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# Targeting Slow Wave Sleep Deficiency in Late-Life Depression: A Case Series With Propofol

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## Abstract

Slow wave sleep (SWS), characterized by large electroencephalographic oscillations, facilitates crucial physiologic processes that maintain synaptic plasticity and overall brain health. Deficiency in older adults is associated with depression and cognitive dysfunction, such that enhancing sleep slow waves has emerged as a promising target for novel therapies. Enhancement of SWS has been noted after infusions of propofol, a commonly used anesthetic that induces electroencephalographic patterns resembling non-rapid eye movement sleep. This paper 1) reviews the scientific premise underlying the hypothesis that sleep slow waves are a novel therapeutic target for improving cognitive and psychiatric outcomes in older adults, and 2) presents a case series of two patients with late-life depression who each received two propofol infusions. One participant, a 71-year-old woman, had a mean of 2.8 minutes of evening SWS prior to infusions (0.7% of total sleep time). SWS increased on the night after each infusion, to 12.5 minutes (5.3% of total sleep time) and 24 minutes (10.6% of total sleep time), respectively. Her depression

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AUTHOR CONTRIBUTIONS

RLR: Data analysis, drafting, review of final manuscript. MK: Data analysis, review of final manuscript. EL: Data analysis, drafting, review of final manuscript. OH: Data analysis, drafting, review of final manuscript. BPL: Drafting, review of final manuscript. EJL: Conceptualization, funding, data acquisition, data analysis, drafting, review of final manuscript. BJAP: Conceptualization, funding, data acquisition, data analysis, drafting, review of final manuscript

SUPPLEMENTARY MATERIALS

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symptoms improved, reflected by a reduction in her Montgomery-Asberg Depression Rating Scale (MADRS) score from 26 to 7. In contrast, the other participant, a 77-year-old man, exhibited no SWS at baseline and only modest enhancement after the second infusion (3 minutes, 1.3% of total sleep time). His MADRS score increased from 13 to 19, indicating a lack of improvement in his depression. These cases Provide proof-of-concept that propofol can enhance SWS and improve depression for some individuals, motivating an ongoing clinical trial (ClinicalTrials.gov NCT04680910).

## BRIEF SUMMARY

Deficiency of slow wave sleep (SWS) in older adults is putatively associated with depression and cognitive dysfunction. Sleep slow waves may serve as a target for novel strategies to improve both depression and cognitive function. This work presents two older adults with treatment-resistant depression who received propofol infusions as a therapeutic probe of the relationships between SWS, depression, and cognitive dysfunction. These cases provide proof-of-concept that propofol can enhance SWS and improve depression for some individuals.

### Keywords

Older adults; slow wave sleep; depression; cognition; anesthesia; propofol; sleep; electroencephalography

## INTRODUCTION

### SWS Deficiency at the Nexus of Cognitive Impairment and Late-Life Treatment-Resistant Depression

Treatment-resistant depression (TRD) in older adults is a leading cause of disability,[1] excess mortality from suicide,[2,3] and dementia.[4–6] The number of patients with late-life TRD (LL-TRD) is likely to increase over time[7,8] as growing proportions of the population reach old age. Using failure of two oral antidepressant classes as a defining characteristic of TRD, it has been shown that additional trials of traditional antidepressants, such as venlafaxine, are unlikely to achieve remission.[9] Moreover, long-term outcomes are dismal, with high recurrence rates.[10] While aripiprazole,[11] electroconvulsive therapy[12] and transcranial magnetic stimulation[13] are alternatives for some, novel treatments are desperately needed.

Cognitive problems are common in LL-TRD. Executive function impairment often coexists with LL-TRD,[14] potentially due to microvascular lesions affecting the white matter tracts connecting prefrontal and subcortical structures.[15] Impaired executive function is associated with poor responses to oral antidepressant treatment, including nonresponse to aripiprazole augmentation.[16,17] Cognitive skills related to executive function, such as alertness and processing speed, are commonly reduced in those with depression and sleep disturbances.[18,19] Cognitive disturbances are associated with functional impairment, progression to Alzheimer’s disease and related dementias, and reduced survival. New treatments should target core pathophysiology. Sleep disruption is an important candidate,[20]

as it contributes not only to difficult-to-treat depression[21] but also to deficits in alertness and executive function.[22]

