Meta-Analysis of the Antidepressant Effects of Acute Sleep Deprivation

Elaine M. Boland, PhD[a,b]; Hengyi Rao, PhD[c]; David F. Dinges, PhD[b]; Rachel V. Smith, PhD[a]; Namni Goel, PhD[b]; John A. Detre, MD[c]; Mathias Basner, MD, PhD[b]; Yvette I. Sheline, MD[b]; Michael E. Thase, MD[a,b]; and Philip R. Gehrman, PhD[a,b,*]

ABSTRACT

Objective: To provide a quantitative meta-analysis of the antidepressant effects of sleep deprivation to complement qualitative reviews addressing response rates.

Data Sources: English-language studies from 1974 to 2016 using the keywords *sleep deprivation* and *depression* searched through PubMed and PsycINFO databases.

Study Selection: A total of 66 independent studies met criteria for inclusion: conducted experimental sleep deprivation, reported the percentage of the sample that responded to sleep deprivation, provided a priori definition of antidepressant response, and did not seamlessly combine sleep deprivation with other therapies (eg, chronotherapeutics, repetitive transcranial magnetic stimulation).

Data Extraction: Data extracted included percentage of responders, type of sample (eg, bipolar, unipolar), type of sleep deprivation (eg, total, partial), demographics, medication use, type of outcome measure used, and definition of response (eg, 30% reduction in depression ratings). Data were analyzed with meta-analysis of proportions and a Poisson mixed-effects regression model.

Results: The overall response rate to sleep deprivation was 45% among studies that utilized a randomized control group and 50% among studies that did not. The response to sleep deprivation was not affected significantly by the type of sleep deprivation performed, the nature of the clinical sample, medication status, the definition of response used, or age and gender of the sample.

Conclusions: These findings support a significant effect of sleep deprivation and suggest the need for future studies on the phenotypic nature of the antidepressant response to sleep deprivation, on the neurobiological mechanisms of action, and on moderators of the sleep deprivation treatment response in depression.

J Clin Psychiatry 2017;78(8):e1020–e1034
https://doi.org/10.4088/JCP.16r11332

[a]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania
[b]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
[c]Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
**Corresponding author:* Philip R. Gehrman, PhD, Department of Psychiatry, University of Pennsylvania, 3535 Market St, Ste 670, Philadelphia, PA 19104 (gehrman@exchange.upenn.edu).

Antidepressant medication is typically reported as the most common treatment strategy for depression.[1] However, antidepressant effects are slow to manifest, often taking several weeks to yield clinical improvement.[2] Moreover, early clinical improvement plays a key role in stable long-term treatment outcomes,[3] highlighting the need for treatment strategies that can produce more rapid antidepressant effects. In contrast, acute sleep deprivation, either total (eg, being deprived of sleep for approximately 36 hours) or partial (being allowed to sleep for only 3 to 4 hours followed by 20 to 21 hours of wakefulness) is a well-known nonpharmacologic treatment for depression that produces clinical improvement in depression symptoms within a single 24-hour period and, as such, is one of the most rapid antidepressant interventions known.[4] First reported in 1818 by German psychiatrist Johann Christian August Heinroth,[5] research into the utility of sleep deprivation was inspired by Schulte, who in the mid-1960s reported the antidepressant effects of sleep loss in a case study of a teacher whose depression eased after a sleepless night.[6] This report was followed several years later by the first trial of sleep deprivation for endogenous depression[7] and then by nearly 2 decades of focused research aimed at understanding and prolonging this rapid treatment response. Wu and Bunney[8] subsequently summarized research in this area and reported an average antidepressant response rate to sleep deprivation of 59% across studies. Unfortunately, these effects are transient in most individuals and are reversed following a subsequent night of sleep.

Variations in the administration of sleep deprivation have been tested since the discovery of its antidepressant effect. Early studies[7,9,10] primarily relied on a single night of acute total sleep deprivation and found that mood gradually improved overnight, reaching euthymic levels by the morning as assessed by either self-report (usually Visual Analog Scale [VAS] ratings) or by clinician ratings (typically a modified version of the Hamilton Depression Rating Scale [HDRS][11] that removed the sleep-related items). Studies of the effects of 1 night of partial sleep deprivation (eg, sleep restricted to generally a < 5-hour time window in the first or second half of the night) were later conducted to explore whether shorter durations of sleep deprivation would be equally effective and to determine if the time of night (early vs late) of partial sleep deprivation affected the antidepressant response.[12] Studies of partial sleep deprivation prior to 1990 yielded mixed results.[8] Since then, it has been generally accepted that partial sleep deprivation is roughly equivalent to total sleep deprivation in efficacy as long as the deprivation occurs in the latter part of the night.[13,14] As a means of attempting to prolong the effects of sleep deprivation, studies have also employed repeated administrations of both total sleep deprivation[15–17] and partial sleep deprivation.[18] Findings have been mixed, however, with reported increases and decreases in responding to repeated applications of sleep deprivation.[14]

Clinical Points

- Sleep deprivation has been shown to have rapid antidepressant effects for roughly 40% to 60% of individuals; however, this response rate has not been analyzed quantitatively since 1990 despite the addition of over 75 studies to the literature.
- Sleep deprivation can be a useful clinical tool for depressed patients if the effects can be sustained; more research must be done to explore ways of extending the antidepressant effect and/or preventing depressive relapse following sleep.

Sleep deprivation has been explored as a potential treatment for both unipolar and bipolar depression. Wu and Bunney[8] reported that sleep deprivation was effective in producing a rapid antidepressant response among individuals with bipolar depression with comparable efficacy to unipolar depression. It was noted in this report, however, that sleep deprivation in bipolar disorder was associated with switches to hypomanic or manic episodes in approximately 30% of cases. More recent research has demonstrated that the switch to hypomanic or manic episodes is much lower (eg, a 5.8% switch to hypomania and a 4.9% switch to mania) among medicated bipolar patients.[19] Studies likewise explored differential effects of sleep deprivation in individuals treated with or without pharmacotherapy. Overall, 83% of unmedicated and 59% of medicated patients relapsed following a single night of sleep post–sleep deprivation, indicating that the antidepressant effect of sleep deprivation is not sustained in the majority of patients.[8]

Since the publication of the review by Wu and Bunney,[8] over 75 studies have been conducted to further explore the effects of sleep deprivation and identify ways of prolonging and enhancing its antidepressant response. Detailed qualitative reviews of these studies have been conducted,[4,14,20] offering comprehensive discussions of what is currently understood about the efficacy of sleep deprivation across mood disorder populations and predictors of sleep deprivation response. These and other studies of sleep deprivation[21,22] frequently cite a 40% to 60% and up to a 70% response rate.[23] However, to date, a formal quantitative meta-analysis of these studies has not been conducted. While recent reviews have concluded that sleep deprivation may be more effective in bipolar samples,[14] and have reported comparable efficacy between total sleep deprivation and partial sleep deprivation,[14] with slightly better results for total sleep deprivation,[20] these statements have not been examined quantitatively across studies of sleep deprivation.

The purpose of this report is to provide a quantitative analysis (ie, pooled estimate) of the antidepressant effects of sleep deprivation in depressed samples. In this report, overall efficacy of sleep deprivation across studies was computed. In addition, analyses examined how the sleep deprivation response may be affected by the type and timing of sleep deprivation performed (total vs early or late partial sleep deprivation), the nature of the clinical sample (unipolar, bipolar, or a combination), medication status, and age and gender of the sample. Importantly, we also explored how response to sleep deprivation may differ across studies as a function of the definition of "response" utilized in each study. In the more than 30 years since the discovery of the antidepressant effects of sleep deprivation, the field has yet to reach a consensus definition of what constitutes adequate response to sleep deprivation treatment. Thus, we explored whether definition of response was an important factor in sleep deprivation response rates.

