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Polysomnography and criteria for the antidepressant response to sleep deprivation

Camellia P. Clark* and **Shahrokh Golshan**
Department of Psychiatry, VA San Diego Healthcare System, University of California, 3350 La Jolla Village Dr., San Diego, CA 92161, USA

Abstract

Background—One night of total or partial sleep deprivation (SD) produces a temporary remission in 40–60% of patients with major depression. Yet no attempts to determine the optimum response criterion(a) for the antidepressant response to SD have been published.

Methods—Twenty-three unmedicated major depression patients received polysomnography (PSG) on an adaptation night; a baseline night; a partial SD (PSD) night (awake after 3 a.m.); and a "recovery" night. Subjects received the Hamilton Depression Rating Scale (HDRS17) at standard times during baseline and PSD days and at 8 a.m. after the "recovery" night. Response was defined as percent decrease in the modified HDRS17 (HDRS17Mod) (omitting sleep and weight loss items) from baseline to the minimum following PSD. Using cutoffs of 30%, 35%, 40%, and 50% to dichotomize responders and nonresponders, PSG variables were analyzed for between-group differences.

Results—All cutoffs differentiated responders' and nonresponders' mood response to PSD despite similar baseline values. Sleep continuity measures most consistently differed between responders and nonresponders on baseline and recovery nights. None of the response cutoffs tested were clearly "best" in terms of detecting the most PSG differences between groups.

Limitations—More subjects may be needed.

Conclusions—Given the increasing interest in SD for clinical and research applications, as well as its proposed use for subtyping depression, further study to determine the optimal response criterion (a) for the antidepressant response to SD is warranted. Planned pooling of multisite data on standardized SD protocols could help determine the optimal cutpoint for response.

Keywords

Depressive disorder; Major; Hamilton depression rating scale; Sleep deprivation; Polysomnography

1. Introduction

One night of total or partial sleep deprivation (SD) produces a temporary remission in 40–60% of patients with current major depression. This intriguing phenomenon has been well documented in numerous studies over the past three decades, totaling over 1700 patients, including hundreds who were not taking medication (Gillin, 1983; Wu and Bunney, 1990; Leibenluft and Wehr, 1992). The antidepressant effects of total SD (TSD) and partial SD (PSD) generally begin within hours-much more rapidly than any other currently available antidepressant treatments (Post et al., 1987). Following SD, patients generally return to their original severity of depression after one night sleep or less (Wu and Bunney, 1990). Although

* Corresponding author. Tel.: +1 858 552 8585x2580; fax: +1 858 642 6393. *E-mail address:* cclark@vapop.ucsd.edu (C.P. Clark).

brief duration of this response limits the clinical feasibility of SD, repeated applications offer an alternative to medication for those who cannot tolerate medication side effects and a means of augmentation in treatment-resistant depression. The antidepressant effects of SD can be prolonged with repeated administrations or with phototherapy, phase advance of the sleep-wake cycle, lithium, and anti-depressants. SD also speeds the onset of response to antidepressant medications (Wirz-Justice et al., 2005).

Although the mechanisms of SD's antidepressant action are unknown, several classes of theories have been proposed. Each theory has its strengths and weaknesses, and they are not mutually exclusive. *Phase advance of the internal clock* or the "internal coincidence model" suggests that SD alleviates circadian dysfunction in depression (Wehr and Wirz-Justice, 1980). The two-process model states that the sleep-wake cycle is regulated by two processes: *Process C*, a circadian factor, and *Process S*, a factor dependent on time awake since prior sleep. Depressed patients are thought to have problems building up levels of Process S properly; SD would increase the buildup of Process S (Borbely and Wirz-Justice, 1982). The *overarousal* hypothesis postulates that depression is associated with pathologically increased physiologic arousal, which is decreased by SD, at least in responders (Gillin et al., 1995). Changes in function of neurotransmitters (Kasper et al., 1988; Ebert et al., 1994) have also been hypothesized to mediate the antidepressant effects of SD.

SD permits the study of patients in depressed vs. remitted states within a brief period of time. Controls can undergo exactly the same procedure as depressed patients, with both subject groups remaining unmedicated. More recently, the antidepressant response to SD has been proposed as a possible biological marker for subtyping depression (Gillin et al., 2001). The increasing interest in SD for clinical and research applications underscores the importance of how to quantify response and dichotomize responders vs. nonresponders.

A review of the literature (Clark and Braun, manuscript in preparation) indicates that modified versions of the Hamilton Depression Rating Scale (HDRS) (omitting sleep and weight loss items) are the most common ratings used to distinguish responders vs. nonresponders to SD. The validity of the HDRS has been questioned, and it has certain disadvantages (Zimmerman et al., 2005). For example, even if one omits the sleep and weight items, the HDRS was not originally designed to reflect changes within a few hours' time. Nevertheless, the HDRS is the most widely used depression scale in clinical trials of antidepressant medications, and researchers and clinicians around the world are familiar with its use.

