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RE: Systematic Review/Meta-analysis of Effects of Psilocybin on Depression and Anxiety


Depression and anxiety raise risks of early death in patients with life-threatening diseases. Major depressive disorder (MDD), with persistent negative thoughts and emotions, affects mood, cognition, motivation, and behavior. Chronic psychological distress reduces treatment adherence and quality of life, prolongs hospital stays, and increases suicidality. Benzodiazepines and antidepressants are used for depression and anxiety in patients with life-threatening diseases. Antidepressants are slow to act, with high relapse rates and significant adverse effects (AEs). Treatment resistant depression (TRD) options include combining, augmenting, or switching drugs, or use of electroconvulsive or other neurostimulation techniques. Higher doses and combined drugs increase risk of AEs.

In March 2019, the FDA approved Spravato® (Jannsen Pharmaceuticals; Beerse, Belgium) for symptoms of MDD, TRD, and suicidality. A nasal spray used with an oral antidepressant, its active compound, S-ketamine, is a non-competitive N-methyl-aspartate (NMDA) glutamate receptor antagonist. Ketamine, a dissociative anesthetic, has euphoric effects that have attracted "recreational" use. Other molecules studied in mood disorders include 3,4-methylenedioxymethamphetamine (MDMA) and psychedelics like lysergic acid diethylamide (LSD) and psilocybin (PSL; from PSL [Psilocybe spp., Strophariaceae] mushrooms). A 2020 meta-analysis (MA) of PSL in depression and anxiety lacked data on patients' prior psychopathologies and PSL's physiological effects. The authors sought to remedy these defects in a systematic review (SR) and MA of clinical trials.

Electronic database searches in January 2020 yielded 722 potentially relevant reports, including eight from reference lists. After duplicate removal (-52) and title and abstract screening (-638), 32 were evaluated for quality (-26). Risk of bias was assessed using Cochrane tools. However, if 26 not meeting criteria were excluded, as stated, six should remain, not seven as claimed. Read in full text, four secondary analyses were excluded.
Three studies included are split into 11 effect sizes (ES) based on post-PSL follow-up times. Forest plots show study-specific ES with 95% confidence intervals (CI). For outcomes of interest, pooled ES in terms of weighted mean difference (WMD) between pre- and post-treatment means of PSL and controls was assessed. Weight given to each study was determined by the precision of its estimates of ES.

Two studies were randomized, double-blind clinical trials; one, a pilot. All were published between 2011-2016. Patients with aggressive cancer and related depression and/or anxiety received PSL (0.2-0.4 mg/kg body weight [bw], or one or three mg/70 kg/bw). Synthetic PSL was given in oral capsules, avoiding nausea and vomiting that often accompany PSL mushroom use. Two studies used niacin 250 mg as control; in one, PSL was used at different dose ratios in two arms. Studies had low risk of bias in most domains, but all had unclear risk of selection bias and one, of allocation concealment. Funnel plots, trim-and-fill, and Egger's regression found publication bias (P > 0.05) for all measures of PSL’s effects on depression and anxiety in terminally ill patients.

Patients had been diagnosed with mood disorders including MDD, generalized anxiety disorder, and others. Beck’s Depression Index (BDI) and State-Trait Anxiety Inventory (STAI-Trait) scores were primary outcomes. Two studies also used STAI-State. Studies were homogenous ($I^2 = 0\%$); a fixed-effects model was used. Pooled effects did not differ in sensitivity analyses (leave-one-out method). For BDI, for 11 ES in 92 patients, intervention was significantly favored vs. control (WMD = -4.589; 95% CI -4.207 to -0.971; P = 0.002). For STAI-Trait, for 11 ES in 92 patients, intervention was significantly favored vs. control (WMD = -5.906; 95% CI -7.852 to -3.960; P < 0.001). For STAI-State, for nine ES in 41 patients, intervention was significantly favored vs. control (WMD = -6.032; 95% CI -8.900 to -3.164; P < 0.001). PSL at all doses tested improved BDI and STAI-Trait scores, but not dose-dependently. The effect was statistically significant vs. controls for BDI at 0.4 mg/kg PSL; for STAI-Trait, 0.3-0.4 mg/kg. PSL induced statistically significant score reductions for 38-189 days for BDI; 14-189 days, STAI-Trait. STAI-State was not included in subgroup analysis.

Secondary outcomes included systolic and diastolic blood pressure (SBP; DBP), and heart rate (HR). PSL increased all three measures significantly; SBP and DBP, for up to five and six hours after intake, and HR, most markedly three to four hours after, with all tending to normalization after ≥ 6 hours. Increases were consistent with PSL effects on the sympathetic nerve system. PSL is unlikely to alter electrocardiograph readings, body temperature, the ionic balance, blood glucose, or cholesterol levels. No AEs were reported in studies included, but PSL AEs have been reported, most of them transient, influenced by many factors. A trained therapy team is essential in seeking PSL benefits.

PSL has been used by humans for millennia to alter consciousness. In preliminary evidence, PSL benefits not only anxiety and depression, but obsessive-compulsive disorder, substance abuse, cluster headaches, and autism. The PSL molecule, similar to endogenous serotonin, was formerly approved for psychopharmacological and clinical research. It was placed in US Schedule 1 of controlled substances in the early 1970s due to rising non-medical use, stifling research. However, research continues. The authors urge that any PSL-containing drugs approved should be listed in Schedule IV.

—Mariann Garner-Wizard

Referenced article can be accessed at https://www.mdpi.com/2227-9059/8/9/331.