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Efficacy of sleep deprivation in patients with depression including bipolar depression

Ioannou M, Greenbrook JTV, Larson T, Magnusson K, Stadig I, Schmitz L, Sjögren P, Steingrimsson S, Svensson M, Szábo Z, Wartenberg C

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Efficacy of sleep deprivation in patients with depression including bipolar depression

[Effekter av sömndeprivation som behandling vid depression (inklusive bipolär depression)]

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1. Abstract

Background

A key treatment goal in depression including bipolar depression is to alleviate depressive symptoms. In depression, the major treatment strategies are psychopharmacological therapy, psychotherapy and electroconvulsive therapy. Bipolar disorder is usually treated with mood stabilisers. A challenge in treatment is the latency period between start of medication to its full effect. Sleep deprivation with or without subsequent light therapy has been considered as a treatment option for depression including bipolar depression.

Objectives: The objective of this Health Technology Assessment (HTA) was to assess whether total sleep deprivation with or without subsequent light therapy is an effective treatment for patients with depression or bipolar depression compared with no sleep deprivation or other treatment - by itself or in addition to standard treatment. Mortality, self-harm, and depression symptoms were considered critical outcomes for decision making. Important outcomes were quality of sleep, health-related quality of life (HRQl), medication use, everyday functioning, length of hospital stay, complications, and patients' experiences during treatment. Diurnal rhythm was considered a less important outcome.

Methods: A systematic literature search was conducted in March 2019 in PubMed, Embase, the Cochrane Library, Cinahl, PsycINFO, and several HTA databases. The certainty of evidence was assessed using the GRADE approach.

Main results: Six RCTs (n= 215 patients) and one cohort study investigated sleep deprivation as add-on to standard treatment versus standard treatment alone. Three RCTs (n=148 patients) compared sleep deprivation with other treatment. In all, seven RCTs were included, two of which had three treatment arms and contributed to both comparisons. Seven case series were included to evaluate complications of sleep deprivation, and one qualitative study contributed information on patients' experiences during treatment. None of the studies reported data regarding the critical outcomes mortality and self-harm. Depressive symptoms were assessed with the Hamilton Depression Rating Scale (HDRS). For sleep deprivation as add-on treatment versus no treatment; and sleep deprivation versus antidepressant medication divergent results or no differences were found. However, a significant reduction in depressive symptoms was reported in one study comparing sleep deprivation followed by chronotherapeutic maintenance treatment (light therapy and sleep time stabilization) versus exercise of limited duration and intensity.
Two studies assessed quality of sleep, with non-validated instruments only. Assessment of HRQL and everyday functioning in two studies did not reveal any consistent differences between sleep deprivation and control group. Medication and diurnal rhythm were not systematically investigated in any of the included studies. In a qualitative study of participants' experience during treatment several patients described a transient initial antidepressant effect and highlighted the importance of social support during sleep deprivation. Systematic documentation of complications is limited.

Concluding remarks: Mortality and self-harm have not been investigated in the included studies on sleep deprivation in patients with depression. Based on six RCTs, with several study limitations and imprecision, sleep deprivation compared with no add-on treatment may have little transient or no effect on depressive symptoms (low certainty of evidence, GRADE ⊕⊕◯◯). Based on one RCT in patients starting antidepressant medication, sleep deprivation with subsequent chronotherapeutic maintenance may reduce depressive symptoms compared with exercise of limited intensity and duration (low certainty of evidence, GRADE ⊕⊕◯◯). It is uncertain whether sleep deprivation affects depressive symptoms compared to medication, and whether sleep deprivation affects the level of functioning, HRQl, or duration of hospital stay compared with no or other treatment (very low certainty of evidence, GRADE ⊕◯◯◯). Medication use and diurnal rhythm were not systematically studied, and information on complications was sparse.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Ett centralt mål i behandlingen av depression och bipolär depression är att reducera de depressiva symptomen. Huvudsakliga behandlingsstrategier vid depression är läkemedelsbehandling, psykoterapi och ECT. Bipolär sjukdom behandlas vanligtvis med stämningsstabiliserande läkemedel. En utmaning i behandlingen är latenstiden tills läkemedel får full effekt. Sömndeprivation med eller utan efterföljande ljusterapi har övervägts som behandlingsmöjlighet både vid depression och bipolär depression.

Syfte
Syftet med denna HTA-rapport var att utvärdera om total sömndeprivation med eller utan efterföljande ljusterapi är en effektiv behandling för patienter med depression eller bipolär depression jämfört med ingen sömndeprivation eller annan behandling. Kritiska utfallsvariabler i analysen var mortalitet, självskadebeteende och depressiva symptom. Viktiga utfallsvariabler var sömnkvalitet, funktions-förmåga, läkemedelsförbrukning, hälsorelaterad livskvalitet, längd av hospitalisering, komplikationer, och patientens upplevelse av behandlingen. Dygnsrytmen inkluderades som en mindre relevant utfallsvariabel.

Metod
En systematisk litteratursökning genomfördes i Mars 2019 i PubMed, Embase, Cochrane Library, Cinahl, PsycINFO, Web of Science, och ett antal HTA-databaser. Studiernas kvalitet utvärderades och GRADE-systemet användes för att bedöma tillförlitligheten hos de sammanvägda resultaten.

Resultat
Sex randomiserade kontrollerade studier (n=215 patienter) och en kohortstudie undersökte sömndeprivation som tilläggsbehandling till standardbehandling vs enbart standardbehandling. Tre randomiserade kontrollerade studier (n=148 patienter) som jämförde sömndeprivation med annan behandling inkluderades. Totalt sju randomiserade studier inkluderades, därav två studier som omfattade tre behandlingsgrupper och bidrog till båda jämförelserna. Sju fallserier inkluderades för att utvärdera komplikationer vid sömndeprivation, och en kvalitativ studie bidrog med information om patienternas upplevelse av behandlingen.
Ingen studie redovisade data för de kritiska utfallsvariabler mortalitet eller självskadebeteende. Depressiva symptom undersöktes med hjälp av Hamilton Depression Rating Scale (HDRS) vid flera tidpunkter i studierna. Gällande jämförelsen av sömndeprivation som tilläggsbehandling vs ingen tilläggsbehandling och sömndeprivation vs antidepressiva läkemedel observerades divergenta resultat eller inga skillnader. Däremot rapporterades en signifikant minskning i depressiva symptom i en studie som jämförde sömndeprivation följd av kronoterapeutisk behandling (ljusterapi och stabilisering av sovtid) versus fysisk träning av begränsad längd och intensitet.
Två studier undersökte sömnkvalitet, dock enbart med icke-validerade instrument. Mätningar av hälsorelaterad livskvalitet och funktions-förmågan visade inga konsistenta skillnader mellan sömndeprivation och kontrollgruppen i två studier. Läkemedelsförbrukning och dygnsrytm har inte studerats systematiskt i de inkluderade studierna. I en kvalitativ studie av deltagarnas upplevelse av behandlingen beskrev flera patienter en övergående initial antidepressiv effekt och betonade vikten av socialt stöd under interventionen. I de inkluderade studierna finns enbart en begränsad systematisk dokumentation av komplikationer vid sömndeprivation.

Sammanfattande kommentarer
Mortalitet och självskadebeteende har inte undersökts i de inkluderade studierna om sömndeprivation i patienter med depression eller bipolär depression. Jämfört med ingen tilläggsbehandling kan sömndeprivation ha en liten övergående eller ingen effekt på depressiva symptom, baserad på sex randomiserade kontrollerade studier med olika begränsningar avseende studiekvalitét och precision (lågt vetenskapligt underlag; GRADE ⊕⊕OO). Baserad på en randomiserad kontrollerad studie i patienter som påbörjat antidepressiv medicinering, kan sömndeprivation med efterföljande

kronoterapeutisk behandling möjligtvis minska depressiva symptom jämfört med begränsad fysisk träning (lågt vetenskapligt underlag; GRADE ⊕⊕OO). Det är osäkert ifall sömndeprivation påverkar depressiva symptom jämfört med läkemedelsbehandling, och om sömndeprivation påverkar funktionsnivån, HRQOL och längden av hospitalisering jämfört med ingen eller annan behandling (mycket lågt vetenskapligt underlag GRADE ⊕OOO). Läkemedelsförbrukning och dygnsrytm har inte undersökts systematiskt och informationen om komplikationer är mycket begränsad.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, October 30th 2019.

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

No data regarding the outcomes mortality, self harm, medication use, or diurnal rhythm were retrieved.

Outcomes	Study design No. of studies (No. of patients)	Absolute effect	Certainty of evidence GRADE[1]
Sleep deprivation vs no sleep deprivation as add on treatment			
Depressive symptoms within 1 week	6 RCTs (215)	Standardised mean difference -0.17 (95% CI -0.75 to 0.41), ns Sub-group analysis excluding a study in elderly patients with late onset depression: Standardised mean difference -0.48 in favour of TSD (95% CI -0.82 to -0.14), p=0.006	⊕⊕◯◯[2]
After more than 1 week	6 RCTs (215)	Standardised mean difference -0.04 (95% CI -0.33 to 0.24), ns	⊕⊕◯◯[2]
Quality of Sleep	1 RCT (64)	Between-group difference in weeks 2-9 ns	⊕◯◯◯[3]
HRQL	1 RCT (64)	Between-group difference in WHO-5 ns	⊕◯◯◯[3]
Everyday functioning	1 RCT (64)	Between-group difference in GAF ns	⊕◯◯◯[3]
Sleep deprivation vs other treatment			
Depressive symptoms	**Sleep deprivation vs medication** 2 RCTs (73)	**Sleep deprivation vs medication:** Between-group difference in HDRS ns in both studies,	⊕◯◯◯[3]
	Sleep deprivation + chrono-therapeutic maintenance vs exercise 1 RCT (75)	**Sleep deprivation + chronotherapeutic maintenance vs exercise:** Between-group difference in HDRS ns week 1 but subsequently sign. advantage for TSD up to week 29.	⊕⊕◯◯[4]
Quality of Sleep	1 RCT (75)	**Sleep deprivation + light therapy vs exercise:** Sign. more patients with increased quality of sleep days 1-8 after TSD than in control F_1=10.5, p <0.001	⊕◯◯◯[3]
HRQL	1 RCT (75)	**Sleep deprivation + light therapy vs exercise:** Between-group difference in WHO-5 week 2 sign. in favour of TSD, week 8 ns.	⊕◯◯◯[3]
Everyday functioning	1 RCT (75)	**Sleep deprivation + light therapy vs exercise** Between-group difference in GAF ns	⊕◯◯◯[3]

CI: Confidence Interval''; GAF: Global Assessment of Functioning - HDRS: Hamilton Depression Rating Scale; HRQL: Health-related Quality of Life; ns: not significant, RCT: Randomized Controlled Trial;;

[1]Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[2]Downgraded two steps for some imprecision, some inconsistencies, some indirectness and serious study limitations (e.g. unclear randomisation, high drop-out, limitations in blinding).

[3] Downgraded three steps for serious imprecision, some indirectness and serious study limitations (e.g. unclear randomisation, lack of information on procedures in control group, high drop-out, limitations in blinding).

[4] Downgraded two steps for single study with some indirectness and some study limitations

4. Abbreviations/Acronyms

APA	American Psychiatric Association
CLOCK	Circadian Locomotor Output Cycles protein Kaput
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
GAF	Global Assessment of Functioning
HAMD	Hamilton Depression Rating Scale
HDRS	Hamilton Depression Rating Scale
ICD	International Statistical Classification of Diseases and Related Health Problems
LT	Light therapy
SD	Sleep deprivation
SSRIs	Selective serotonin reuptake inhibitors
SPS	Sleep Phase Stabilisation
SPF	Swedish Psychiatric Association (*Svenska Psykiatriska Föreningen*)
STS	Sleep Time Stabilisation
rTMS	Repetitive Transcranial Magnetic Stimulation
TSD	Total Sleep Deprivation
VGR	Region Västra Götaland
WHO	World Health Organisation
WT	Wake Therapy

5. Background

Disease/disorder of interest and its degree of severity

Depression is a leading cause of disability worldwide (WHO, 2017), causing a high burden of disease and substantial societal cost (Ekman et al., 2013; Whiteford et al., 2013). It is the major cause of death by suicide (WHO, 2017), and is highly correlated with cardiovascular and chronic disease-related mortality (Machado et al., 2018).

Depression, as other psychiatric conditions, is commonly diagnosed in line with a number of symptoms described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) and International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) (APA, 2013; WHO, 1992). Mood disorders are divided into the two main subtypes of low (depressed) or elevated mood (mania or hypomania). According to DSM-5, a patient may suffer from episodes of depression only (known as unipolar depression, major depressive disorder or recurrent depression) or episodes of either low or elevated mood (bipolar disorder). These mood changes differ from normal mood fluctuations by the severity of symptoms, longer duration and decrease in everyday life functioning and social interactions (APA, 2013).

The most serious complications of depression are suicide and self-harm. Symptoms include anxiety, memory and psychomotor dysfunction (APA, 2013). Disturbances in sleep and wake patterns, tiredness, insomnia and early morning awakening are also common (APA, 2013). Different phenotypes of sleep disturbances can be distinguished in patients with depression ranging from hypersomnia to insomnia. Research has identified various abnormalities in the circadian rhythm in patients with mood disorders (Takaesu, 2018; Vadnie and McClung, 2017; Wirz-Justice et al., 2005) This includes altered levels of important neuroendocrine regulators, which leads to a loss of timing in the circadian system and disturbed sleep.

The connection between the clinical state and changes in the circadian rhythm has been found to be most distinct in patients with bipolar disorder (Wirz-Justice et al., 2013).

Prevalence and incidence

According to the World Health Organization, around 4.4% of the world's population suffer from depression, and approximately 800,000 die by suicide every year. The one-year prevalence in Europe is estimated around 5% (Paykel et al., 2005). In Sweden, the lifetime risk has been estimated to be 36% for women and 23% for men (Mattisson et al., 2005). Recent years have seen an increase in depressive symptoms among youth in Sweden (SCB, 20180404), and a corresponding increase in prescription of antidepressant medication (Socialstyrelsen, 2019a).

Lifetime prevalence of bipolar disorder is estimated to be 1.0–2.4% worldwide, depending on the diagnostic criteria used (Merikangas et al., 2007). The one-year prevalence of bipolar disorder is around 1% (Pini et al., 2005). The annual incidence rate of diagnosed bipolar disorder in Sweden has increased gradually since the early 1990s, with an approximate 3.5-fold increase up to 2009 (IR: 9.1/10000 individuals, 2009). This suggests an advance in recognition of bipolar disorder, an ailment commonly misdiagnosed as other mental disorders, such as depression (Ghaemi et al., 2000).