To date no empirical studies of the optimum response criterion(a) for the antidepressant response to SD have been published (Clark and Braun, manuscript in preparation). It seems intuitive that the best cutoff (e.g., percent decrease in a given rating scale) would yield the greatest differences, in polysomnography (PSG), imaging, etc.; it is possible that the best cutoff for one purpose (e.g., PSG) might not be the best cutoff for another purpose (e.g., functional imaging studies). Based on the literature we used cutoffs of 30% (Kasper et al., 1988; Volk et al., 1997), 35% (Philipp and Werner, 1979), 40% (Gillin et al., 1989; Wu et al., 1999), and 50% (Ebert et al., 1991; Holsboer-Trachsler et al., 1994) decrease in the 17-item Hamilton Depression Rating Scale (HDRS17) (omitting sleep and weight loss items) to examine group differences between responders and nonresponders to one night of PSD in our SPECT study of Major Depression.

2. Methods

2.1. Subjects

Twenty-three unmedicated patients with current major depression and 14 normal controls entered the study. Polysomnographic measures on the depressed subjects were reported

previously based on a response criterion of ≥30% decrease in the modified HDRS17 (HDRS17Mod) (omitting items #4–6, sleep, and #16, weight loss) (Clark et al., 1998). All patients met full diagnostic criteria for current DSM-IV major depressive disorder (unipolar) and had a baseline HDRS17≥16. Control subjects had no psychiatric disorder based on structured interview. All subjects received the Structured Clinical Interview for DSM-III-R or the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) as well as full medical history, physical examination and laboratory evaluation, including ECG, urinalysis, and urine drug screen.

We excluded subjects for bipolar disorder; comorbid psychiatric or substance use disorders; pregnancy; lactation; epilepsy; primary sleep disorders; irregular sleep–wake patterns; circulatory conditions which could affect brain perfusion (e.g., hypertension, unexplained syncope, hypotensive episodes, etc.); or use within 2 weeks of medications or substances which could affect sleep pattern, electroencephalogram (EEG), and/or SPECT. (No patient took fluoxetine during the 6 weeks prior to the study.) Other exclusion criteria included brain injury, hypoxia, history of meningitis, migraines, or developmental disorders. All subjects gave full informed consent for this study, which was approved by the UCSD Human Subjects Committee.

2.2. Mood ratings

Subjects were rated for contemporaneous mood with the HDRS17 at 8 a.m., 2 p.m. and 5 p.m. during baseline and PSD days, upon awakening (3 a.m.) during the PSD night, and at 8 a.m. after the "recovery" night. (The term "recovery night" refers to recovery of at least part of the sleep debt, not to recovery from the depressive episode itself (Wu and Bunney, 1990).) Trained clinicians used the Structured Interview Guide to the HDRS (Williams, 1988). Clinical response was defined as percent decrease in the HDRS17Mod from baseline to the minimum score (greatest decrease in depressive symptoms) following PSD.

2.3. Polysomnography

All subjects spent four nights in the sleep laboratory: an adaptation night; a baseline night; a PSD night (in which they had to remain awake from 3 a.m. on); and a night of "recovery" sleep. On each night, we used standard PSG recording montage, including EEG (C3 or C4), bilateral electro-oculogram (EOG), and submental electromyogram (EMG). On the adaptation night, we also screened subjects for sleep apnea and nocturnal myoclonus by means of pulse oximetry and bilateral anterior tibial EMG. Records were scored visually by standard criteria (Rechtschaffen and Kales, 1968) as previously described (Gillin et al., 1994) and were excluded for significant artifacts or recording problems.

2.4. Statistics

Data were analyzed using SPSS 11.0 (Chicago, IL). All continuous variables were examined for approximate normal distribution before performing between-group *t*-tests. Nonparametric statistics were used whenever necessary because of deviations from normal distributions or small numbers of participants. Chi-square statistics were used to test for differences in proportions between groups, e.g., for demographic analyses.

All sleep architecture variables were analyzed for between-group differences between responders and nonresponders. Separate analyses were performed for cutoffs of 30%, 35%, 40%, and 50% on percent decrease HDRS17Mod. Because of the exploratory nature of this study, we did not correct for multiple comparisons.

3. Results

Because this paper focuses on the antidepressant effects of SD, data on healthy controls are not reported here.

3.1. Demographics and clinical description

Basic demographic and clinical data for the entire patient group is shown in Table 1.

In this all unipolar cohort, no patient had psychotic features, and no one met DSM-III-R (or DSM-IV) specifiers for melancholic, postpartum, or seasonal subtype.

