. Six records of Triple Chronotherapy in addition to conventional treatment, published between 2009 and 2018, were included in the revision. All studies reported significant improvements on HAM–D scores at the end of treatment, with 50% to 84% response rates. Efficacy of treatment was confirmed on follow-up by three studies, with 58% to 61% response rates. Remission rates varied from 33,3% to 77%. Reported side effects were negligible across studies.

**Limitations:** Available trials are very few and only one included a control group treated with a daily exercise program.

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**Conclusions:** The limited literature suggests that Triple chronotherapy might be a safe and effective addition to conventional antidepressant interventions, although well–designed, randomized controlled trials are needed.

**Keywords**: Sleep Deprivation; Sleep–phase advance; Bright Light Therapy; Circadian rhythms; Chronobiology; Depression

## INTRODUCTION

Depressive disorders are thought to affect up to 350 million people worldwide (WHO, 2015), with a relevant impact on individuals' quality of life and socio-occupational functioning. Depression is the single largest contributor to nonfatal health loss and the leading cause of disability worldwide (Friedrich, 2017), as well as the most common condition associated with suicide fatality (Hawton et al., 2013). Despite a broad availability of antidepressant treatments including pharmacological molecules, psychosocial interventions, psychotherapy and ECT (APA, 2010), some patients may not respond adequately or may experience adverse events (Connolly & Thase, 2011; Fava M., 2003). In clinical practice, one of the major problems faced by medical and nursing teams is the relatively long latency of antidepressant effects; this makes the treatment of severe forms highly challenging, especially when suicidal risk is considered relevant. Treatment resistance represents an additional problem: one meta-analysis reported an average response rate only marginally superior to 50% in adults with major depressive disorder (Papakostas & Fava, 2009). Despite the robust evidence on the rapid efficacy of ECT for the treatment of both unipolar and bipolar depressive patients

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with pharmacological treatment resistance, approximately half of those successfully treated with ECT relapse within 6 months (Bourgon, 2000), and cognitive side effects can include a persisting retrograde amnesia (Andrade et al., 2016).

A large number of Randomized Controlled Trials (RCTs) has also shown that psychotherapy is effective in depressive disorders, resulting in moderate to large effect sizes (Barth et al., 2013; Cuijpers et al., 2013a), although an average of 5–7 weeks is necessary to reach remission (Rush et al., 2006). This context highlights the need to identify alternative interventions with limited adverse effects to support or achieve remission from depressive symptoms during acute stages.

Circadian rhythm abnormalities are known to play a significant role in the pathogenesis of affective disorders such as Major Depression or Bipolar Depression, and their stabilization can become a crucial aspect of effective interventions on mood (Benca et al., 1992; Pillai et al., 2011). Chronotherapeutics, defined as controlled exposure to environmental factors that can influence biological rhythms and exert a therapeutic effect on mental disorders, are developing in this direction (Benedetti et al., 2007). One of the most highly researched chronotherapeutic approaches is Wake Therapy or Sleep Deprivation (SD) (Wu et al., 2009, 2001; Giedke & Schwärzler, 2002). Previous reviews suggested this intervention to be rapid and effective, with reduction of depressive symptoms in up to 80% of patients and rare side effects after a single night of Total Sleep Deprivation (TSD) (Benedetti et al., 2007; Wirz-Justice et al., 2009). Despite a relative superiority of TSD, efficacy has also been shown for partial Sleep Deprivation, in which case sleep should be no longer than 3 hours (Giedke et al., 2003). In selected cases, sustained effects in time have been shown with TSD (Wehr T., 1990; Muller P., 1995), although its systematic diffusion has been limited by reports of effects that only

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last a few days or even hours (Wu & Bunney, 1990). Antidepressant drugs, Bright Light Therapy (BLT) or Sleep Phase Advance (SPA) have all been hypothesized to prolong the effect (Giedke & Schwärzler, 2002). BLT exploits light's natural capacity to regulate sleep-wake rhythms and the secretion of hormones such as melatonin and serotonin through exposure to ultraviolet–filtered light of intensity up to 10.000 lux (Shirani & St. Louis, 2009). SPA consists in manipulating the sleep–wake cycle by supporting sleep earlier than the patient's usual bedtime and wakefulness before the usual waking time (Cunningham et al., 2019).

