Meta-Analysis of the Antidepressant Effects of Acute Sleep Deprivation

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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.

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Antidepressant medication is typically reported as the most common treatment strategy for depression. However, antidepressant effects are slow to manifest, often taking several weeks to yield clinical improvement. Moreover, early clinical improvement plays a key role in stable long-term treatment outcomes, 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. The first reported in 1818 by German psychiatrist Johann Christian August Heinroth, 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. This report was followed several years later by the first trial of sleep deprivation for endogenous depression and then by nearly 2 decades of focused research aimed at understanding and prolonging this rapid treatment response. Wu and Bunney 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 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. Studies of partial sleep deprivation prior to 1990 yielded mixed results. 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. As a means of attempting to prolong the effects of sleep deprivation, studies have also employed repeated administrations of both total sleep deprivation and partial sleep deprivation. Findings have been mixed, however, with reported increases and decreases in responding to repeated applications of sleep deprivation.
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,\(^{14}\) with slightly better results for total sleep deprivation,\(^{14}\) 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...
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 (MADRS22; n = 2), the Adjective Mood Scale (AMS25; n = 3), the Bonjanovský and Chloupková Depression Rating Scale26 (n = 1), the Bunney-Hamburg Scale27 (n = 1), the Sleep Deprivation Rating Scale28 (n = 1), the Bjorum and Lindberg Scale9 (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,
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 studies15,16,30–33 reported response rates on both medicated and nonmedicated patients; 1 study34 compared groups of total sleep deprivation and partial sleep deprivation responders; and 1 study35 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Sample Type</th>
<th>Mean Age, y</th>
<th>% Female</th>
<th>Type of Sleep Deprivation</th>
<th>Medication (yes/no)</th>
<th>Outcome Measure</th>
<th>Proportion Responders (95% CI)</th>
<th>Timing of Depression Measurement</th>
<th>Proportion Responders (95% CI)</th>
<th>Mean Pre/Post Depression Scores ± SD (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies Utilizing a Randomized Non–Sleep Deprivation Control Group</strong></td>
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<tr>
<td>Elsenga and van den Hoofdakker31</td>
<td>1983</td>
<td>10</td>
<td>Unipolar</td>
<td>49.1</td>
<td>88</td>
<td>Total</td>
<td>Yes</td>
<td>5-item HDRS</td>
<td>≥ 6 point reduction</td>
<td>Day after TSD</td>
<td>40% (12%–74%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Holsboer-Trachsler et al36</td>
<td>1994</td>
<td>14</td>
<td>Mixed</td>
<td>50.43</td>
<td>43</td>
<td>Multiple late PSD</td>
<td>Yes</td>