Present treatment

The main treatment goal is to eliminate symptoms and re-establish psychosocial functioning (Lam et al., 2009). Major treatment strategies are psychopharmacological therapy, psychotherapy, and electroconvulsive therapy (ECT). First-line medication for patients with unipolar depression is usually antidepressant medication, with selective serotonin reuptake inhibitors (SSRIs) being the most common (Läkemedelskomittén i VGR, 2018).

Patients with bipolar disorder are normally treated with *mood stabilisers*. Among the mood stabilisers commonly used, lithium has been proven effective in preventing relapse and reducing self-harm (Läkemedelskommittén i VGR, 2019). Bipolar depression is usually treated with adjunctive therapy to mood stabilisers (antidepressant medication or Quetiapine). Caution is needed with the use of antidepressant medication (e.g. SSRIs) in bipolar depression, as there is a risk of inducing *mood or polarity switching* from depression to mania (Läkemedelskomittén i VGR, 2019). ECT may be needed in refractory or more severe forms of bipolar depression. The clinical response to lithium is suggested to be correlated to chronotype and cellular circadian rhythms (McCarthy et al., 2019).

There are two major therapeutic challenges related to the psychopharmacological treatment of depression and currently available antidepressant medications. The first issue is the matter of efficacy, as less than one-third of patients receiving standard antidepressants in clinical trials experience remission after up to four months of treatment (Thase et al., 2005). The delayed onset of the antidepressant effect is another challenge. Although SSRIs, when compared with placebo, show early onset of antidepressant effect already after one week, 5 to 7 weeks may be needed to achieve full effect (Hieronymus et al., 2016; Machado-Vieira et al., 2010). The latency period, between start of medication to its full effect, is considered critical, as it has been found to be related to increased risk for suicidal behaviour and worse treatment outcomes (Machado-Vieira et al., 2010; Trivedi et al., 2006). Thus, alleviating depressive symptoms as early as possible should be regarded as a prioritised treatment goal.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

In Sweden, the vast majority of patients (about 70%) with unipolar depression are diagnosed and treated as outpatients by general practitioners (SBU, 2004). Patients with therapy-refractory depression, high risk of suicide, or comorbid psychiatric conditions are usually referred to psychiatric specialists for more specialised care. A first evaluation normally takes place within three months after referral (Socialstyrelsen, 2019b). The patient undergoes a new assessment at the referred psychiatric unit. Patients may also initiate a self-referral to the tertiary care system. In some cases, patients may need acute hospital admission due to the intensity of symptoms, severe functional impairment, and refractory to treatment, or risk of suicide. Compulsory care is required in some cases, especially in depression with psychotic features. Hospital admission is usually acute (non-elective) after visit at the psychiatric emergency room, although direct or non-elective admission may be available in some cases with ongoing outpatient psychiatric care.
Patients with bipolar disorder, who are residents in the region Västra Götaland, receive outpatient care at subspecialised psychiatric units. The screening for bipolar disorder usually takes place at the primary healthcare level, and further psychiatric assessment is needed in most cases. Inpatient admission may be needed to treat manic, depressive or mixed episodes. During the course of bipolar illness, patients often lack insight into their own condition and compulsory care may be needed in some cases. In recent years, efforts have been made to improve continuity of care for patients and simplify the care pathways within Region Västra Götaland (VGR). In Gothenburg (Sahlgrenska University Hospital's catchment area) there are two specialised inpatient units dedicated to the care of patients with bipolar disorder, in close collaboration with an outpatient unit for this patient population.

Number of patients per year who undergo current treatment regimen

Prescription of antidepressant medication, especially SSRIs, is relatively high in Sweden. Among adults in 2015, more than 12% of women and 6% of men were undergoing treatment with antidepressant medication (Socialstyrelsen, 2019a). The total cumulative incidence of antidepressant initiation for the most common antidepressants in Sweden during the period 2009 and 2013/2014 (depending on data source) was 234 per 1000 population (compared to 213 in Denmark and 162 in Germany) (Forns et al., 2019).

According to online data from the National Patient Registry, admission rates of adults patients with depression (bipolar disorder excluded) were up to 131 inpatient admissions per 100,000 citizens in VGR in 2017, with an average length of 21.6 hospital stay days (Socialstyrelsen, 2019c). Admission rates for adult patients with bipolar disorder were about 64.5 inpatient admissions per 100,000 citizens in VGR in 2017. The average length of admission is often longer for these patients (32.6 days in 2017) (Socialstyrelsen, 2019c).

Present recommendations from medical societies or health authorities

In Sweden, national guidelines for depression from the National Board of Health and Welfare (Socialstyrelsen, 2017) state that treatment options depend on the type of depression and its severity (mild, moderate or severe). In recurrent depressive disorder or severe depression, antidepressant medication, ECT, and lithium are strongly recommended. Repetitive transcranial magnetic stimulation (rTMS) (a relatively new noninvasive form of brain stimulation) may also be a treatment option for treating severe depression, yet with smaller effect size than ECT.

Psychotherapy should be offered in cases of mild or moderate forms of depressions, and physical exercise or antidepressant medication can be prescribed as alternative treatment options. Notably, the National Board of Health and Welfare's guidelines underscore the need of improving access to psychotherapy for less severe forms of depression.

Bipolar disorder has not been included in the latest version of the National Board of Health and Welfare's national guidelines for depression (Socialstyrelsen, 2017). The Swedish Psychiatric

Association (SPF) has published guidelines for diagnosis and treatment of bipolar disorder in 2014 (SPF, 2014). Mood stabilisers (i.e. lithium), adjunctive treatment with antidepressant medication or Quetiapine, and ECT are the suggested treatment options for bipolar depression. The treatment recommendations in VGR are in line with the SPF's guidelines (Läkemedelskomittén i VGR, 2019).

Sleep deprivation is currently not mentioned in the Swedish guidelines on treatment of unipolar and bipolar depression.

6. Health Technology at issue: Sleep deprivation/wake therapy

Sleep deprivation, defined as voluntary sleep restriction for therapeutic purposes, has been investigated as an antidepressant treatment for four decades. It falls under chronotherapeutic interventions in which biological rhythms and sleep are manipulated through controlled exposure to environmental stimuli in order to treat mood disorders. These interventions target several mechanisms common to the action of antidepressant medication. Changes in the activity of the same monoaminergic and glutamatergic systems as those observed during antidepressant drug treatment have been reported. Although these marked changes in the neurobiology of the brain have been observed, it is still uncertain which biological changes are needed to recover from depression.

Although instantaneous overnight remission of depressive symptoms after sleep deprivation has been widely reported, the intervention has not been established as treatment because patients usually relapse after recovery sleep. New studies indicate that the relapse can be prevented by combining sleep deprivation with other treatments, such as daily light therapy (starting during sleep deprivation or after recovery sleep), sleep phase advances or concurrent administration of a variety of medications (Wirz-Justice et al., 2005). This has led to a plethora of treatment protocols without clear consensus which should be preferred.

Treatment can be a single or a repeated sleep deprivation (two or three nights per week with recovery nights in between), total (all night) or partial (second half of night) (Boland et al., 2017). The patient thus stays awake all night or is woken at 1 AM and stays awake all morning, as well as the next full day. It is important to avoid naps during sleep deprivation treatment as this can compromise the outcome of the intervention (Martiny et al., 2012). This is the main reason why this treatment method has mainly been used in a hospital setting such as inpatient wards or sleep centres. During the no-sleep nights, patients are encouraged to remain awake by participating in physical and social activities (e.g. playing games, surfing the internet, watching TV). Interaction with personnel or patients staying awake two and two together are usual measures of increasing adherence to the protocol.

If effective, implementation of the method (especially as an adjunctive treatment) in the inpatient psychiatric care units could be considerably beneficial for the patients. It could induce faster onset of improvement of depressive symptoms and potentially shorten length of admission.

7. Focused question

Is sleep deprivation (wake therapy) an effective treatment of depression and bipolar depression (defined according to DSM criteria)?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Adult (≥18 years) patients with depression including bipolar depression (defined according to DSM criteria)
I	Sleep deprivation/wake therapy (for at least one night under supervision at the hospital; with or without subsequent light therapy), with or without standard treatment (excluding ECT)
C	C1: No sleep deprivation, with or without standard treatment (excluding ECT) C2: Other treatment* than sleep deprivation, with or without standard treatment (excluding ECT).
O	Critical for decision making • Mortality (including suicide) • Self-harm • Depressive symptoms (assessed by validated instrument) Important for decision making • Quality of sleep • Health-related quality of life measured with validated instruments • Medication use • Everyday functioning (restored Activities of Daily Living, return to work) according to validated scales or administrative data • Length of hospital stay • Complications (Note – worsening in depressive symptoms is evaluated as part of effect measures and not as part of complications) • Patients' experience during treatment (based on qualitative studies) Less important for decision making • Diurnal rhythm

*Other treatment – e.g. exercise or medication

8. Methods

Systematic literature search (Appendix 1)

During March 2019 two authors (KM, IS) performed systematic searches in PubMed, Embase, the Cochrane Library, Cinahl, PsycInfo and a number of HTA databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies have been critically appraised using a checklist from the Swedish Agency for HTA and assessment of social services (SBU) for assessment of randomised controlled trials. The results of each study have been summarised per outcome in Appendix 4. When possible, data have been pooled for meta-analysis in RevMan 5.3 using a random effects model. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). Certainty of evidence for each outcome was assessed using the GRADE approach (Atkins et al., 2004; GRADE Work group). Methodological assessment of the qualitative study was performed using the template for qualitative studies provided by SBU.

Patient involvement

The PICO was reviewed in a meeting with three representatives from the patient organisation IBIS (Intresseförening Bipolär Sjukdom) - including feedback from a patient and patients' relatives view. Meeting participants were informed about the HTA project and asked to provide input on the PICO. They confirmed that the outcomes at issue were relevant and emphasised the value of antidepressant treatment with early onset.

Ongoing research

A search in Clinicaltrials.gov (2019-06-07) using the search terms (chronotherapy OR "sleep deprivation" OR "sleep deprived" OR "wake therapy") AND (depression OR depressive OR depressed OR antidepression OR antidepressive OR antidepressed) identified 61 trials. A search in WHO ICTRP (2019-06-07) using the search terms chronotherap* AND depress* OR chronotherap* AND antidepress* OR chronotherap* AND anti-depress* OR sleep depriv* AND depress* OR sleep depriv* AND antidepress* OR sleep depriv* AND anti-depress* OR wake therap* AND depress* OR wake therap* AND antidepress* OR wake therap* AND anti-depress* identified 30 trials. In total 70 unique ongoing trials were identified.

9. Results

9.1 Search results and study selection (Appendix 1)

The literature search identified 2,133 articles after removal of duplicates. After reading the abstracts 2,055 articles were excluded. An additional 43 articles were excluded by two authors after reading the articles in full text. The remaining 35 articles were sent to all participants of the project group, and 19 articles (describing seven RCTs, one cohort study, seven case series and one qualitative study) were finally included in the assessment (Appendix 2). In addition, two systematic reviews (SR) were commented upon.

9.2 Included studies (Appendix 2)

In the following, results for each outcome are presented separately for the comparison of sleep deprivation vs no sleep deprivation (C1) and for the comparison of sleep deprivation vs other treatment (C2). Note that two publications contributed to both comparisons as they included three treatment arms.

For C1 six RCTs were included with a total of 215 patients, comparing sleep deprivation as add-on to medication or standard treatment with no add-on treatment (Benedetti et al.,1997, Elsenga et al., 1982, Kundermann et al., 2008, Kragh et al., 2017, Reynolds et al., 2005, Wu et al., 2009). Only one of these studies (Kragh et al., 2017) had no limitations regarding directness, precision and risk of bias. All other studies had minor or major risk of bias – mainly due to limitations in blinding, and high or incompletely described dropout rates. The directness was limited in four of the studies e.g. due to differing sleep deprivation protocols (one up to six wake nights) and patient populations (e.g. one study in elderly patients with late-onset depression). Furthermore, two studies had small sample sizes limiting the precision. Two studies – Kragh et al., 2017, and Wu, 2009 - combined sleep deprivation with chronotherapeutic interventions (light therapy, sleep time stabilization). Apart from the RCTs one cohort study was included in the analysis.

For C2 three RCTs were included with a total of 148 patients comparing sleep deprivation with other active treatment.Two studies (Elsenga et al., 1982, and Reynolds et al., 2005) compared sleep deprivation with medication. The third study compared sleep deprivation combined with subsequent chronotherapeutic maintenance (light therapy and sleep time stabilization) with exercise as active comparator (this study was reported in three different publications (Martiny et al., 2012, 2013, and 2015). The risk of bias was judged to be minor in all three studies (some limitations in blinding, and some questions regarding the control treatments). Questions regarding directness were raised for two studies (one study only included elderly patients, and for the study comparing sleep deprivation with exercise of only limited duration and intensity). Furthermore, one of the three studies had a small sample size limiting the precision.

Original data were retrieved for three studies (Kragh et al., 2017; Kundermann et al., 2008; Reynolds et al., 2005) after direct contact with the authors.

Apart from the studies above, seven case series (Benedetti et al., 2005, Colombo et al., 1999, Colombo et al., 2000, Fähndrich, 1981, Rudolf et al., 1978, Suzuki et al., 2018, and Svendsen, 1976) were included to evaluate complications of sleep deprivation, and one qualitative study (Kragh et al., 2017 b) contributed information regarding patients' experience during treatment.

9.2 Results per outcome and comparison

Outcomes, critical for decision-making

9.3.1. Mortality (including suicide) and self-harm

None of the included studies reported data regarding mortality or self-harm.

9.3.2. Depressive symptoms (Appendix 4.1)

Depressive symptoms were investigated using the Hamilton Depression Rating Scale (HDRS) at baseline and several subsequent times during the studies. The HDRS questionnaire is a commonly used and psychometrically tested scale for evaluation of patients following treatment for depression (Hamilton, 1960; Obeid et al., 2018). In HDRS ratings, the clinician evaluates the patients' symptoms during the last week. The HDRS ratings were assessed by clinicians/raters in all studies. In this

HTA, we distinguish between the initial treatment evaluation within the first week after the first sleep deprivation, and subsequent assessments after two or more weeks.