For each response cutoff (30%, 35%, 40%, and 50%) we analyzed each of these variables in responders vs. nonresponders. None of the demographic or clinical variables significantly differed between groups except for age, which differed only for the 30% and 35% cutoffs. In both cases, responders were younger than nonresponders [30% cutoff: responders 37.2±9.9 vs. nonresponders 48.0±9.7, t=−2.7, df=21, 2-tailed P=0.015; 35% cutoff: responders 37.8±10.1 vs. nonresponders 46.5±10.6, t=−2.0, df=21, 2-tailed P=0.058].

3.2. Mood ratings

Cutoffs of 30%, 35%, 40%, and 50% on percent decrease HDRS17Mod yielded 11 responders and 12 nonresponders, 10 responders and 13 nonresponders, 7 responders and 16 nonresponders, and 3 responders and 20 nonresponders, respectively. (See Table 2).

Regardless of the percent cutoff used, responders' and nonresponders' depression severity was similar at baseline but diverged significantly with PSD. For all the cutoffs used, sleep-deprived HDRS17Mod was significantly lower for responders than for nonresponders ($-4.2 \leq t \leq -3.0$, df=21). The responder group also showed greater decrease ($3.2 \leq t \leq 5.3$, df=21) and percent decrease ($3.8 \leq t \leq 5.6$, df=1) in the HDRS17Mod for all four cutoffs used. In other words, each cutoff displayed face validity for describing differences in the course of depressive symptom severity with SD.

3.3. Polysomnography

3.3.1. Baseline night—For the response cutoffs tested, minutes awake after sleep onset and sleep efficiency were the PSG variables which differed (or tended to differ) most consistently between responders and nonresponders, with nonresponders exhibiting more disrupted sleep. (See Table 3).

All other PSG measures either were not significantly different for any cutoff or differed at only one cutoff. At the 35% cutoff, no sleep architecture variables differed between the two groups.

3.3.2. Recovery night—Sleep efficiency and minutes awake after sleep onset again were among the PSG variables that most consistently differed between responders and nonresponders across response cutoff levels. Nonresponders' sleep again reflected more disruption than that of the responder group, with differences in sleep efficiency and minutes awake after sleep onset evident using more stringent response criteria (40% and 50%). The other sleep architecture measures which differed most consistently for the recovery night included percent Stage 4 and percent slow wave sleep (SWS), with nonresponders' SWS measures lower than responders' values at the more liberal response cutoffs (30% and 35%). None of the other sleep architecture variables differed on more than one response cutoff.

3.3.3. Change from baseline to recovery night—We also wished to explore the impact of using different percent cutoffs on detecting differences between responders and

nonresponders in sleep changes from the baseline night to the recovery night. Change scores for each PSG variable were calculated as baseline minus recovery night values, e.g., change in SWS=baseline SWS−recovery SWS. For each percent cutoff (30%, 35%, 40%, 50%), all PSG change scores were tested for between-group differences. No apparent pattern emerged for differences between responders and nonresponders on PSG variable change scores. No change scores significantly differed for the 40% response cutoff, and the few variables which differed or tended to differ at the 30% cutoff did not overlap with those few apparent differences at the 35% cutoff.

3.3.4. Reanalysis taking age into account—Given the effects of age on sleep (e.g., decreasing SWS with increasing age) we reanalyzed all the PSG data for the percent cutoffs (30% and 35%) for which responders were younger than nonresponders for baseline and recovery nights and for change scores, using age as a covariate. The results did not change for any baseline and change PSG variables. For the recovery night, covarying with age altered the results only for percent Stage 4 and percent slow wave sleep, which lost their trends toward differences. This was the case for both the 30% and 35% cutoff ANCOVAs. However, because minutes awake after sleep onset and sleep efficiency differed only at the higher response cutoffs, these results were not affected.

4. Discussion

If one evaluates response cutoffs by identifying the greatest difference between responders and nonresponders in a given area (e.g., PSG), none of the four cutoffs tested was clearly the best. For both baseline and recovery nights, differences in minutes awake after sleep onset and sleep efficiency were more apparent at the higher response cutoffs. Although Table 3 shows two-tailed statistics, nonresponders showed more “depressed” sleep (e.g. lower sleep efficiency) than responders on baseline and recovery night (Benca et al., 1992). This would seem to be at variance with data that responders’ total SD showed “a more ‘depressed’ EEG sleep pattern” than nonresponders (Duncan et al., 1980). However, their study used a multivariate analysis, and responders were “significantly more depressed” than nonresponders at baseline.