Some preliminary studies hypothesized that Triple Chronotherapy, i.e. the combination of SD, SPA and BLT, could produce a rapid and stable improvement of depressive symptoms (Benedetti et al, 2005; Echizenya et al. 2013; Wu et al., 2009). Therefore, the extension of SD effects might be a useful aid to standard interventions or an alternative for those cases in which they are not feasible. A recent systematic review suggested that chronotherapy may be an effective treatment option for depression, although the search was restricted to randomized controlled trials and case-control studies (Humpston et al. 2020; Colleen & McClung, 2013). In this study, we aimed to systematically review all of the available evidence on Triple Chronotherapy interventions targeted to depressive symptoms in Major Depression and Bipolar Depression. We chose this particular protocol due to the possibility of a relatively effortless implementation in any setting, compared to protocols combining several nights of sleep deprivation, which require higher staff involvement and patient compliance.

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## METHODS

We conducted this review following the PRISMA statement for systematic reviews (Moher D et al., 2009).

### Search strategy

A comprehensive systematic computer-based search was conducted on PubMed, Scopus and Embase (December 11, 2019) using relevant keywords: depression, sleep deprivation, chronotherapy and related terms (see Supplementary materials for additional details).

### Eligibility criteria

We included all the primary literature articles retrieved directly through database searches combining terms related to the effectiveness of a Triple Chronotherapy intervention with SD, BLT and SPA for depression, either administered alone or in combination with any other treatment. Secondary literature articles cited in the primary articles were also screened for inclusion.

Studies were included regardless of specific execution modalities or combination sequence of interventions adopted by the authors. Furthermore, articles including any control group were retained, regardless of its definition (i.e. active control or placebo). The eligible population included individuals of any gender or age with Major Depressive Disorder or Bipolar Depression, as defined in the original studies. No time or study design restrictions were applied. Articles in languages other than English or

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Italian language were excluded, as were those that failed to report standardized depression rating scale scores in their outcomes.

**Study selection**

After title and abstract screening, 25 potentially eligible studies were retrieved for full-text screening. Two members of the team (PF, ST) independently screened the abstract of the identified records. In case of disagreement, the record was included to allow its evaluation at the next screening phase. Full text of potentially eligible studies were then independently screened by two members of the team (PF, ST). Any disagreement was resolved by consensus with a third member of the team (ADA). Nineteen studies were excluded for failure to match the eligibility criteria reported in the previous section.

**Data extraction and outcome**

A data extraction sheet was created to record the following information: first author and publication year, number and sociodemographic characteristics of participants, recruitment setting, definition and details of intervention and control groups, evaluation tools, primary and secondary outcomes. We defined our primary outcome as the response and remission rates after treatment, measured with standardized depression rating scales. The secondary outcome was the severity of suicidal thinking, regardless of the assessment tool.

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**Quality assessment**

The quality of included studies was independently assessed by two members of the team (PF, ST) with the Clinical appraisal tools (i.e. Checklist for Randomized Controlled Trials, Checklist for Quasi-Experimental Studies) developed by the Joanna Briggs Institute (Tufanaru et al. 2017). In case of disagreement, a third member of the team was consulted (ADA).

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies) includes nine questions. JBI Critical Appraisal Checklist for Randomized Controlled Trials includes 13 questions. We agreed to score one point for each answer rated as "yes". In order to differentiate low–to–moderate from high quality studies we chose the following thresholds: 6 out of 9 items in the quasi-experimental studies checklist and 9 out of 13 items in the randomized controlled studies checklist. This score partition in is not recommended by the JBI and was only employed to estimate the overall quality of the included studies.

**RESULTS**

The search strategy identified 321 records, 126 of which were removed as duplicates. After title and abstract screening, 25 potentially eligible studies were assessed at the full-text screening. Nineteen studies were excluded for failure to match inclusion criteria, so six studies were included in the revision (Figure 1). The methodological quality of the included studies was assessed: all six obtained satisfying scores (≥6 for quasi-experimental studies and ≥9 for randomized controlled studies). Unclear or unreported points for each study are shown in the

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Supplementary Table, whereas major findings are reported in Table 1. Included studies were published between 2009 and 2019. Two were randomized controlled studies (RCTs) while the remaining four were quasi-experimental without a control group. Moscovici et al. (2009) and Wu et al. (2009) recruited outpatients, whereas the other studies focused on patients hospitalized in an acute psychiatric setting. One study (Hurd et al. 2019) was conducted on adolescents while the majority of included studies focused on adult individuals.