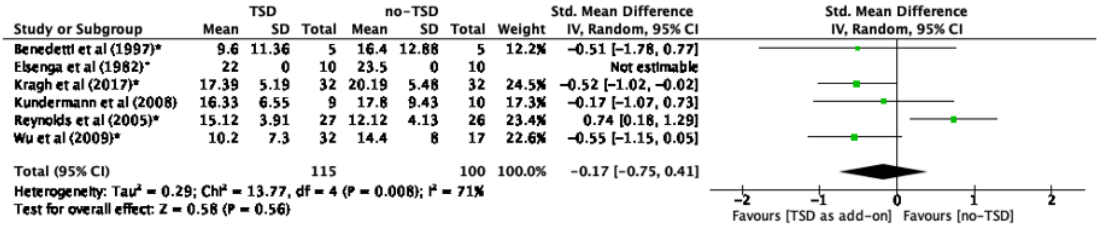
C1: Sleep deprivation vs no sleep deprivation

Six RCTs (Benedetti et al.,1997, Elsenga et al., 1982, Kundermann et al., 2008, Kragh et al., 2017, Reynolds et al., 2005, Wu et al., 2009) and one cohort study (Gorgulu et al., 2006) investigated the effect of sleep deprivation as add-on to medication or standard treatment on depressive symptoms. Only one of these studies (Kragh, 2017) was assessed to have no or minor limitations regarding directness, precision and risk of bias. In the studies depressive symptoms were assessed for a study duration of 2 to 9 weeks.

Effects of sleep deprivation during the first week after treatment start
Four RCTs reported statistically significant differences between the treatment groups during the first week which in three studies were in favour of sleep deprivation (Benedetti et al 1997, Kragh et al., 2017, and Wu et al., 2009) and in one study in favour of the comparator (Reynolds et al., 2005). The remaining two studies reported no significant difference between the treatment groups.

A meta-analysis of the post-treatment data during the first week was non-significant for sleep deprivation + standard treatment compared with standard treatment only (SMD= -0.17 [95% CI -0.75 to 0.41]; p=0.56) with high heterogeneity (Figure 1). At the time of analysis, no reliable variability data were available for one of the studies (Elsenga, 1982) which therefore does not contribute to the meta-analysis. Note, the meta-analysis is based on post-treatment assessments only, as information regarding mean change from baseline and the corresponding standard deviation is missing in almost all publications. This approach is less powerful than the statistical analyses used in the individual publications, which consider repeated measures at different time points (see Appendix 4.1, showing significant between group differences week 1 for Benedetti et al 1997, Elsenga et al 1982, Kragh et al 2017, Reynolds et al 2005, and Wu et al 2009).

Figure 1. Meta-analysis of the HDRS scores during the first week after start of treatment with sleep deprivation as add-on to standard treatment compared with standard treatment only.



*Indicates statistically significant result reported in publication

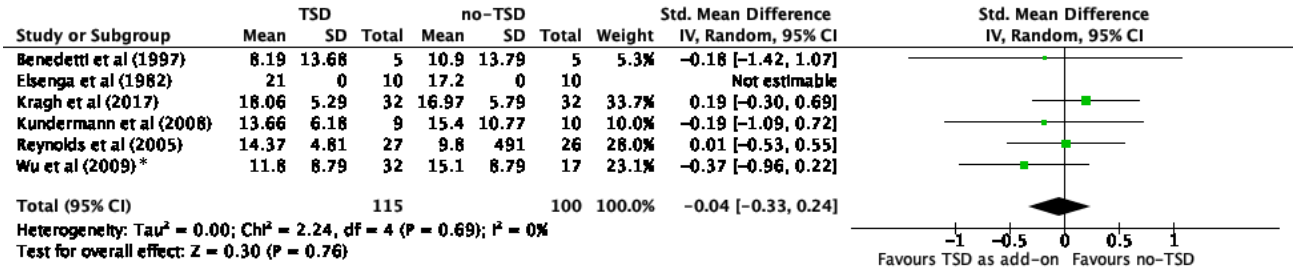
The RCT by Reynolds et al. (2005) was found to be the main source of the statistical heterogeneity. Apart from the fact that this is the only RCT significantly favouring no sleep deprivation, the study shows substantial differences from the other studies: by protocol, the study restricted the population to elderly patients with late onset adult depression. Furthermore, the treatment investigated the effect of a single night of sleep deprivation without any other chronotherapeutic maintenance strategy. In addition, antidepressant medication was initiated at a low dose during the first two days. In a post-hoc sensitivity analysis excluding Reynolds et al. (2005), the heterogeneity resolved (I^2 =0%) and the overall effect reached statistical significance with standardized mean difference? (SMD) of -0.48 (95% CI -0.82 to - 0.14; p=0.006) in favour of sleep deprivation.

However, considering the PICO for this HTA report, the conclusion is based on the broader analysis including all relevant studies rather than an ad-hoc sub-group analysis.

Conclusion: In patients with depression or bipolar depression, sleep deprivation given in addition to standard treatment may result in little or no difference in depressive symptoms compared with no add-on treatment during the first week after treatment start.
Low certainty of evidence (GRADE ⊕⊕◯◯).

Effects of sleep deprivation more than one week after treatment start
In five out of six RCTs, no significant effects of sleep deprivation were observed in the subsequent weeks after sleep deprivation (Benedetti et al.,1997, Elsenga et al., 1982, Kundermann et al., 2008, Kragh et al., 2017, and Reynolds et al., 2005). One RCT reported a maintained effect of sleep deprivation (Wu et al., 2008). This study recruited patients with bipolar depression with ongoing treatment with mood stabilisers and used a chronotherapeutic protocol (sleep deprivation in combination with light therapy and sleep phase advance). Meta-analysis of the HDRS scores two to three weeks after first sleep deprivation did not reach significance (SMD=- 0.04 [95% CI -0.33 to 0.24]; p=0.76), with low heterogeneity (Figure 2).
In the cohort study (Gorgolu et al., 2009) the sleep deprivation group showed larger symptom reduction than the control group during the first two weeks after first sleep deprivation. No difference in depression symptom scores was found six weeks after sleep deprivation.

Figure 2. Meta-analysis of the HDRS scores two to three weeks after start of treatment with sleep deprivation as add-on to standard treatment compared with standard treatment.



* Indicates statistically significant result reported in publication

Conclusion: In patients with depression, sleep deprivation in addition to standard treatment may have little or no persisting effect on depressive symptoms, after more than one week, compared with no add-on treatment.
Low certainty of evidence (GRADE ⊕⊕◯◯).

C2: Sleep deprivation vs other treatment

Sleep deprivation vs medication

Two RCTs with minor study limitations including 73 patients compared sleep deprivation and concurrent administration of placebo with initiation of antidepressant medication (Elsenga et al.,1982; Reynolds et al., 2005). No difference was found between sleep deprivation compared with antidepressant medication during the two-week follow-up in the studies.

Conclusion: It is uncertain whether sleep deprivation compared with medication affects depressive symptoms in patients with depression.
Very low certainty of evidence (GRADE ⊕◯◯◯).

Sleep deprivation vs exercise

Another study with minor study limitations (described in three publications focusing different study periods – Martiny et al.2012; Martiny et al., 2013; Martiny et al., 2015) compared sleep deprivation followed by chronotherapeutic maintenance with exercise. All patients were hospitalized for two weeks and started antidepressant medication with a fixed dose of duloxetine in the first week. In the second week at hospital, patients received treatment according to randomization: The sleep

deprivation group had 3 wake therapy nights within one week, combined with light therapy and sleep time stabilization throughout the subsequent study period. Patients in the exercise group had an individually tailored daily exercise program planned with a physiotherapist and were subsequently seen weekly to follow up their exercise performance. The patients in the sleep deprivation-group showed a rapid, significant and larger reduction in depression scores than the patients in the exercise group during the 29-week follow up, although the effect diminished over time. In this study, response was defined as a 50% reduction in HDRS from baseline. Initially, the proportion of responders was higher in the sleep deprivation group than in the exercise group (75% vs 25%). This difference diminished after completion of the intervention (42% vs 10%). However, at week 29 the proportion of responders was still significantly higher in the sleep deprivation group than in the exercise group (61.9%/37.9%, OR=2.6, p=0.01).

Conclusion: In patients with depression starting antidepressant medication, sleep deprivation with subsequent chronotherapeutic maintenance may result in reduced depressive symptoms compared with exercise. Low certainty of evidence (GRADE ⊕⊕◯◯).

Outcomes, important for decision-making

9.3.3. Quality of sleep (Appendix 4.2)

The outcome quality of sleep was investigated in one RCT comparing sleep deprivation as add on to medication (Kragh et al., 2017) with no add on treatment (C1) and in one RCT (reported in Martiny et al., 2012; and Martiny et al., 2015) comparing sleep deprivation with exercise (C2). In both studies quality of sleep was self-reported using non-validated instruments. Both studies reported positive effects of the combination of sleep deprivation, light therapy and sleep time stabilization on patients' sleep duration, sleep maintenance and self-reported sleep quality. A significant advance of sleep-wake cycle was observed in one study (Martiny et al., 2015), indicating less problems falling asleep. Kragh et al. (2017) report a decrease in awakenings during the night and less day time sleeping in the first weeks after sleep deprivation.

Conclusion: It is uncertain whether sleep deprivation affects the quality of sleep in patients with depressioncompared with no treatment or with other treatment.
Very low certainty evidence (GRADE ⊕◯◯◯).

9.3.4. Health-related quality of life (Appendix 4.3)

HRQL was measured with validated instruments in one RCT comparing sleep deprivation as add on to medication with no-add on treatment (C1) and in one RCT comparing sleep deprivation to exercise (C2). Both studies (Kragh et al., 2017; Martiny et al., 2015) evaluated similar chronotherapeutic interventions (combination of sleep deprivation, light therapy and sleep time stabilization) and measured HRQL with the WHO-5 scale. Only one study (Martiny et al., 2015) showed significantly better self-reported HRQL in the sleep deprivation treatment group than in the control group.

Conclusion: It is uncertain whether sleep deprivation affects the health-related quality of life measured in patients with depression compared with no treatment or with other treatment.
Very low certainty evidence (GRADE ⊕◯◯◯).

9.3.5. Medication use

None of the included studies investigated the need for, or changes in medication use before and after intervention. Data on psychotropic medication were reported in two studies (Kragh et al., 2017; Martiny et al., 2015) mainly serving as control information for a possible cofounder. No significant differences between intervention and control groups were reported.

9.3.6. Everyday functioning (restored ADL, return to work) according to validated scales or administrative data (Appendix 4.4)

Everyday functioning was investigated by using GAF assessments in one RCT comparing sleep deprivation as add on to medication with no add on treatment (C1) and in one RCT comparing sleep deprivation to exercise (C2). The two studies (Kragh et al., 2017; Martiny et al., 2015) had similar intervention protocols for the sleep deprivation groups but they report GAF scores in different post-treatment time periods (9 weeks and 29 weeks after sleep deprivation, respectively). No significant effect on everyday functioning was found.

Conclusion: It is uncertain whether sleep deprivation affects the everyday functioning in patients with depression compared with no treatment or with other treatment.
Very low certainty evidence (GRADE ⊕◯◯◯).

9.3.7. Length of hospital stay (Appendix 4.5)

One RCT (Kragh et al., 2017) investigated the length of hospital stay in patients treated with sleep deprivation as add-on compared with no add-on treatment (C1). No significant difference was found between groups. Noticeably, the median length of hospital stay was numerically longer for the sleep deprivation group. No studies investigated this outcome for C2.

Conclusion: It is uncertain whether sleep deprivation in addition to standard treatment affects the length of hospital stay compared with no add-on treatment in patients with depression.
Very low certainty of evidence (GRADE ⊕◯◯◯).

9.3.8. Complications (Appendix 4.6)

The systematic documentation of complications is limited in the included studies. Data is provided in three RCTs (Wu et al., 2009; Martiny et al., 2015; Kragh et al., 2017), one cohort study (Gorgulu et al., 2009), and 7 case series (Benedetti et al., 2005; Colombo et al., 1999; Colombo et al., 2000; Fähndrich, 1981; Rudolf et al., 1978; Suzuki et al., 2018; Svendsen, 1976).

A complication of special interest is the polarity/mood switching in patients with bipolar depression, as sleep disturbance is a common prodromal symptom of relapse in mania. Summarized over all included case series above, the average switch rate in bipolar patients during sleep deprivation treatment (650 patients with bipolar disorder) was 5.5%. The publications do not provide any information as to when the polarity switch occurred in relation to the sleep deprivation. No conclusive data could be retrieved on mood switching in unipolar patients treated with sleep deprivation.

Regarding the tolerability and feasibility of the treatment, relevant data were retrieved from three RCTs (Wu et al., 2009, Martiny et al., 2015; Kragh et al., 2017) and one cohort study (Gorgulu et al., 2009). Of the 152 patients who were treated with sleep deprivation, 17 (11.2%) were reported as dropouts. The reasons for dropout were not specified in all cases but ECT treatment and failure to adhere to study protocol were mentioned. A comparison with the control groups is not possible, since information on dropouts in the control groups is very limited. One patient in the control group developed polarity switch (Martiny et al., 2015).

Two studies (Martiny et al., 2015, Kragh et al., 2017) described development or worsening of anxiety in a small number of patients as a result of the sleep deprivation.

9.3.9. Patients' experience during treatment (based on qualitative studies)

Only one study (Kragh et al., 2017b) was found to focus on patients' qualitative experiences of sleep deprivation when taking part in an RCT . The quality of the study was evaluated as moderate due to lack of information on ethical rational (i.e. power imbalances during interviewing) and theoretical foundation (i.e. insufficient presentation of manifest analysis). The participants' overall experiences were reported to be positive. A rapid but transient antidepressant effect was experienced by some patients whereas others described long-term benefits, such as improved sleep and diurnal rhythms. Social support was found to be important for implementation of the sleep deprivation treatment. Negative experiences were limited, and mostly related to disappointment surrounding inadequate or transient responses.

Less important for decision making

9.3.10 Diurnal rhythm

None of the studies investigated the effect of sleep deprivation on diurnal rhythms. In one study (Kundermann et al., 2008) the cortisol and prolactin levels were measured during the study period for examining the effects of sleep deprivation in the normalization processes of the serotoninergic dysfunction. However, no certain conclusion could be drawn on effect of sleep deprivation on diurnal rhythms.

10. Ethical aspects

A possible immediate but transient relief from depressive symptoms raises important ethical questions surrounding the clinical relevance of the method. Hopelessness is a critical burden in depression and is highly associated with suicidal ideation and attempts. By addressing and modifying hopelessness, suicidality can be reduced (Beck et al, 1979; Nekanda-Trepka et al., 1983). However, whilst immediate relief of depressive symptoms could be an important means of working toward reinstalling hope, the transient nature of the positive effects of sleep deprivation could also aggravate patients' despair. This could potentially result in the treatment causing more harm than good, if patients were to lack access to continuity of care.
Thus, adequate follow-up measures would need to be in place, were sleep deprivation to be offered as adjunctive treatment. Nevertheless, none of the included studies, nor any of the case series that were assessed for inclusion, reported any severe complications. The rate of switch into mania after sleep deprivation in patients with bipolar depression appears to be lower than occurrence with antidepressant medication (Niitsu et al., 2015). Nevertheless, the presence of this phenomenon still justifies some concerns for the risk of switching, and thus, this would need to be more adequately explored prior to the method becoming a standardized treatment for patients with bipolar depression.