<td>17-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>6 weeks after final PSD</td>
<td>43% (18%–71%)</td>
<td>Pre: 23.0 ± 3.7 Post: 14.0 ± 8.6 (39.1%)</td>
</tr>
<tr>
<td>Kuhs et al18</td>
<td>1996</td>
<td>27</td>
<td>Mixed</td>
<td>43.3</td>
<td>41</td>
<td>Multiple late PSD</td>
<td>Yes</td>
<td>10-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>2 weeks after final PSD</td>
<td>67% (46%–83%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Calliurt and Guducu37</td>
<td>2005</td>
<td>13</td>
<td>Unipolar</td>
<td>38.46</td>
<td>79</td>
<td>Late partial (4h TIB)</td>
<td>Yes</td>
<td>21-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>92% (63%–100%)</td>
<td>Means not provided: reports 85.81% decrease in HDRS scores</td>
</tr>
<tr>
<td>Reynolds et al32</td>
<td>2005</td>
<td>27</td>
<td>Unipolar</td>
<td>70.6</td>
<td>70</td>
<td>Total</td>
<td>Yes</td>
<td>13-item HDRS</td>
<td>HDRS ≤ 10</td>
<td>Day after TSD</td>
<td>22% (9%–42%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Reynolds et al32</td>
<td>2005</td>
<td>27</td>
<td>Unipolar</td>
<td>71.4</td>
<td>70</td>
<td>Total</td>
<td>No</td>
<td>13-item HDRS</td>
<td>HDRS ≤ 10</td>
<td>Day after TSD</td>
<td>41% (22%–61%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Smith et al33</td>
<td>2009</td>
<td>7</td>
<td>Unipolar</td>
<td>68.8</td>
<td>100</td>
<td>Total</td>
<td>Yes</td>
<td>13-item HDRS</td>
<td>HDRS ≤ 10</td>
<td>Day after TSD</td>
<td>40% (32%–49%)</td>
<td>Pre: 15.7 ± 3.6 Post: 13.6 ± 4.2 (13.4%)</td>
</tr>
<tr>
<td>Smith et al33</td>
<td>2009</td>
<td>6</td>
<td>Unipolar</td>
<td>68.8</td>
<td>50</td>
<td>Total</td>
<td>No</td>
<td>13-item HDRS</td>
<td>HDRS ≤ 10</td>
<td>Day after TSD</td>
<td>39% (27%–51%)</td>
<td>Pre: 16.3 ± 4.8 Post: 13.0 ± 5.4 (20.3%)</td>
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<td><strong>Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group</strong></td>
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<tr>
<td>Baghai et al13</td>
<td>2003</td>
<td>56</td>
<td>Unipolar</td>
<td>49.2</td>
<td>66</td>
<td>Late partial (TIB unclear)</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>64% (50%–77%)</td>
<td>Pre: 11.6 ± 0.9 Post: 7.1 ± 1.1 (38.7%)</td>
</tr>
<tr>
<td>Baumgartner et al13</td>
<td>1990</td>
<td>14</td>
<td>Mixed</td>
<td>39.7</td>
<td>64</td>
<td>Total</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (23%–77%)</td>
<td>Pre: 11.0 ± 3.6 Post: 8.0 ± 6.3 (27.3%)</td>
</tr>
<tr>
<td>Beck et al19</td>
<td>2010</td>
<td>14</td>
<td>Unipolar</td>
<td>46.2</td>
<td>43</td>
<td>Late partial (TIB unclear)</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>50% (23%–77%)</td>
<td>Pre: 21.8 ± 4.7 Post: 12.6 ± 8.4 (42.2%)</td>
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<tr>
<td>Beck et al19</td>
<td>2010</td>
<td>14</td>
<td>Unipolar</td>
<td>43.9</td>
<td>64</td>
<td>Late partial (TIB unclear)</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>43% (18%–71%)</td>
<td>Pre: 21.7 ± 6.6 Post: 15.7 ± 9.1 (27.6%)</td>
</tr>
<tr>
<td>Benedetti et al15</td>
<td>1999</td>
<td>20</td>
<td>Bipolar</td>
<td>48.2</td>
<td>60</td>
<td>Multiple TSD administrations</td>
<td>Yes</td>
<td>21-item HDRS</td>
<td>HDRS score &lt; 8</td>
<td>5 days after final TSD</td>
<td>50% (27%–73%)</td>
<td>Pre: 23.4 ± 3.3 Post: 8.3 ± 2.2 (63.9%)</td>
