

#10 Propofol Enhancement of Slow Wave Sleep as a Putative Mechanism for Treating Depression in Older Adults: A Pilot Study

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Background/Introduction: Propofol is a commonly used anesthetic that serves as a positive allosteric modulator of GABAA receptors. Rodent models have demonstrated the ability of propofol to address homeostatic needs for non-rapid eye movement sleep. In small clinical trials, propofol has shown some promise as a novel antidepressant and enhancer of slow wave sleep (SWS) in patients with insomnia. While sleep disturbances have been recognized as a core pathophysiology of depression, it remains unknown whether promoting SWS may be important for enhancing response to oral antidepressants. We utilized propofol as a therapeutic probe in a mechanistic trial to address whether 1) propofol may augment an oral antidepressant regimen in geriatric patients with treatment-resistant depression, and 2) whether antidepressant effects are mediated through SWS enhancement.

Methods: Sixteen depressed participants, age 60 years and older who failed at least 2 oral antidepressant trials, were enrolled in an open-label trial. Participants were instructed to maintain a consistent oral antidepressant regimen throughout the study period. Two 2-hour propofol infusions were administered 2-6 days apart, with real-time monitoring to target maximal induction of slow waves on 64-channel high-density electroencephalographic (EEG). The Eleveld pharmacokinetic (PK) model was utilized for target-controlled infusions to allow stepwise titration of propofol based on the EEG, enable stable modeled brain effect-site concentrations, and post-hoc evaluation of drug exposure durations. Wireless wearable headbands were utilized to acquire at-home EEG during overnight sleep before and up to two weeks after infusions. Recordings were scored manually by AASM-registered technologists. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Assessments were performed within one week before the infusions and approximately 1-, 3-, and 10-weeks afterwards. Changes from baseline were calculated. Exposure durations were calculated for different ranges of modeled brain PK effect-site concentrations. Linear regressions and slope tests were utilized to evaluate associations. Nonparametric Mann-Whitney U-tests were utilized to evaluate difference in medians. The investigation was registered on ClinicalTrials.gov (NCT04680910).

Results: There were no serious adverse events and only one withdrawal. Results were based on the fifteen participants who completed both infusions. Post-infusion MADRS scores were reduced compared to baseline at 1-week (median change -4, 95%CI [-7,1], $p=0.014$), 3-weeks (median change -5, 95%CI [-13,1], $p=0.026$), and at 10-weeks (median change -3, 95%CI [-11,1], $p=0.010$). Weight-adjusted average propofol dose negatively correlated with MADRS changes at 1-week ($r^2=0.32$, $p=0.029$), 3-weeks ($r^2=0.52$, $p=0.003$), and 10-weeks ($r^2=0.41$, $p=0.010$) after the second infusion (**Figure 1**). Average change in duration of SWS on infusion nights correlated with post-infusion reductions in MADRS scores at 1-week ($r^2=0.27$, $p=0.047$) and 3-weeks ($r^2=0.28$, $p=0.040$). Duration of exposure at moderate modeled propofol effect-site concentrations (2.5-4.5 mcg/ml) correlated with SWS enhancement on nights following infusions ($r^2=0.28$, $p=0.04$) and MADRS changes at 3-weeks ($r^2=0.42$, $p=0.009$).

Conclusions: These open-label trial findings suggest that serial propofol infusions may augment oral antidepressant therapy in geriatric patients in a dose-dependent manner. Enhancement of post-infusion SWS is a potential mechanism for subsequent antidepressant response. These safety, feasibility, and response data support an ongoing experimental double-blind randomized controlled trial (ClinicalTrials.gov NCT06867549).

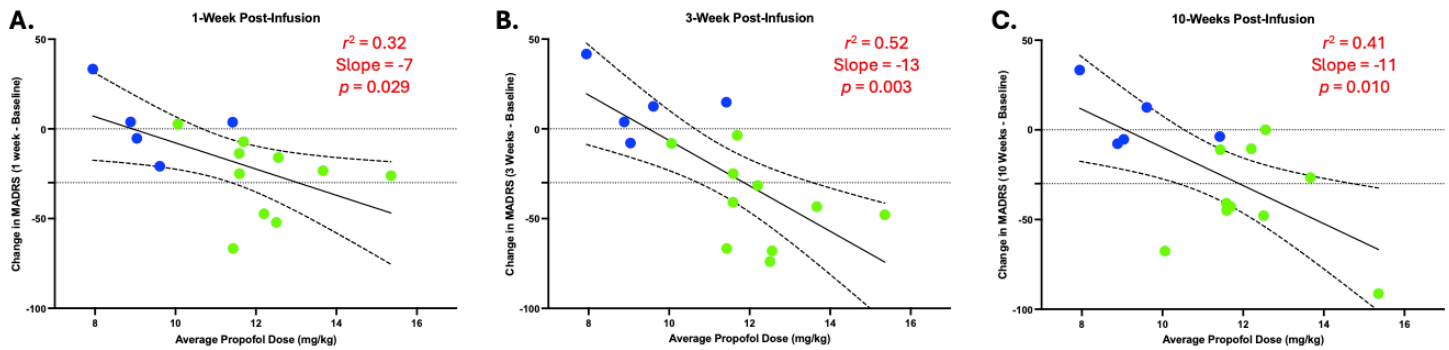


Figure 1. Average weight-based propofol dose as a predictor of relative change in MADRS at 1-, 3-, and 10-weeks after the second infusion. A. Percentage change in baseline MADRS at 1-week correlates inversely with average propofol dose administered during the two infusions. **B.** A stronger association is noted at 3-weeks post-infusion. **C.** Average propofol dose predicts percentage change at 10-weeks. Blue symbols indicate 5 non-responders, with 30% of baseline threshold indicated on the graphs. Green symbols denote 10 responders, defined as individuals who had at least 30% change in baseline MADRS during the 10-week follow-up period.