Whilst the human circadian rhythm has received some popular attention, the nature of sleep deprivation as a treatment method would need to be adequately presented to patients, in order to adhere to foundational principles of informed consent. To a person suffering from depressive symptoms, such as insomnia, tiredness, and psychomotor retardation, the proposition to stay awake in 36 hours may instinctively raise some doubts surrounding the method. Adequate information would need to be provided so that patients feel comfortable in pursuing the method. This holds importance both in obtaining consent, but also in patient-participation, as in contrast to other antidepressant treatments, sleep deprivation requires considerable determination and engagement from the patient in adhering to treatment.

Notably, all studies included in the present analysis described sleep deprivation as a well-tolerated treatment. However, reporting on complications and drop-out is deficient in most studies and information on patients who discontinue treatment is lacking.
In summary, further explorations surrounding the potential of sleep deprivation as adjunctive treatment for depression should be considered. In such explorations, important ethical aspects relating to treatment efficacy, informed consent, patient participation, and economic prioritization should be considered.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

Sleep deprivation /wake therapy is not an established treatment at the Sahlgrenska University Hospital. However, it has been used at some psychiatric inpatient units within the framework of research or experimental treatment (Christodoulou et al., 2015). The general impression is that the method could easily be introduced to the patients and personnel without additional costs or supplementary application. In relation to the publications included in this HTA, the support offered to patients in these studies has been limited. The procedure needed can relatively easily be introduced for inpatients. The regular staff should be able to monitor patients during the procedure.

Present use of the technology in other hospitals in Region Västra Götaland
Currently, there is no regular use of the method in the region.

Consequences of the new health technology for personnel
If sleep deprivation /wake therapy should be implemented on a regular and extended basis, additional personnel may be required. A larger scale introduction will probably require further education and training of personnel.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland
It is too early to ascertain consequences at this stage. If sleep deprivation /wake therapy will be shown to be an effective treatment, the number of referrals to clinics where these interventions are given may increase. However, as sleep deprivation may be considered an easily implemented technique, it is more probable that the procedure would gain traction and be disseminated to other facilities in the region.

12. Economic aspects

Present costs of currently used technologies
The average cost for a patient with depressive disorders and\or bipolar disorder is (year 2017) 52,000 up to 54,000 SEK (ICD-codes: F30, F31, F32), which includes both in- and outpatient care costs and is an average from 15 Swedish health care regions. On average, only a small share (10-20%) of patients have any inpatient care costs, so the cost per patient among the sub-group with inpatient costs is substantially higher.

Expected costs of the new health technology (see I: in PICO)
Two main scenarios are considered in the economic analysis:

(a) Sleep deprivation as an adjunctive treatment in an inpatient psychiatric care unit

(b) Sleep deprivation as an inpatient treatment for patients who are currently treated in an outpatient setting (assuming hospitalization for 5 days to allow for 3 nights with sleep deprivation separated by nights without sleep deprivation)

The following considerations consider direct costs of the health technology only.

As for the first scenario (a), it is assumed that with minor organizational adjustments it would be possible to adopt sleep deprivation without adding any staff hours or requiring additional staff categories. If this is possible from an organizational perspective, this implies that there is no added economic cost for sleep deprivation as an adjuvant treatment in an inpatient psychiatric care unit setting.
For the second scenario (b), the demand for inpatient stays (days) will increase, with the associated increase in economic costs. With a cost per inpatient day as reported by the inpatient psychiatric care unit at the Sahlgrenska University Hospital of around 6,000 SEK and an assumed total of 5 inpatient days per patient treated, the added cost of sleep deprivation would be approx. 30,000 SEK per patient.

Total change in costs

The total change in costs in scenario (a) is assumed to be null. In scenario (b), the total change in costs would depend on how many patients are being offered sleep deprivation as an additional treatment. For every 10 patients offered sleep deprivation treatment, and otherwise treated in an outpatient setting, the total change in costs would be around 300,000 SEK.

Possibility to adopt and use the new technology within the present budget

Sleep deprivation as an adjunctive treatment for patients in an inpatient psychiatric care unit is possible to adopt within the present budget, i.e. without displacing other health care services. Sleep deprivation as a treatment for patients otherwise in an outpatient setting is not possible to adopt within the present budget and would require additional funding and/or imply that other health care services are displaced.

Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost-consequence or budget-impact analysis studies of the new technology were identified in the published literature.

13. Discussion

Summary of main results

The aim of this HTA was to assess the efficacy of sleep deprivation with or without subsequent light therapy in patients with depressive symptoms including bipolar depression. We included seven RCTs and one cohort study in our data analysis. Seven case series contributed to evaluating the occurrence of complications.

No conclusions could be drawn on treatment effect on mortality and self-harm as none of the included studies reported relevant outcome data. No study reported suicide attempt or death during treatment, and suicide risk was an exclusion criterion in many of the studies.

Regarding depressive symptoms, the findings at the overall level do not show an advantage of sleep deprivation as adjunctive treatment to standard treatment compared to placebo (SMD= -0.17[-0.75 to 0.41]; p=0.56). Due to inconsistencies, study limitations, some indirectness and imprecision, our confidence in this finding is low (GRADE ⊕⊕◯◯).

In a post-hoc sub-group analysis excluding a study in elderly patients with depression (Reynolds, 2005), the combination of sleep deprivation and standard treatment showed a transient antidepressant effect in the first week compared with standard treatment alone (-0.48 ([-0.82 to - 0.14]; p=0.006)). In any case, any add-on effect of sleep deprivation seems to be transient and diminished after the first week. Note that two of the studies (Kragh et al., 2017, and Wu 2009) combined sleep deprivation with subsequent light therapy, one of these studies reports transient, the other sustained effects of the combination treatment.
A single study compared sleep deprivation with exercise – both provided after start of antidepressant medication. This study had some study limitations and the intervention regarding exercise had considerable limitations both in intensity and duration. The study reports a similar initial reduction in depressive symptoms as seen in the sub-group analysis above. This study combined sleep deprivation with subsequent light therapy and sleep time stabilization and reports a sustained difference between groups during 20 weeks follow up. Based on this study we have low confidence in the finding that sleep deprivation with subsequent sleep time stabilization and light therapy may result in reduced depressive symptoms compared with exercise (GRADE ⊕⊕◯◯).

Even though sleep deprivation has been compared with medication in two studies, it is uncertain if sleep deprivation compared with these treatments reduces depressive symptoms (very low certainty of evidence (GRADE ⊕◯◯◯).
As for the other outcomes evaluated in this HTA, it is uncertain whether, quality of sleep, HRQL, everyday functioning, and length of hospital stay, are affected, with certainty of evidence for these findings being very low (GRADE ⊕◯◯◯). Other outcomes – medication use, and diurnal rhythm were not systematically assessed in the included studies.

Overall completeness and applicability of evidence

When evaluating the applicability of evidence, aspects of the included studies – as the *study population*, the *sleep deprivation-protocols*, the *use of HDRS as symptom rating scale* and the *standard treatment* have to be considered.

The *study population* varied across the included studies - mainly in terms of the diagnosis, age and suicidality of the included patients. Regarding diagnosis: two studies included patients with bipolar disorder (Benedetti et al., 1997, Wu et al., 2009); three studies recruited only patients with unipolar depression (Gorgolu et al., 2009, Kundermann et al., 2008, Reynolds et al., 2005); two studies included patients with uni- or bipolar depression (Martiny et al., 2015, Kragh et al., 2017); in one study no exact information regarding the kind of depression was available (Elsenga et al., 1982). One study was conducted in an elderly psychiatric population. Only two studies did not have suicidality as an exclusion criterion (Benedetti et al., 1997, Gorgulu et al., 2009). It can be noted, that the variety in sleep disturbances in patients with depression – ranging from insomnia to hypersomnia – has not been considered explicitly in the included studies. Anxiety is a common, agonizing symptom of depression and Martiny et al. (2015) commented that a high level of anxiety may be contraindicated for sleep deprivation. For the other studies, it is unclear how many patients suffered from anxiety.
The *treatment protocol* varied from a single wake night (Reynolds et al., 2005) up to 6 wake nights within three weeks (Kundermann et al., 2008). Subsequent maintenance strategies varied: some studies combined sleep deprivation with medication only, whilst three trials (Kragh et al 2017, Martiny et al 2015, and Wu 2009) provided additional chronotherapeutic interventions (light therapy, sleep phase advance, and or sleep time stabilization). Overall, the most favorable results were reported after sleep deprivation for 3 wake nights within one week in combination with medication and other chronotherapeutic interventions. It should be emphasized that the support offered to patients during wake nights differed considerably – in some studies various activities (requiring room and personnel) were offered, whereas patients in other studies merely were instructed to stay awake with very limited further support.

The limitation of *using HDRS as depression rating scale* is worth consideration. The scale has been criticized, as changes in HDRS score may be observed even if a clinically relevant change in depression is lacking (Bagby et al., 2004; Hieronymus et al., 2016; Pettersson et al., 2015). Namely, the HDRS score may decrease due to changes in a subset of items related to sleep or appetite without corresponding changes in core symptoms such as depressed mood, and anhedonia. Moreover, a modified version of HDRS has been used in three of the included studies (Elsenga et al., 1982, Kundermann et al., 2008, Wu et al., 2009) and the comparability of these results may be affected.

In studies investigating sleep deprivation as adjunctive treatment, the underlying *standard treatment* was similar to clinical praxis in Sweden. The only exception was a study (Benedetti et al., 1997) were an antidepressant (fluoxetine) was administrated to patients with bipolar depression without concurrent treatment with mood stabilizers.
Summarizing the comments above, the applicability of the evidence to the context of Swedish healthcare is regarded as limited.

An important question is whether sleep deprivation has a clinically relevant effect. In evaluating placebo-controlled clinical trials of antidepressant medication, the American Food and Drug Administration (FDA) and Swedish Medical Products Agency considered an average two-point difference in HDRS-17 score as the minimal important difference (from placebo to endpoint in the short-term studies) (Melander et al., 2008; Montgomery et al., 2009). Meta-analyses of currently used antidepressant medication compared with placebo regarding HDRS reported an SMD of 0.30-0.35 in patients with mild to moderate depression (Socialstyrelsen, 2017). In this context, the effect size in the post-hoc meta-analysis of sleep deprivation as add-on treatment in non-elderly psychiatric population would qualify as clinically relevant. However, the confidence interval is wide and the overall confidence in this finding is low. Furthermore, the included studies reported transient effects several days after sleep deprivation – this duration needs to be evaluated in relation to the need for additional treatment options during the first weeks it takes until antidepressant medication gains effect. Still, even if sleep deprivation only reduces depression symptoms for a limited duration, this may be of clinical value in absence of other treatment options. Also, it remains to be seen, if sleep deprivation may be repeated for renewed effect in patients who respond to this treatment.

Apart from mood switching, no other serious complication has been reported in the included studies. Polarity switching is a fundamental and defining characteristic of bipolar disorder (Goodwin et al., 2007). It can occur spontaneously or precipitated by stress or concurrent treatment (Salvadore et al., 2010). The switch rate to mania during treatment with placebo has been estimated to 4.2% for patients with bipolar disorder (Peet, 1994). According to Benedetti (2018), the switch rate to mania may rise to 15–40% during treatment with antidepressants.
In the studies included in this HTA-report a switch rate around 5,5% was reported. Yet, this observation is limited by the heterogeneity of treatment modalities and insufficient reporting of complications in most of the publications. Moreover, no study was specifically designed to assess the risk of manic switch. With respect to the clinical relevance, the risk of manic switch should not be seen as an absolute contraindication for inpatient treatment of patients with bipolar disorder.

Agreements and disagreements with other studies and reviews

In the literature search, two systematic reviews were identified. Boland et al. (2017) conducted a meta-analysis of the antidepressant effects of sleep deprivation with focus on short-term response rates and correlations of response to factors such as medication status, type of sleep deprivation, age, and gender. The review by Boland et al. (2017) differs from this HTA-report with regard to the PICO: e.g. Boland et al. excluded studies with chronotherapeutic augmentation to sleep deprivation but included studies with partial sleep deprivation. In their publication, Boland et al. (2017) observe that the response to sleep deprivation was not correlated to the type of sleep deprivation, medication status, diagnosis, age or gender of the study population. The other systematic review (Mencurini et al., 2018)

focused the depressive mood and circadian rhythm disturbances in patients with seasonal affective disorder reporting a positive but transient effects of sleep deprivation on depressive mood in this population. None of the studies included in the present HTA report are assessed in the review by Mencurini et al. (2018).

Implications for research

The findings of this report suggest a need for further research on sleep deprivation in patients with depression. As conclusions are limited by the heterogeneity of treatment modalities and study population, further well-designed RCTs are required to investigate the optimal treatment protocol and patient subgroups who could benefit from the treatment. As the method is based on chronobiological foundation, it should be relevant to evaluate biological markers (for example monitoring rest- activity cycles by actigraphy) and genotype (e.g. circadian CLOCK gene polymorphisms). Elderly may respond differently to chronotherapies, as circadian rhythms alter with age (Campos Costa et al., 2013). Moreover, late-life depression may differ from early-life depression in etiology and response to treatment (Blazer, 2003). Further studies can also be considered to evaluate the role of chronotherapeutic interventions in elderly psychiatric patients.

14. Future perspectives

Scientific knowledge gaps

A number of questions need to be addressed in future studies:

- Is the effect observed in some of the included studies due to sleep deprivation or to a placebo effect?
- Is the effect on depressive symptoms as measured by HDRS, reported in some of the included studies, mainly due to effects on sleep-related items?
- Are there specific sub-groups of patients with depression for whom sleep deprivation is effective?
- Which sleep deprivation protocol is most effective and has most lasting effect?
- Which maintenance strategy is most effective and when should it be applied (related to sleep deprivation) in order to maintain an antidepressant response (i.e light therapy during or direct after sleep recovery, timing of initiation of antidepressants or lithium, combination of sleep deprivation with sleep phase advance?)
- Can sleep deprivation be repeated after initial adequate response in order to achieve more long-term maintenance?

Ongoing research

In total 70 unique ongoing trials were identified in the search, however,only one of these ongoing trials was relevant for the question at issue. A RCT which started 2015, is currently conducted at the Sahlgrenska university hospital (ClinicalTrials.gov identifier *NCT02503124*.). According to the study design, admitted patients suffering from a depressive episode are randomized to either a 36 hours sleep-deprivation combined with six days bright light therapy in addition to treatment as usual, including medication, or to treatment as usual only. This study should be regarded as a clinical trial of effectiveness as it is oriented towards everyday clinical practice and conditions with broad eligibility criteria. The study is estimated to be completed in 2020.