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<td>Benedetti et al15</td>
<td>1999</td>
<td>20</td>
<td>Bipolar</td>
<td>48.35</td>
<td>70</td>
<td>Multiple TSD administrations</td>
<td>No</td>
<td>21-item HDRS</td>
<td>HDRS score &lt; 8</td>
<td>5 days after final TSD</td>
<td>25% (9%–49%)</td>
<td>Pre: 26.0 ± 4.9 Post: 14.3 ± 7.9 (45%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Sample Type</th>
<th>Mean Age, y</th>
<th>% Female</th>
<th>Type of Sleep Deprivation</th>
<th>Medication (yes/no)</th>
<th>Outcome Measure</th>
<th>Response Criteria</th>
<th>Timing of Depression Measurement</th>
<th>Proportion Responders (95% CI)</th>
<th>Mean Pre/Post Depression Scores ± SD (% change)</th>
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<tbody>
<tr>
<td><strong>Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group</strong></td>
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<tr>
<td>Benedetti et al³⁰</td>
<td>2001</td>
<td>13</td>
<td>Bipolar</td>
<td>N/A⁵</td>
<td>N/A⁶</td>
<td>Multiple TSD administrations</td>
<td>Yes</td>
<td>MADRS</td>
<td>MADRS score &lt; 6</td>
<td>2 days after final TSD</td>
<td>38% (14%–68%)</td>
<td>Pre: 30.5 ± 4.4 Post: 13.5 ± 11.9 (35.8%)</td>
</tr>
<tr>
<td>Benedetti et al³⁰</td>
<td>2001</td>
<td>14</td>
<td>Bipolar</td>
<td>N/A⁵</td>
<td>N/A⁶</td>
<td>Multiple TSD administrations</td>
<td>No</td>
<td>MADRS</td>
<td>MADRS score &lt; 6</td>
<td>2 days after final TSD</td>
<td>7% (&lt;1%–34%)</td>
<td>Pre: 30.3 ± 6.4 Post: 17.7 ± 9.5 (41.5%)</td>
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<tr>
<td>Benedetti et al³⁰</td>
<td>2008</td>
<td>80</td>
<td>Bipolar</td>
<td>46.86</td>
<td>66</td>
<td>Multiple TSD administrations</td>
<td>Yes</td>
<td>17-item HDRS</td>
<td>HDRS score &lt; 8</td>
<td>2 days after final TSD</td>
<td>53% (41%–64%)</td>
<td>Pre: 21.0 ± 4.0 Post: 8.9 ± 7.6 (41.5%)⁷</td>
</tr>
<tr>
<td>Bernier et al⁴¹</td>
<td>2009</td>
<td>11</td>
<td>Unipolar</td>
<td>22.91</td>
<td>100</td>
<td>Late partial (2.5 h TIB)</td>
<td>Yes</td>
<td>17-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>45% (17%–77%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Bouhuys et al⁴²</td>
<td>1989</td>
<td>17</td>
<td>Unipolar</td>
<td>49.10</td>
<td>88</td>
<td>Total</td>
<td>No</td>
<td>AMS</td>
<td>5-point reduction</td>
<td>Day after TSD</td>
<td>44% (20%–70%)</td>
<td>Data not provided⁸</td>
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<td>Bouhuys et al⁴³</td>
<td>1990</td>
<td>16</td>
<td>Mixed</td>
<td>45.1</td>
<td>75</td>
<td>Total</td>
<td>No</td>
<td>AMS</td>
<td>5-point reduction</td>
<td>Day after TSD</td>
<td>40% (28%–52%)</td>
<td>Data not provided⁹</td>
</tr>
<tr>
<td>Brückner and Wiegand⁴⁵</td>
<td>2010</td>
<td>34</td>
<td>Mixed</td>
<td>50</td>
<td>53</td>
<td>Total</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>56% (38%–73%)</td>
<td>Pre: 40.7 ± 11.9 Post: 35.1 ± 14.0 (13.7%)</td>
</tr>
<tr>
<td>Clark et al⁴⁶</td>
<td>2006</td>
<td>17</td>
<td>Unipolar</td>
<td>42.8</td>
<td>58</td>
<td>Late partial (TIB unclear)</td>
<td>No</td>
<td>17-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>29% (10%–56%)</td>
<td>Pre: 16.0 ± 3.2 Post: 10.5 ± 3.1 (34.5%)⁹</td>
</tr>
<tr>
<td>Danos et al⁴⁷</td>
<td>1994</td>
<td>17</td>
<td>Unipolar</td>
<td>48.3</td>
