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Psilocybin, psychological distress, and suicidality

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Hendricks et al. (2015) found that having ever used any classic psychedelic substance—namely, dimethyltryptamine (DMT), ayahuasca, lysergic acid diethylamide (LSD), mescaline, peyote or San Pedro, or psilocybin—was associated with a significantly reduced likelihood of past month psychological distress (weighted OR = .81 (.72–.91)), past year suicidal thinking (weighted OR = .86 (.78–.94)), past year suicidal planning (weighted OR = .71 (.54–.94)), and past year suicide attempt (weighted OR = .64 (.46–.89)) in the United States adult population. Although these findings comport with an emerging literature suggesting classic psychedelics may be effective in the treatment of mental health conditions and prevention of self-harm, they do not speak to the potential risk profile or therapeutic applications of psilocybin in particular, which is the most commonly examined classic psychedelic in contemporary clinical research. Considering that psilocybin may be a candidate for future approved medical use in the United States, the United Kingdom, and other nations (Bogenschutz et al., 2015; Grob et al., 2011; Johnson et al., 2014; see also Nutt et al., 2013), an analysis of the specific relationships of psilocybin use with psychological distress and suicidality may help inform decisions by the United States Food and Drug Administration and regulatory bodies of other nations. The objectives of the current research, therefore, were to extend the analysis of Hendricks et al. (2015) by evaluating the associations of lifetime psilocybin use, per se, with past month psychological distress, past year suicidal thinking, past year suicidal planning, and past year suicide attempt in the United States adult population. Methods and data analysis were similar to those of Hendricks et al. (2015). Participants in the current study were adult (18 years old) respondents of the National Survey on Drug Use and Health pooled across years 2008 through 2012 with valid data on the variables of interest. To isolate unique associations with psilocybin use, four mutually exclusive groups of respondents were examined: 1. Psilocybin Only (those reporting lifetime use of psilocybin but no other classic psychedelic); 2. Psilocybin & Other Psychedelics (those reporting lifetime use of psilocybin in addition to other classic psychedelics); 3. Non-Psilocybin Psychedelics Only (those reporting lifetime

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use of any classic psychedelic with the exception of psilocybin); and 4. No Psychedelics (those reporting no lifetime use of any classic psychedelic substance). The primary outcome variables were past month psychological distress (yes = 1 or no = 0), past year suicidal thinking (yes = 1 or no = 0), past year suicidal planning (yes = 1 or no = 0), and past year suicide attempt (yes = 1 or no = 0).

Multivariate logistic regression tested the relationships of group membership with the outcome variables while controlling for age, gender, ethnoracial identity, educational attainment, annual household income, marital status, self-reported engagement in risky behavior, and lifetime illicit use of cocaine, other stimulants, sedatives, tranquilizers, heroin, pain relievers, marijuana, 3, 4-methylenedioxymethamphetamine (MDMA)/ecstasy, phencyclidine (PCP), and inhalants. For each regression model, six planned contrasts were conducted: 1) Psilocybin Only vs. No Psychedelics; 2) Psilocybin Only vs. Psilocybin & Other Psychedelics; 3) Psilocybin Only vs. Non-Psilocybin Psychedelics Only; 4) Psilocybin Only and Psilocybin & Other Psychedelics (i.e. all respondents reporting lifetime use of psilocybin) vs. No Psychedelics; 5) Psilocybin Only and Psilocybin & Other Psychedelics vs. Non-Psilocybin Psychedelics Only; and 6) Psilocybin Only and Psilocybin & Other Psychedelics vs. No Psychedelics and Non-Psilocybin Psychedelics Only.

In a recently published study, Johansen and Krebs (2015) investigated the relationships between psychedelic use and mental health problems. Nesvåg et al. (2015) suggest the analyses by Johansen and Krebs (2015) introduced overadjustment bias by controlling for lifetime other illicit substance use. Although overadjustment typically biases results toward the null (Schisterman et al., 2009), this critique also could apply to the prior study showing positive rather than null effects (Hendricks et al., 2015) as well as to the present analyses. Overadjustment bias can be defined as “control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome” (Schisterman et al., 2009: 488). From this perspective, controlling for lifetime other illicit substance use would represent overadjustment as described by Nesvåg et al. (2015) in our analyses if lifetime other illicit substance use were a *consequence* of lifetime classic psychedelic or psilocybin use. Yet, we are unaware of any data indicating that classic psychedelic or psilocybin use is a *cause* of other illicit substance use. Indeed, the accumulated evidence suggests common factors underlie substance use behavior (e.g. impulsivity and disagreeableness; Iacono et al., 2008; Kotov et al., 2010; Morral et al., 2002; Vanyukov et al., 2012; Verdejo-García et al., 2008), and as stated in Hendricks et al. (2015), several lines of research indicate that classic psychedelics including psilocybin have anti-addictive effects. In our estimation, failure to control for lifetime other illicit substance use would represent a failure to account for suicide risk factors (i.e. substance misuse and impulsive-aggressive personality characteristics; see Hendricks et al., 2015) that overlap with, but do not appear to be caused by, classic psychedelic or psilocybin use. We therefore hold that inclusion of the aforementioned covariates is appropriate and likely does not introduce overadjustment bias.

