

# PSYCHIATRY ALERTS NOS

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## Ketamine Anesthesia and ECT Outcomes

Compared with propofol-based anesthesia, ketamine-based anesthesia reduced the number of ECT sessions needed for response in patients with treatment-resistant depression in a randomized trial.

**Methods:** Study participants had a diagnosis of treatment-resistant depression, a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of  $\geq 20$ , and had been referred to a university hospital for ECT treatment. Patients were randomly assigned to anesthesia with either ketamine or propofol, both used in conjunction with remifentanyl and succinylcholine. The study pharmacist prepared the anesthesia beforehand, and the anesthesiologist was permitted to vary the doses of the other agents, without being aware of the randomized treatment. All patients were enrolled for 8 ECT sessions, 2 or 3 times per week, with unilateral or bilateral electrode placement and ECT parameters determined by the attending psychiatrist. The MADRS was administered 1 day after each ECT session and 30 days after the final session. The primary study outcome was the number of ECT sessions needed to achieve response, defined as a  $\geq 50\%$  reduction in MADRS score. Remission was defined as a MADRS score of  $\leq 10$ . The study was terminated after an interim analysis due to early efficacy results.

**Results:** Of the 27 study participants, all 14 patients in the ketamine group and 10 of 13 in the propofol group met MADRS criteria for response. The median number of treatments before response was 2 for ketamine and 4 for propofol ( $p=0.01$ ). All patients in the ketamine arm achieved remission, which occurred after a median of 3 treatments. In the propofol group, 7 patients achieved remission after a median of 7 sessions. A single patient in each group experienced a relapse of depression during the 30-day follow-up. There were no significant differences between the 2 anesthetics in adverse effects, which included hemodynamic changes, nausea/vomiting, and headache. Ketamine resulted in no dissociation and only rare memory impairment, but the dose was relatively low. Average time from anesthesia induction to discharge readiness was the same in both groups, about 1 hour.

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**Discussion:** Earlier studies and meta-analyses of ketamine-based anesthesia in ECT have had conflicting results. Inconsistencies may have resulted from differences in electrode placement, stimulus parameters, ketamine dosing, or the use of sedatives that can suppress seizures and reduce the efficacy of ECT. Although the present results are positive, they require replication. In addition, the potential adverse cardiovascular effects of hemodynamic changes associated with ketamine administration should be evaluated.

**Study Rating\*—17 (100%):** This study met all criteria for a randomized controlled trial.

Gamble J, Bi H, Bowen R, Weisgerber G, et al: Ketamine-based anesthesia improves electroconvulsive therapy outcomes: a randomized-controlled study. *Canadian Journal of Anesthesia* 2018; doi 10.1007/s12630-018-1088-0. From the University of Saskatchewan, Canada. **Funded by the University of Saskatchewan; and the Royal University Hospital Foundation. The authors declared no competing interests.**

**Common Drug Trade Names:** ketamine—*Ketalar*; propofol—*Diprivan*; remifentanyl—*Ultiva*; succinylcholine—*Anectine*

\*See Reference Guide.

## TMS Augmented by Behavioral Activation Therapy

Results of a pilot study suggest that adding behavioral activation therapy (BAT), modified to be delivered during transcranial magnetic stimulation sessions, is feasible and has the potential to improve outcomes in patients with resistant depression.

**Background:** Both TMS and BAT have been shown to be effective in the treatment of major depression. TMS has been shown to increase reward learning and may have the ability to "prime" patients to be more sensitive to reinforcements from BAT activities. Ordinarily, BAT is delivered in 45–60 min weekly sessions by providers trained in counseling. The present study was undertaken to investigate whether BAT could be adapted to be delivered by TMS technicians during sessions.