<td>100</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>53% (28%–77%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Ebert et al⁴⁸</td>
<td>1991</td>
<td>10</td>
<td>Unipolar</td>
<td>38.9</td>
<td>50</td>
<td>Total</td>
<td>No</td>
<td>18-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (19%–81%)</td>
<td>Data not provided⁹</td>
</tr>
<tr>
<td>Ebert et al⁴⁹</td>
<td>1993</td>
<td>14</td>
<td>Unipolar</td>
<td>36.3</td>
<td>0</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>57% (29%–82%)</td>
<td>Data not provided⁹</td>
</tr>
<tr>
<td>Ebert et al⁵⁰</td>
<td>1994</td>
<td>10</td>
<td>Bipolar</td>
<td>33.4</td>
<td>0</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (19%–81%)</td>
<td>Pre: 22.5 ± 4.0 Post: 13.0 ± 2.7 (42.3%)⁹</td>
</tr>
<tr>
<td>Ebert et al⁵¹</td>
<td>1994</td>
<td>20</td>
<td>Bipolar</td>
<td>40</td>
<td>0</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>55% (32%–77%)</td>
<td>Pre: 28.2 ± 2.2 Post: 21.5 ± 2.1 (23.8%)⁹</td>
</tr>
<tr>
<td>Ebert et al⁵²</td>
<td>1996</td>
<td>12</td>
<td>Unipolar</td>
<td>40.4</td>
<td>0</td>
<td>Total</td>
<td>No</td>
<td>16-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>67% (35%–90%)</td>
<td>Pre: 28.8 ± 1.8 Post: 16.0 ± 3.2 (44.4%)</td>
</tr>
<tr>
<td>Elenga and Van den Hoofdakker⁵³</td>
<td>1988</td>
<td>33</td>
<td>Unipolar</td>
<td>49.3</td>
<td>64</td>
<td>Total</td>
<td>Yes</td>
<td>21-item HDRS</td>
<td>≥ 6 point reduction</td>
<td>Day after TSD</td>
<td>27% (13%–46%)</td>
<td>Data not provided</td>
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</tbody>
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(continued)
Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Sample Type</th>
<th>Mean Age, y</th>
<th>% Female</th>
<th>Type of Sleep Deprivation</th>
<th>Medication (yes/no)</th>
<th>Outcome Measure</th>
<th>Response Criteria</th>
<th>Timing of Depression Measurement</th>
<th>Proportion Responders (95% CI)</th>
<th>Mean Pre/Post Depression Scores ± SD (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies Not Utilizing a Randomized Non–Sleep Deprivation Control Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fritzsche et al 54</td>
<td>2001</td>
<td>40</td>
<td>Mixed</td>
<td>47.1</td>
<td>65</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (34%–66%)</td>
<td></td>
</tr>
<tr>
<td>Gerner et al 55</td>
<td>1979</td>
<td>25</td>
<td>Mixed</td>
<td>45</td>
<td>N/A</td>
<td>Total</td>
<td>No</td>
<td>Unnamed scale</td>
<td>Positive mean change</td>
<td>Day after TSD</td>
<td>64% (43%–82%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Giedke et al 34</td>
<td>2003</td>
<td>22</td>
<td>Mixed</td>
<td>N/A</td>
<td>N/A</td>
<td>Late partial</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>27% (11%–50%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Giedke et al 34</td>
<td>2003</td>
<td>17</td>
<td>Mixed</td>
<td>N/A</td>
<td>N/A</td>
<td>Total</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>53% (28%–77%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Gillin et al 66</td>
<td>1989</td>
<td>19</td>
<td>Mixed</td>
<td>42</td>
<td>11</td>
<td>Total</td>
<td>Yes</td>
<td>19-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>32% (13%–57%)</td>
<td></td>
</tr>
<tr>
<td>Hemmeter et al 17</td>
<td>2007</td>
<td>27</td>
<td>Unipolar</td>
<td>44.1</td>
<td>44</td>