**Triple–chronotherapy and control interventions**

The triple–chronotherapy intervention was carried out in addition to standard psychopharmacological treatment in all studies except for Moscovici and Kotler (2009). In the two RCTs, the control group underwent standard treatment (Wu et al., 2009) or an alternative physical intervention planned by a physiotherapist, in addition to medication (Martiny et al., 2013). The triple–chronotherapy intervention adopted in three studies (Sahlem et al.,2014; Wu et al., 2009; Hurd et al., 2019) consisted in the following schedule for recruited subjects:

- One night of TSD (*Wake Therapy)* with wake maintenance from awakening (Day 0) to 6 p.m. of the following day (Day 1);
- Three days of SPA: sleep phase from 6 p.m. (Day 1) to 1 a.m. (Day 2), from 8 p.m. (Day 2) to 3 am (Day 3) and from 10 p.m. (Day 3) to 5 p.m. (Day 4);
- BLT: 30 minutes of exposure to a light intensity of 10.000 lux (Sahlem et al., 2014; Hurd et al., 2019) or 120 minutes at 5.000 lux (Wu et al., 2009) for the whole duration of treatment. The beginning of treatment was planned at 7 a.m. in one study (Hurd et al., 2019), whereas Sahlem et al. (2014) and Wu et al. (2009) defined BLT time

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on the basis of individual chronotype calculated by preventive administration the Morningness-Eveningness questionnaire (MEQ) (Horne & Ostberg, 1976). Echizenya et al. (2013) proposed the same intervention by anticipating SPA by one hour after Wake Therapy and extending BLT to two hours upon awakening, on each day of treatment. One study (Martiny et al., 2013) implemented three days of TSD alternating each with three days of early sleep adjustment (8 p.m. – 8 a.m. sleeping time) as a milder version of SPA. The BLT intervention (30 minutes with 10.000 lux intensity) was repeated each morning, with individualized starting time based on the patient's MEQ score. Moscovici et al. (2009) proposed a partial SD on the first day with awakening in the second half of the night associated with BLT at increasing intensity from 400 to 10.000 lux, from 3 a.m. to 6.30 a.m.; on the following 3 days sleeping time was anticipated to 7 p.m. (SPA) and BLT maintained as on the first day, throughout.

**Evaluation criteria and main outcomes**

All studies evaluated the efficacy of Triple–chronotherapy reporting the response rate, defined as an improvement on the Hamilton Depression (HAM–D) Rating scale equal to or greater than 50% from baseline scores. Remission, defined with different cut-offs according to the HAM–D version employed, was reported in every study except Echizenya et al. (2013), who instead evaluated relapse rates, defined as ≥ 50% worsening of the HAM–D after initial response to treatment. Evaluations were done at baseline and at the end of treatment in every study. Four

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studies (Echizenya et al., 2013; Sahlem et al., 2014; Wu et al., 2009, Martiny et al., 2013) evaluated patients daily from baseline up to the end of treatment and four studies (Moscovici & Kotler, 2009; Echizenya et al., 2013; Wu et al., 2009; Hurd et al., 2019) monitored patients at different time points after the end of treatment, over a time span of 1 to 7 weeks.

All studies reported significant improvements on HAM–D scores at the end of treatment: response rates ranged from 50% to 84% (Moscovici & Kotler, 2009; Echizenya et al., 2013; Sahlem et al., 2014; Martiny et al., 2013; Hurd et al., 2019) and were significantly superior to control group scores (Wu et al., 2009; Martiny et al., 2013). Efficacy of treatment was confirmed on follow-up by Echizenya et al. (2013), who reported a response rate of 61.5% at 13 and 23 days, and by Moscovici & Kotler (2009), who reported a 58.3% response rate. These results are in line with those by Wu et al., 2009, who confirmed statistically significant response rates in favour of the chronotherapy intervention compared to the control group at 7 weeks. Remission rates, evaluated in five studies (Moscovici & Kotler, 2009; Sahlem et al.,2014; Martiny et al., 2013; Hurd et al., 2019; Wu et al., 2009), varied from 33,3% to 77%. Hurd et al. (2019) reported a reduction of remission rates from 77% at the end of treatment to 50% at the one-month follow-up. Martiny et al. (2013) reported a reduction of both response and remission rates 3 days after hospital discharge, which were nonetheless significantly better compared to the control group. In the only study that reported relapse rates (Echizenya et al., 2013), only one patient who had initially responded to treatment had a relapse after 2 weeks. Interestingly, one study (Martiny et al., 2013) reported a statistically significant worsening of HAM-D scores in those subjects who had brief naps during the intervention.