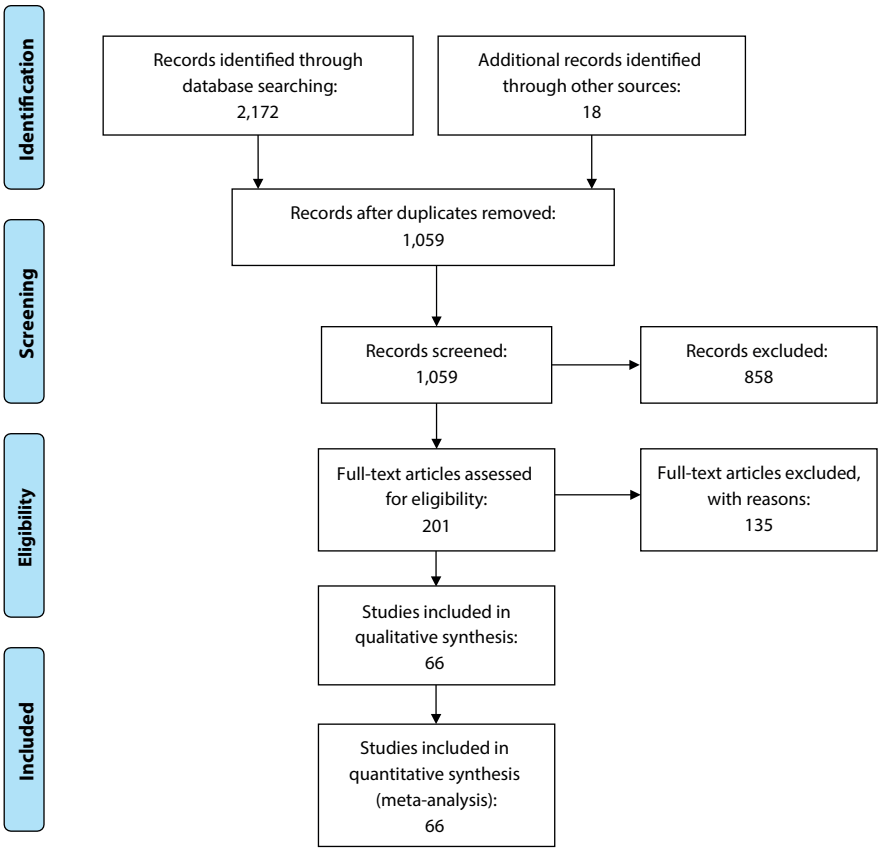
METHOD

Literature Review and Data Collection

A comprehensive search for English-language studies of experimentally induced sleep deprivation in depressed samples was conducted with the PsycINFO and PubMed databases, utilizing reference lists and Google Scholar databases as supplementary sources. Keywords *sleep deprivation* and *depression* were utilized, resulting in a total of 2,172 records meeting both of these search terms (Figure 1). The abstracts of these articles were reviewed to determine if the study was a clinical trial of the antidepressant effects of sleep deprivation. This yielded 200 full-text articles assessed for inclusion in analyses. Studies were then excluded if (1) no data were provided on the proportion of individuals who responded to sleep deprivation (42 studies); (2) sleep deprivation was augmented with chronotherapeutics (eg, phase advance, bright light therapy) and/or repetitive transcranial stimulation or electroconvulsive therapy and response data were not provided for sleep deprivation alone (20 studies); (3) no a priori definition was provided of how "responder" was operationalized or multiple definitions were utilized (18 studies); (4) the study utilized or overlapped with a previously reported sample (17 studies); (5) the study was conducted on a sample of healthy subjects (10 studies); (6) the sample was smaller than 5 participants (9 studies); (7) the sample was not purely depressed or bipolar (eg, seasonal affective, schizoaffective, premenstrual dysphoric disorder) (6 studies); (8) the sample comprised solely responders to sleep deprivation (5 studies); (9) the study did not report data immediately after sleep deprivation in cases of single-administrations (3 studies); (10) the study utilized rapid eye movement (REM) sleep deprivation (3 studies); and (11) the study did not use a defined rating scale for response (2 studies).

Each article was reviewed, and data were extracted on sample size, mean age and gender distribution, number and proportion of responders and nonresponders, type and timing of sleep deprivation (eg, total, partial, and early vs late partial sleep deprivation), type of sample (eg, unipolar depression, bipolar depression, or mixed), medication status, outcome measure used (eg, a modified HDRS that excludes sleep and weight items, VAS), and definition of antidepressant response (eg, percentage reduction in baseline score). If a study included groups of individuals receiving different types of sleep deprivation or if groups

Figure 1. PRISMA Flow Diagram of Study Selection



of participants differed in terms of diagnosis or medication status, separate entries were included in the dataset from the same study. Thus, although there were 66 studies, we included 75 separate entries for analyses.

Data Analyses

Categorical variables were generated on the basis of common themes in the data for purposes of exploring univariate and multivariate effects among the nonrandomized studies, as there were too few randomized studies to conduct reliable analyses. In the variables described below, "n" refers to number of entries, not distinct studies. The variable for definition of response included 4 levels: 1 = 30% or less reduction in pre–sleep deprivation depression (n = 31); 2 = 40% or less reduction (n = 11); 3 = 50% reduction (n = 9); and 4 = "nonpercentage-based criteria" (n = 24). The nonpercentage category included specific score criteria (eg, HDRS < 8) and a specific point reduction (eg, 6-point decrease from baseline) as well as more general criteria such as "positive mean change" (eg, qualitative definitions of response such as "patient reported that sleep deprivation had helped" and "patient and physician agreed on response" or simply a positive mean change from baseline depression score). Studies overwhelmingly utilized the HDRS as an outcome measure; however, 10 studies (11 entries) utilized other measures. As such, we created a categorical variable for outcome measure that had 2 levels: 1 = HDRS (n = 64) and 2 = "Other" (n = 11). "Other" outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS[24]; n = 2), the Adjective Mood Scale (AMS[25]; n = 3), the Bonjanovský and Chloupková Depression Rating Scale[26] (n = 1), the Bunney-Hamburg Scale[27] (n = 1), the Sleep Deprivation Rating Scale[28] (n = 1), the Bjorum and Lindberg Scale[9] (n = 1), and unnamed depression rating scales (n = 2). Although studies varied in the version of the HDRS that was utilized (see Table 1), all HDRS-derived scales were considered a single variable in meta-regression. Sample type included 3 levels: 1 = unipolar depression (n = 42); 2 = bipolar depression (n = 7); and 3 = mixed sample (n = 26). Type of sleep deprivation was categorized into 3 levels: 1 = single administration of total sleep deprivation (n = 51), 2 = multiple administrations of total sleep deprivation (n = 7); and 3 = partial sleep deprivation (n = 15). Of the 15 partial sleep deprivation studies included, only 1 study utilized early partial sleep deprivation (partial sleep deprivation administered in the first half of the night) and, thus, early and late partial sleep deprivation variables were not created. Medication status was dichotomized into on-medication (n = 36) and off-medication (n = 37).

Meta-analyses were conducted on the overall proportion of individuals who exhibited an antidepressant response to sleep deprivation and on the proportion of responders in each category detailed above. A meta-regression was conducted using a Poisson mixed-effects model, with age,

gender, type of sleep deprivation, sample type, outcome measure, and response criteria as independent variables. The number of responders was used as the outcome, with the natural log of the study sample size as the offset. Due to the limited number of study entries (n = 75), all combinations of covariates producing models of 7 degrees of freedom or less were examined. Response criteria and outcome measure were significantly correlated (Pearson correlation coefficient [r] = 0.64; $P < .0001$) and were therefore not included in any of the same models. Heterogeneity across studies was assessed using the I^2 statistic,[29] and publication bias was examined visually using funnel plots. Meta-analyses were conducted using MedCalc Version 16.4.3 (MedCalc Software bvba, Ostend, Belgium). Regression analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina). Statistical significance was denoted as a P value less than .05.

RESULTS

Descriptive Statistics

A total of 66 independent studies were included (Table 1). As stated previously, some study samples were split if they possessed unique criteria. This occurred in 8 studies. Six studies[15,16,30–33] reported response rates on both medicated and nonmedicated patients; 1 study[34] compared groups of total sleep deprivation and partial sleep deprivation responders; and 1 study[35] compared early to late partial sleep deprivation. Study sample size ranged from 6 to 80, with a mean sample size of 22.81 (standard deviation [SD] = 14.14). Included studies were conducted from 1976 to 2012. The mean age of participants across all studies was 45.9 years (SD = 15.54 years), and the mean proportion of female participants was 60% (SD = 0.29, or 29%). Percent change in depression ratings (ie, from baseline to post–sleep deprivation) is provided in Table 1. Data were available for 43 entries, and ranged from 13.4% to 85.8% (mean = 39.6%) among randomized studies and from 10.9% to 73.2% (mean = 36.6%) among nonrandomized studies.

The funnel plot for nonrandomized studies appeared symmetrical; however, the randomized funnel plot indicated some asymmetry. As there were only 9 entries in that analysis, however, power was considered too low to distinguish actual asymmetry from chance. Thus, we note that results should be interpreted with caution. As heterogeneity was high across studies (I^2 statistic for inconsistency = 57.56% for nonrandomized studies and 72.6% for randomized studies), random effects results are reported here. Out of 141 participants in randomized trials, 63 responded to sleep deprivation, with a random effects total of 44.52% (95% CI, 29.10%–60.10%). Among 1,593 participants in nonrandomized studies, 812 responded to sleep deprivation, with a random effects total of 50.40% (95% CI, 46.59%–54.22%). Results are presented visually in Figure 2.

Results of categorical meta-analyses as well as 95% confidence intervals for nonrandomized studies are presented in Figure 3. The overall response rate to total sleep deprivation was 50.4%, and the response rate to partial sleep deprivation was 53.1%. Multiple administrations of total sleep deprivation yielded an overall response rate of 37.8%.

In unipolar depressed samples, the response rate to sleep deprivation was 50.6%. Among bipolar depressed samples, the response rate was 37.7%, and in samples that used a mixture of unipolar and bipolar depressed patients, the response rate was 53.1%.

The response rate to sleep deprivation in studies that utilized a 30% reduction in baseline depression score was 53.7%, 50.9% in studies utilizing a 40% reduction criterion, 50.1% in studies utilizing a 50% reduction criterion, and 44.5% in studies that utilized a nonpercentage-based outcome criterion. Among studies that utilized the HDRS to quantify response, the response rate was 51.2%. Among studies that used other outcome measures, the response rate was 46.2%.

Meta-Analysis/Meta-Regression

Results from the mixed effects Poisson regression, using all possible combinations of covariates as described earlier, were nonsignificant, indicating that neither type of depression (unipolar, bipolar, or a combined sample), medication status, age, gender, type of sleep deprivation, outcome measure (HDRS or other), nor definition of response yielded statistically significant differential response rates to sleep deprivation.

DISCUSSION

Results from quantitative analyses of studies over a 36-year period indicate that sleep deprivation is effective in rapid reduction of depressive symptoms in approximately half of all depressed patients. Partial sleep deprivation is equally as effective as total sleep deprivation; however, because 14 of the 15 studies involving partial sleep deprivation utilized late partial sleep deprivation, we were unable to quantify response rates of early versus late partial sleep deprivation, or of either type of partial sleep deprivation relative to total sleep deprivation. Medication status does not appear to confer added benefit or reduction in efficacy. The effect of sleep deprivation is also roughly equivalent across differing definitions of antidepressant response. Additionally, although the number of randomized trials is small relative to nonrandomized trials (6 vs 60, respectively), total response rates are not meaningfully different. Thus, no matter how response is quantified, how sleep deprivation is delivered, or whether the patient has bipolar or unipolar depression, sleep deprivation has a nearly equivalent response rate.