<td>Late partial</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>52% (32%–71%)</td>
<td></td>
</tr>
<tr>
<td>Hernandez et al 58</td>
<td>2000</td>
<td>15</td>
<td>Unipolar</td>
<td>68.5</td>
<td>67</td>
<td>Total</td>
<td>No</td>
<td>13-item HDRS</td>
<td>HDRS score ≤ 6</td>
<td>Day after TSD</td>
<td>67% (38%–88%)</td>
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</tr>
<tr>
<td>Hochli et al 59</td>
<td>1986</td>
<td>10</td>
<td>Mixed</td>
<td>40.2</td>
<td>70</td>
<td>Total</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (18%–81%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Kaschka et al 60</td>
<td>1989</td>
<td>22</td>
<td>Unipolar</td>
<td>41</td>
<td>68</td>
<td>Total</td>
<td>Yes</td>
<td>21-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>41% (21%–64%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Kasper et al 61</td>
<td>1988</td>
<td>41</td>
<td>Mixed</td>
<td>50.4</td>
<td>69</td>
<td>Total</td>
<td>No</td>
<td>16-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>50% (32%–68%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Kasper et al 62</td>
<td>1990</td>
<td>41</td>
<td>Mixed</td>
<td>49.9</td>
<td>71</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>49% (33%–65%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Kuhs et al 63</td>
<td>1985</td>
<td>39</td>
<td>Mixed</td>
<td>44.15</td>
<td>52</td>
<td>Total</td>
<td>Yes</td>
<td>10-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>41% (26%–58%)</td>
<td>Data not provided</td>
</tr>
<tr>
<td>Larsen et al 7</td>
<td>1976</td>
<td>19</td>
<td>Unipolar</td>
<td>N/A</td>
<td>53</td>
<td>Total</td>
<td>Yes</td>
<td>BLS</td>
<td>≥ 3 point reduction</td>
<td>Day after TSD</td>
<td>32% (13%–57%)</td>
<td>Data not provided</td>
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<tr>
<td>Müller et al 64</td>
<td>1993</td>
<td>9</td>
<td>Mixed</td>
<td>49</td>
<td>55</td>
<td>Total</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>66% (30%–93%)</td>
<td>Pre: 8.2 ± 3.7 Post: 4.2 ± 3.6 (48.8%)</td>
</tr>
<tr>
<td>Neumeister et al 65</td>
<td>1996</td>
<td>20</td>
<td>Mixed</td>
<td>47.6</td>
<td>70</td>
<td>Late partial</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>70% (46%–88%)</td>
<td>Data not provided</td>
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<tr>
<td>Neumeister et al 66</td>
<td>1998</td>
<td>30</td>
<td>Mixed</td>
<td>42.6</td>
<td>80</td>
<td>Total</td>
<td>Yes</td>
<td>16-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>73% (54%–88%)</td>
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<tr>
<td>Orth et al 68</td>
<td>2001</td>
<td>18</td>
<td>Unipolar</td>
<td>43.6</td>
<td>55</td>
<td>Total</td>
<td>No</td>
<td>SDDRS</td>
<td>30% reduction in baseline ratings</td>
<td>Day after TSD</td>
<td>56% (31%–78%)</td>
<td>Pre: 20.7 ± 5.2 Post: 13.1 ± 5.5 (36.7%)</td>
</tr>
<tr>
<td>Parekh et al 67</td>
<td>1998</td>
<td>27</td>
<td>Mixed</td>
<td>38.7</td>
<td>59</td>
<td>Total</td>
<td>No</td>
<td>17-item HDRS</td>
<td>30% decrease in baseline HDRS</td>
<td>Day after TSD</td>
<td>44% (25%–65%)</td>
<td>Pre: 21.8 ± 5.3 Post: 17.1 ± 6.7 (21.5%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample Type</th>
<th>No. of Patients</th>
<th>Age, y % Female</th>
<th>Type of Sleep Deprivation</th>
<th>Medication (yes/no)</th>
<th>Outcome Measure</th>