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Two studies assessed the severity of suicidal risk by administering the Columbia Suicide Severity Rating Scale (CSSRS). Sahlem et al. (2014) reported a significant improvement of scores at the end of the intervention. In Hurd et al. (2019), the number of subjects with suicidal thoughts fell from 100% at baseline to 10% at the end of treatment. A worsening was reported at a 1-week follow-up (24%) and after one month (50%).

**Discussion**

In this review we aimed to evaluate the efficacy of a Triple Chronotherapy intervention in achieving response and remission in individuals with Major Depressive Disorder or Bipolar Depression; 6 studies met our eligibility criteria and were included in the review. The modalities through which the intervention was implemented were different. In particular, Martiny et al. (2013) and Moscovici et al. (2009) proposed a triple intervention with different timing and modalities compared to the other 4 studies. Despite this, all studies reported significant improvement of HAM–D scores at the end of treatment. Although approximately half of those diagnosed with depression respond to SD within 24 hours, relapse is frequently observed after a single night of sleep (Boland et al., 2017). The effect of SPA is also rapid and limited in duration, whereas BLT is effective and sustained when administered for 2 to 5 weeks (Al–Karawi & Jubair. 2016). Therefore, combination of the three interventions could strengthen and sustain the effect of each single component, although comparative studies are currently lacking. The medium– to long–term effect of a combined intervention also needs further study because systematic follow-ups were only reported in 4 studies, with differing time

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points. Nonetheless, results from 3 studies confirmed the intervention's efficacy and only one study (Hurd et al., 2019) reported reduced remission rates one week after the end of the intervention. Furthermore, evaluation of relapse proposed by Echizenya et al. (2013) may represent a further outcome to assess in the long term. Several lines of evidence support the use of SD and SPA in the treatment of depression (Dallaspezia et al., 2015). BLT is routinely employed in the treatment of Seasonal Affective Disorder (Menculini et al., 2018) and has recently gained attention for its efficacy in difficult-to-treat unipolar (Echizenya et al., 2013) and bipolar depressive syndromes (Sit et al., 2018). The substantial lack of risks associated with BLT makes it a candidate treatment for those populations in which medication is ineffective or potentially harmful, among which geriatric patients (Chang et al., 2018) and pregnant or breastfeeding women (Crowley SK & Youngstedt, 2012). Ongoing studies will also define its potential in treating adolescent depression (Holtmann et al., 2018) and preventing the onset of perinatal depression (Baiardi et al., 2016). The underlying mechanisms of action remain unclear for all three interventions. The Suprachiasmatic Nucleus (SCN) is considered the brain's master circadian pacemaker, and its endogenous rhythm is largely modulated by the environmental light-dark cycle (Lucas et al., 2015). BDNF-mediated synaptic potentiation and regulation of SCN responsivity to light-induced phase shifts (Schiena et al., 2015) and modulation of clock-gene expression (Bunney et al., 2015) have been proposed as chronobiological mechanisms underlying rapid antidepressant responses to Sleep Deprivation and NMDA-receptor antagonist Ketamine. SPA might act by improving "internal timing" and is supported by the observation that earlier parental set bedtimes are a protective factor against depression and suicidal ideation during adolescence (Dallaspezia et al., 2015). Indeed,

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a strong relationship between evening chronotype and bipolar mood disorders has been reported by a recent systematic review (Melo et al., 2017) and a meta-analysis found evening chronotype to be associated with an increased likelihood of any mood disorder and with the severity of depressive symptoms in affected subjects (Au & Reece, 2017). BLT is thought to promote the resynchronization of SCN oscillations and to stimulate serotonergic neurotransmission that might be impaired in depressed patients (Wu et al., 2017) (Lam et al., 1996).

Whereas chronotherapeutic approaches are used by many clinicians for seasonal affective disorder or unipolar depression, their use in bipolar depression is more recent and controversial. Evidence of a circadian dysfunction in Bipolar Disorder supporting the use of chronotherapy as an effective and powerful tool to manage the depressive phase is actively growing (Yorguner et al., 2017; Sit et al., 2018; Zhou et al., 2018). Several authors support its use in addition to a mood stabilizer, although the risk of manic/hypomanic switch rate might be lower than 4% (Benedetti et al., 2018). The majority of studies reviewed here included both unipolar and bipolar depressed patients while Wu et al (2009) included only bipolar patients and Moscovici et al (2009) only unipolar ones. In the Wu et al. (2009) study 2 out of 32 subjects presented a mild manic switch whereas Sahlem et al. (2014) and Hurd et al. (2019) reported mild insomnia and transitory daytime sleepiness after SPA in an unspecified number of subjects.

