Sleep and circadian profiles stratify antidepressant response to ketamine in young people: bridging clinical care and public health

Planning J.V. Saw[1], Elise McGlashan[2], Orli S. Schwartz[1], Christopher G. Davey[1]

[1]Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia

[2]School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia

Abstract

Background: Major depressive disorder is a leading cause of disability among young people, yet current treatments demonstrate limited efficacy.[1] Subcutaneous ketamine shows promise for treatment-resistant depression, but individual variability in response remains poorly understood.[2] Sleep and circadian disturbances are prevalent in youth depression and may influence antidepressant outcomes through mechanisms involving synaptic plasticity and circadian regulation.[3]

Aim: To investigate whether baseline and post-treatment sleep and circadian activity metrics moderate or mediate the antidepressant effects of subcutaneous ketamine in young people with moderate-to-severe depression.

Methods: Data were drawn from 110 young people aged 16-25 years old enrolled in the SKY-D trial, a multi-site, double-blind randomised controlled trial (RCT) comparing subcutaneous ketamine with active control (midazolam).[4] Subjective sleep quality (Pittsburgh Sleep Quality Index) and chronotype (Reduced Morningness-Eveningness Questionnaire) were assessed at baseline. Objective metrics were derived from wrist-worn actigraphy across three domains: circadian and activity patterns, sleep continuity, and sleep fragmentation and light exposure. Depression was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, 24 hours, and 1 week post-first treatment. In this exploratory analysis, moderation models examined whether baseline sleep metrics predicted differential treatment responses, with sensitivity analyses excluding statistical outliers identified via Mahalanobis distance. All models were adjusted for baseline MADRS.

Results: Ketamine produced a greater acute reduction in depressive symptoms at 24 hours (mean difference -4.7 MADRS points, p =0.021), but this was not sustained at 1 week (25.1 vs 27.2, p =0.179). Despite this, objective sleep and circadian metrics significantly moderated ketamine's 1-week response. Three baseline actigraphy-derived metrics remained robust moderators after sensitivity analyses: longer sleep period time, lower 24-hour physical activity, and lower maximum light exposure each predicted greater antidepressant response to ketamine versus midazolam at 1 week. Simple slope analyses supported clinically meaningful effects for sleep period and physical activity: among participants with longer baseline sleep (+1 SD), ketamine was associated with ~4 points greater improvement in MADRS compared with midazolam (p =0.038), and among those with lower baseline activity (-1 SD), ketamine was associated with ~ 3.3 points greater improvement (p =0.038). For maximum light exposure, the overall moderation remained significant (p=0.032), but the simple slope was marginal (p =0.057). Subjective sleep quality and chronotype did not moderate outcomes, and post-treatment sleep changes did not mediate response.

Conclusion: Objective sleep and circadian characteristics may help identify young people more likely to respond to ketamine's antidepressant effect. These moderation effects emerged despite no overall treatment difference, suggesting actigraphy-based assessment could inform stratified treatment approaches.[5] Future research should investigate whether targeting these modifiable determinants through adjunctive interventions can enhance outcomes and whether these predictors generalise across ketamine regimens and administration routes.

References

1. Hetrick SE, McKenzie JE, Bailey AP, Sharma V, Moller CI, Badcock PB, et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis. Cochrane Database Syst Rev 2021;5(5):CD013674.
2. Xu Y, Hackett M, Carter G, Loo C, Gálvez V, Glozier N, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2016;19(4):pyv124.

3. Lovato N, Gradisar M. A meta-analysis and model of the relationship between sleep and depression in adolescents: recommendations for future research and clinical practice. Sleep Med Rev 2014;18(6):521-529.
4. Schwartz OS, Amminger P, Baune BT, Bedi G, Berk M, Cotton SM, et al. The Study of Ketamine for Youth Depression (SKY-D): study protocol for a randomised controlled trial of low-dose ketamine for young people with major depressive disorder. Trials 2023;24(1):686.
5. Duncan WC Jr, Slonena E, Hejazi NS, Brutsche N, Yu KC, Park L, et al. Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biol Psychiatry 2017;82(5):361-369.