## SWS Deficiency as a Mechanistic Pathway for Cognitive Dysfunction in Older Adults

Sleep is a daily critical period for restoring physiologic and brain functions that promote good mental and cognitive health. It is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. NREM Stage 3 (N3),[23] synonymous with slow wave sleep (SWS), is characterized by oscillating cortical electrical activity that generates large-amplitude, low-frequency electroencephalographic (EEG) waves. SWS is linked to subjective feelings of restorative sleep,[24] reduced neurohumoral stress response,[25] and memory consolidation.[26] Synaptic remodeling critical for learning and memory is thought to occur during SWS,[27] such that sleep slow waves may serve as markers of synaptic plasticity.[28] In addition, memories are putatively replayed during SWS through hippocampal-dependent pathways.[29] Emerging evidence suggests that enhancing sleep slow waves improves declarative memory.[30] More recently, sleep slow waves have been shown to regulate the biochemical milieu within the brain through the glymphatic system[31] by stimulating cerebrospinal fluid waves.[32] The physiologic processes that link SWS to cognitive performance have important implications for aging patients, who tend to have less SWS relative to younger individuals.[33] Healthy glymphatic flow during SWS may reduce deposition of dementia-associated proteins, such as amyloid-beta[31] and tau.[34] Slow wave activity (SWA), a measure of power in sleep slow waves, is inversely correlated with tau and amyloid-beta deposition in older adults, suggesting that measures of SWS have utility as mechanistic markers for aging-related pathways to cognitive impairment.[35] Pharmacologic SWS enhancement may have a beneficial effect on both cognitive function and mood in LL-TRD (Figure 1).

## SWS as a Novel Antidepressant Target

SWS abnormalities have long been associated with depression. In nondepressed individuals, SWS dominates early sleep cycles, with replacement by REM later in the sleep period. SWA peaks in the first cycle and declines with each successive SWS cycle, reflecting decreasing sleep pressure and restoration of synaptic homeostasis.[36] In contrast, patients with depression typically exhibit maximum SWA during later N3 cycles, supporting the hypothesis that depressed patients have impaired homeostasis of synaptic plasticity.[37] Reduced SWA, particularly in the first cycle,[38] has been considered part of the core pathophysiology of depression, even when accounting for age.[39] This characteristic shift in peak SWA can be quantified through the delta sleep ratio (DSR). The DSR is the ratio of SWA for the first and second N3 cycles,[38] with a ratio greater than 1.5 observed in those without depression. The DSR has been used as a predictor for treatment response[40] and vulnerability to recurrence.[38] Reduced SWS is a known risk factor for depression,[41] with coincident REM intrusion into early sleep cycles and increased REM duration. Many antidepressants augment SWS, including lithium,[42] trazodone,[43] nefazodone, mirtazapine,[44] sertraline,[45] and clomipramine.[46] Furthermore, newer antidepressants, such as ketamine[47] and agomelatine,[48] increase SWS duration or SWA. It has been proposed that addressing SWS deficiency is crucial for sustaining an antidepressant response.[49] Restoring SWS to the early cycles of overnight sleep facilitates normalization of REM sleep architecture;

subsequent REM delay and reduced REM duration is observed with antidepressant response. Overall, objective metrics based on EEG sleep slow waves are associated with depression, treatment response, and cognitive functioning. Despite these observations, no studies have specifically targeted SWS to treat LL-TRD.

**Propofol as a Therapeutic Probe of Sleep, Depression, and Cognitive Dysfunction—**Propofol is a commonly used sedative in anesthetic practice. Low doses induce a shift toward lower EEG frequencies, with patterns resembling NREM Stage 2 (N2) sleep. Higher doses induce EEG slow waves resembling those of N3/SWS.[50] Even greater doses induce burst suppression, a pattern in the EEG waveform characterized by episodes of zero-voltage EEG (signifying suppression of cortical activity) interspersed with bursts of mixed-frequency activity. With this escalation of dose, response to noxious stimulation decreases.