Available studies presented a satisfactory albeit not high methodological quality. Only 2 RCTs were retrieved whereas other studies had several critical issues such as lack of a control group, small sample size, high attrition rate on follow-up evaluations, or differing management of psychopharmacological treatment regimens. The good

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average clinical response and remission rates obtained support a practical utility of the intervention that also proved to be safe, given a substantial lack of side effects across studies. All examined studies reported a lack of significant side effects during and after the Triple–chronotherapy intervention.

**Conclusions**

Mood disorders, especially depression, are the most burdensome and frequent mental health issues worldwide. Due to its high prevalence and to the impact on affected individuals' quality of life, depression is considered a global health problem of paramount importance. Problems related to treatment resistance and long latency to response have opened up new pathways for research into alternative or additional interventions for acute stages of illness. Furthermore, some fragile populations have unsatisfactory response rates or potentially dangerous side effects with conventional antidepressant treatments. These include but are not limited to adolescents, elderly patients and pregnant or breastfeeding women. Results of this review suggest that Triple Chronotherapy – the combination of Total Sleep Deprivation, Sleep Phase Advance and Bright Light Therapy – is safe and effective in producing a rapid and stable improvement in depressive symptoms, especially in addition to standard pharmacological treatments. The long–term evaluation of outcomes is currently underexplored and has thus far yielded contrasting findings.

In general, despite a satisfying quality, available studies are very few so well-designed RCTs that can generate further evidence on the efficacy of Triple Chronotherapy to sustain its implementation in clinical practice are necessary.

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**Contributors**

PF and ST designed the search methodology and independently screened the abstract of the identified records. EGO supervised eligibility criteria and quality check. ADA and PF wrote the first draft of the manuscript. CC and CP revised the manuscript; OG and AD supervised all study procedures. All co–authors had full editorial control during the writing of the manuscript and finally approved it.

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The study received no funding.

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None

**Conflict of interest**

The authors declare no conflict of interest.