The results regarding sleep deprivation response among bipolar participants as well as via multiple sleep deprivation administrations warrant some discussion, however. Although some qualitative reviews have suggested that sleep deprivation may be slightly more effective in bipolar samples, our results indicated inferior, although not significantly so, results in bipolar patients relative to unipolar patients. It would be incorrect, however, to conclude that sleep deprivation is not an effective treatment for bipolar depression. Because our

Table 1. Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

Author	Year	No. of Patients	Sample Type	Mean Age, y	% Female	Type of Sleep Deprivation	Medication (yes/no)	Outcome Measure	Response Criteria	Timing of Depression Measurement	Proportion Responders (95% CI)	Mean Pre/Post Depression Scores ± SD (% change)
Studies Utilizing a Randomized Non–Sleep Deprivation Control Group												
Elsenga and van den Hoofdakker[31]	1983	10	Unipolar	49.1	88	Total	Yes	5-item HDRS	≥6 point reduction	Day after TSD	40% (12%–74%)	Data not provided[a]
Elsenga and van den Hoofdakker[31]	1983	10	Unipolar	51.2	88	Total	No	5-item HDRS	≥6 point reduction	Day after TSD	30% (6%–65%)	Data not provided[a]
Holsboer-Trachsler et al[36]	1994	14	Mixed	50.43	43	Multiple late PSD administrations (4 h TIB)	Yes	17-item HDRS	50% reduction in baseline HDRS	6 weeks after final PSD	43% (18%–71%)	Pre: 23.0 ± 3.7 Post: 14.0 ± 8.6 (39.1%)
Kuhs et al[18]	1996	27	Mixed	43.3	41	Multiple late PSD administrations (TIB unclear)	Yes	10-item HDRS	50% reduction in baseline HDRS	2 weeks after final PSD	67% (46%–83%)	Data not provided[a]
Caliyurt and Guducu[37]	2005	13	Unipolar	38.46	79	Late partial (4 h TIB)	Yes	21-item HDRS	50% reduction in baseline HDRS	Day after PSD	92% (63%–100%)	Means not provided; reports 85.81% decrease in HDRS scores
Reynolds et al[32]	2005	27	Unipolar	70.6	70	Total	Yes	13-item HDRS	HDRS ≤ 10	Day after TSD	22% (9%–42%)	Data not provided[a]
Reynolds et al[32]	2005	27	Unipolar	71.4	70	Total	No	13-item HDRS	HDRS ≤ 10	Day after TSD	41% (22%–61%)	Data not provided[a]
Smith et al[33]	2009	7	Unipolar	68.8	100	Total	Yes	13-item HDRS	HDRS ≤ 10	Day after TSD	40% (32%–49%)	Pre: 15.7 ± 3.6 Post: 13.6 ± 4.2 (13.4%)
Smith et al[33]	2009	6	Unipolar	68.8	50	Total	No	13-item HDRS	HDRS ≤ 10	Day after TSD	39% (27%–51%)	Pre: 16.3 ± 4.8 Post: 13.0 ± 5.4 (20.3%)
Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group												
Baghai et al[13]	2003	56	Unipolar	49.2	66	Late partial (TIB unclear)	No	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	64% (50%–77%)	Pre: 11.6 ± 0.9 Post: 7.1 ± 1.1 (38.7%)[b]
Baumgartner et al[38]	1990	14	Mixed	39.7	64	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	50% (23%–77%)	Pre: 11.0 ± 3.6 Post: 8.0 ± 6.3 (27.3%)
Beck et al[39]	2010	14	Unipolar	46.2	43	Late partial (TIB unclear)	No	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	50% (23%–77%)	Pre: 21.8 ± 4.7 Post: 12.6 ± 8.4 (42.2%)
Beck et al[39]	2010	14	Unipolar	43.9	64	Late partial (TIB unclear)	Yes	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	43% (18%–71%)	Pre: 21.7 ± 6.6 Post: 15.7 ± 9.1 (27.6%)
Benedetti et al[15]	1999	20	Bipolar	48.2	60	Multiple TSD administrations	Yes	21-item HDRS	HDRS score < 8	5 days after final TSD	50% (27%–73%)	Pre: 23.4 ± 3.3 Post: 8.5 ± 8.2 (63.9%)
Benedetti et al[15]	1999	20	Bipolar	48.35	70	Multiple TSD administrations	No	21-item HDRS	HDRS score < 8	5 days after final TSD	25% (9%–49%)	Pre: 26.0 ± 4.9 Post: 14.3 ± 7.9 (45%)

(continued)

Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

Author	Year	No. of Patients	Sample Type	Mean Age, y	% Female	Type of Sleep Deprivation	Medication (yes/no)	Outcome Measure	Response Criteria	Timing of Depression Measurement	Proportion Responders (95% CI)	Mean Pre/Post Depression Scores ± SD (% change)
Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group												
Benedetti et al[30]	2001	13	Bipolar	N/A[c]	N/A[c]	Multiple TSD administrations	Yes	MADRS	MADRS score < 6	2 days after final TSD	38% (14%–68%)	Pre: 30.5 ± 4.4 Post: 13.5 ± 11.9 (55.8%)
Benedetti et al[30]	2001	14	Bipolar	N/A[c]	N/A[c]	Multiple TSD administrations	No	MADRS	MADRS score < 6	2 days after final TSD	7% (< 1%–34%)	Pre: 30.3 ± 6.4 Post: 17.7 ± 9.5 (41.5%)
Benedetti et al[40]	2008	80	Bipolar	46.86	66	Multiple TSD administrations	Yes	17-item HDRS	HDRS score < 8	2 days after final TSD	53% (41%–64%)	Pre: 21.0 ± 4.0 Post: 8.9 ± 7.6 (41.5%)[b]
Bernier et al[41]	2009	11	Unipolar	22.91	100	Late partial (2.5 h TIB)	Yes	17-item HDRS	30% reduction in baseline HDRS	Day after PSD	45% (17%–77%)	Data not provided
Bouhuys et al[42]	1989	17	Unipolar	49.10	88	Total	N/A	Bf-S	Difference score of 6 points	Day after TSD	53% (29%–77%)	Data not provided
Bouhuys et al[43]	1990	16	Mixed	45.1	75	Total	No	AMS	5-point reduction	Day after TSD	44% (20%–70%)	Data not provided[a]
Bouhuys et al[44]	1995	72	Mixed	47.3	58	Total	Yes	AMS	Difference score of 6 points	Day after TSD	40% (28%–52%)	Pre: 40.7 ± 11.9 Post: 35.1 ± 14.0 (13.7%)
Brückner and Wiegand[45]	2010	34	Mixed	50	53	Total	Yes	6-item HDRS	50% reduction in baseline HDRS	Day after TSD	56% (38%–73%)	Pre: 9.9 ± 2.7 Post: 5.4 ± 2.0 (45.5%)[b]
Clark et al[46]	2006	17	Unipolar	42.8	58	Late partial (TIB unclear)	No	17-item HDRS	40% reduction in baseline HDRS	Day after PSD	29% (10%–56%)	Pre: 16.0 ± 3.2 Post: 10.5 ± 3.1 (34.5%)[b]
Danos et al[47]	1994	17	Unipolar	48.3	100	Total	Yes	16-item HDRS	30% reduction in baseline HDRS	Day after TSD	53% (28%–77%)	Data not provided
Ebert et al[48]	1991	10	Unipolar	38.9	50	Total	No	18-item HDRS	50% reduction in baseline HDRS	Day after TSD	50% (19%–81%)	Data not provided[a]
Ebert et al[49]	1993	14	Unipolar	36.3	0	Total	Yes	16-item HDRS	30% reduction in baseline HDRS	Day after TSD	57% (29%–82%)	Pre: 28.2 ± 2.2 Post: 19.7 ± 4.8 (30.3%)[b]
Ebert et al[50]	1994	10	Bipolar	33.4	0	Total	Yes	16-item HDRS	40% reduction in baseline HDRS	Day after TSD	50% (19%–81%)	Pre: 22.5 ± 4.0 Post: 13.0 ± 2.7 (42.3%)[b]
Ebert et al[51]	1994	20	Bipolar	40	0	Total	Yes	16-item HDRS	40% reduction in baseline HDRS	Day after TSD	55% (32%–77%)	Pre: 28.2 ± 2.2 Post: 21.5 ± 2.1 (23.8%)[b]
Ebert et al[52]	1996	12	Unipolar	40.4	0	Total	No	16-item HDRS	40% reduction in baseline HDRS	Day after TSD	67% (35%–90%)	Pre: 28.8 ± 1.8 Post: 16.0 ± 3.2 (44.4%)
Elsenga and Van den Hoofdakker[53]	1988	33	Unipolar	49.3	64	Total	Yes	21-item HDRS	≥6 point reduction	Day after TSD	27% (13%–46%)	Data not provided

(continued)

Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

Author	Year	No. of Patients	Sample Type	Mean Age, y	% Female	Type of Sleep Deprivation	Medication (yes/no)	Outcome Measure	Response Criteria	Timing of Depression Measurement	Proportion Responders (95% CI)	Mean Pre/Post Depression Scores ± SD (% change)
Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group												
Fritzsche et al[54]	2001	40	Mixed	47.1	65	Total	Yes	16-item HDRS	30% reduction in baseline HDRS	Day after TSD	50% (34%–66%)	Pre: 17.3 ± 5.1 Post: 11.3 ± 4.2 (34.5%)[b]
Gerner et al[55]	1979	25	Mixed	45	N/A	Total	No	Unnamed scale	Positive mean change	Day after TSD	64% (43%–82%)	Data not Provided
Giedke et al[34]	2003	22	Mixed	N/A[c]	N/A[c]	Late partial (TIB unclear)	Yes	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	27% (11%–50%)	Data not provided[a]
Giedke et al[34]	2003	17	Mixed	N/A[c]	N/A[c]	Total	Yes	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	53% (28%–77%)	Data not provided[a]
Gillin et al[56]	1989	19	Mixed	42	11	Total	Yes	19-item HDRS	40% reduction in baseline HDRS	Day after TSD	32% (13%–57%)	Pre: 17.5 ± 7.5 Post: 12 ± 5 (31.4%)[b]
Hemmeter et al[57]	2007	27	Unipolar	44.1	44	Late partial (5.5 h TIB)	Yes	6-item HDRS	40% reduction in baseline HDRS	Day after PSD	52% (32%–71%)	Pre: 25.6 ± 7.8 Post: 18.4 ± 7.7 (28.2%)
Hernandez et al[58]	2000	15	Unipolar	68.5	67	Total	No	13-item HDRS	HDRS score ≤ 6	Day after TSD	67% (38%–88%)	Data not provided[a]
Höchli et al[59]	1986	10	Mixed	40.2	70	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	50% (18%–81%)	Data not provided[a]
Kaschka et al[60]	1989	22	Unipolar	41	68	Total	Yes	21-item HDRS	30% reduction in baseline HDRS	Day after TSD	41% (21%–64%)	Data not provided[a]
Kasper et al[61]	1988	32	Mixed	50.4	69	Total	No	16-item HDRS	30% reduction in baseline HDRS	Day after TSD	50% (32%–68%)	Data not provided[a]
Kasper et al[62]	1990	41	Mixed	49.9	71	Total	Yes	16-item HDRS	30% reduction in baseline HDRS	Day after TSD	49% (33%–65%)	Data not provided[a]
Kuhs et al[63]	1985	39	Mixed	44.15	52	Total	Yes	10-item HDRS	30% reduction in baseline HDRS	Day after TSD	41% (26%–58%)	Data not provided[a]
Larsen et al[9]	1976	19	Unipolar	N/A	53	Total	Yes	BLS	≥3 point reduction	Day after TSD	32% (13%–57%)	Data not provided
Müller et al[64]	1993	9	Mixed	49	55	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	66% (30%–93%)	Pre: 8.2 ± 3.7 Post: 4.2 ± 3.6 (48.8%)
Neumeister et al[65]	1996	20	Mixed	47.6	70	Late partial (4.5 h TIB)	Yes	16-item HDRS	40% reduction in baseline HDRS	Day after PSD	70% (46%–88%)	Data not provided[a]
Neumeister et al[66]	1998	30	Mixed	42.6	80	Total	Yes	16-item HDRS	40% reduction in baseline HDRS	Day after TSD	73% (54%–88%)	Data not provided[a]
Orth et al[28]	2001	18	Unipolar	43.6	55	Total	No	SDDRS	30% reduction in baseline ratings	Day after TSD	56% (31%–78%)	Pre: 20.7 ± 5.2 Post: 13.1 ± 5.5 (36.7%)
Parekh et al[67]	1998	27	Mixed	38.7	59	Total	No	17-item HDRS	30% decrease in baseline HDRS	Day after TSD	44% (25%–65%)	Pre: 21.8 ± 5.3 Post: 17.1 ± 6.7 (21.5%)[b]

(continued)

Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

Author	Year	No. of Patients	Sample Type	Mean Age, y	% Female	Type of Sleep Deprivation	Medication (yes/no)	Outcome Measure	Response Criteria	Timing of Depression Measurement	Proportion Responders (95% CI)	Mean Pre/Post Depression Scores ± SD (% change)
Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group												
Post et al[10]	1976	19	Unipolar	N/A	N/A	Total	No	Unnamed depression scale	2 point decrease in nurse ratings	Day after TSD	53% (29% –76%)	Pre: 9.5 ± 0.6 Post: 6.7 ± 0.6 (29%)[b]
Reist et al[68]	1994	21	Unipolar	39	0	Total	No	17-item HDRS	35% reduction in baseline HDRS	Day after TSD	71% (48%–89%)	Pre: 20 ± 3.6 Post: 13.6 ± 3.2 (32.3%)[b]
Reynolds et al[69]	1987	15	Unipolar	70	88	Total	No	17-item HDRS	30% reduction in baseline HDRS	Day after TSD	40% (16%–68%)	Pre: 24.5 ± 3.8 Post: 16.2 ± 6.0 (33.8%)
Riemann et al[70]	1990	17	Mixed	39.1	71	Total	No	6-item HDRS	30% reduction in baseline depression	Day after TSD	53% (28%–77%)	Data not provided
Riemann et al[71]	1991	48	Mixed	46.1	71	Total	No	6-item HDRS	30% reduction in baseline depression	Day after TSD	63% (47%–76%)	Data not provided[a]
Riemann et al[72]	1993	24	Mixed	49.2	68	Total	No	6-item HDRS	30% reduction in baseline depression	Day after TSD	58% (37%–78%)	Pre: 8.3 ± 3.9 Post: 5.3 ± 3.9 (36.1%)
Riemann et al[23]	1999	57	Mixed	42.3	N/A	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	77% (64%–87%)	Data not provided[a]
Roy-Byrne et al[73]	1984	16	Unipolar	39	75	Total	No	BHS	Mean change of 2 or more points	Day after TSD	38% (15%–65%)	Data not provided[a]
Salomon et al[74]	1994	11	Unipolar	44.3	45	Total	No	18-item HDRS	25% reduction in baseline HDRS	Day after TSD	36% (11%–69%)	Pre: 28.5 ± 10.6 Post: 25.4 ± 13.2 (10.9%)
Schilgen et al[12]	1980	30	Unipolar	47.6	N/A	Late partial (4.5 h TIB)	Yes	BCS	Negative mean difference	Day after PSD	77% (58%–90%)	Data not provided[a]
Schüle et al[75]	2001	33	Unipolar	48/9	58	Late partial (4.5 h TIB)	No	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	45% (28%–64%)	Pre: 24.3 ± 5.8 Post: 16.4 ± 8.6 (32.7%)
Schüle et al[22]	2003	29	Unipolar	53.7	59	Late partial (2.5–4.5 h TIB)	No	6-item HDRS	30% reduction in baseline HDRS	Day after PSD	69% (49%–85%)	Pre: 11.5 ± 3.3 Post: 7.1 ± 2.8 (38.2%)[b]
Schumann et al[76]	2001	52	Unipolar	45.97	63	Total	Mixed	6-item HDRS	50% reduction in baseline HDRS	Day after TSD	31% (19%–45%)	Data not provided[a]
Shelton and Loosen[77]	1993	20	Unipolar	42.9	55	Total	No	13-item HDRS	30% reduction in baseline HDRS	Day after TSD	60% (36%–81%)	Pre: 21.2 ± 5.6 Post: 12.7 ± 4.9 (40%)[b]
Smeraldi et al[16]	1999	20	Unipolar	44.9	60	Multiple TSD administrations	Yes	21-item HDRS	HDRS < 8	4 days after final TSD cycle	75% (51%–91%)	Pre: 24.7 ± 3.3 Post: 6.6 ± 5.6 (73.2%)
Smeraldi, et al[16]	1999	20	Unipolar	51.6	65	Multiple TSD administrations	No	21-item HDRS	HDRS < 8	4 days after final TSD cycle	15% (3%–38%)	Pre: 25.7 ± 5.3 Post: 16.6 ± 6.7 (35.4%)

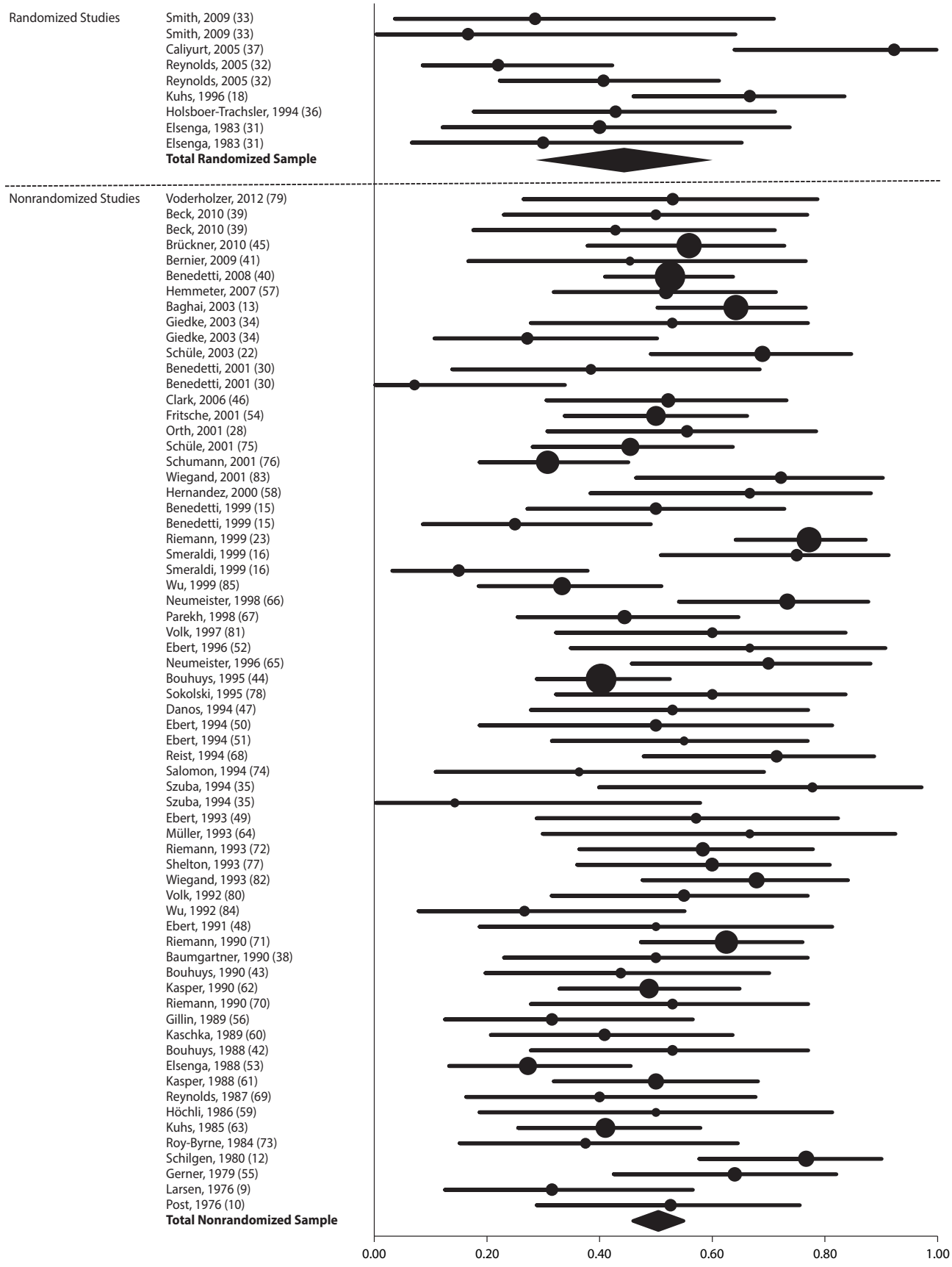
(continued)

Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

Author	Year	No. of Patients	Sample Type	Mean Age, y	% Female	Type of Sleep Deprivation	Medication (yes/no)	Outcome Measure	Response Criteria	Timing of Depression Measurement	Proportion Responders (95% CI)	Mean Pre/Post Depression Scores ± SD (% change)
Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group												
Sokolski et al[78]	1995	15	Unipolar	46.3	13	Total	No	16-item HDRS	8.5 point decrease in HDRS	Day after TSD	60% (32%–84%)	Pre: 25.9 ± 5 Post: 18.4 ± 5.7 (29%)[b]
Szuba et al[35]	1994	9	Mixed	28.9	88	Late partial (4 h TIB)	Yes	6-item HDRS	50% decrease in baseline HDRS	Day after PSD	78% (40%–97%)	Pre: 10.8 ± 3.7 Post: 6.1 ± 4.0 (43.5%)
Szuba et al[35]	1994	7	Mixed	31	86	Early partial (5 h TIB)	Yes	6-item HDRS	50% decrease in baseline HDRS	Day after PSD	14% (0.3%–58%)	Data not provided[a]
Voderholzer et al[79]	2012	15	Unipolar	34	66	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	53% (27%–79%)	Data not provided[a]
Volk et al[80]	1992	20	Unipolar	48.5	60	Total	Yes	18-item HDRS	30% reduction in baseline HDRS	Day after TSD	55% (32%–77%)	Pre: 26.0 ± 9.9 Post: 21.1 ± 11.7 (18.8%)[b]
Volk et al[81]	1997	15	Mixed	54.9	67	Late partial (TIB unclear)	Yes	18-item HDRS	30% reduction in baseline HDRS	Day after PSD	60% (32%–84%)	Pre: 18.9 ± 5.8 Post: 14.3 ± 6.1 (24.3%)[b]
Wiegand et al[82]	1993	28	Unipolar	48.7	66	Total	No	6-item HDRS	30% reduction in baseline HDRS	Day after TSD	68% (48%–84%)	Data not provided[a]
Wiegand et al[83]	2001	18	Unipolar	45.7	50	Total	Yes	6-item HDRS	50% reduction in baseline HDRS	Day after TSD	72% (47%–90%)	Pre: 13.7 ± 2.9 Post: 5.7 ± 4.4 (58.4%)
Wu et al[84]	1992	15	Unipolar	31.9	80	Total	No	18-item HDRS	40% reduction in baseline HDRS	Day after TSD	27% (8%–55%)	Pre: 20.6 ± 6.6 Post: 13.0 ± 5.8 (36.9%)[b]
Wu et al[85]	1999	36	Unipolar	30.13	69	Total	No	18-item HDRS	40% reduction in baseline HDRS	Day after TSD	33% (19%–51%)	Pre: 23.6 ± 5.7 Post: 14.9 ± 6.0 (36.9%)[b]

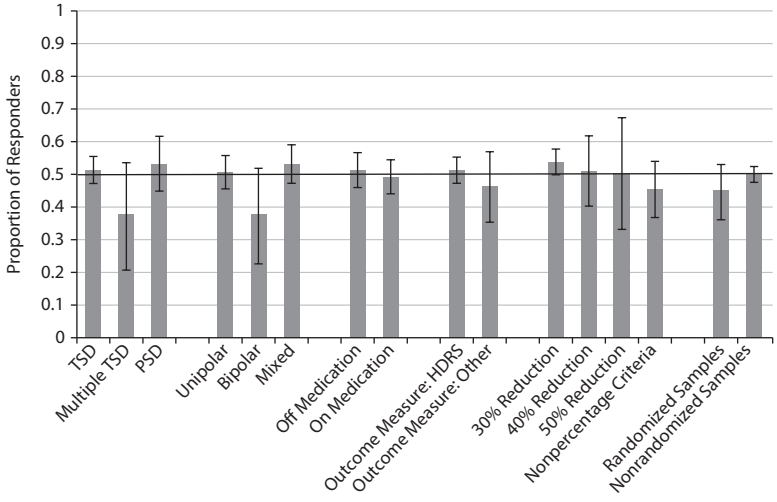
[a]Data provided visually in a figure, but we were unable to calculate exact pre/post means, both pre– and post–sleep deprivation means were not provided, or data were provided only for responders.
[b]Data averaged across groups (eg, phenotypes, genotypes, responders/nonresponders).
[c]Age and gender data available for full sample, but not broken down by respective category (eg, TSD vs PSD; on or off medications).
Abbreviations: AMS = Adjective Mood Scale, BCS = Bonjanovský and Chloupková Scale, Bf-S = Befindlichkeitsskala Depression Scale, BHS = Bunney-Hamburg Scale, BLS = Bjorum and Lindberg Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N/A = not applicable, PSD = partial sleep deprivation, SDDRS = Sleep Deprivation Depression Rating Scale, TIB = time in bed, TSD = total sleep deprivation, VAS = Visual Analog Scale.

Figure 2. Proportion of Responders to Sleep Deprivation[a]



[a]Lines represent 95% confidence intervals. Size of markers indicates weight based on sample size. Diamonds represent random pooled effects.

Figure 3. Proportion of Responders to Sleep Deprivation Across Categories[a]



[a]Bars indicate random effect response rates. Error bars represent 95% confidence intervals.
Abbreviations: PSD = partial sleep deprivation, TSD = total sleep deprivation.

analysis was concerned specifically with the effects of sleep deprivation, we excluded a large number of studies (16) in which chronotherapeutics (eg, sleep phase advance, light therapy) were applied in conjunction with sleep deprivation because we were unable to tease apart the effects of sleep deprivation versus the effects of the additional treatment. The majority of these studies involved bipolar samples and reported response rates from 45% to 79%, much higher than the 37% response rates we obtained in our meta-analyses.[21,86–89] Additionally, of the studies we included that utilized multiple sleep deprivation administrations, 5 of the 7 entries (3 of the 4 studies) included bipolar samples. Given the nearly equivalent response rates between bipolar samples and multiple total sleep deprivation administrations (37.7% and 37.8%, respectively), it is unclear whether the sample type or the method of administration is driving the effect. Among the previously mentioned studies incorporating sleep deprivation and chronotherapeutics, sleep deprivation is often administered multiple times. Thus, taken together, it may be that individuals with bipolar disorder are more likely to benefit from sleep deprivation when it is administered with chronotherapy over a series of administrations, but this cannot be determined based on the currently available literature base.

Our findings provide an updated estimate of the response to sleep deprivation that takes into account the abundance of studies that have been published on sleep deprivation since the last quantitative review was published.[8] Wu and Bunney,[8] as well as several qualitative reviews post 1990 (see references 14 and 20) articulate a 40% to 60% response rate; however, our analyses provide a more precise estimate of 44% to 50%, depending on whether randomized treatment arms are utilized. These comprehensive and in-depth reviews noted patterns across studies suggesting a slight advantage of sleep deprivation for bipolar patients[14] as well as some indication that total sleep deprivation may have a slight advantage over partial sleep deprivation[20]; however, our quantitative analyses indicate equivalent response rates across samples and modalities. However, other qualitative observations are supported by our analyses. The consensus in the field is that medications do not appear to influence the effects of sleep deprivation,[18] which we also found in our analyses. Additionally, our results showed that definition of antidepressant response did not influence response rates. A similar conclusion was drawn in a 2007 report by Clark and Golshan,[90] who found that 30%, 35%, 40%, and 50% cutoff definitions for response could all differentiate responders and nonresponders to partial sleep deprivation, suggesting that sleep deprivation response is an "all or none" phenomenon rather than a continuum of response magnitudes.

Although it is widely held that severity of depression does not influence response to sleep deprivation,[14] we were not able to assess this quantitatively due to the wide variability of depression measures used, both in type of assessment and in number of items utilized (eg, various versions of the HDRS). Improved continuity of depression measurement within the sleep deprivation literature going forward will help pave the way for assessing the influence of depression severity across studies.