15. Participants in the project

The question was nominated by
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Administrative support
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Declaration of interests
The authors declare no conflicts of interest.

Project time
The HTA was accomplished during the period of 2019-02-26 –2019-12-02.
Literature searches were made in March 2019.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Is wake therapy (sleep deprivation) an effective treatment of depression and bipolar depression (defined according to DSM criteria)?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Adult (≥18 years) patients with depression and bipolar depression (defined according to DSM criteria)
I	Wake therapy / Sleep deprivation (for at least one night under supervision at the hospital; with or without subsequent light therapy), with or without standard treatment (excluding ECT)
C	C1: No sleep deprivation, with or without standard treatment (excluding ECT) C2: Other treatment than sleep deprivation, with or without standard treatment (excluding ECT).
O	<u>Critical for decision making</u> Mortality (including suicide) Self harm Degree of depressive symptoms (assessed by validated instrument) <u>Important for decision making</u> Quality of sleep Health-related quality of life measured with validated instruments Medication use Everyday functioning (restored Activities of Daily Living, return to work) according to validated scales or administrative data Length of hospital stay Complications (Note – worsening in depressive symptoms is evaluated as part of effect measures and not as part of complications.) Patients' experience during treatment (based on qualitative studies) <u>Less important for decision making</u> Diurnal rhythm

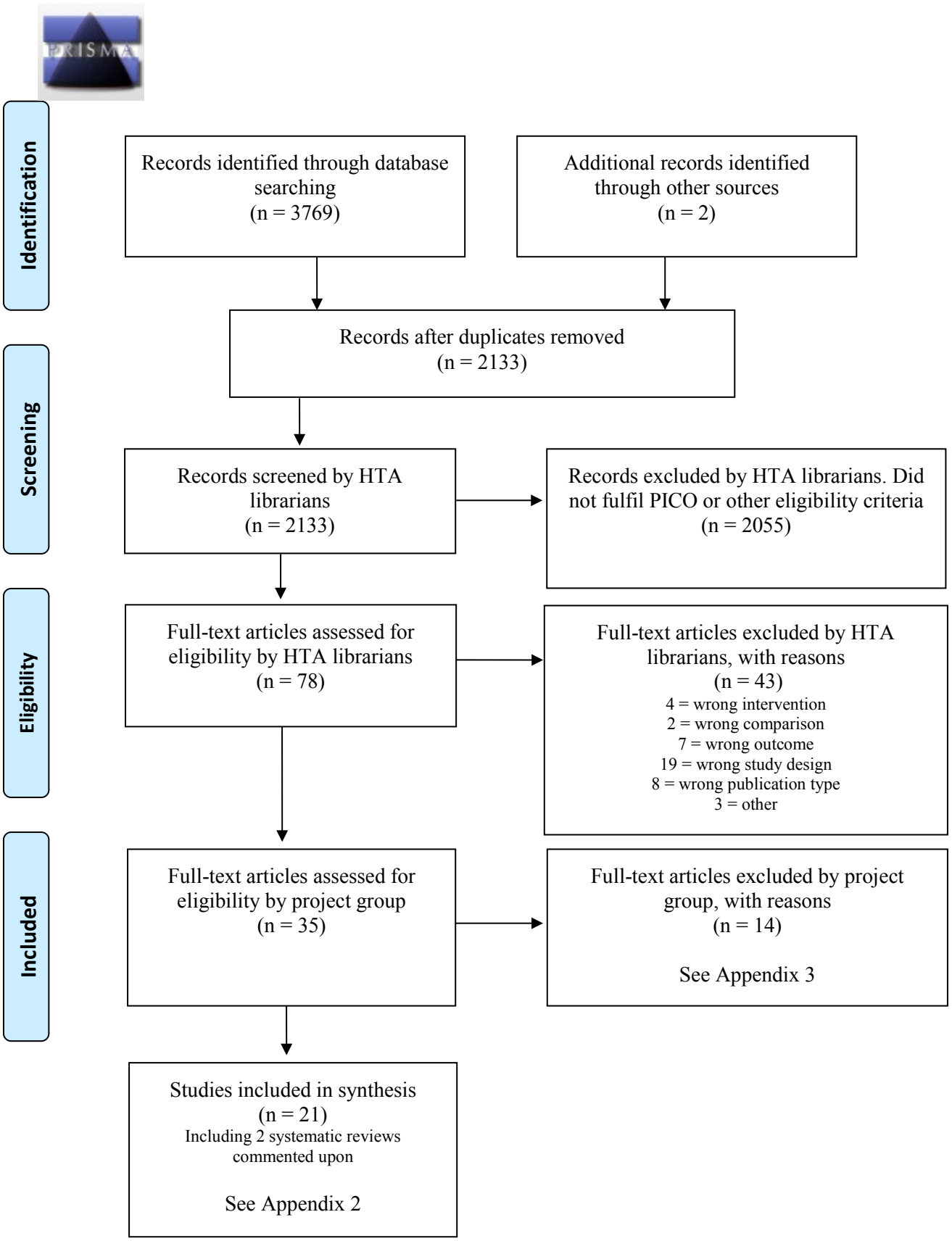
<u>Eligibility criteria</u>

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies
Case series etc. if ≥ 100 patients

Language:
English, German, French, Swedish, Norwegian, Danish

Publication date: 1995-

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: PubMed
Date: 15 Mar 2019
No. of results: 912

Search	Query	Items found
#10	**Search #7 NOT #8 Filters: Danish; English; Norwegian; Swedish**	**912**
#9	Search #7 NOT #8	1058
#8	Search (((animals[mh]) NOT (animals[mh] AND humans[mh])))	4557419
#7	Search #3 AND #6	1198
#6	Search #4 OR #5	471969
#5	Search (depression*[tiab] OR depressive*[tiab] OR depressed[tiab] OR antidepress*[tiab] OR anti-depress*[tiab])	436071
#4	Search (Depression[Mesh] OR Depressive Disorder[Mesh])	199398
#3	Search #1 OR #2	9484
#2	Search (sleep depriv*[tiab] OR wake therap*[tiab] OR chronotherap*[tiab])	8988
#1	Search Chronotherapy[Mesh] OR Sleep Phase Chronotherapy[Mesh]	938

Database: Embase 1974 to 2019 March 14 (OvidSP)
Date: 15 Mar 2019
No. of results: 1282

#	Searches	Results
1	exp chronotherapy/	2651
2	exp sleep therapy/	512
3	(sleep depriv* or wake therap* or chronotherap*).ab,ti.	12976
4	1 or 2 or 3	15199
5	exp postnatal depression/	1745
6	exp involutional depression/	258
7	exp major depression/	57235
8	exp endogenous depression/	883
9	exp depression/	427240
10	exp bipolar depression/	5706
11	exp perinatal depression/	2384
12	exp long term depression/	5038
13	exp treatment resistant depression/	2422
14	(depression* or depressive* or depressed or antidepress* or anti-depress*).ab,ti.	573997
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	713790
16	4 and 15	2089
17	(animal not (animal and human)).sh.	1029853
18	16 not 17	2080
19	(child not (child and adult)).sh.	1062538
20	18 not 19	2023
21	**limit 20 to ((danish or english or norwegian or swedish) and (article or article in press or conference paper or note or "review"))**	**1282**

Database: CINAHL (EBSCOhost)
Date: 15 Mar 2019
No. of results: 216

#	UNDRAN	RESULTAT
S9	**S3 AND S7** **Avgränsare - Språk: Danish, English, Norwegian, Swedish**	**216**
S8	S3 AND S7	219
S7	S4 OR S5 OR S6	148,723
S6	TI (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*) OR AB (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*)	123,682
S5	(MH "Seasonal Affective Disorder")	564
S4	(MH "Depression+")	94,819
S3	S1 OR S2	2,391
S2	TI (sleep depriv* OR wake therap* OR chronotherap*) OR AB (sleep depriv* OR wake therap* OR chronotherap*)	2,275
S1	(MH "Chronotherapy")	181

Database: PsycInfo (EBSCOhost)
Date: 15 Mar 2019
No. of results: 1111

#	UNDRAN	RESULTAT
S8	**S3 AND S6** **Avgränsare - Språk: Danish, English, Norwegian, Swedish; Exkludera doktorsavhandlingar**	**1,111**
S7	S3 AND S6	1,255
S6	S4 OR S5	295,834
S5	TI (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*) OR AB (depression* OR depressive* OR depressed OR antidepress* OR anti-depress*)	290,265
S4	DE "Major Depression" OR DE "Depression (Emotion)" OR DE "Treatment Resistant Depression" OR DE "Late Life Depression" OR DE "Endogenous Depression" OR DE "Seasonal Affective Disorder"	140,912
S3	S1 OR S2	7,428
S2	TI (sleep depriv* OR "wake therap*" OR chronotherap*) OR AB (sleep depriv* OR "wake therap*" OR chronotherap*)	5,402
S1	DE "Sleep Deprivation"	5,574

Database: The Cochrane Library
Date: 15 Mar 2019
No. of results: 248
Cochrane reviews 4
Trials 244

ID	Search	Hits
#1	MeSH descriptor: [Chronotherapy] explode all trees	118
#2	MeSH descriptor: [Sleep Phase Chronotherapy] explode all trees	5
#3	(sleep depriv* OR "wake therapy" OR "wake therapies" OR chronotherap*):ti,ab,kw (Word variations have been searched)	1763
#4	#1 OR #2 OR #3	1763
#5	MeSH descriptor: [Depression] explode all trees	9970
#6	MeSH descriptor: [Depressive Disorder] explode all trees	10503
#7	(depression* OR depressive* OR depressed OR antidepress* OR anti-depress*):ti,ab,kw (Word variations have been searched)	64588
#8	#5 OR #6 OR #7	64633
#9	**#4 AND #8**	**248**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
15 Mar 2019
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 2 new records

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Project: Total sleep deprivation (TSD) as treatment of depression

Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study groups; Intervention vs control	Patients (n)	Mean age ± SD (years)	Men (%)	Outcome variables
Benedetti, 2005 Italy	Case series		I: 3 TSD cycles + LT + standard	Bipolar depressed patients (60)	I: 46±11		Complications
Benedetti, 1997 Italy	RCT	28 days (final assessment ca 2 weeks after last TSD cycle	I: 3 TSD cycles + fluoxetine C: fluoxetine	Hospitalized bipolar depressed patients (10)	I: 40 ± 12 C: 42 ± 10	33%	HDRS
Boland, 2017	Systematic review						
Colombo, 1999 Italy	Case series		I: 3 TSD cycles + standard treatment	Bipolar depression (206)	I:46±12	34%	Complications
Colombo, 2000 Italy	Case series	1 week	I: 3 TSD cycles + standard treatment	Bipolar depression (115)		33%	Complications
Elsenga, 1982 Netherlands	RCT	15 days	Ia: 4 TSD cycles +clomipramine Ib: 4 TSD cycles + placebo C: clomipramine	Hospizalized depressed patients (30)	Ia; 49±14 Ib: 51±18 C:51±13	20%	HDRS
Fähndrich, 1981 Germany	Case series	4 days	I: TSD + standard	Unipolar or bipolar depression (80)	49, range 20 - 78	41%	Complications
Gorgulu, 2009 Turkey	Cohort study	42 days	I: 3 TSD cycles +sertraline C: sertraline	Patients with major depression (41)	I; 40±12 C:33±11	37%	HDRS, complications
Kragh, 2017a Denmark	RCT	9 weeks	I: 3 TSD cycles + standard treatment C: Standard treatment	Hospitalized patients with depression (64)	I: 38 (± 12) C: 40 (± 12)	57%	HDRS, HrQoL, length of stay, level of functioning, quality of sleep, complications

Project: Total sleep deprivation (TSD) as treatment of depression

Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study groups; Intervention vs control	Patients (n)	Mean age ± SD (years)	Men (%)	Outcome variables
Kragh, 2017b Denmark	Qualitative study		I: 3 TSD cycles + standard treatment	Hospitalized patients with depression (13)	37 (range: 18-66)	62%	*Comment:overlap of study population with Kragh et al 2017*
Kundermann, 2008 Germany	RCT	3 weeks	I: 6 TSD cycles + CBT C: CBT	Hospitalized patients with depression (19)	37±8	57%	HDRS
Kundermann, 2009 Germany	RCT	3 weeks	I: 6 TSD cycles + CBT C: CBT	Hospitalized patients with depression (18)	I: 37 ±8 C: 37 ±8	62%	*Comment: Overlap of study population with Kundermann 2008*
Martiny, 2012 Denmark	RCT	9 weeks	I: 3 TSD cycles + LT + duloxetine C: Daily exercise + duloxetine	Hospitalized patients with depression (75)	I:47 ±13 C:49 ±11	41%	HDRS, level of functioning, HrQoL, Quality of sleep, complications
Martiny, 2013 Denmark	RCT	1 week	I: 3 TSD cycles + LT + duloxetine C: Daily exercise + duloxetine	Hospitalized patients with depression (75)	I:47 ±13 C:49 ±11	41%	Complications *Comment: same study population a Martiny 2012*
Martiny, 2015 Denmark	RCT	20 weeks	I: 3 TSD cycles + LT + duloxetine C: Daily exercise + duloxetine	Hospitalized patients with depression (75)	I:47 ±13 C:49 ± 11	41%	HDRS, level of functioning, Quality of sleep, complications *Comment: same study population as Martiny 2012*
Menculini, 2018	Systematic review						
Reynolds, 2005, USA	RCT	2 weeks	Ia: 1TSD cycle + placebo Ib: 1TSD cycle + paroxetine C: Paroxetine	Outpatients with late-life depression (80)	Ia:71±8 Ib:71±7 C:70±7	32%	HDRS,
Rudolf, 1978 Germany	Case series Mixed method (including qualitative information)	Night with TSD	I: 1 TSD cycle	Patients with depression, the majority hospitalized (67)	I: 48	39%	Complications

Project: Total sleep deprivation (TSD) as treatment of depression

Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study groups; Intervention vs control	Patients (n)	Mean age ± SD (years)	Men (%)	Outcome variables
Suzuki, 2018 Japan	Case series	6 days	I: 3 TSD cycles + LT	Hospitalized patients with bipolar depression (220)	I: 47 ±11	35%	Complications
Svendsen, 1976 Denmark	Case series	TSD until discharge	I: 1 to 6 TSD cycles	Hospitalized or patients or outpatients with unipolar or bipolar depression (77	I: range 20 - 72	19%	Complications
Wu, 2009 USA	RCT	7 weeks	I: 1 TSD cycle + LT + SPA + medication C:medication	Out-patients with bipolar major depressive episode (49)	I: 39 ± 13 C:40 ± 14	74%	HDRS, complications