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Figure 1. PRISMA Flowchart

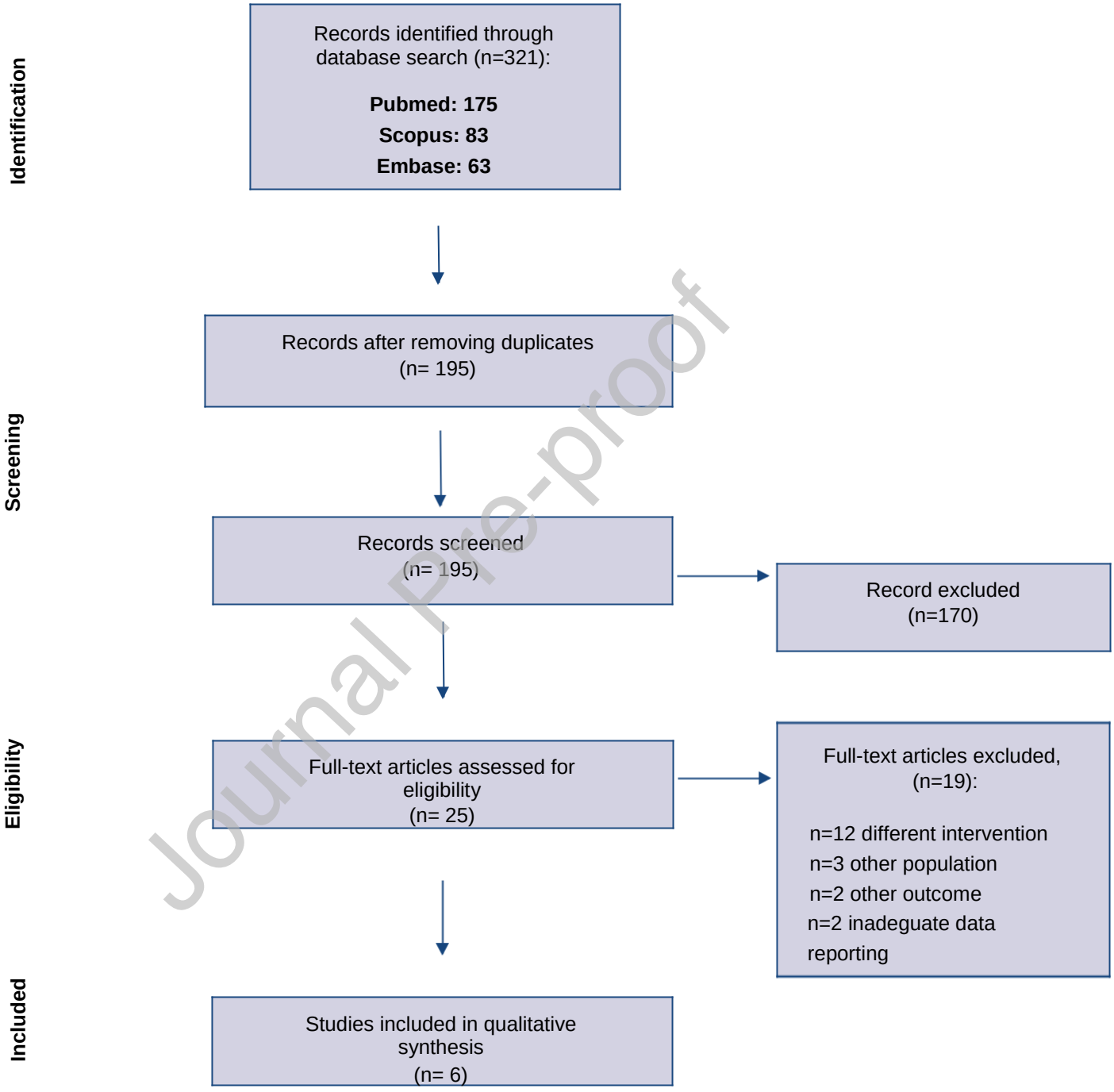


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Table 1. Characteristics of the included studies

| Author and Year (quality appraisal *) | Study design | Setting and period | Sample | Intervention and Comparison | Main outcomes | Main results | Effect size SDM (95% CI) |
|---|---|---|---|---|---|---|---|
| Moscovici & Kotler, 2009 (6/9) | Quasi-experimental study | Beer–Yaakov Mental Hospital. Telaviv<br><br>University, Telaviv, Israel | n=12<br><br>Age range: 18-70<br><br>Mean age: 43.3 ±10.12 SD, 10 F<br><br>Diagnosis: Depressive episode (ICD-10 criteria) | *Intervention group:*<br><br>TCT**<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light therapy (gradual increase from 0 to 5000 lux during the night and 10.000 lux for 30 minutes (from 06.00 to 06.30)<br><br>*Control group:* none | Primary: 21-Item Hamilton depression rating scale (HAMD21)<br><br>Other: Montgomery-Asberg Depression Clinician Rating Scale (MADRS)<br><br>Secondary: ZUNG Self-rating depression scale (SDS) | Significant reduction ($p<0.001$) in HAMD21, MADRS and SDS scores was found at the end of treatment and maintained at the follow-up after 4 weeks 4 subjects meeting criteria for remission at the end of the treatment, 7 at follow-up | 2.84 (1.76-3.92)[a]<br><br>Week 3-4 |
| Wu et al., 2009 (9/13) | Randomised Controlled Trial | University of California Irvine (UCI) and University of California San Diego (UCSD) Medical Centers | n=49<br>Age range: not avaible<br><br>Mean age: CAT (Chrono Tp) 39 ±13.31; MED (Tp as normal) 40 ± 14.1; 20 F<br><br>Diagnosis: Bipolar disorder Major depressive episode (DSM-IV criteria) | *Intervention group:*<br><br>TCT** + TAU ***<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light for 120 minutes (5.000 lux)<br><br>*Control group:* TAU *** | Primary: 19-Item Hamilton depression rating scale (HAMD19) | Significant decrease in HAMD19 scores in the intervention group versus the control group was maintained over a 7-week follow-up period | 1.04 (0.55-1.53)[b]<br><br>0.54 (−0.06 – 1.14)[c]<br><br>Week 7-9 |