<th>Outcome Criteria</th>
<th>Response Criteria</th>
<th>Timing of Depression Measurement</th>
<th>Mean Pre/Post Depression Scores (± SD)</th>
<th>% change (95% CI)</th>
<th>Proportion Responders (% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post et al</td>
<td>1976</td>
<td>19 Unipolar</td>
<td>N/A</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>Unnamed depression scale</td>
<td>2 point decrease in nurse ratings</td>
<td>Day after TSD</td>
<td>Pre: 9.5±0.6 Post: 6.2±0.6</td>
<td>Pre: 3.8±0.2 Post: 3.2±0.2</td>
<td>52% (29%–76%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Reist et al</td>
<td>1994</td>
<td>21 Unipolar</td>
<td>39</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>17-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>Pre: 25±1.6 Post: 13±1.3</td>
<td>Pre: 3±3.9 Post: 3±3.9</td>
<td>53% (28%–77%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Reynolds et al</td>
<td>1987</td>
<td>17 Unipolar</td>
<td>39</td>
<td>71 Total</td>
<td>No</td>
<td>No</td>
<td>17-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>Pre: 16.2±6.0</td>
<td>Pre: 16.2±6.0</td>
<td>40% (16%–68%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Riemann et al</td>
<td>1990</td>
<td>19 Unipolar</td>
<td>71</td>
<td>Total</td>
<td>Yes</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>Data not provided</td>
<td>Data not provided</td>
<td>58% (28%–77%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Roy-Byrne et al</td>
<td>1984</td>
<td>16 Unipolar</td>
<td>39</td>
<td>75 Total</td>
<td>No</td>
<td>No</td>
<td>BHS</td>
<td>Mean change of 2 or more points</td>
<td>Day after PSD</td>
<td>Data not provided</td>
<td>Data not provided</td>
<td>38% (15%–65%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Salomon et al</td>
<td>1994</td>
<td>11 Unipolar</td>
<td>45</td>
<td>Total</td>
<td>No</td>
<td>No</td>
<td>18-item HDRS</td>
<td>25% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>Pre: 2±1.6 Post: 0±1.6</td>
<td>Pre: 5±3.8 Post: 5±3.8</td>
<td>30% (11–59%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Schilgen et al</td>
<td>1980</td>
<td>16 Unipolar</td>
<td>47</td>
<td>N/A Total</td>
<td>No</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Yes 8CS</td>
<td>Data not provided</td>
<td>Data not provided</td>
<td>30% (15–55%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Schumann et al</td>
<td>2001</td>
<td>52 Unipolar</td>
<td>45.9±5.7</td>
<td>63 Total</td>
<td>No</td>
<td>No</td>
<td>6-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>Data not provided</td>
<td>Data not provided</td>
<td>31% (19%–45%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Shellenbeger et al</td>
<td>1993</td>
<td>19 Unipolar</td>
<td>45.9±5.7</td>
<td>63 Total</td>
<td>No</td>
<td>No</td>
<td>13-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>Data not provided</td>
<td>Data not provided</td>
<td>31% (19%–45%)</td>
<td>95% CI (32%)</td>
</tr>
<tr>
<td>Smeraldi et al</td>
<td>1999</td>
<td>20 Unipolar</td>
<td>44.9±5.6</td>
<td>60 Multiple TSD administrations</td>
<td>Yes</td>
<td>21-item HDRS HDRS&lt;8</td>
<td>4 days after final TSD cycle</td>
<td>Pre: 2±1.6 Post: 0±1.6</td>
<td>Pre: 5±3.8 Post: 5±3.8</td>
<td>Pre: 2±1.6 Post: 0±1.6</td>
<td>Pre: 5±3.8 Post: 5±3.8</td>
<td>31% (19%–45%)</td>
<td>95% CI (32%)</td>
</tr>
</tbody>
</table>