TSD: Total sleep deprivation, HDRS: Hamilton Depression Rating Scale, o.d.: once daily, LT: Light therapy, SPA: Sleep Phase Advance

Project: Total sleep deprivation as treatment of depression
Appendix 3. Excluded articles

Author, year	Reason for exclusion
Bech, 2014	Wrong study design (validation study)
Benedetti,1999	Case series without information on complications
Bouhuys,1995	Case series without information about complications
Giedke, 2003	Wrong comparator
Harrington , 2018	Wrong population
Haug, 1988	Wrong study design – case series
Milstein, 1979	Unspecific population
Pflug, 1976	Case series without information about complications
Pflug, 1978	Case series without information about complications,
Putilov 2005	Wrong study design
Trautmann, 2018	Case series without information about complications

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) as add on vs no add on									
Benedetti, 1997 Italy	RCT	I:5 C:5	0	**TSD (3 nights)+ Fluoxetine** **HDRS-17*** Baseline: 25.2 (SE:1.60) 1st TSD (Day 7): 14.0 (SE: 4.8), Δ=-11.2 1 w after 1st TSD (Day 14): 9.6 (SE:5.08), Δ=-15.6 Day 21 8.19 (SE: 6.12), Δ=-17.0 Day 28 6.27 (SE: 5.86), Δ=-18.9	**Fluoxetine** **HDRS-17*** Baseline: 26.2 (SE:3.89) Day 7: 22.2 (5.70), Δ=-4 *Between group difference: p=0.016* Day 14: 16.4 (5.76), Δ=-9.8 *Between group difference:* p=0.044 Day 21 10.9 (SE:6.17), Δ=-15.3 *Between group difference: ns* Day 28 9.2 (SE: 6.48), Δ=-17 *Between group difference: n*s	Bipolar patients *Sleep deprivation-protocol:* 3 TSD cycles in 6 days No response or remission data *Data provided visually in a diagram	?	?	-

* + No or minor problems
? Some problems
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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Elsenga, 1982 Netherlands	RCT	I:10 C:10	Not reported	**TSD (4 nights) + cloripramine** **HDRS-17*** Baseline (day1): 30.8 Week 1: 22, Δ=-8.8 Week 2:21, Δ=-9.8 **Response** Day3 (Day after TSD): 40% (95%CI: 12%-74%) **HDRS-5*** Baseline (day1): 17.5 Day2 (during TSD):15.5, Δ=-2 Day 3 (after recovery sleep): 14.5, Δ=-3 Day 5:13.6, Δ=-3.9 Week 1 (7 days post 1st TSD): 13.5, Δ=-4 Day12 (11 days after 1st TSD):11, Δ=-6.5 Week 2: 10.5, Δ=-7	**Cloripramine** **HDRS-17*** Baseline: 26.7 Week1: 23.5, Δ= -3.2 Between group difference: t(1,54)=-2.06, P<0.05 Week2: 17.2,Δ=-9.5, Between group difference n.s. **Response** Day3: 20% Week 1 (3 days after 2nd TSD) Between group difference: 21%, t(1,54)=-2.11, P<0.04, sign. Week 2 (after 4th TSD): Between group difference: ns **HDRS-5*** Baseline:15.5 Day 2:14.8, Δ=-0.7 Day 3:14, Δ=-1.5, Between group difference: n.s. Day 5: 12.7, Δ=-2.8, Between group difference: t (1,17)=3.31, p<0.01, Week 1: 11.5, Δ=-4 Day12:9.2, Δ=-6.3, Between group difference: n.s. Week 2: 9, Δ=-6.5, Between group difference: n.s.	*Scales:* HDRS-17 (¨loss of weight¨-item replaced of ¨anaesthesia¨ HDRS-5 (or SH) (depressed mood, anxiety and tension, retardation, agitation, work and interests) *Sample-note:* Inpatients. No distinction between uni- or bipolar patients. *TSD-protocol:* 2 TSD/week in 2 weeks *Data provided visually in a figure. *Response*: ≥ 6 point reduction in HRDS-5	+	?	?

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Gorgulu 2009 Turkey	Cohort study	I:19 C:22	2 drop-outs 2 with-drawls	**TSD (3 nights) + sertraline** HDRS-17 Baseline: 25.23 (SD:4.46) Day 1(TSD): 17.42 (SD:6.07), Δ=-7.81 Day 7 (6 days after 1st TSD): 7.37 (SD: 4.02), Δ=-17.86 Day 14: 8.68 (SD:5.56), Δ=-16.55 Day 42: 6.53 (SD.7.21), Δ=-18.7	**Sertraline** HDRS-17 Baseline: 24.32 (SD:5.02) Between group difference: ns Day 1: No data provided Day 7: 15.73 (SD 6.10), Δ=-8.59 Between group difference: sign. Day 14: 12.85 (SD:5.75), Δ=-11.47 Between groups difference: p=0.02, sign Day 42: 6.41 (SD4.26), Δ=-17.91 Between groups difference: p=0.95, n.s.	*Unipolar depression* *Scale:*HDRS-17 *TSD-protocol:* 3 TSD within 1 week Inpatient treatment-outpatient follow up (except for 2 C-patients)	?	-	?
Kragh, 2017 Denmark	RCT	I: 32 C:32	C: drop-outs n=14 (due to ECT n=6) I: drop-outs n=10 (due to ECT n=3)	**TSD (3 nights), LT, STS + standard** **HDRS-17*** Baseline 22.84 (SE:0.89) Week 1 (1 week after 1st TSD): 17.39 (SE:0.92), Δ= - 5.45 Week2: 18.05 (SE:0.94), Δ=-4.79 Week3*:18.52 (SE:0.99), Δ=-4.32 Week4* :16.70 (SE:1.02), Δ=-6.14 Week5* (1 month after TSD): 17.07 (SE:1.03), Δ=-5.77 Week9 (2 months after TSD) 13.09 (SE: 1.057), Δ=-9.75	**Standard** **HDRS-17*** Baseline: 22.49 (SE:089) Week 1 20.19 (SE:0.97), Δ= - 2,3 *Between group difference: p=0.04, sign.* Week2: 16.97 (1.02), Δ=-5.58 Week3*:16.24 (SE:1.11), Δ=-6.25 Week4*:14.77 (SE:1.15), Δ=-7.72 Week5*:16.35(SE:), Δ=-6.14 Week 9*:14.19 (SE:1.195), Δ=-8.3 Between group difference Week 2-9: ns	Note includes 2 out-patients hospitalized for the treatment Suicidal patients excluded Scales: HDRS-6 and HDRS-17 95% CIs reported in the paper converted to SD (taking into account the final drop-out rates in the sample; as the exact time of dropouts was not reported)	+	?	+

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? Some problems
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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Continued: Kragh, 2017 Denmark				**HDRS-6** Baseline 11.2 (SD: 2.63) Week 1 (1 week after TSD): 8.5 (SD:2.25), Δ=-2.7 Week2: 9.1 (SD: 2.26), Δ= -2.1 Week9: 6.5 (SD: 2.4), Δ=-4.7 **Response** Week1 (1 week after TSD): 9.4% Week 8: 22% Week 9: 34% **Remission**	**HDRS-6** Baseline 10.9 (SD: 2.63) Week 1: 9.2 (SD:2.01),Δ= -1.7, *Between group difference:p=0.36 n.s.* Week 2: 8.1 (SD: 2.1), Δ= -2.8 *Between group difference: p=0.19 n.s.* *Week 9: 6.3 (SD:2.5),* Δ=-4.6, *Between group difference: p=0.8 n.s.* **Response** Week 1: 0%, *Between group difference:p=0.08, n.s.* Week 8:16%,*Between group difference:p=0.64 n.s.* Week 9:19%,*Between group difference: p=0.16 n.s.* *Between group difference Week 3,4,5,6,7: n.s.* **Remission** *Between group difference Week19: n.s.*	*Data provided after contact with the author **Response** (HDRS-17<50% from baseline) **Remission** (HDRS-17<8)			

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? Some problems
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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Kunder-mann, 2008 Germany	RCT	I:9 C:10	1 drop- out	**TSD (6 nights) + CBT** **HDRS-17** Baseline*: 26.2 (SD:5.6) Week1 (6 days after 1st TSD)* :16.3, (SD:6.6), Δ=-10.1 Week2* :13.6 (SD:6.2), Δ=-12.4 Week3* :11.8 (SD:5.1), Δ= -14.6 **BDI** Baseline: 28.8 (SD:1.7) Week1* :20.0 (SE:2.2), Δ=-8.8 Week2*:19.9 (SE:4.4), Δ=-8.9 Week3* :14.9 (SE:3.4), Δ=-13.9 **Response** 3/9	**CBT** **HDRS-17** Baseline*: 25.8 (SD:2.4) Between groups difference: p=0.83, n.s. Week1*: 17.8 (SD:9.4), Δ=-8.2 Between group difference: n.s. Week2* :15.4 (SD:10.8), Δ=-10.4 Between group difference: n.s. Week3* :10.3 (SD:8.9), Δ=15.6 Between group difference: n.s. **BDI** Baseline: 31.6 (SD:2.6) Between group difference p=0.39,n.s. Week1: 17.2 (SE.2.9), Δ=-14.4 Between group difference: n.s. Week2* :21.4 (SE:4.8), Δ=-10.2 Between group difference: n.s. Week3* :20.9 (SE:4.8), Δ=-10.7 Between group difference: n.s. **Response** 6/10 Between group difference: x^2=0.900, p=0.637, n.s.	*Sample-note:* Unipolar depression, patients were drug-free. Suicidal tendencies was exclusion criteria *Scales:*HDRS-17, BDI: Beck depression Inventory (self-rating) *TSD-protocol:* 6 nights of SD separated by 2-3 nights of sleep. (2 TSDs/week) *CBT:* 3-weeks program (5 sessions/w): behavioural activation, cognitive reconstruction, social skills training *Data provided by the author *Response*: ≥ 50% reduction in HDRS after the 3-week period. *Note:* Trial reported in 2 articles	?	?	-

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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Reynolds, 2005 USA	RCT	I:27 C:26	18 drop-outs 1 with-drawl	**TSD (1night) + paroxetine** **HRDS-17** Baseline: 21.0 (SD: 3.1) Day 0 (after recovery sleep) 18.4, Δ=-2.6 Week 1 (1 week after TSD)*: 15.12(SD: 3.91), Δ=-5.88 Week2*: 14.37 (SD:4.81), Δ=-6.63 Response (day 14): 22% (N=6)(CI:7-38) Remission (day 14): 11%,(CI:0-23)	**Paroxetine** **HRDS-17** Baseline:18.9 (SD:2.5) Between group difference: p= 0.037 Day 0: 13.3, Δ=-5.6 Week1 *: 12.12(SD:4.13), Δ=-6.78 Between group difference: n.s. Week2*:9.80 (SD:4.91), Δ=-9.1 Between group difference: p=0.12 n.s. Response (day 14): 46% (N=12), (CI=27-65) Between group difference p=0.16 n.s. Remission: 38%, (CI:20-57) Between group difference: p=0.07 sign.	*Sample Note:* only elderly patients (> 60 y), unipolar depression *TSD-protocol:* 1 single TSD HRDS-17 (or HAM-D) *Data provided after contact with the author *Response:* HRDS<10, day 14 *Remission:* HRDS<7, day 14	?	?	+
Wu, 2009 USA	RCT	I: 32 C: 17	n=5 all in TSD group, due to re-location, failure to adhere to protocol and in-tolerance to medi-cation (n=2).	**TSD (1 night) + LT+ Sleep phase advance + medication** **HRSD-19** Baseline (day 0):19 (SD: 6.7) Day 1 (TSD): 14.5 (SD: 6.2), Δ=-4.5 Day 2 (after recovery sleep/SPA from TSD): 11.2 (SD:6.9), Δ=-7.8 Day 7: 10.2 (SD: 7.3), Δ=-8.8	**Medication** **HRSD-19** Baseline: 18.5 (SD: 7.1) *Between group difference: p=0.8, n.s.* Day 1: 16 (SD:8.7), Δ=-2.5 *Between group difference; p=0.27, n.s.* Day 2:15.1 (SD:7.1), Δ=-3.4 *Between group difference: p=0.3 n.s.* Day 7: 14.4 (SD: 8), Δ=-4.1 *Between group difference:p=0.001 sign.*	*Note:* Patients with a history of suicidal behaviour excluded. Only outpatients included. yet 4 TSD-patients receive inpatient chronotherapy Medication: Antidepressant (sertraline mostly) + mood stabilizers (Lithium mostly)	+	?	?

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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
continued: Wu, 2009 USA				Week 2: 11.8 (SD: 8.8), Δ=-7.2 Week3: 12.6 (SD: 9),Δ=--6.4 Week 4: 12.6 (SD: 9.8), Δ=-6.4 Week 5: 11.5 (SD: 10), Δ=-7.5 Week 6: 11.7 (SD: 9.9), Δ=-7.3 Week 7: 10.1 (SD: 9.6), Δ=-8.9 **Remission:** 12/32 (37.5%)	Week2: 15.1 (SD: 8.8), Δ=-3.4 Week 3: 16.9 (SD: 10.2), Δ=-1.6 *Between group difference: p=0.01 sign.* Week 4: 17.4 (SD:9.1), Δ=-1.1 *Between group difference: p=0.01 sign.* Week 5: 14.3 (SD: 11), Δ=-4.2 *Between group difference: p= 0.05 sign.* Week 6: 14.3 (SD10.2), Δ=-4.2 *Between group difference: p=0.03 sign.* Week 7: 15.2 (SD:10.2), Δ=-3.3 *Between groups difference: p=0.02 sign.* **Response:** *Between group difference: Day 7 (p=0.007), Week 7 (p=0.02)* **Remission:** *0/17 (0%)*	HDRS-19: abbreviated version of HDRS-24, excluding items pertaining to sleep, weight loss, diurnal variation *Response:* 50% decrease in HRSD *Remission:* Response and ≤7 (at the end of 7 weeks)			

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? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) vs Other treatment									
Elsenga, 1982 Netherlands	RCT	I:10 C:10		**TSD (4 nights) +Placebo** **HDRS-5*** Baseline (day1): 17.5 Day2 (during TSD):13.5, Δ=-4 Day 3 (after recovery sleep): 16.2, Δ=-1.3 Week 1 (7 days after 1st TSD): 15, Δ=-2.5 Day12(11 days after 1st TSD): 14.5, Δ=-3 Week 2 (14 days after 1st TSD): 13, Δ=-4.5 **HDRS-17*** Baseline (day1): 29.8, Week 1: 29, Δ= -0.8 Week2: 27.5, Δ= -2.3 Response (day after TSD): 30% (95%CI 6-65%)	**Clomipramine** **HDRS-5*** Baseline: 15.5 Day 2: 14.8, Δ=-0.7 Day 3: 14, Δ=-1.5 Week 1: 11.5, Δ=-4, Between group difference: n.s. Day12: 9.2, Δ=-6.3 Week 2: 9, Δ=-6.5, Between group difference: n.s. **HDRS-17*** Baseline: 26.7 Week1: 23.5, Δ= -3,2Between group difference:n.s. Week2: 17.2, Δ=-9.5,Between group difference:n.s. Response (day after TSD) 20%	*Sample-note:* Inpatients. No distinguish between unipolar or bipolar patients. *Scales:* *HDRS-5*:(or SH) (items:depressed mood, anxiety and tension, retardation, agitation, work and interests) *HDRS-17:* (¨loss of weight¨-item replaced of ¨anaesthesia¨ *TSD-protocol:* 2 TSD/week in 2 weeks *Data from visual inspection of figure. *Response:* ≥ 6-point reduction in HRDS-5	+	?	?