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|---|---|---|---|---|---|---|---|
| Echizenya et al., 2013 (6/9) | Quasi-experimental study | Akita University Hospital, Hondo, Akita-City, Japan | n=13<br><br>Age range: 29-62<br><br>Mean age: 42.0 ±10.8 SD, 5 F<br><br>Diagnosis: Major depressive episode Bipolar disorder (DSM-IV criteria) | *Intervention group:*<br><br>TCT** + TAU***<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light for 120 minutes (5.000 lux)<br><br>*Control group:* TAU*** | Primary: 17-Item Hamilton depression rating scale (HAMD17)<br><br>Other: Zung Self-rating depression scale (SDS) | Significant improvement of depressive symptoms was observed with a reduction of HAMD17 and SDS scores at the end of treatment 8 patients maintained the responsiveness at follow-up | 2.28 (1.36-3.20[a]<br>Week 3-4 |
| Martiny et al., 2013 (10/13) | Randomised Controlled Trial | Copenhagen University Hospital, Copenhagen Denmark September 2005-August 2008 | n=75<br>Age>18 years<br>Age range: not avaible<br><br>Diagnosis: Major depression | *Intervention group:*<br><br>TCT** + TAU***<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light for 30 minutes (10.000 lux)<br><br>*Control group:* TAU*** + EP**** | Primary: 6-Item Hamilton depression rating scale (HAMD6) | The response rate in the intervention group at the end of the treatment was 41.9% versus 10.1% in the control group. Remission rates were 19.4% and 4.7% respectively | 2.33 (1.82–2.84)[b]<br><br>0.60 (0.14–1.07)[c]<br><br>Week 7-9 |
| Sahlem et al., 2014 (6/9) | Quasi-experimental study | Medical University of South Carolina (MUSC) October 2013-march 2014 | n=10<br>Age: 18-75<br>Age range: not avaible<br><br>Mean age: 44 ±16.4 SD; 6 F<br><br>Diagnosis: Unipolar or Bipolar depression (MINI neuropsychiatric examination criteria) | *Intervention group:*<br><br>TCT** + TAU***<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light for 30 minutes (10.000 lux)<br><br>*Control group:* none | Primary: 17-Item Hamilton depression rating scale (HAMD17)<br><br>Other: Columbia Suicide Severity Rating Scale (CSSRS) | Both HAMD17 and CSSRS scores were significantly reduced (p=0.002 and p=0.01) and the end of the intervention 6 individuals met criteria for remission at the end of treatment | 2.43 (1.18–3.68)[a]<br><br>Day 5-7 (no long-term follow-up) |

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|---|---|---|---|---|---|---|---|
| Hurd et al., 2019 (6/9) | Quasi-experimental study | Psychiatric Youth Inpatient Unit, Billings Clinic, Billigs, Montana. July 2016-March 2017 | n=31<br>Age range: 12-17<br><br>Diagnosis: Non-psychotic depressive episode (DSM-V criteria) | *Intervention group:*<br><br>TCT** + TAU***<br><br>TCT: one night of sleep deprivation followed by 3 days of sleep phase advancement and daily bright light therapy (1using a 10.000 lux light box)<br><br>*Control group:* none | Primary: 17-Item Hamilton depression rating scale (HAMD17)<br><br>Other: Columbia Suicide Severity Rating Scale (CSSRS) Screen for Child Anxiety Related Emotional Disorders (SCARED-5) Self-Harm Likert Scale | HAMD17 scores were significantly reduced at the end of the intervention ($p<0.01$) and the follow up after 1 week ($p<0.01$) and 1 month ($p<0.001$). 26 patients (84%) experienced a clinical response, 24 achieved remission at the end of the intervention<br><br>Secondary outcomes (SCARED-5, CSSRS, Self-Harm Likert Scale) showed significant at the end of the intervention that was sustained at the follow up periods | 3.23 (2.32-4.1)[a]<br><br>Day 30 |

* Score of the methodological quality of the study according to the Clinical appraisal tool proposed by "The Joanna Briggs Institute"
** Triple Chronotherapy procedure
*** Treatment as usual
**** Daily exercise program (at least 30 minutes) with a physiotherapist
[a] Within-group standardised effect sizes for case series. HAMD, Hamilton Depression Rating Scale; SMD, Standardised Mean Difference; CI, Confidence Interval
[b] Within-group standardised effect sizes for RCTs. HAMD, Hamilton Depression Rating Scale; SMD, Standardised Mean Difference; CI, Confidence Interval
[c] Between-group standardised effect sizes for RCTs. HAMD, Hamilton Depression Rating Scale; SMD, Standardised Mean Difference; CI, Confidence Interval

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