*Studies Not Utilizing a Randomized Non-Sleep Deprivation Control Group*
### Table 1 (continued). Characteristics of Studies of the Antidepressant Effects of Sleep Deprivation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Sample Type</th>
<th>Mean Age, y</th>
<th>% Female</th>
<th>Type of Sleep Deprivation</th>
<th>Medication (yes/no)</th>
<th>Outcome Measure</th>
<th>Response Criteria</th>
<th>Timing of Depression Measurement</th>
<th>Proportion Responders (95% CI)</th>
<th>Mean Pre/Post Depression Scores ± SD (%) change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolski et al [78]</td>
<td>1995</td>
<td>15</td>
<td>Unipolar</td>
<td>46.3</td>
<td>13</td>
<td>Total</td>
<td>No</td>
<td>16-item HDRS</td>
<td>8.5 point decrease in HDRS</td>
<td>Day after TSD</td>
<td>Pre: 25.9 ± 5 Post: 18.4 ± 5.7 (29%)</td>
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</tr>
<tr>
<td>Szuba et al [35]</td>
<td>1994</td>
<td>9</td>
<td>Mixed</td>
<td>28.9</td>
<td>88</td>
<td>Late partial (4 h TIB)</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>50% decrease in baseline HDRS</td>
<td>Day after PSD</td>
<td>Pre: 10.8 ± 3.7 Post: 6.1 ± 4.0 (43.5%)</td>
<td></td>
</tr>
<tr>
<td>Szuba et al [35]</td>
<td>1994</td>
<td>7</td>
<td>Mixed</td>
<td>31</td>
<td>86</td>
<td>Early partial (5 h TIB)</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>50% decrease in baseline HDRS</td>
<td>Day after PSD</td>
<td>14% (0.3%–5.8%)</td>
<td></td>
</tr>
<tr>
<td>Voderholzer et al [79]</td>
<td>2012</td>
<td>15</td>
<td>Unipolar</td>
<td>34</td>
<td>66</td>
<td>Total</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>53% (27%–79%)</td>
<td></td>
</tr>
<tr>
<td>Volk et al [80]</td>
<td>1992</td>
<td>20</td>
<td>Unipolar</td>
<td>48.5</td>
<td>60</td>
<td>Total</td>
<td>Yes</td>
<td>18-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>55% (32%–77%)</td>
<td></td>
</tr>
<tr>
<td>Volk et al [81]</td>
<td>1997</td>
<td>15</td>
<td>Mixed</td>
<td>54.9</td>
<td>67</td>
<td>Late partial (TIB unclear)</td>
<td>Yes</td>
<td>18-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after PSD</td>
<td>60% (32%–84%)</td>
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</tr>
<tr>
<td>Wiegand et al [82]</td>
<td>1993</td>
<td>28</td>
<td>Unipolar</td>
<td>48.7</td>
<td>66</td>
<td>Total</td>
<td>No</td>
<td>6-item HDRS</td>
<td>30% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>68% (48%–84%)</td>
<td></td>
</tr>
<tr>
<td>Wiegand et al [83]</td>
<td>2001</td>
<td>18</td>
<td>Unipolar</td>
<td>45.7</td>
<td>50</td>
<td>Total</td>
<td>Yes</td>
<td>6-item HDRS</td>
<td>50% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>72% (47%–90%)</td>
<td></td>
</tr>
<tr>
<td>Wu et al [84]</td>
<td>1992</td>
<td>15</td>
<td>Unipolar</td>
<td>31.9</td>
<td>80</td>
<td>Total</td>
<td>No</td>
<td>18-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>27% (8%–55%)</td>
<td></td>
</tr>
<tr>
<td>Wu et al [85]</td>
<td>1999</td>
<td>36</td>
<td>Unipolar</td>
<td>30.13</td>
<td>69</td>
<td>Total</td>
<td>No</td>
<td>18-item HDRS</td>
<td>40% reduction in baseline HDRS</td>
<td>Day after TSD</td>
<td>33% (19%–51%)</td>
<td></td>
</tr>
</tbody>
</table>