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Martiny, 2012 Denmark	RCT	I:37 C:38		**TSD (3 nights) +LT+Duloxetine** **HAM-D_6** Baseline (day1):12.1 (SE: 0.2) Day 2 (during 1st TSD): 6.2(SE: 0.5), Δ=-5.9 Day 3 (after sleep recovery):5.5(SE:0.4), Δ=-6.6 **Response** Day1 (baseline): 0% Day2 (during TSD): 58.7% Day3 (after recovery sleep):64.6% Day8 (1 w after 1st TSD): 41.9% **Remission** Day1 (Baseline): 0% Day 2 (during TSD): 38.6% Day 3 (after recovery sleep): 64.6% (23/35) Day8(1 w after 1st TSD): 19.4%	**Exercise+Duloxetine** **HAM-D_6** Baseline(day2): 8.7 (SE:0.5) Day 2: 8.7 (SE:0.5), Δ=0, Between group difference: p=0.007 Day 3: 8.7 (SE:0.4), Δ=0 Between group difference: p<0.0001 **Response** Day1 (baseline):0% Day2: 13.7% Day 3: 16.9%, Between group difference: OR 9.0 (95%CL 3.7-21.8), p<0.001 Day 8: 10.1% Between group difference: OR 6.4; CL 2.3-17.4, p=0.0002 **Remission** Day 1: 0% Day 2: 2.9% Day 3: 3.7% , Between group difference: OR:20.8 (95%CL 5.6-77.1), p<0.001 Day 8: 4.7%, Between groups difference OR:4.9; CL1.4-17.0; p=0.1	*Sample-note:* Unipolar depression Includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged *Scale:* HAM-D_6 *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation *Response:* 50% reduction from baseline score *Remission:* ≤4 HAM-D_6-score	? Out-pat.	?	+

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Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Martiny, 2013 Denmark	RCT	I: 37 C:38	1 patient in I:-group was not included in analysis due to logistic prob-lems in the ward.	**TSD (3 nights) +LT+Duloxetine** **HDRS$_{17}$** Week1 (prior to TSD): 20.7(SE:0.82) Week 2 (1 w after 1st TSD): 12.6 (SE:0.79), Δ=-8.1 Week 3: 12.1 (SE:0.67), Δ=-8.6 Week4: 11.6(SE:0.58), Δ=-9.1 Week5: 11.0(SE:0.54), Δ=-9.7 Week6: 10.5(SE0.55), Δ=-10.2 Week7: 10.0(0.61), Δ=-10.7 Week8: 9.5(SE:0.71), Δ=-11.2 Week 9: 9.0(SE0.83), Δ=-11.7 **Response** Week1(baseline): 0% Week2(1 w after 1st TSD): 41.4% Week3: 46% Week4: 50% Week5: 55% Week6: 59% Week7: 64% Week8: 68% Week9: 71%	**Exercise+Duloxetine** **HDRS$_{17}$** Week1: 21 (SE:0.80), between group difference p=0.89, n.s. Week2: 16.5 (SE:0.75), Δ=-4.4, Between groups differences: p=0.0004 Week 3: 15.9 (SE:0.64), Δ=-5, Between group differences: p<0.0001 Week4: 25.2 (0.55), Δ=-4.3 Week5:14.6(SE:0.51), Δ=-6.3 Week6: 13.9(SE:0.51), Δ=-7 Between group difference week3-6, p<0.0001 Week7: 13.3(SE:0.57), Δ=-7.6, Between group difference: p=0.0001 Week8: 12.6(SE0.66), Δ=-8.3, Between groups difference, p=0.001 Week 9: 12.0 (SE:0.78), Δ=-8.9, Between groups difference: p=0.008 **Response** Week1: 0% Week2:13%, Between group difference: p=0.003 Week3: 16%, Between group difference: p=0.001 Week4: 20%, Between group difference:p=0.0007 Week5: 24%, Between group difference: p=0.0006 Week6: 29%, Between group difference,p=0.001 Week7: 35%, Between group difference: p=0.004 Week8: 41%, Between groups difference: p=0.01 Week9: 47%, Between groups difference: p=0.04	Same trial as above. *Sample-note:* Unipolar Depression. Includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation *Scale:* HDRS$_{17}$	?	?	+

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Continued: Martiny, 2013 Denmark				**Remission** Week1: 0% Week2: 24 Week3: 27% Week4: 29% Week5: 32% Week6: 36% Week7: 39% Week8: 42% Week9: 46%	**Remission** Week1: 0% Week2: 5%,Between group difference: p=0.004 Week3: 7%, Between group difference: p=0.002 Week4: 8%, Between group difference, p=0.001 Week5: 10%,Between group difference,p=0.0008 Week6: 13%, Between group difference:p=0.001 Week7: 16%, Between group difference: p=0.003 Week8: 19%, Between group difference: p=0.01 Week9: 23%, Between groups difference: p=0.04	*Response*: <50% from baseline score on $HDRS_{17}$ *Remission*: <8 score on $HDRS_{17}$			
Martiny, 2015 Denmark	RCT	I: 37 C: 38	I: 7 C: 4	**TSD (3 nights) +LT+Duloxetine** **$HDRS_{17}$** Baseline (prior to TSD): 20.7(SE:0.82) Week9: 9.0(SE:0.8), Δ=-11.7 Week13: 8.7(SE:0.8), Δ=-12 Week17: 8.4(SE0.8), Δ=-12.3 Week21: 8.1(SE:0.8), Δ=-12.6 Week25: 7.8(SE:0.9), Δ=-12.9 Week29: 7.5(SE:0.9), Δ=-13.2 **Response** Week9(8 weeks from TSD): 64% Week13: 66.3% Week17: 68.5% Week21: 70.6% Week25: 72.7% Week29: 74.6% **Remission** Week9(8 weeks from TSD): 44.8% Week 13: 48.3 Week17: 51.7% Week21: 55.2% Week25: 58.6% Week29: 61.9%	**Exercise+Duloxetine** **$HDRS_{17}$** Baseline: 20.9 (SE:0.80) Week9: 11.6 (SE:0.8), Δ=-9.3 Week13: 11.3 (SE:0.7), Δ=-9.6 Week17: 11.0 (SE:0.8), Δ=-9.9 Week21: 10.7 (SE:0.8), Δ=-10.2 Week25: 10.4 (0.8), Δ=-10.5 Week29: 10 (0.9), Δ=-11 Between group difference: p=0.02 **Response** Week9: 52.2% Week13: 54.7% Week17: 57.2% Week21: 59.6% Week25: 62.0% Week29: 64%, Between group difference, p=0.22 **Remission** Week9: 23.4% Week13: 26.0% Week17: 28.8% Week21: 31.7% Week25: 34.7% Week29: 38%, Between group difference: p=0.01	**Same trial as above**, Unipolar depression, 20-week follow up. Dropout was somewhat higher in TSD-group but not related to depression scores	?	?	+

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.1 Outcome variable: Depression

Author year country	Study design	Number of patients n=	Drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Reynolds, 2005 USA	RCT	I:27 C:26		**TSD (1 night) + Placebo** **HRDS-17** Baseline: 20.8 (SD: 3.7) Week 1(1 week after TSD)*: 12.88 (SD: 5.7), Δ= -7.92 Week2*: 12.63 (SD: 5.77), Δ= -8.17 **Response (day 14):** 41% (CI:22-59) **Remission (day 14):** 22% (CI:7-38)	**Paroxetine** **HRDS-17** Baseline: 18.9 (SD:2.5) Between group difference p= 0.037 Week 1*: 12.12 (SD: 4.13), Δ= -6.78, Between group difference: n.s. Week2*: 9.80 (SD: 4.91), Δ= -9.1 Between group difference: n.s. **Response (day 14)** 46% (CI =27-65) Between group difference: p=0.16 **Remission (day 14):** 38% (CI:20-57) Between group difference: p=0.07	*Sample:* only elderly patients (> 60 y), unipolar depression *TSD-protocol:* 1 TSD *Scale:* HRDS-17 (or HAM-D) *Response:* HRDS<10, day 14 *Remission:* HRDS<7, day 14 *Data provided after contact with the author	?	?	+

CI: Confidence interval, LT: Light Therapy, NA: Not assessed, yr= year, est=estimated, mo=months, SD: Standard deviation, STS: Sleep time stabilization, TSD: Total sleep deprivation,

Project: Total sleep deprivation as treatment of depression
Appendix 4.2 Outcome variable: Quality of sleep

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) vs other treatment									
Martiny, 2012,2015 Denmark	RCT			**TSD (+LT+STS)** **Sleep onset** Baseline: 11:43 pm, SD:1:53) Day1-8 (During intervention phase): Δ=-79.6(SD:99.4) min Week 9: 10:55pm(SD:1:20), Δ=- 72 min (P<0.001) **Sleep offset** Baseline: 7:28 am(SD:1:53) Day1-8 (During intervention phase): Δ=30.0(SD:89.1) min Week9: 7:14 am(SD: 1:17), Δ=14 min (p=0.02) **Sleep duration** Baseline: 7:44(SD=1:60) Day1-8 (During intervention phase): Δ=49.6(SD:126.9) min Week9: 8:19 (SD=1:17), Δ=35 min(P<0.001) **Sleep quality**	**Exercise** **Sleep onset** Baseline: 11:46 pm (SD:1:60) Day 1-8: Δ=-39.7(SD:125.6) min Between groups difference: F_1=10.1, p=0.002 Week9: 11:53pm (1:30) Δ=7 min(p=0.68) **Sleep offset** Baseline: 7:28 am (SD:1:49) Δ=-3.0(SD.132.8) min Between groups difference F_1=0.6, p=0.43 Week9: 7:45 (SD:1:48) Δ=-31min (p=0.09) **Sleep duration** Baseline: 7:42 (SD=1:37) Δ=42.7(SD:123.0) min Between groups difference: F_1=2.6, p=0.11 Week 9: 7:53(SD=1:60) Δ= 11 min (p=0.008) **Sleep quality** Between group comparison - day1-8: increased: F_1=10.5, p=0.0002	Note includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged LT: Light Therapy STS: Sleep Time Stabilisation Sleep onset, sleep offset, sleep duration= time in minutes or hh:mm Sleep quality: Self perceived and scored 0-10 (10 = best)	?	?	+

Project: Total sleep deprivation as treatment of depression
Appendix 4.2 Outcome variable: Quality of sleep

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) as add on vs no no-add on-									
Kragh, 2017 Denmark	RCT	n=64 C: n=32 I: n=32	I: dropouts n=10 (due to ECT n=3) C: dropouts n=14 (due to ECT n=6)	**TSD, LT, STS + standard** **Sleep onset (mean)** Week1: 20:32 (CI 20:10-20:53) Week9 23:59 (CI 23:35-00:25) **Sleep offset** Week1: 07:30am (CI 07:01-08:00) Week9: 07:24 (CI 06:56-07:57) **Sleep quality** Week1: 6.8 (CI 6.3- 7.3) **Duration of sleep** Week 1: 5.9 h (SD 5.2) Week9: 7:09h(CI 6.39-7.42) **Awakenings during night** Week 1: 2.8 Week 9: 1.9 (CI 1.3-2.5)	**Standard** **Sleep onset** Week1: 00:04 (CI 23:53-00:25) Between groups difference (p=0.0001) Week9: 23:40 (CI 23:11-00:08) Between groups difference: ns **Sleep offset** Week1: 07:25 (CI 06:51-07:58) Week9: 07:53 (CI 07:17-08:26) Between group difference week1-9: ns **Sleep quality** Week1: 5.4 (CI 4.9-5.8) Between groups difference: p=0.0001 Week2-9: Between groups difference: ns **Duration of sleep** Week 1: 6.6 h(0.18) Week9: 7.32h (CI 6.54-8.06) Between groups differences week1-9: ns **Awakenings during night** Week1: 3.3 Between groups difference: ns Week 9: 3.3 (CI 2.6-3.9) Between groups difference: sign	Note includes 2 out-patients hospitalized for the treatment *Sleep quality:* self-reported on a 0-10 scale	+	?	-

Project: Total sleep deprivation as treatment of depression
Appendix 4.2 Outcome variable: Quality of sleep

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Continued: Kragh, 2017 Denmark				**Avoidance of sleep during daytime (y/n)** Week 1: 33.3 % Week 2: 28% Week 3: 25% Week4:28% Week5-6: 31% Week 7: 31% Week 8: 38% Week9: 13% **Duration of daytime sleep** Week 1,2 Week 3: 66 min (CI 34.9-97.4) Week 6: 70 min (CI 34.4-106.7)	**Avoidance of sleep during daytime (y/n)** Week 1: 13%, Between group difference: p=0.04, Week2: 6.3 % Between group difference:p=0.02 Week3: 3%, Between groups difference:p=0.01 Week4: 3%, Between groups difference:p=0.01 Week 5-6: 13% Between groups difference:p=0.07 Week 7: 13% Week 8: 16%, Between groups difference:p=0.05 Week 9: 6% Between groups difference: p=0.39 **Duration of daytime sleep** Week 1,2: Between group difference: ns Week 3: 117 min (CI 89.4-143.7) Between groups difference: p=0.02 Week6: 119 min (CI: 86.6-151.8) Between groups difference: sign (p=0.05) Week 4,5,7,8,9: Between group difference: ns				

TSD: Total sleep deprivation

Project: Total sleep deprivation as treatment of depression
Appendix 4.3 Outcome variable: Quality of life