Although the mean response rate to sleep deprivation across studies was approximately 50%, there was significant variability in individually reported response rates, ranging from as low as 7% to as high as 78%. The calculated I^2 statistic, a measure of the percentage of variance attributable to study heterogeneity, indicated that approximately 73% and 58% of the variance stemmed from heterogeneity across randomized and nonrandomized studies, respectively. The characteristics we tested as predictors of response quite likely contributed to this high level of heterogeneity, as studies differed considerably in definition of response, type of sleep deprivation applied, and sample characteristics. However, there are likely many other factors that contributed to the heterogeneity that we were not able to examine as they were not systematically reported. It is also likely that the relatively small sample sizes of most of the included studies contributed a substantial portion of this heterogeneity. The mean sample size across studies was approximately 23, and approximately 66% of the studies had sample sizes below this number. Thus, small individual sample sizes very likely contributed to the wide range of response rates. It is possible, however, that other study characteristics not examined in these analyses might explain some of the heterogeneity. For example, there may be particular subtypes of depression or bipolar disorder that are more or less responsive to sleep deprivation. Alternatively, other patient characteristics may influence treatment response. These analyses point to the need for future studies to include more comprehensive assessment of potential

predictors of treatment outcome in order to identify those patients most likely to benefit from sleep deprivation.

This study is not without limitations. We were able to analyze only a small portion of the numerous sleep deprivation studies conducted due to availability of response rate data as well as language restrictions, and considerable heterogeneity across studies limited direct comparisons of categorical variables. Other studies of the antidepressant effects of sleep deprivation did not include sufficient information to be included in these analyses. Our results are limited to published reports only, thus potentially biasing conclusions. Although we provide descriptive data for each study on the percent change in depression ratings, we were unable to generate a meta-analysis of this effect because correlation coefficients of within-person changes in depression scores were not provided in the studies reviewed. Among included studies, an overwhelming majority (91%) did not use control groups. Thus, it is possible that demand characteristics or other psychosocial factors could have influenced outcomes among nonrandomized studies. The inclusion of correlated subgroups from the same studies into the meta-analyses, along with the marked heterogeneity across studies, suggests that the pooled effects should be interpreted with some caution. It is also possible that our nonsignificant meta-regression findings do not indicate equivalent efficacy of sleep deprivation. It is possible that the categorical data we chose to analyze (eg, type of sleep deprivation, use of medications, outcome measures) were not relevant, were overly heterogeneous, and/or represented too small samples sizes to effect significant findings. Additionally, the dichotomization of our covariates may have resulted in null findings. Thus, we have established that there are not significant differences among the variables chosen, but it cannot be ruled out that other variables and/or alternative types of analyses may uncover significant predictors of response. For example, the overwhelming majority of studies failed to report the baseline sleep characteristics of depressed samples. Indeed, it is quite possible that existing insomnia and associated chronic sleep debt may moderate the antidepressant effects of sleep deprivation. Moreover, very few studies reported on objective measures of sleep (eg, degree of deprivation of non-REM vs REM sleep) or on markers of circadian phase, making it difficult to determine if the stage of sleep deprivation and/or altered circadian phase (eg, typically sleeping during the day vs night) affects response to sleep deprivation. Studies also frequently combined depressed patients with longer treatment histories with individuals who had never used antidepressant medication, thus begging the question whether treatment resistance may moderate the antidepressant response to sleep deprivation. Furthermore, given the wide heterogeneity of depression measurement scales (both type of scale and number of items used within scales), we were also unable to examine whether depression severity impacted sleep deprivation response across studies. Finally, this analysis did not analyze claims across studies that sleep following sleep deprivation results in a return of depressive symptomatology.

Sleep deprivation remains one of the most rapid antidepressant treatments, with our analyses showing 50% of patients achieving significant symptom reduction (45% in randomized trials). There has not been widespread adoption of sleep deprivation as a clinical treatment, however, because improvements are typically lost following a subsequent night of sleep. Indeed, research shows that greater than 80% of those who respond to sleep deprivation relapse following a night of sleep.[14] Studies have thus been aimed at researching ways of prolonging the antidepressant effect. As mentioned previously, some literature suggests that combining sleep deprivation with chronotherapeutics is effective in sustaining clinical gains. These interventions include bright light therapy[21,91] and a phase advance[23,92] of the sleep period. A recent meta-analysis of the effects of light therapy both alone and in conjunction with sleep deprivation suggests that light therapy is effective in improving severity of illness in individuals with bipolar disorder[93]; however, to our knowledge, no meta-analysis has been conducted on the efficacy of light therapy or phase advance in unipolar depressed subjects.

Our overall meta-analysis revealed that approximately 50% of 1,593 participants (45% of 141 participants in randomized trials) evaluated in 66 separate published studies over a 36-year period had a positive affective response to sleep deprivation (Figure 2) and that, other than possibly older age, no demographic or outcome characterization influenced this result. Variability among studies notwithstanding, the stability of this finding across decades and laboratories suggests that the response to sleep deprivation in depressed individuals may be phenotypic, which has not been given adequate consideration. To determine whether this is the case, one would ideally study sleep deprivation in depressed individuals at least 2 or more times, utilizing intraclass correlations to establish the degree of phenotypic (stable within-subject) variability in response. To our knowledge, such a study has not yet been reported. However, the likelihood that the antidepressant response to sleep deprivation may be phenotypic is suggested by studies on the highly phenotypic nature of neurobehavioral responses to both acute total sleep deprivation and chronic partial sleep deprivation in healthy individuals (see reference 94 for an overview). These phenotypic responses include psychomotor vigilance performance and cognitive processing throughput,[95] which are very sensitive to sleep loss,[96] physiological sleep propensity,[97] and energy balance responses.[98] The high intraclass correlations consistently found for neurobehavioral responses to sleep deprivation (both acute total sleep deprivation and chronic partial sleep deprivation) suggest that these phenotypic differences may include genetic components[94,95,99,100] and be targets for biomarkers.[101–103]

Finally, the mechanisms through which sleep deprivation exerts its antidepressant effects have been the focus of more recent examinations (see references 14 and 104 for thorough, comprehensive reviews of this important work); however, a consensus has yet to identify a single mechanism of action. For example, Bunney and Bunney[104]

suggest that the antidepressant effect of sleep deprivation is manifested through a "reset" of the body's circadian rhythms, specifically via CLOCK gene transcription. This line of research is supported by work demonstrating that chronotherapeutics (eg, phase advance, light therapy) are often effective in extending the antidepressant effects of sleep deprivation.[91,92] Still other studies of neurobiological correlates of sleep deprivation target specific brain regions (eg, medial prefrontal cortex, ventral anterior cingulate cortex)[48,50,80,83,84] and specific neurotransmitter systems (eg, dopaminergic system)[50] as playing important roles in the antidepressant response to sleep deprivation. It is difficult to synthesize the mechanistic literature because of the heterogeneity of biomarkers or neuroimaging methods assessed. Our analyses failed to bring to light evidence that would bring greater clarity to these mechanisms, however; thus, it is clear that more work needs to be done to identify precisely how sleep deprivation brings about such rapid and significant reductions in depression severity. Multimodal neuroimaging has been successfully used to demonstrate changes in brain function underlying the effects of acute sleep deprivation in healthy subjects,[105–108] and these same paradigms can readily be applied to patients with depression. There are also tremendous opportunities to further biomarker approaches such as neuroimaging, metabolomics, and genomics to differentiate responders from nonresponders. As mentioned, there has been some work in this area (eg, references 40 and 109–113); however, more work can be done to further elucidate the neural substrates of depression, to help disentangle the wide heterogeneity of symptom presentation and treatment response in depression, and to contribute to the development of new strategies to leverage sleep deprivation or related neuromodulatory interventions to improve treatment specificity and outcomes.

The availability of an antidepressant treatment that has rapid effects in 50% of patients would mark a radical improvement in clinical practice, *if* we can find ways to maintain the effects over time. Researchers have focused on sustaining the often ephemeral effects of sleep deprivation, either with multiple administrations of total sleep deprivation or partial sleep deprivation for example; however, more work needs to be done to bring the field to more of a consensus as to how best to apply such administrations. As Hemmeter et al[14] note in their review of studies of repeated administrations of sleep deprivation, how a depressed individual responds clinically to a single administration of sleep deprivation is not often predictive of how that individual will respond to subsequent administrations. Indeed, temporal trends either have not been observed or have been contradictory, demonstrating both increased as well as decreased response to subsequent sleep deprivation trials. This is yet another area in which studies that focus on phenotypic response to sleep deprivation can benefit the field, such that more refined and personalized sleep deprivation administration recommendations can be applied in clinical practice. When these phenotypic studies incorporate full descriptions of the levels of baseline sleep disturbance among participants, it may also further our knowledge of the antidepressant response to Cognitive Behavioral Therapy for Insomnia (CBT-I), an intervention that has shown some efficacy as an adjunctive depression treatment for individuals with depression and insomnia.[114,115] CBT-I includes a therapeutic sleep restriction component that limits time in bed to no less than 5 hours; however, the neurobiological mechanism of action leading to antidepressant effects is not understood. Assessing the level of baseline sleep disturbance in sleep deprivation as well as phenotypic response to total sleep deprivation, partial sleep deprivation, and CBT-I may help uncover important mechanisms of action of both sleep deprivation and restriction and enable providers to improve treatment matching practices.

Submitted: November 8, 2016; accepted February 24, 2017.

Published online: September 19, 2017.

Potential conflicts of interest: The authors report no conflicts of interest.

Funding/support: Analysis, data collection and interpretation, manuscript review and preparation supported by Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs (Dr Boland); National Institutes of Health (NIH) grants R01 HL102119 and P30 NS045839 (Dr Rao), R01 MH107571 (Drs Rao, Dinges, Thase, and Gehrman), R01MH098260 (Dr Sheline), and P41 EB015893 and R01 MH080729 (Dr Detre); National Aeronautics and Space Administration (NASA) (grants NNX15AK76A, NBPF02701, NNX08AY09G, NBPF03401, NBPF02501, NNX14AM81G, NNX16AI53G); National Heart, Lung, and Brain Institute (U01 HL125388); National Institute on Drug Abuse (1 R21 DA040902-01A1); the Office of Naval Research N00014-11-1-0361 and the National Aeronautics and Space Administration NNX14AN49G (Dr Goel); National Space Biomedical Research Institute (NSBRI) through NASA NCC 9-58 (Dr Basner); and grant support from Merck and Philips Healthcare/Respironics.