**Methods:** The investigators developed a protocol in which BAT was modified to fit the structure of daily TMS sessions. Treatment was provided by nurses or Bachelor's-level technicians who had completed about 10 hours of training. Patients were introduced to BAT during the first week of TMS, and engagement in activities began in week 2. Patients' progress was assessed during the first 5–10 min of each session, before starting TMS, and the next behavioral goal was discussed after TMS. Target activities were selected using an abbreviated version of the Pleasant Events Schedule. Depression was assessed as part of routine care, using the self-report Inventory of Depressive Symptomatology (IDS-SR), the 9-item Patient Health Questionnaire (PHQ-9), and the Snaith-Hamilton Pleasure Scale (SHAPS), a 14-item self-report measure of anhedonia. Criteria for response were a  $\geq 50\%$  decrease from baseline in the IDS-SR and the PHQ-9. A  $\geq 50\%$  change in SHAPS score indicates a significant decrease in anhedonia.

**Results:** A preliminary analysis was performed on data collected over 14 weeks from 11 patients, all women. Patients had completed a mean of 33 TMS sessions. They set a mean of 18 behavioral activation goals and completed a mean of 14. A total of 6 patients (55%) met clinical criteria for response. Mean decreases on the standardized depression measures ranged from 39% for the SHAPS to 55% for the PHQ-9. Although it did not reach statistical significance, patients' percent of goal completion correlated positively with change in measures of depression severity. After treatment completion, many patients said they intended to continue applying behavioral activation in their daily lives. TMS technicians reported anecdotally that BAT did not impair the flow of TMS delivery and that it enhanced the quality and efficiency of daily clinical assessments.

**Discussion:** Although the study was inadequately powered to demonstrate a significant relationship between BAT participation and depression symptom measures, the overall positive

direction of the correlations suggests that further investigation is warranted. Future studies should compare the combination of BAT and TMS with standard TMS alone in a larger sample.

Russo G, Tirrell E, Busch A, Carpenter L: Behavioral activation therapy during transcranial magnetic stimulation for major depressive disorder. *Journal of Affective Disorders* 2018;236 (August 15):101–104. From Alpert Medical School of Brown University, Providence, RI; and other institutions. **This study was conducted without specific funding. The authors declared no competing interests.**

## Smartphone Intervention for Serious Mental Illness

In a randomized trial in patients with serious mental illness, a smartphone-based self-management intervention and a clinic-based program had similar effects. Both treatments had high patient satisfaction, but the mobile phone-based health (mHealth) intervention higher rates of patient engagement.

**Methods:** FOCUS, the mHealth intervention, was compared with the Wellness Recovery Action Plan (WRAP), a clinic-based group intervention widely used for patients with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. The interventions were delivered over 12 weeks at a large mental health services agency in the Midwestern U.S. FOCUS consists of a smartphone app, a clinician dashboard, and an mHealth support specialist. The app has daily self-management prompts and assessments and on-demand video or audio content about auditory hallucinations, mood, sleep, social functioning, and medication. Study participants received brief weekly calls from an mHealth specialist for technical and clinical support. WRAP is an in-person group program led by trained facilitators, with similar goals and techniques to FOCUS. Patients were randomly assigned to 1 of the 2 interventions in 12-week parallel-group cycles. The primary clinical outcome, assessed by blinded raters, was change from baseline to post-treatment (3 months) and follow-up (6 months) in general psychopathology, measured using the brief Symptom Checklist-9 (SCL-9).

**Results:** A total of 163 patients (mean age, 49 years; 59% men) were randomized. About half of participants had schizophrenia or schizoaffective disorder, 28% had bipolar disorder, and 23% had major depression. More than two-thirds had previously used a smartphone.

After randomization, 90% of patients randomized to FOCUS started using the app, compared with the 58% of the WRAP group who attended the first clinic session ( $p < 0.001$ ). Although daily use of FOCUS declined during the trial, patients used the app on at least half of the days in every week, averaging 5.4 days in the first week and 3.8 days in the final week. Patients were more likely to fully engage in FOCUS than WRAP for  $\geq 8$  weeks (56% vs 40%;  $p = 0.03$ ). Mean posttreatment satisfaction was similar for the 2 interventions.

Results of treatment did not differ between the 2 groups for any of the primary or secondary clinical outcomes at 3 months. Mean SCL-9 scores decreased significantly from baseline to 3 months and 6 months in both the FOCUS and WRAP groups. The 2 interventions were associated with similar significant improvements on the Beck Depression Inventory and the Recovery Assessment Scale at 6 months. Neither group demonstrated significant improvement in Psychotic Symptom Rating Scales score or quality of life at 3 months, although these measures did reach significance at 6 months in the FOCUS group.