Sleep-like states achieved during propofol infusions[51] may satisfy some homeostatic sleep needs. Other functions of sleep slow waves, such as the ability to entrain sleep spindles, may not be satisfied by propofol.[50] Studies in sleep-deprived rodents have shown that propofol facilitates recovery from SWS deficiency,[52] suggesting that propofol may engage intrinsic mechanisms for regulating SWS. These results mirror anecdotes of patients feeling rested and restored after propofol sedation. The similarities between sleep and propofol sedation have motivated a trial of propofol to treat refractory insomnia.[53] In these patients (28–68 years of age), propofol infusions from 10 P.M. to midnight on five consecutive days had a durable effect on subsequent sleep architecture, enhancing nighttime SWS for up to 6 months after the last infusion.[53] Effects on cognition and comorbid psychiatric disorders were not assessed. The potential for SWS enhancement distinguishes propofol from dexmedetomidine, another sedative that can generate EEG states that mimic sleep. In addition, evidence for antidepressant effects exists for propofol but not dexmedetomidine.

A recent clinical trial has demonstrated propofol's antidepressant potential in patients 18–45 years of age.[54] The administration of 10 propofol infusions targeting burst suppression yielded antidepressant responses, with some sustained for up to 3 months. Associated changes in SWS and cognition remain unknown. Burst suppression is often avoided intraoperatively, as a sign of excessive anesthetic exposure; the degree of intraoperative burst suppression has been associated with postoperative cognitive dysfunction.[55] Targeting EEG slow waves, rather than burst suppression, may address SWS deficits and enhance subsequent overnight SWS. In addition, avoiding burst suppression may minimize risk of potentially unfavorable cognitive outcomes. Overall, prior studies have utilized five or more infusions,[53,54] targeted a different EEG marker,[54] and have not specifically recruited geriatric patients.[53,54] In contrast, we are repurposing propofol as a therapeutic probe of the relationships between SWS, depression, and cognitive dysfunction in the aged. We present two cases showing varied responses to this approach, demonstrating proof-of-concept and potential limitations.

## CASE DESCRIPTIONS

Two older adults with longstanding LL-TRD were referred after failing to improve in a clinical trial.[56] They were recruited as pilot participants in the Slow Wave Induction by Propofol to Eliminate Depression (SWIPED) investigation (ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04680910).

After informed consent was obtained, both participants underwent a history and physical examination to rule out any contraindications for two sessions of intravenous propofol general anesthesia. Baseline and postinfusion sleep recordings were acquired using the first-generation version of the Dreem, a wireless wearable headband equipped with dry EEG electrodes.[57] Sleep EEG recordings were manually scored in 30-second epochs by certified sleep technologists, using modified American Academy of Sleep Medicine (AASM) criteria.[57,58] EEG data were imported into EEGLAB,[59] using custom-written MATLAB scripts. After temporal downsampling to 250 Hz, a 0.1 −0.6 Hz band-stop filter was applied to reduce respiratory artifact. Spectral analysis was performed using the Chronux toolbox[60] (5-second nonoverlapping time windows, time-bandwidth of 3, and 5 tapers). Five-second epochs with amplitude greater than 250 mcV were excluded. SWA was calculated as 0.5–4 Hz power in the F7-F8 EEG per 30-second N2/N3 epoch during first and second cycles of sleep. Average SWA was calculated across the first 30 minutes of N2/N3 for the first and second cycles of the sleep recordings, with the DSR as the ratio of the first and second cycle SWA. Prior to each propofol infusion, both participants fasted overnight to minimize aspiration risk. Sedation sessions were directly supervised by a board-certified anesthesiologist. They began with placement of an intravenous catheter, standard monitors in accordance with American Society of Anesthesiologist guidelines, and a 64-channel high-density EEG cap. EEG signals were monitored in real time using a Net Amps and Net Station software to optimize safe induction of slow waves while avoiding burst suppression. After infusions, participants recovered under nursing supervision and were discharged home.

### Case 1

The patient was a 71-year-old Caucasian non-Hispanic female who had suffered from depression since approximately 15 years of age. She reported previous trials of fluoxetine, citalopram, venlafaxine, paroxetine, escitalopram, bupropion, and transcranial magnetic stimulation. She presented in an episode characterized by depressed mood, anhedonia, disturbed sleep, fatigue/low energy, feelings of worthlessness/guilt, and difficulty concentrating that had persisted for several years. The patient did not achieve lasting remission despite several adequate treatment trials, including: 1) 90 mg duloxetine augmented by aripiprazole 7.5 mg, 2) monotherapy with nortriptyline, and 3) citalopram 40 mg and bupropion 150 mg. She continued citalopram and bupropion for the duration of the study.

