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File: ■ Psilocybin (*Psilocybe* spp., Strophariaceae)
■ Depression
■ Sleep

HC 022146-672

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RE: Daytime Psilocybin Use Interacts with the Sleep Cycle

Dudysová D, Janků K, Šmotek M. The effects of daytime psilocybin administration on sleep: Implications for antidepressant action. *Front Pharmacol*. December 3, 2020;11:602590. doi: 10.3389/fphar.2020.602590.

Sleep is correlated with mood; poor sleep with mood disorders. Psilocybin (PSL; from *Psilocybe* spp., Strophariaceae mushrooms), a serotonergic agonist with possible antidepressant activity, may interact with sleep, and may induce neuroplasticity. A basic mechanism of neuronal adaptation, neuroplasticity is reduced in depression. Slow wave activity (SWA), a marker of the intensity of non-rapid eye movement (NREM) slow wave sleep (SWS), is thought to support synaptic homeostasis and memory functions that are dependent on neuroplasticity. The efficacy of many antidepressants may be related to SWA. Serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) reduce rapid eye movement (REM) sleep duration (SD), and increase sleep latency (SL). Other antidepressants have little or no effect on REM sleep but reduce SL, improve sleep efficiency (SE), and boost SWS.

This randomized, double-blind, placebo (PLA)-controlled, crossover clinical trial (RCT) is the first to report PSL's sleep effects. Macro- and microstructural sleep changes were studied using subjective sleep stage measures and whole-night polysomnography (WNPS) with 19-channel electroencephalography (EEG). Twenty participants (10 male-identifying; aged 28–53 years) took PLA and PSL in separate sessions and underwent WNPS ~ 12 hours after each. Recruitment, demographics, randomization, blinding, and PLA/PSL administration, including, presumably, order of agent administration, are detailed in an earlier report* but not here. Participants did not use any medicines regularly, had no major disorders, and met other criteria. Menstruating participants were tested at times not overlapping with their menses, to reduce hormonal effects; menopausal and postmenopausal adults were excluded. Participants were asked to refrain from psychotropic substances between an initial interview and test sessions, excessive alcohol use in the week before tests, and coffee (*Coffea arabica*, Rubiaceae), tobacco (*Nicotiana tabacum*, Solanaceae), and food intake the morning before tests.

PSL was given in individually calibrated capsules at ~ 9 a.m. on test days. Doses of ~ 0.26 mg/kg body weight were increased 1 mg for every 5 kg and were within 15–22 (mean 18.35 ± 2.21) mg. Psychedelic effects lasting ~ 6.5-8 hours dissipated well before WNPS began. Sessions were held ≥ 28 days apart (mean = 49 days) to avoid any long-lasting PSL effects on sleep. In preparation, 18 participants underwent an adaptation night ≥ 2 days before their

first WNPS session (median = 7.5 days); WNPS procedures are detailed. After each study night, SL, SD, and sleep quality (SQ) were self-rated via Likert scales and sleep stage durations, SL, and SE were computed from WNPS results.

One participant was excluded due to excessive daytime sleepiness; two, technical issues. Data from 17 participants were used. SL, total sleep time (TST), SE, and number of sleep cycles did not significantly differ between PLA and PSL. REM SL significantly increased after PSL (P = 0.048). Duration and proportion of sleep stages did not differ significantly between PLA and PSL, but trended to reduced REM, stage 1 NREM, and stage 3 NREM sleep and increased stage 2 NREM sleep after PSL. Absolute delta power during SWS in the first sleep cycle was significantly lower after PSL then PLA at the average electrode (P = 0.003) and at locally averaged frontal, parietal, temporal, and occipital derivations. After corrections, significant decreases remained at parietal (P = 0.001), temporal (P = 0.004), and occipital (P = 0.006) derivations.

No significant decrease in relative delta was seen at the average electrode but was seen in averaged parietal derivations (P = 0.039) after PSL. There was a trend to reduced relative delta in averaged central derivations for PSL (P = 0.081). There were no significant differences in power spectral density during any sleep stage in relative or absolute power at any frequency band. In total NREM sleep (stages 1–3), significant increases of relative but not absolute power were seen in frontal and parietal sigma band, but after corrections, no changes in absolute or relative power were significant in any band at any derivation. There were no changes in subjective TST or SQ, but significant changes in subjective SL, rated as an average 10.5 minutes longer after PSL vs. PLA (P = 0.028). There were no significant interactions between gender and condition in sleep macrostructure. Nonetheless, in first sleep cycle SWA, female-identifying participants had significantly higher relative delta power than male-identifying, regardless of PLA/PSL condition across all electrodes. This effect was not found locally at frontal, parietal, occipital, or temporal electrodes after corrections. In subjective sleep reports, male-identifying participants had poorer SQ after PSL (P = 0.002); female-identifying did not.

The authors hypothesize that, like SSRIs and some other antidepressants, PSL would reduce REM sleep and prolong REM SL; results were consistent with this notion. They also theorize that PSL would promote SWA in the first sleep cycle; however, results showed significantly lower delta power vs. PLA. This is akin to results for some other serotonin receptor agonists that reduce SWA. PSL's effects on neuron formation are dose- and time-related. Different doses or timing may boost SWS, as seen with SSRIs. Future PSL studies should explore mood effects' links with sleep changes and ideally use a parallel group design with a larger number of participants.

The authors declare no conflicts of interest.

—Mariann Garner-Wizard

*Bravermanová A, Viktorinová M, Tylš F, et al. Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing – study on P300 and mismatch negativity in healthy volunteers. *Psychopharmacol* (Berl). February 2018;235(2),491–503. doi:10.1007/s00213-017-4807-2.

Referenced article can be accessed at https://www.frontiersin.org/articles/10.3389/fphar.2020.602590/full.