Role of the sponsor: None.

Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect the views of the United States Government.

REFERENCES

1. Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry*. 2010;67(12):1265–1273.
2. Gelenberg AJ, Chesen CL. How fast are antidepressants? *J Clin Psychiatry*. 2000;61(10):712–721.
3. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand*. 2002;105(3):164–172.
4. Wirz-Justice A, Van den Hoofdakker RH. Sleep deprivation in depression: what do we know, where do we go? *Biol Psychiatry*. 1999;46(4):445–453.
5. Steinberg H, Hegerl U. Johann Christian August Heinroth on sleep deprivation as a therapeutic option for depressive disorders. *Sleep Med*. 2014;15(9):1159–1164.
6. Schulte W. Kombinierte Psycho-und Pharmakotherapie bei Melancholikern. In: *Probleme der pharmakopsychiatrischen Kombinations-und Langzeitbehandlung*. Basel, Switzerland: Karger Publishers; 1966:150–169.
7. Pflug B, Tölle R. Therapy of endogenous depressions using sleep deprivation: practical and theoretical consequences [in German]. *Nervenarzt*. 1971;42(3):117–124.
8. Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am J Psychiatry*. 1990;147(1):14–21.
9. Larsen JK, Lindberg ML, Skovgaard B. Sleep deprivation as treatment for endogenous depression. *Acta Psychiatr Scand*. 1976;54(3):167–173.
10. Post RM, Kotin J, Goodwin FK. Effects of sleep deprivation on mood and central amine metabolism in depressed patients. *Arch Gen Psychiatry*. 1976;33(5):627–632.
11. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
12. Schilgen B, Tölle R. Partial sleep deprivation as therapy for depression. *Arch Gen Psychiatry*. 1980;37(3):267–271.
13. Baghai TC, Schule C, Zwanzger P, et al. Influence of a functional polymorphism within the angiotensin I-converting enzyme gene on partial sleep deprivation in patients with major depression. *Neurosci Lett*. 2003;339(3):223–226.
14. Hemmeter UM, Hemmeter-Spernal J, Krieg JC.

Sleep deprivation in depression. *Expert Rev Neurother*. 2010;10(7):1101–1115.
15. Benedetti F, Colombo C, Barbini B, et al. Ongoing lithium treatment prevents relapse after total sleep deprivation. *J Clin Psychopharmacol*. 1999;19(3):240–245.
16. Smeraldi E, Benedetti F, Barbini B, et al. Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression: a placebo-controlled trial. *Neuropsychopharmacology*. 1999;20(4):380–385.
17. van den Burg W, Bouhuys AL, van den Hoofdakker RH, et al. Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder. *J Affect Disord*. 1990;19(2):109–117.
18. Kuhs H, Färber D, Borgstädt S, et al. Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression: a randomised study. *J Affect Disord*. 1996;37(1):31–41.
19. Colombo C, Benedetti F, Barbini B, et al. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res*. 1999;86(3):267–270.
20. Giedke H, Schwärzler F. Therapeutic use of sleep deprivation in depression. *Sleep Med Rev*. 2002;6(5):361–377.
21. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry*. 2005;66(12):1535–1540.
22. Schüle C, di Michele F, Baghai T, et al. Influence of sleep deprivation on neuroactive steroids in major depression. *Neuropsychopharmacology*. 2003;28(3):577–581.
23. Riemann D, König A, Hohagen F, et al. How to preserve the antidepressive effect of sleep deprivation: a comparison of sleep phase advance and sleep phase delay. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(5):231–237.
24. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
25. von Zerssen D, Koeller DM. *Klinische Selbstbeurteilungsskalen (KSb-S) aus dem Münchener Psychiatrischen Informations-system (PSYCHIS München). Manuale*. Weinheim, Germany: Beltz Test; 1976.
26. Bonjanovský J, Chloupková K. Bewertungsskala der Depressionszustände. *Eur Neurol*. 1966;151:54–61.
27. Bunney WE Jr, Hamburg DA. Methods for reliable longitudinal observation of behavior. *Arch Gen Psychiatry*. 1963;9:280–294.
28. Orth DN, Shelton RC, Nicholson WE, et al. Serum thyrotropin concentrations and bioactivity during sleep deprivation in depression. *Arch Gen Psychiatry*. 2001;58(1):77–83.
29. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11(2):193–206.
30. Benedetti F, Campori E, Barbini B, et al. Dopaminergic augmentation of sleep deprivation effects in bipolar depression. *Psychiatry Res*. 2001;104(3):239–246.
31. Elsenga S, van den Hoofdakker RH. Clinical effects of sleep deprivation and clomipramine in endogenous depression. *J Psychiatr Res*. 1982-1983;17(4):361–374.
32. Reynolds CF 3rd, Smith GS, Dew MA, et al. Accelerating symptom-reduction in late-life depression: a double-blind, randomized, placebo-controlled trial of sleep deprivation. *Am J Geriatr Psychiatry*. 2005;13(5):353–358.
33. Smith GS, Reynolds CF 3rd, Houck PR, et al. Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression: a randomized, placebo-controlled study. *Psychiatry Res*. 2009;171(1):1–9.
34. Giedke H, Klingberg S, Schwärzler F, et al. Direct comparison of total sleep deprivation and late partial sleep deprivation in the treatment of major depression. *J Affect Disord*. 2003;76(1–3):85–93.
35. Szuba MP, Baxter LR Jr, Altshuler LL, et al. Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. *Psychiatry Res*. 1994;51(3):283–295.
36. Holsboer-Trachsler E, Hemmeter U, Hatzinger M, et al. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment—neurobiological and psychometric assessment of course. *J Psychiatr Res*. 1994;28(4):381–399.
37. Caliyurt O, Guducu F. Partial sleep deprivation therapy combined with sertraline induces more rapid improvements in quality of life items in major depressive disorder. *J Affect Disord*. 2005;88(1):75–78.
38. Baumgartner A, Riemann D, Berger M. Neuroendocrinological investigations during sleep deprivation in depression, II: longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. *Biol Psychiatry*. 1990;28(7):569–587.
39. Beck J, Hemmeter U, Brand S, et al. Modafinil reduces microsleep during partial sleep deprivation in depressed patients. *J Psychiatr Res*. 2010;44(13):853–864.
40. Benedetti F, Barbini B, Bernasconi A, et al. Serotonin 5-HT2A receptor gene variants influence antidepressant response to repeated total sleep deprivation in bipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(8):1863–1866.
41. Bernier D, Bartha R, Devarajan S, et al. Effects of overnight sleep restriction on brain chemistry and mood in women with unipolar depression and healthy controls. *J Psychiatry Neurosci*. 2009;34(5):352–360.
42. Bouhuys AL, Beersma DGM, van den Hoofdakker RH. Observed behavior as a predictor of the response to sleep deprivation in depressed patients. *Psychiatry Res*. 1989;28(1):47–61.
43. Bouhuys AL, Flentge F, Van den Hoofdakker RH. Effects of total sleep deprivation on urinary cortisol, self-rated arousal, and mood in depressed patients. *Psychiatry Res*. 1990;34(2):149–162.
44. Bouhuys AL, van den Burg W, van den Hoofdakker RH. The relationship between tiredness prior to sleep deprivation and the antidepressant response to sleep deprivation in depression. *Biol Psychiatry*. 1995;37(7):457–461.
45. Brückner TU, Wiegand MH. Motor activity in depressed patients during therapeutic sleep deprivation. *Eur Psychiatry*. 2010;25(8):465–467.
46. Clark CP, Brown GG, Archibald SL, et al. Does amygdalar perfusion correlate with antidepressant response to partial sleep deprivation in major depression? *Psychiatry Res*. 2006;146(1):43–51.
47. Danos P, Kasper S, Scholl HP, et al. Clinical response to sleep deprivation and auditory-evoked potentials—preliminary results. *Pharmacopsychiatry*. 1994;27(2):70–71.
48. Ebert D, Feistel H, Barocka A. Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99m-HMPAO SPECT. *Psychiatry Res*. 1991;40(4):247–251.
49. Ebert D, Kaschka W, Stegbauer P, et al. Prolactin response to sulpiride before and after sleep deprivation in depression. *Biol Psychiatry*. 1993;33(8–9):666–669.
50. Ebert D, Feistel H, Kaschka W, et al. Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation—preliminary results. *Biol Psychiatry*. 1994;35(11):880–885.
51. Ebert D, Feistel H, Barocka A, et al. Increased limbic blood flow and total sleep deprivation in major depression with melancholia. *Psychiatry Res*. 1994;55(2):101–109.
52. Ebert D, Albert R, Hammon G, et al. Eye-blink rates and depression: is the antidepressant effect of sleep deprivation mediated by the dopamine system? *Neuropsychopharmacology*. 1996;15(4):332–339.
53. Elsenga S, Van den Hoofdakker RH. Body core temperature and depression during total sleep deprivation in depressives. *Biol Psychiatry*. 1988;24(5):531–540.
54. Fritzsche M, Heller R, Hill H, et al. Sleep deprivation as a predictor of response to light therapy in major depression. *J Affect Disord*. 2001;62(3):207–215.
55. Gerner RH, Post RM, Gillin JC, et al. Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J Psychiatr Res*. 1979;15(1):21–40.
56. Gillin JC, Kripke DF, Janowsky DS, et al. Effects of brief naps on mood and sleep in sleep-deprived depressed patients. *Psychiatry Res*. 1989;27(3):253–265.
57. Hemmeter U, Hatzinger M, Brand S, et al. Effect of flumazenil-augmentation on microsleep and mood in depressed patients during partial sleep deprivation. *J Psychiatr Res*. 2007;41(10):876–884.
58. Hernandez CR, Smith GS, Houck PR, et al. The clinical response to total sleep deprivation and recovery sleep in geriatric depression: potential indicators of antidepressant treatment outcome. *Psychiatry Res*. 2000;97(1):41–49.
59. Höchli D, Riemann D, Zulley J, et al. Is there a relationship between response to total sleep deprivation and efficacy of clomipramine treatment in depressed patients? *Acta Psychiatr Scand*. 1986;74(2):190–192.
60. Kaschka WP, Flügel O, Negele-Anetsberger J, et al. Total sleep deprivation and thyroid function in depression. *Psychiatry Res*. 1989;29(2):231–234.
61. Kasper S, Sack DA, Wehr TA, et al. Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. *Biol Psychiatry*. 1988;24(6):631–641.
62. Kasper S, Voll G, Vieira A, et al. Response to total sleep deprivation before and during treatment with fluvoxamine or maprotiline in patients with major depression—results of a double-blind study. *Pharmacopsychiatry*. 1990;23(3):135–142.
63. Kuhs H. Dexamethasone suppression test and sleep deprivation in endogenous depression. *J Affect Disord*. 1985;9(2):121–126.
64. Müller HU, Riemann D, Berger M, et al. The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. *Acta Psychiatr Scand*. 1993;88(1):16–20.
65. Neumeister A, Goessler R, Lucht M, et al. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol*