Two baseline overnight sleep EEG recordings demonstrated a paucity of SWS sleep (average 2.8 minutes). SWS composed only 0.7% of her total sleep time, compared to a normative 7%–9% for those 70–80 years of age[33] (Table 1). The patient tolerated intravenous propofol infusions without any adverse events. On the first infusion, a total of 1,006 mg of propofol were administered over 1 hour and 42 minutes. On the second infusion, a total of 1,035 mg

of propofol were administered over 1 hour and 34 minutes. EEG slow waves were observed during both infusions. Using an automated detection algorithm,[61] 2 seconds and 96 seconds of burst suppression were detected during the first and second infusions, respectively. Postinfusion overnight at-home sleep studies showed SWS enhancement on the night after each infusion, to 12.5 minutes (5.3% of total sleep time) and 24 minutes (10.6% of total sleep time, a nearly 10fold increase), respectively (Table 1, Figure 2). This participant also demonstrated a reduction in REM sleep duration and total sleep time. She also showed an earlier sleep onset and offset compared to baseline (Figure 2). The average preinfusion DSR was 0.92 while the average DSR postinfusion was 1.64. These measures mirrored changes in her depression assessments. Prior to the first infusion, her Montgomery-Åsberg Depression Rating Scale (MADRS) score was 26, which improved to 7 after the first infusion and remained at 7 nine months later.

### Case 2

The patient was a 77-year-old Caucasian non-Hispanic male with unipolar depression and untreated obstructive sleep apnea. He presented with reduced interest/pleasure, changes in appetite, disturbed sleep, fatigue/low energy, feelings of worthlessness/guilt, and difficulty concentrating. He noted that his depression symptoms started at approximately 15 years of age. Over the past two years, his therapy had included unsuccessful trials of bupropion (up to 300 mg) and escitalopram (10 mg). More recently, the patient had failed to remit after trials of 1) bupropion up to 450 mg, 2) nortriptyline, 3) venlafaxine 150 mg augmented with aripiprazole up to 15 mg, and 4) sertraline up to 200 mg then augmented with lithium carbonate up to 450 mg. He remained on lithium and sertraline for the duration of the SWIPED trial.

Baseline sleep recordings showed a short total sleep time and absent SWS (Table 1). During the first propofol infusion, the patient had moderate airway obstruction that required chin lift maneuvers but otherwise tolerated the session well. Due to intermittent airway obstruction, he received 779 mg of propofol over 1 hour and 4 minutes. For the second infusion, he received 652 mg propofol over 1 hour and 33 minutes. These doses were comparatively less than that administered to the patient in Case 1. EEG slow waves were not readily identified during either infusion. Burst suppression was only detected during the second infusion (3 seconds total). Postinfusion sleep recordings showed only modest SWS enhancement after the second infusion (3 minutes, 1.3% of total sleep time). He had an increased total sleep time (Table 1) and earlier sleep onset (Supplementary Figure 1). Due to his fragmented sleep, corresponding cycles of sleep were challenging to discern, with DSR showing wide variability. DSR for preinfusion Night 1 was 1.4 and 2.0 for Night 2. The postinfusion DSR values were 1.6 (Night 1) and 0.41 (Night 2). Before the first propofol infusion, his MADRS score was 13, which increased to 19 after the first infusion. Six months later, his MADRS score was 20.

## DISCUSSION

Disrupted SWS is at the nexus of depression and cognitive dysfunction in older adults, making it a promising treatment target for LL-TRD. Targeting SWS may correct core

depression pathophysiology. Rather than intervening upon a particular neurotransmitter system, we aim to promote SWS to facilitate optimal cognitive and mental health. Using propofol as a therapeutic probe to engage endogenous sleep circuitry may yield new pharmacologic and nonpharmacologic avenues for rapidly alleviating TRD. This strategy mirrors that of the neurosteroid brexanolone[62] to correct pathophysiology associated with postpartum depression.