**Study Rating\*—17 (100%):** This study met all criteria for a randomized controlled trial.

Ben-Zeev D, Brian R, Jonathan G, Razzano L, et al: Mobile health (mHealth) versus clinic-based group intervention for people with serious mental illness: a randomized controlled trial. *Psychiatric Services* 2018; doi 10.1176/appi.ps.201800063. From the University of Washington, Seattle; and other institutions. **Funded by the Patient-Centered Outcomes Research Institute. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Treating Nightmare Disorders

Nightmare disorders are common, affecting 4% of the U.S. adult population. Diagnostic criteria proposed in the third edition of the International Classification of Sleep Disorders are repeated occurrences of extended, extremely dysphoric dreams; rapid alertness on awakening; and clinically significant distress or impairment in important areas of functioning. Nightmares may occur without comorbid psychopathology or may be associated with such disorders as depression, anxiety, substance abuse, borderline personality, PTSD, and schizophrenia-spectrum disorders. PTSD-associated nightmares have been the most studied.

An updated position paper from the American Academy of Sleep Medicine acknowledges that there is limited direct evidence for most of the available treatment options. The task force based its treatment recommendations on clinical expertise and qualitative assessment of the evidence, rather than using an evidence grading system. Of the many treatments available (see table), only 1 is recommended by the position paper task force: image rehearsal therapy for PTSD-associated nightmares and nightmare disorder. A few medications are "not recommended" for nightmare disorder because of evidence that they are ineffective or harmful. Most treatment options are categorized as "may be used," based on less clear evidence or consensus. The treatments in the table are listed in alphabetical order as there is no order of preference.

The only "recommended" therapy, image rehearsal therapy, is a modified CBT technique that involves altering the content of a nightmare by creating a new set of positive images and rehearsing the rewritten dream scenario daily while awake. Multiple randomized trials have evaluated the effects of this treatment on various outcomes. In a 6-month trial in 168 women survivors of sexual assault, 3 sessions of image rehearsal therapy reduced nightmare frequency by about 65%. Other trials with smaller sample sizes have described similar results. Patient populations have included veterans with PTSD and

Treatment options for nightmares in adults with PTSD-associated nightmares		
Behavioral or Psychological		
Recommended	Image rehearsal therapy	
May be used	Cognitive behavioral therapy (CBT) CBT for insomnia Exposure, relaxation, and rescripting therapy Eye movement desensitization and reprocessing	
Pharmacologic		
May be used	Aripiprazole Clonidine Cyproheptadine Fluvoxamine Gabapentin Nabilone Olanzapine	Phenelzine Prazosin <sup>‡</sup> Risperidone Topiramate Trazodone Tricyclic antidepressants
Treatment options for nightmare disorder		
Behavioral or Psychological		
Recommended	Image rehearsal therapy	
May be used	CBT Exposure, relaxation, and rescripting therapy Hypnosis Lucid dreaming therapy Progressive deep muscle relaxation	Sleep dynamic therapy Self-exposure therapy Systematic desensitization Testimony method
Pharmacologic		
May be used	Nitrazepam Prazosin <sup>‡</sup> Triazolam	
Not recommended	Clonazepam Venlafaxine	
<sup>‡</sup> Downgraded from a previous "recommended" status based on a recent negative study in >300 veterans with PTSD		

patients with chronic nightmares, generalized anxiety disorder, or various comorbid psychiatric disorders. A single trial in veterans with PTSD reported no benefit.