Psychiatry. 1996;39(1):16–21.
66. Neumeister A, Praschak-Rieder N, Hesselmann B, et al. Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. *Arch Gen Psychiatry*. 1998;55(2):167–172.
67. Parekh PI, Ketter TA, Altshuler L, et al. Relationships between thyroid hormone and antidepressant responses to total sleep deprivation in mood disorder patients. *Biol Psychiatry*. 1998;43(5):392–394.
68. Reist C, Chen CC, Chhoeu A, et al. Effects of sleep on the antidepressant response to sleep deprivation. *Biol Psychiatry*. 1994;35(10):794–797.
69. Reynolds CF 3rd, Kupfer DJ, Hoch CC, et al. Sleep deprivation effects in older endogenous depressed patients. *Psychiatry Res*. 1987;21(2):95–109.
70. Riemann D, Berger M. The effects of total sleep deprivation and subsequent treatment with clomipramine on depressive symptoms and sleep electroencephalography in patients with a major depressive disorder. *Acta Psychiatr Scand*. 1990;81(1):24–31.
71. Riemann D, Wiegand M, Berger M. Are there predictors for sleep deprivation response in depressed patients? *Biol Psychiatry*. 1991;29(7):707–710.
72. Riemann D, Wiegand M, Lauer CJ, et al. Naps after total sleep deprivation in depressed patients: are they depressiogenic? *Psychiatry Res*. 1993;49(2):109–120.
73. Roy-Byrne P, Uhde TW, Post RM, et al. Relationship of response to sleep deprivation and carbamazepine in depressed patients. *Acta Psychiatr Scand*. 1984;69(5):379–382.
74. Salomon RM, Delgado PL, Licinio J, et al. Effects of sleep deprivation on serotonin function in depression. *Biol Psychiatry*. 1994;36(12):840–846.
75. Schüle C, Baghai T, Zwanzger P, et al. Sleep deprivation and hypothalamic-pituitary-adrenal (HPA) axis activity in depressed patients. *J Psychiatr Res*. 2001;35(4):239–247.
76. Schumann G, Benedetti F, Voderholzer U, et al. Antidepressive response to sleep deprivation in unipolar depression is not associated with dopamine D3 receptor genotype. *Neuropsychobiology*. 2001;43(3):127–130.
77. Shelton RC, Loosen PT. Sleep deprivation accelerates the response to nortriptyline. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17(1):113–123.
78. Sokolski KN, Reist C, Chen CC, et al. Antidepressant responses and changes in visual adaptation after sleep deprivation. *Psychiatry Res*. 1995;57(3):197–207.
79. Voderholzer U, Fiebich BL, Dersch R, et al. Effects of sleep deprivation on nocturnal cytokine concentrations in depressed patients and healthy control subjects. *J Neuropsychiatry Clin Neurosci*. 2012;24(3):354–366.
80. Volk S, Kaendler SH, Weber R, et al. Evaluation of the effects of total sleep deprivation on cerebral blood flow using single photon emission computerized tomography. *Acta Psychiatr Scand*. 1992;86(6):478–483.
81. Volk SA, Kaendler SH, Hertel A, et al. Can response to partial sleep deprivation in depressed patients be predicted by regional changes of cerebral blood flow? *Psychiatry Res*. 1997;75(2):67–74.
82. Wiegand M, Riemann D, Schreiber W, et al. Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. *Biol Psychiatry*. 1993;33(6):467–476.
83. Wiegand MH, Lauer CJ, Schreiber W. Patterns of response to repeated total sleep deprivations in depression. *J Affect Disord*. 2001;64(2–3):257–260.
84. Wu JC, Gillin JC, Buchsbaum MS, et al. Effect of sleep deprivation on brain metabolism of depressed patients. *Am J Psychiatry*. 1992;149(4):538–543.
85. Wu J, Buchsbaum MS, Gillin JC, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*. 1999;156(8):1149–1158.
86. Benedetti F, Dallaspezia S, Fulgosi MC, et al. Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol Int*. 2007;24(5):921–937.
87. Benedetti F, Calabrese G, Bernasconi A, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. *Psychiatry Res*. 2009;173(3):238–242.
88. Benedetti F, Riccaboni R, Locatelli C, et al. Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. *J Clin Psychiatry*. 2014;75(2):133–140.
89. Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry*. 2009;66(3):298–301.
90. Clark CP, Golshan S. Polysomnography and criteria for the antidepressant response to sleep deprivation. *J Affect Disord*. 2007;101(1–3):195–200.
91. Colombo C, Lucca A, Benedetti F, et al. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res*. 2000;95(1):43–53.
92. Berger M, Vollmann J, Hohagen F, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *Am J Psychiatry*. 1997;154(6):870–872.
93. Tseng PT, Chen YW, Tu KY, et al. Light therapy in the treatment of patients with bipolar depression: a meta-analytic study. *Eur Neuropsychopharmacol*. 2016;26(6):1037–1047.
94. Basner M, Rao H, Goel N, et al. Sleep deprivation and neurobehavioral dynamics. *Curr Opin Neurobiol*. 2013;23(5):854–863.
95. Van Dongen HPA, Baynard MD, Maislin G, et al. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep*. 2004;27(3):423–433.
96. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull*. 2010;136(3):375–389.
97. Banks S, Van Dongen HPA, Maislin G, et al. Neurobehavioral dynamics following chronic sleep restriction: dose-response effects of one night for recovery. *Sleep*. 2010;33(8):1013–1026.
98. Spaeth AM, Dinges DF, Goel N. Phenotypic vulnerability of energy balance responses to sleep loss in healthy adults. *Sci Rep*. 2015;5:14920.
99. Goel N, Banks S, Mignot E, et al. DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue. *Neurology*. 2010;75(17):1509–1519.
100. Kuna ST, Maislin G, Pack FM, et al. Heritability of performance deficit accumulation during acute sleep deprivation in twins. *Sleep*. 2012;35(9):1223–1233.
101. Goel N. "Omics" approaches for sleep and circadian rhythm research: biomarkers for identifying differential vulnerability to sleep loss. *Curr Sleep Med Rep*. 2015;1:38–46.
102. Weljie AM, Meerlo P, Goel N, et al. Oxalic acid and diacylglycerol 36:3 are cross-species markers of sleep debt. *Proc Natl Acad Sci U S A*. 2015;112(8):2569–2574.
103. Mullington JM, Abbott SM, Carroll JE, et al. Developing biomarker arrays predicting sleep and circadian-coupled risks to health. *Sleep*. 2016;39(4):727–736.
104. Bunney BG, Bunney WE. Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms. *Biol Psychiatry*. 2013;73(12):1164–1171.
105. Ma N, Dinges DF, Basner M, et al. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. *Sleep*. 2015;38(2):233–240.
106. Chee MW, Tan JC. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. *Neuroimage*. 2010;51(2):835–843.
107. Chee MW, Tan JC, Zheng H, et al. Lapsing during sleep deprivation is associated with distributed changes in brain activation. *J Neurosci*. 2008;28(21):5519–5528.
108. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness, I: effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res*. 2000;9(4):335–352.
109. Benedetti F, Serretti A, Colombo C, et al. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am J Psychiatry*. 1999;156(9):1450–1452.
110. Benedetti F, Colombo C, Serretti A, et al. Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry*. 2003;54(7):687–692.
111. Benedetti F, Dallaspezia S, Lorenzi C, et al. Gene-gene interaction of glycogen synthase kinase 3-β and serotonin transporter on human antidepressant response to sleep deprivation. *J Affect Disord*. 2012;136(3):514–519.
112. Dallaspezia S, Locatelli C, Lorenzi C, et al. Sleep homeostatic pressure and PER3 VNTR gene polymorphism influence antidepressant response to sleep deprivation in bipolar depression. *J Affect Disord*. 2016;192:64–69.
113. Wolf E, Kuhn M, Normann C, et al. Synaptic plasticity model of therapeutic sleep deprivation in major depression. *Sleep Med Rev*. 2016;30:53–62.
114. Taylor DJ, Lichstein KL, Weinstock J, et al. A pilot study of cognitive-behavioral therapy of insomnia in people with mild depression. *Behav Ther*. 2007;38(1):49–57.
115. Manber R, Edinger JD, Gress JL, et al. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep*. 2008;31(4):489–495.