The above case series offers mixed support and proof-of-concept that propofol can enhance SWS and improve depression. Of the two patients, one exhibited induction of EEG slow waves during propofol infusions, enhancement of SWS on postinfusion nights, and a sustained improvement in depression lasting at least several months. While it is possible that burst suppression contributed to her antidepressant response, the duration of burst suppression observed here was less than 20% of the target duration that improved depression in a prior study that utilized ten propofol infusions.[54] The second patient did not demonstrate EEG slow waves during infusions, SWS enhancement on postinfusion nights, nor improvement in depression. He received a lower total propofol dose. Both participants showed a potential cumulative effect of serial infusions, as the duration of SWS increased more after the second infusion than the first. A corresponding shift of the DSR from low values into the range expected for nondepressed individuals (> 1.5) was observed for Case 1, while Case 2 showed limitations in evaluating this metric. Future study will be needed to assess whether patients with low preinfusion DSR values will be most responsive to any propofol-induced SWS enhancement. These data provide evidence that targeting slow waves during infusions may have a different effect on sleep homeostasis than targeting other EEG patterns. The case series supports two distinct but related hypotheses, 1) that targeting EEG slow waves during propofol infusions may facilitate subsequent SWS enhancement, and 2) that SWS enhancement may improve depression. The latter can also be expressed as a precision medicine hypothesis, that patients with LL-TRD and concomitant SWS deficiency will show an antidepressant effect from propofol only if their SWS improves. This hypothesis is consistent with the experimental therapeutics agenda of the National Institute of Mental Health, which proposes that novel treatments should both engage a target (in this case SWS enhancement) and improve an outcome (depression).

We acknowledge limitations and alternative explanations for improvement. The improvements for Case 1 could have been related to a placebo effect, but this is somewhat unlikely given the duration of the response.

There are several explanations for the lack of SWS enhancement in Case 2. This patient did not show EEG slow waves during propofol infusions, which may be necessary for subsequent SWS enhancement. He did not show SWS before infusions, but baseline SWS may be required for enhancement. This patient’s OSA may be a contributing factor, as well. The many abnormalities in sleep architecture that are associated with OSA may hinder SWS enhancement. These data demonstrate that this approach may lead to clinical improvements in only a subset of patients, depending on their baseline characteristics (e.g., the presence of SWS at baseline or lack of OSA).

We acknowledge additional changes in sleep architecture following propofol infusions. Both participants had earlier sleep onset after infusions compared to preinfusion times. The earlier times of sleep onset and offset after infusions could reflect phase advance in circadian rhythms. Total sleep time decreased after infusions for Case 1 but increased for Case 2, such that sleep restriction could have contributed to the effects (Table 1). However, sleep restriction typically has a short duration of effect, which is inconsistent with the persistence of the response in Case 1 seven weeks after the intervention. REM duration also generally decreased after propofol infusions. These changes will require future consideration.

Our next step in this research is an ongoing Phase I trial of 15 patients with LL-TRD. This trial expands evaluation of psychiatric outcomes to include anhedonia and cognitive function and includes a more extensive follow-up period. Prior to enrollment, participants will be screened for current depression symptoms with the Patient Health Questionnaire-9 (PHQ-9). At enrollment, the study team will administer the Columbia Suicide Severity Rating Scale (C-SSRS), MADRS, Montreal Cognitive Assessment (MoCA), and Snaith-Hamilton Pleasure Scale (SHAPS) to assess baseline suicidality, depression severity, cognitive ability, and anhedonia, respectively. In addition, participants will record two nights of baseline sleep using the Dreem headband. Participants will then undergo high-density EEG monitoring during two propofol infusions administered 2−6 days apart. Propofol will be individually dosed to maximize induction of EEG slow waves during infusions. The Feeling Scale will be employed to gauge participants' affect before and after infusions. The C-SSRS, MADRS, and SHAPS will be repeated approximately seven days after the second infusion. On the night of each infusion, participants will record overnight sleep EEG. They will record up to five additional nights over three weeks following the second infusion. We will assess for SWS enhancement and changes in DSR. Postintervention psychiatric assessments, including the C-SSRS, MADRS, MoCA, and SHAPS, will be performed approximately three weeks after the second infusion. The study visit will also entail a high-density EEG recording without propofol sedation. Finally, outcomes will be assessed approximately ten weeks after the second infusion. This Phase I trial will lay the groundwork for a subsequent randomized controlled trial elucidating the relationships between disrupted SWS, depression, and cognitive dysfunction in those with LL-TRD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## DISCLOSURE

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BJAP has a patent pending on control of anesthetic state modulation and an agreement with Elemind on the use of nonpharmacologic potentiation of EEG slow waves. EJL reports consulting fees from Merck, Boehringer-Ingelheim, Pritikin ICR, IngenioRx, and Prodeo, grant funding from Janssen, the COVID Early Treatment Fund, and Fast-Grants, and a patent pending on sigma-1 receptor agonists for COVID-19. BPL reports consulting fees from Merck and Eli Lilly. He is also on the Scientific Advisory Board for Beacon Biosignals. RLR, OH, and EL

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## DATA STATEMENT

These data were presented by poster at the Center on Biological Rhythms and Sleep Research Symposium in St. Louis, MO, May 2022 and during the Foundation for Anesthesia Education and Research poster session at the American Society of Anesthesiologists Annual Meeting in New Orleans, LA, October 2022.