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) vs other treatment									
Martiny, 2015 Denmark	RCT	I:37 C:38		**TSD (+LT+STS)** **WHO-5** Week1 (prior to TSD): 24.5 Week2 (after TSD): 48, Δ=23.5 Week 3: 49, Δ=24.5 Week 4: 51,Δ=26.5 Week5: 52, Δ=27.5 Week 6, 53, Δ=28.5 Week 7: 54, Δ=29.5 Week 8: 55, Δ=30.5 Week9: 56, Δ=31.5	**Exercise** **WHO-5** Week1: 19 Week 2: 33, Δ=14, Between groups difference F_{71}=6.49, p=0.01 Week 3: 35.5, Δ=16.5 Between groups difference P<0.01 Week 4: 37.5, Δ=18.5 Between groups difference P<0.01 Week5: 41.5, Δ=22.5 Between groups difference P<0.01 Week 6: 43.5, Δ=24.5 Between groups difference p<0.05 Week7: 45.5, Δ=26.5 Between groups difference: ns Week 8: 48, Δ=29 Between groups difference: ns Week 9: 52, Δ=33 Between groups difference: ns	WHO-5: World health Organisation Well being index *Sample-note:* includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation	?	?	+

Project: Total sleep deprivation as treatment of depression
Appendix 4.3 Outcome variable: Quality of life

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) as add-on vs no-TSD									
Kragh, 2017 Denmark	RCT	I:32 C: 32	I: dropouts n=10 (due to ECT n=3) C: dropouts n=14 (due to ECT n=6)	**TSD, LT, STS + standard** **WHO-5** Week 0: 14.4 (CI 8.8 – 19.7) Week 9: 34.0 (CI 27.4 – 40.5)	**Standard** **WHO-5** Week 0: 15.6 (CI 9.9 – 21.2) Week 9: 35.2 (CI 27.8 – 42.5) Between group difference in WHO-5: n.s.	*Sample-note:* Note includes 2 out-patients hospitalized for the treatment *Scale:* WHO-5 World health Organisation Well being index *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation	+	?	+

TSD: Total sleep deprivation, n.s.: not significant

Project: Total sleep deprivation as treatment of depression
Appendix 4.4 Outcome variable: Everyday functioning

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) vs other treatment									
Martiny, 2012,2015 Denmark	RCT	I:37 C:38		**TSD (+LT+STS)** **GAF-F score** Baseline: 52,4 (SD: 11,2) Week 29: 76,7 (16,8)	**Exercise** **GAF-F score** Baseline: 53,3 (SD:9,4) Week 29: 71,6 (14) Between group difference: n.s.	Unipolar depression *Sample-note:* includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation	?	?	-
Sleep deprivation (TSD) as add-on vs no-TSD									
Kragh, 2017 Denmark	RCT	I: 32 C: 32	I: dropouts n=10 (due to ECT n=3) C: dropouts n=14 (due to ECT n=6)	**TSD, LT, STS + standard GAF** Baseline: 57,1 (SD 10,2) Week 9: 60 (CI 56,6 – 63,5)	**Standard GAF** Baseline: 57,9 (SD 10,1) Week 9: 63,6 (CI 60 - 67) Between group difference n.s.	Note includes 2 out-patients hospitalized for the treatment	+	?	-

TSD: Total sleep deprivation; n.s.: not significant

Project: Total sleep deprivation as treatment of depression
Appendix 4.5 Outcome variable: Length of stay

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Sleep deprivation (TSD) as add-on vs no-TSD									
Kragh, 2017 Denmark	RCT	I:32 C:32		**TSD, LT, STS + standard** **Length of admission (median)** 48 (range 15-198) **Length of admission (median, from study entry until discharge)** 36 days (9-63)	**Standard** **Length of admission** 39 days (15-141), (p=0.15) **Length of admission** 21 days (3-62) p=0.09	*Sample-note:* Note includes 2 out-patients hospitalized for the treatment *TSD-protocol:* 3 TSD within 1 week+ LT+STS *LT:* Light Therapy *STS:* Sleep Time Stabilisation	+	+	+

TSD: Total sleep deprivation

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.6 Outcome variable: Complications

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Sleep deprivation (TSD) as Add on – no add on						
Gorgulu 2009	Cohort study	n=84. Healthy controls n=33, Inpatients n=51	n=11 Technical problems=9 Could not complete study, reason not specified, n=3.	TSD + sertraline 2 patients could not complete study, reason not specified.	Sertraline	51 patients with MD, 33 healthy controls. 1 healthy control could not complete TSD due to abnormal reactions.
Kragh, 2017	RCT	n=64 C: n=32 I: n=32	C: dropouts n=14 (due to ECT n=6) I: dropouts n=10 (due to ECT n=3)	TSD, LT, STS + standard Worsening in anxiety n=1 Self-harm n=1 Tiredness 55%, restlessness 52%, sensitivity 80%, concentration difficulties 74%, memory difficulties 74%, headache 80%. No patients developed manic or hypomanic symptoms.	Standard Not reported	Note includes 2 out-patients hospitalized for the treatment. Unipolar patients. The intervention group had two dropouts due to possible complications. Other comparisons regarding complications between the groups cannot be done.
Wu, 2009	RCT	n=49 C: n=17 I: n=32	n=5 all in TSD group, due to relocation, failure to adhere to protocol and intolerance to medication.	TSD + LT+ Sleep phase advance + medication Brief switch of polarity, n=2. Patients were not excluded from study.	Medication None of the patients experienced adverse events.	Medication: Sertraline + mood stabilizers. 49 outpatients with BPD, during TSD patients were at the hospital.
Sleep deprivation (TSD) vs exercise						
Martiny, 2012	RCT	n=75 C: n=38 I: n=37	Not reported	TSD+LT+Duloxetine Increase in anxiety, n=4.	Exercise+Duloxetine Exercise induced pain, n=1. Switch of polarity, n=1.	Note includes out-patient population that is hospitalized for the 1 week treatment, afterwards discharged. Patients with MD and BPD with mood stabilizing treatment

Project: Total sleep deprivation as treatment of depression
Appendix 4.6 Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
				Running eyes due to LT, n=1. Hypoglykemia in diabetic patient, n=1. Switch of polarity, n=1.		for at least 1 month. No patients dropped out due to manic symptoms. A few patients in the TSD-group developed panic attacks without pre-existing panic disorder, high anxiety might be a relative counterindication according to authors.
Martiny, 2013	RCT	n=75 C: n=38 I: n=37	1 patient in WT-group was not included in analysis due to logistical problems in the ward.	TSD+LT+Duloxetine	Exercise+Duloxetine	**Same trial as above**, reports unblinded. No additional complications are described in this paper, but dropout is reported.
Martiny, 2015	RCT	n=75 C: n=38 I: n=37	n=11 C: n=4 I: n=7	TSD+LT+Duloxetine	Exercise+Duloxetine	**Same trial as above**, 20-week follow up. Dropout was somewhat higher in TSD-group but not related to depression rates.
Case series						
Benedetti, 2005	Case series	n=60	Not reported	TSD + LT + standard Switch of polarity, n=2 No reported complications from LT (lux 400).		Patients with BPD type 1. Patients were divided into three subgroups according to the history of drug resistance. Two patients developed a manic episode, both in group 1 (33/60 patients with no history of drug resistance).
Colombo, 1999	Case series	n=206	Not reported	**TSD + placebo, n=82**, or TSD + pharmacological treatment, n=124. Switch of polarity, n=22 (10,7%).		Patients with BPD, type is not specified. Out of the 124 patients, 34 were treated with Amineptine and 36 with Pindolol. The switch rate was according to paper not associated with medication status, p=0.268. Note: mania 10, hypomania 12, in total 22 patients. Of 22 switches, 10 were in TSD+placebo-group.

* + No or minor problems
? Some problems
- Major problems

Project: Total sleep deprivation as treatment of depression
Appendix 4.6 Outcome variable: Complications

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Colombo, 2000	Case series	n=115	7	TSD + (lithium, patients continued long-term treatment, no new administrations) + 1. No LT, n=35 2. LT 150 lux red light, n=38 3. LT 2500 lux white light, n=42 Switch to mania, n=7 (6,1%)		115 inpatients with BPD, type is not specified. Of the seven patients with switch to mania three had been taking lithium and received LT (2), four were without lithium and had no LT, n=2, or LT (1), n=2.

Project: Total sleep deprivation as treatment of depression
Appendix 4.6 Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Fähndrich, 1981	Case series	n=80	0	TSD + medication Worsening of symptoms, n=4. Increase of guilt delusion, n=2. Increase of symptoms developing paranoia, n=2. Inhibition increased to stupor, n=1.		Unipolar depression, bipolar depression, involutional depression, neurotic depression and depression in schizophrenic patients. Medication = antidepressants, neuroleptics in the schizophrenic group. In total 164 TSD, no protocol was used (number of TSD/patients 2-10).
Rudolf, 1978	Case series	n=67	Not reported	TSD + medication Headache, n=1. Generalized convulsion (in combination with substance withdrawal), n=1.		45 patients with endogenous depression, 22 with neurotic depression (unipolar depression). The majority was inpatients. Some spent the TSD-night alone.
Suzuki, 2018	Case series	n=220	3 Due to switch of polarity.	TSD + LT + Lithium Switch of polarity, n=3 (1.4%).		220 inpatients with BPD type 1. Patients who were not taking lithium started it together with TSD. Note: Overlap with Benedetti 2014, Suzuki 2016 and Dallaspezia 2018. Patients were recruited in San Rafaelle Hospital, between 2002 and 2015.

* + No or minor problems
? Some problems
- Major problems

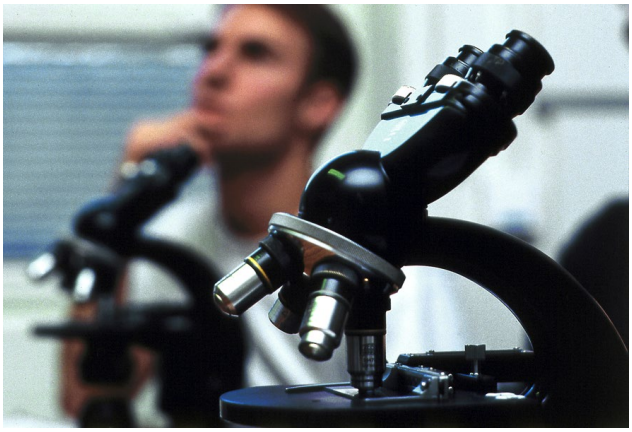
Project: Total sleep deprivation as treatment of depression
Appendix 4.6 Outcome variable: Complications

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Svendsen, 1976	Case series	n=77	0	TSD + medication No complications observed, no switch of polarity.		60 patients with unipolar and 17 with bipolar depression. No side effects at all were observed. Patients were divided into three groups with one TSD, maximum five TSDs or TSD twice a week (maximum six TSDs).

BPD: bipolar depression. BPD type 1: depression in bipolar disorder type 1. LT: light therapy. MD: major depression. TSD: Total sleep deprivation.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

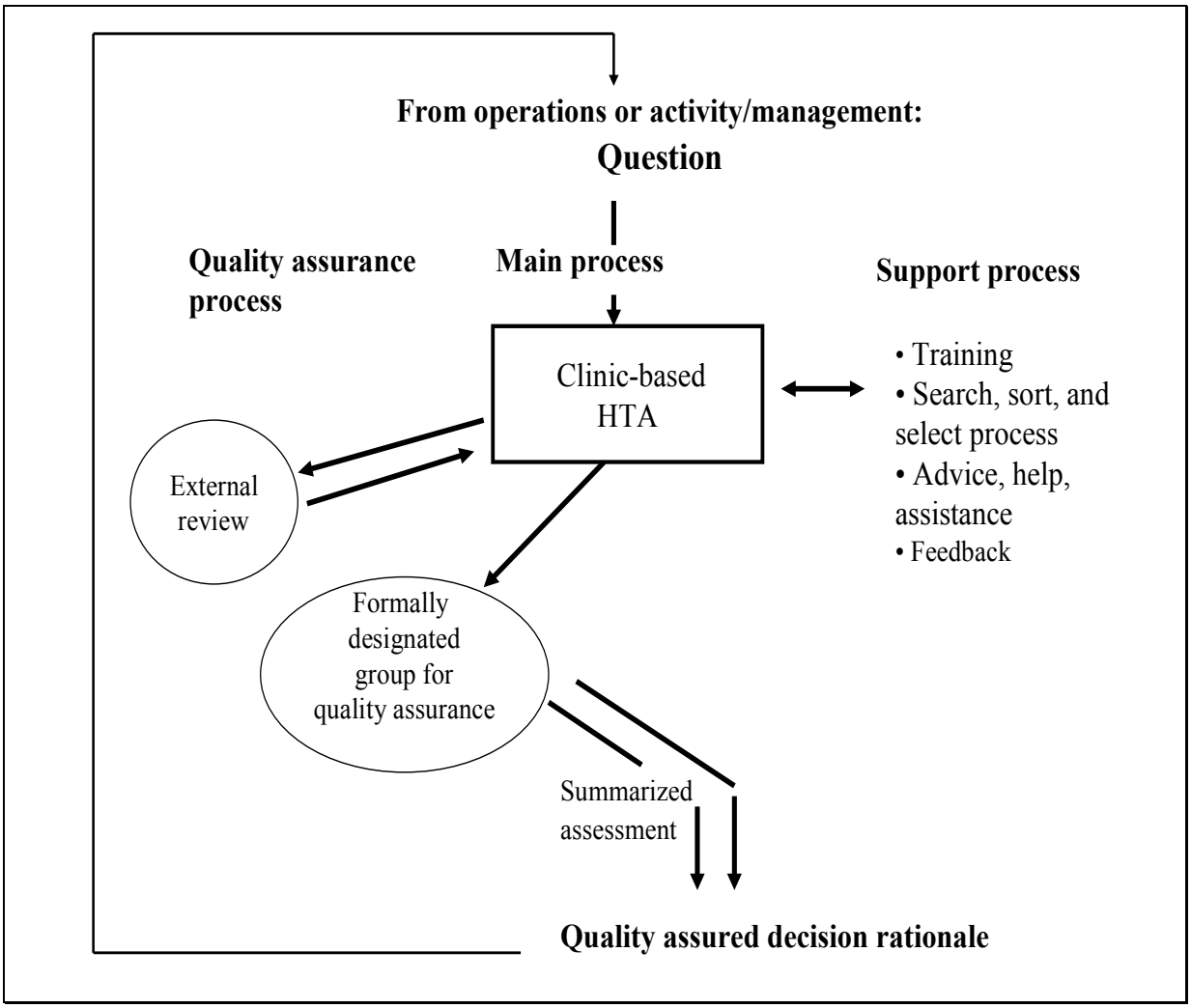
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
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