Of the four response cutoffs tested, no clear “best cutoff” or consistent pattern of more or fewer differences with increasingly stringent cutoffs emerged. However, this may be related to our subject numbers. Although our total number of depressed subjects is in line with many other studies of the antidepressant effects of SD (Clark and Braun, manuscript in preparation), the numbers of responders were small for the higher percent cutoffs. It may be that larger differences between the number of responders for different cutoffs would be necessary to see differences in the results using different percent cutoffs for decreases in HDRS17Mod.

Another limitation of our data is the small number of PSG variables differing between responders and non-responders overall. Although other groups also reported few PSG differences (Gerner et al., 1979; Reynolds et al., 1987; Gillin et al., 1989; Riemann et al., 1991), a small number of potential “true differences” makes it less likely that different response cutoffs will yield different numbers of variables differing between responders and nonresponders.

This is the first attempt to determine the optimum response cutoff for percent decrease in the HDRS17Mod in the SD literature. Perhaps none of the response cutoffs tested are optimal. Though current conditions make it unlikely that a multicenter study would be funded to determine the optimal response criterion. Adoption of standardized SD protocols (e.g., Benedetti, Terman and Wirz-Justice, *Treatment Manual for Chronotherapeutics*, in preparation) would permit pooling multicenter data, facilitating determination of the best cutpoint for SD response.

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Table 1

Characteristics of depressed subjects (*N*=23)

Age	42.4±11.0
Male/female	8/15
White/nonwhite	19/4
Married/single	18/5
Handedness	22 right/1 left
Education (years)	13.7±2.2
Current smoker	5 yes/17 no*
Current alcohol	13 yes/9 no*
Coffee drinker	18 yes/4 no*
Age first major depressive episode (years)	24.0±11.3
Number major depressive episodes	4.0±4.9
Lifetime duration in major depressive episodes (weeks)	97.3±151.1

* Missing data on 1 subject.

Table 2

Different response cutoffs on the modified 17-item Hamilton Depression Rating Scale

Cutoff	*N*	BL H17	BL H24	BL HDRS17Mod	SD HDRS17Mod	(BL-SD) HDRS17Mod	% Drop HDRS17Mod
30%							
Responders	12	19.9±2.8	26.5±4.1	15.2±2.4	7.7±2.4*	7.5±3.0*	47.5±11.2*
Nonresponders	11	19.6±3.1	25.4±4.5	15.9±3.4	13.0±3.6	2.9±3.1	13.7±17.2
35%							
Responders	11	20.1±2.9	26.7±4.2	15.5±2.2	7.9±2.4*	7.6±3.1*	48.8±10.7*
Nonresponders	12	19.4±3.0	25.3±4.4	15.5±3.6	12.3±4.2	3.2±3.1	15.3±17.3
40%							
Responders	8	20.5±3.2	27.3±4.7	16.3±2.0	7.3±2.4*	9.0±2.3*	53.3±8.9*
Nonresponders	15	19.3±2.8	25.3±3.9	15.1±3.3	11.8±3.9	3.3±2.8	19.6±17.7
50%							
Responders	5	20.6±3.8	27.2±5.9	15.8±2.2	5.8±1.6*	10.0±1.4*	57.8±8.4*
Nonresponders	18	19.5±2.7	25.6±3.8	15.4±3.1	11.4±3.6	4.0±3.1	24.0±19.0

BL: Baseline;

H17: 17-item Hamilton Depression Rating Scale;

H24: 24-item Hamilton Depression Rating Scale;

HDRS17Mod: Modified 17-item Hamilton Depression Rating Scale (omitting sleep and weight loss items);

SD: Sleep deprived.

Mean±standard deviation.

% Drop HDRS17Mod was used to dichotomize responders vs. nonresponders.

* $P<0.01$, *t*-test, one-tailed, df=21.

Table 3

Effects of HDRS17Mod response cutoffs on polysomnographic differences

		30%	35%	40%	50%
Baseline					
Wake after sleep onset (minutes)	Responders<nonresponders	*	n.s.	**	*****,****
% Sleep efficiency	Responders>nonresponders	n.s.	n.s.	**	*****
Recovery					
Wake after sleep onset	Responders<nonresponders	n.s.	n.s.	**	****,*
% Sleep efficiency	Responders>nonresponders	n.s.	n.s.	n.s.	
% Stage 4	Responders>nonresponders	******,******	*****,	n.s.	n.s.
% Slow wave sleep	Responders>nonresponders		n.s.	n.s.	n.s.

HDRS17Mod: Modified 17-item Hamilton Rating Scale for Depression (omitting sleep and weight loss items).

* 0.05<*P*<0.10, *t*-test, two-tailed.

** *P*<0.05, *t*-test, two-tailed.

*** *P*<0.05, Mann–Whitney *U*.

**** Trend no longer present with age as covariate.