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## HIGHLIGHTS

- What is the primary question addressed by this study?

  Can propofol enhance slow wave sleep in geriatric patients to address core pathophysiology of depression and associated cognitive dysfunction?

- What is the main finding of this study?

  Two older adults with treatment-resistant depression received two morning infusions of propofol. One of the two demonstrated slow wave sleep enhancement and a sustained improvement of depression.

- What is the meaning of the finding?

  The above case series lays the groundwork for an ongoing open-label Phase I clinical trial by providing proof-of-concept of propofol-induced slow wave sleep enhancement and antidepressant response.

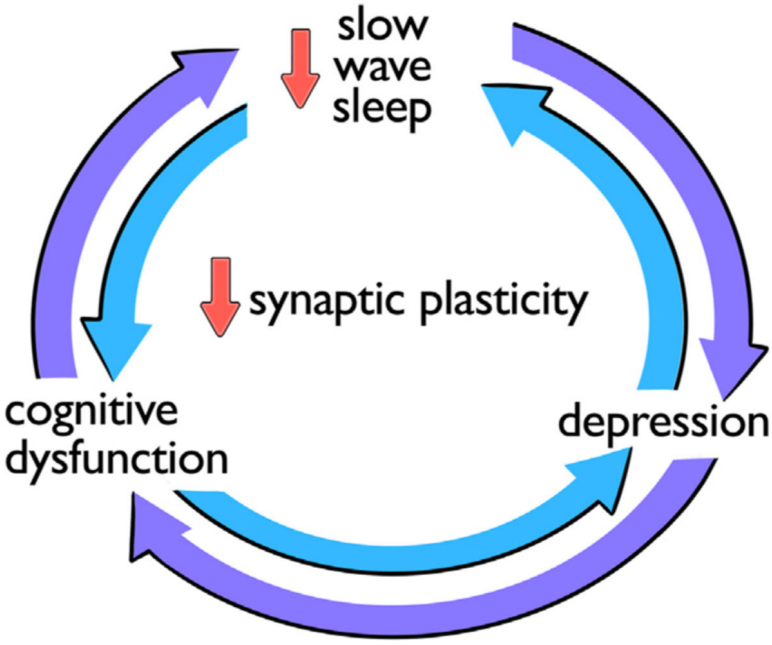


**FIGURE 1.**

Bidirectional relationships are thought to exist between disrupted slow wave sleep, cognitive dysfunction, and depression. Abnormalities in slow wave sleep, a crucial period for synaptic plasticity, is a potential mechanistic link underlying these relationships.