*aData 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.

*bData averaged across groups (eg, phenotypes, genotypes, responders/nonresponders).

‡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

Randomized Studies
- Smith, 2009 (33)
- Smith, 2009 (33)
- Callyurt, 2005 (37)
- Reynolds, 2005 (32)
- Reynolds, 2005 (32)
- Kuh, 1996 (18)
- Holzboer-Trachsler, 1994 (36)
- Elsenga, 1983 (51)
- Elsenga, 1983 (51)

Total Randomized Sample

Nonrandomized Studies
- Voderholzer, 2012 (79)
- Beck, 2010 (39)
- Beck, 2010 (39)
- Brückner, 2010 (45)
- Bernier, 2009 (41)
- Benedetti, 2008 (40)
- Hemmeler, 2007 (57)
- Baghai, 2003 (13)
- Giedke, 2003 (34)
- Giedke, 2003 (34)
- Schüle, 2003 (22)
- Benedetti, 2001 (30)
- Benedetti, 2001 (30)
- Clark, 2006 (46)
- Fritsche, 2001 (54)
- Orth, 2001 (28)
- Schüle, 2001 (75)
- Schumann, 2001 (76)
- Wiegand, 2001 (83)
- Hernandez, 2000 (58)
- Benedetti, 1999 (15)
- Benedetti, 1999 (15)
- Riemann, 1999 (23)
- Smeralidi, 1999 (16)
- Smeralidi, 1999 (16)
- Wu, 1999 (85)
- Neumeister, 1998 (66)
- Parekh, 1998 (67)
- Volk, 1997 (81)
- Ebert, 1996 (52)
- Neumeister, 1996 (65)
- Bouhuys, 1995 (44)
- Sokolski, 1995 (78)
- Danos, 1994 (47)
- Ebert, 1994 (50)
- Ebert, 1994 (51)
- Reist, 1994 (68)
- Salomon, 1994 (74)
- Szuba, 1994 (35)
- Szuba, 1994 (35)
- Ebert, 1993 (49)
- Müller, 1993 (64)
- Riemann, 1993 (72)
- Shelton, 1993 (77)
- Wiegand, 1993 (82)
- Volk, 1992 (80)
- Wu, 1992 (84)
- Ebert, 1991 (48)
- Riemann, 1990 (71)
- Baumgartner, 1990 (38)
- Bouhuys, 1990 (43)
- Kasper, 1990 (62)
- Riemann, 1990 (70)
- Gillin, 1989 (56)
- Kaschka, 1989 (60)
- Bouhuys, 1988 (42)
- Elsenga, 1988 (53)
- Kasper, 1988 (61)
- Reynolds, 1987 (69)
- Höchli, 1986 (59)
- Kuh, 1985 (63)
- Roy-Byrne, 1984 (73)
- Schilgen, 1982 (12)
- Gerner, 1979 (55)
- Larsen, 1976 (9)
- Post, 1976 (10)

Total Nonrandomized Sample

Notes: Lines represent 95% confidence intervals. Size of markers indicates weight based on sample size. Diamonds represent random pooled effects.
Antidepressant Effects of Sleep Deprivation

response rates. A similar conclusion was drawn in a 2007 report by Clark and Golshan, 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, 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 I² 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

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. 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. Wu and Bunney, 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 as well as some indication that total sleep deprivation may have a slight advantage over partial sleep deprivation; 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, which we also found in our analyses. Additionally, our results showed that definition of antidepressant response did not influence

Figure 3. Proportion of Responders to Sleep Deprivation Across Categories

Bars indicate random effect response rates. Error bars represent 95% confidence intervals.

Abbreviations: PSD = partial sleep deprivation, TSD = total sleep deprivation.
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 therapy21,91 and a phase advance23,92 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 disorder95; 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 components94,95,99,100 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 Bunney104
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) and specific neurotransmitter systems (eg, dopaminergic system) 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 al14 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 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.

References