Morgenthaler T, Auerbach S, Casey K, Kristo D, et al: Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine position paper. *Journal of Clinical Sleep Medicine* 2018;14 (June 15):1041–1055. From the Mayo Clinic, Rochester, MN; and other institutions. **Funded by the American Academy of Sleep Medicine. The study authors declared no competing interests.**

**Common Drug Trade Names:** aripiprazole—*Abilify*; clonazepam—*Klonopin*; clonidine—*Catapres*; cyproheptadine—*Periactin*; fluvoxamine—*Luvox*; gabapentin—*Neurontin*; nabilone—*Cesamet*; nitrazepam (not available in the U.S.)—*Mogadon*; olanzapine—*Zyprexa*; phenelzine—*Nardil*; prazosin—*Minipress*; risperidone—*Risperdal*; topiramate—*Topamax*; trazodone—*Desyrel*; triazolam—*Halcion*; venlafaxine—*Effexor*

## Circadian Activity and Mood

In a large, cross-sectional, population-based study, disrupted circadian rhythmicity was associated with depression, bipolar disorder, subjective wellbeing, personality, and cognitive performance. Reduced circadian amplitude, easily measured with a wrist accelerometer, may be a core feature of depressive and bipolar disorders and may help identify patients who could benefit from specific therapies.

**Background:** Circadian disruption is a known feature of mood disorders, but most research to date has focused on sleep-related factors or self-reported preferences for morning or evening activity. Using data from the large U.K. Biobank general population cohort, which includes objectively measured circadian rhythmicity parameters, the present study evaluated associations between circadian rhythmicity and mental health and wellbeing phenotypes, including lifetime history of mood disorder.

**Methods:** Study participants were selected from >500,000 adults enrolled in the U.K. Biobank project. At the baseline assessment, in 2006–2010, participants provided data on demographics, smoking, and other covariates. Accelerometer data were collected during 2013–2015 from >100,000 participants who wore the devices for 7 days during normal life. For the present analysis, the cohort was divided into quintiles based on relative amplitude of activity—i.e., the difference between the most active continuous 10-hour period and the least active 5-hour period in an average 24-hour day. Relative amplitude ranges from 0 to 1, with lower values attributable to increased nighttime activity, reduced daytime activity, or both. Cohort members with sleep disorders or insomnia were excluded from the sample. A total of 91,105 participants also completed an online version of the Mental Health Questionnaire (MHQ) in 2016–2017 and were included in the present analysis. The MHQ assessment, completed an average of 1.85 years after accelerometer recordings, obtained information on childhood trauma, lifetime mood disorders, subjective wellbeing, loneliness, and neuroticism. Brief online cognitive tests were also completed at this time.

**Results:** The mean relative amplitude of circadian activity in the entire population was 0.87 (range, 0.121–0.997). Lower amplitude was associated with higher prevalences of major depressive disorder and bipolar disorder and with higher ratings for neuroticism and loneliness. (See table). Higher amplitudes were

Reduction in relative amplitude and mental health and wellbeing outcomes <sup>†</sup>		
Outcome	Odds Ratio*	Significance
Lifetime major depressive disorder	1.06	p<0.0001
Lifetime bipolar disorder	1.11	p=0.007
Mood instability	1.02	p=0.004
Neuroticism	1.01	p<0.0001
Happiness	0.91	p<0.0001
Health satisfaction	0.90	p<0.0001
Loneliness	1.09	p<0.0001
Reaction time	1.75	p<0.0001

<sup>†</sup>Fully adjusted model (i.e., age, gender, ethnicity, socioeconomic deprivation, smoking status, alcohol intake, body mass index, and childhood trauma). Odds ratios represent the increase in incidence associated with a 1-quintile reduction in relative amplitude of activity.

associated with better subjective ratings of happiness and health satisfaction. Participants with lower-amplitude rhythmicity performed more poorly on the reaction time test, a measure of general neurocognitive function.

**Discussion:** The present study, with its very large sample size and control for various confounders, confirms the association of circadian disruption with mood disorders, risk factors for mood disorders, and neurocognitive impairment. However, because the data are cross-sectional, the results cannot address causality of the association.

Lyall L, Wyse C, Graham N, Ferguson A, et al: Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *Lancet Psychiatry* 2018;5 (June):507–514. From the University of Glasgow, U.K.; and other institutions. **Funded by the Wellcome Trust; and other sources. One study author disclosed a potentially relevant relationships; the remaining 14 authors declared no competing interests.**

\*See Reference Guide.

## Reference Guide

**Odds Ratio:** A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at [www.alertpubs.com](http://www.alertpubs.com).

**"Change is the law of life and those who look only to the past or present are certain to miss the future."—John F. Kennedy**

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