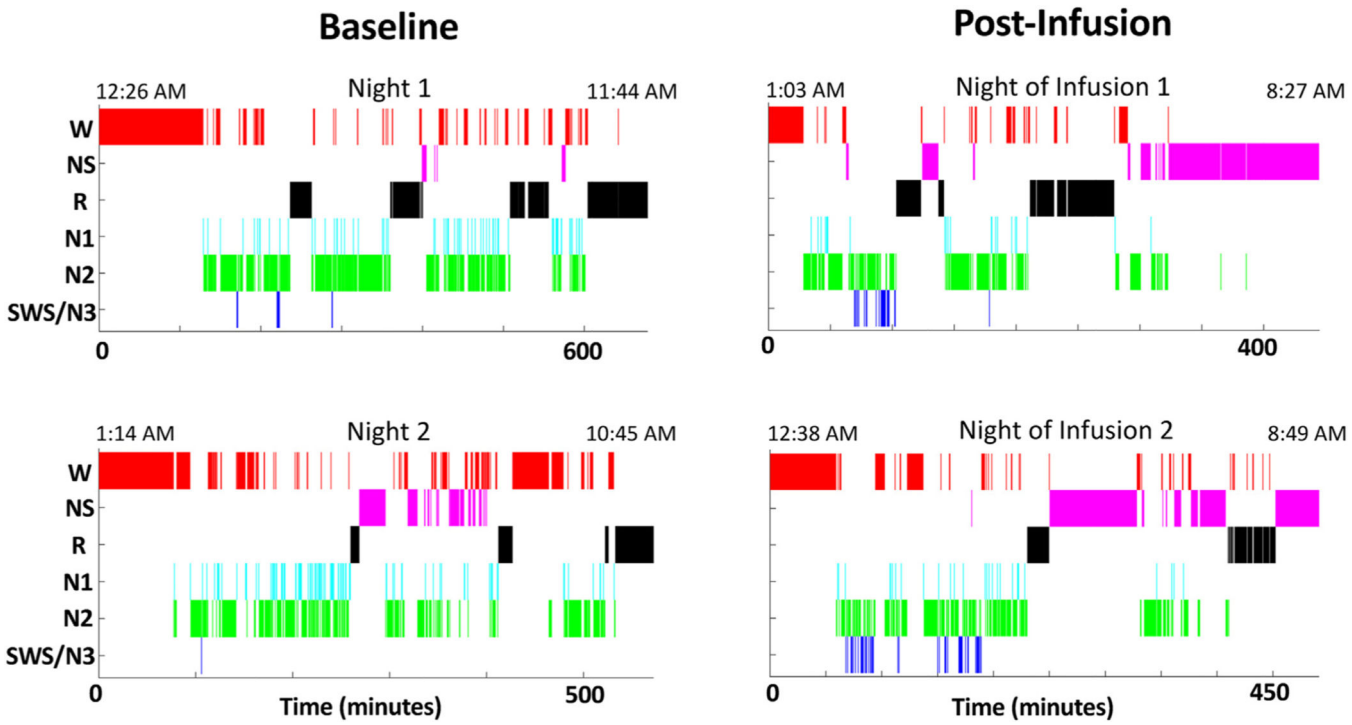


**FIGURE 2.**

Hypnograms were generated from sleep electroencephalographic (EEG) data recorded by a 71-year-old woman with treatment-resistant depression. The patient provided EEG recordings before and after receiving propofol infusions. Both baseline sleep recordings were conducted prior to Infusion 1. Sleep onset occurred at 2:35 A.M. and 2:48 A.M., respectively, for the first and second preinfusion nights. Postinfusion EEG recordings were conducted on the night following each morning propofol infusion. Sleep onset occurred at 1:31 A.M. and 1:37 A.M., respectively, for the first and second postinfusion nights. After each infusion, the patient exhibited slow wave sleep enhancement and earlier sleep onset compared to baseline. W = awake, NS = nonscorable epochs, R = rapid eye movement (REM) sleep, N1 = non-REM stage 1 sleep, N2 = non-REM stage 2 sleep, N3 = non-REM stage 3 sleep, SWS = slow wave sleep.

**TABLE 1.**

Two Older Adults With Treatment-Resistant Depression Recorded at-Home Sleep Electroencephalograms (EEG) Before and After Receiving Morning Propofol Infusions

| | | Average Baseline Minutes (% Total Sleep Time) | Night of Infusion 1 Minutes (% Total Sleep Time) | Night of Infusion 2 Minutes (% Total Sleep Time) |
|---|---|---|---|---|
| **Case 1** | **Total sleep time** | 378.5 | 235 | 226 |
| | **N3/SWS** | 2.8 (0.7) | 12.5 (5.3) | 24 (10.6) |
| | **REM** | 122.5 (32.4) | 88.5 (37.7) | 57 (25.2) |
| **Case 2** | **Total sleep time** | 171.8 | 314.5 | 230.5 |
| | **N3/SWS** | 0 (0) | 0 (0) | 3 (1.3) |
| | **REM** | 52.8 (30.7) | 92.5 (29.4) | 22.5 (9.8) |

Case 1 was a 71-year-old woman. Case 2 was a 77-year-old man. Metrics from two nights of sleep (recorded prior to Infusion 1) were averaged to generate baseline sleep measures. Both participants exhibited slow wave sleep (SWS) deficiency at baseline. Participants conducted additional sleep EEG recordings at home on the nights after each infusion. Case 1 demonstrated SWS enhancement after each propofol infusion. Case 2 demonstrated minimal SWS enhancement after the second propofol infusion. Both participants generally exhibited reduced REM duration after infusions. TST = total sleep time, REM = rapid eye movement sleep, N3 = non-REM stage 3 sleep, SWS = slow wave sleep.

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