Of the 191,832 respondents, 7550 (2.47% weighted) fell into the Psilocybin Only group, 12,724 (6.49% weighted) fell into the Psilocybin & Other Psychedelics group, 6963 (4.59% weighted) fell into the Non-Psilocybin Psychedelics Only group, and 164,595 (86.42%

weighted) fell into the No Psychedelics group. In multi-variate logistic regression models group membership was significantly associated with past month psychological distress (Wald chi-square = 24.41, $p < .0001$), past year suicidal thinking (Wald chi-square = 17.85, $p = .0005$), past year suicidal planning (Wald chi-square = 26.13, $p < .0001$), and past year suicide attempt (Wald chi-square = 10.95, $p = .01$). Results of planned comparisons are presented in Table 1. As shown in this table, the odds of all four outcomes were reduced in the Psilocybin Only group relative to the No Psychedelics group, the odds of past year suicidal thinking and past year suicidal planning were decreased in the Psilocybin Only group relative to the Psilocybin & Other Psychedelics group, and the odds of past month psychological distress were reduced in the Psilocybin Only group relative to the Non-Psilocybin Psychedelics Only group. Furthermore, the odds of all outcomes except for past year suicidal planning were reduced in the Psilocybin Only and Psilocybin & Other Psychedelics groups relative to the No Psychedelics group, and the odds of past month psychological distress was decreased in the Psilocybin Only and Psilocybin & Other Psychedelics groups relative to both the Non-Psilocybin Psychedelics Only group and the No Psychedelics and Non-Psilocybin Psychedelics Only groups. In sum, the contrasts showing multiple significantly improved outcomes in the Psilocybin Only group and among those who have ever used psilocybin suggest that even among the broader class of classic psychedelics, psilocybin may be associated with the greatest therapeutic potential.

The current findings demonstrate that the potentially beneficial effects of classic psychedelic use reported by Hendricks et al. (2015) extend to psilocybin use per se. Furthermore, these findings suggest that lifetime use of psilocybin but no other classic psychedelic may be especially protective with regard to psychological distress and suicidality. This finding is consistent with data indicating that psilocybin may have the most favorable safety profile of all classic psychedelic substances (Gable 1993, 2004). Psilocybin in particular may thus hold promise as an innovative mental health intervention and suicide prophylaxis. For other indications for which psilocybin is currently being studied (cancer-related anxiety/depression and addictions; Bogenschutz et al., 2015; Grob et al., 2011; Johnson et al., 2014), the present results also address a safety concern. That is, based on the highly sensationalized cultural history of classic psychedelics, some in the public may be concerned that controlled clinical prescription application of psilocybin may increase the risk of suicide. The present data do not provide support for this concern and are consistent with recently renewed clinical research suggesting possible therapeutic applications of psilocybin.

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Table 1
Results of planned contrasts among four groups: Psilocybin Only, Psilocybin & Other Psychedelics, Non-Psilocybin Psychedelics Only, and No Psychedelics

Planned contrasts	Outcome variables			
	Psychological distress OR (95% CI)	Suicidal thinking OR (95% CI)	Suicidal planning OR (95% CI)	Suicide attempt OR (95% CI)
Psilocybin Only vs. No Psychedelics	.70 (.60-.81)[†]	.76 (.64-.90)**	.54 (.36-.82)**	.58 (.35-.94)*
Psilocybin Only vs. Psilocybin & Other Psychedelics	.89 (.75-1.05)	.80 (.67-.96)*	.59 (.43-.81)**	.75 (.49-1.14)
Psilocybin Only vs. Non-Psilocybin Psychedelics Only	.76 (.64-.90)**	.89 (.72-1.09)	.83 (.54-1.27)	1.06 (.62-1.80)
Psilocybin Only and Psilocybin & Other Psychedelics vs. No Psychedelics	.74 (.65-.84)[†]	.85 (.75-.96)*	.70 (.49-1.005) [§]	.66 (.45-.98)*
Psilocybin Only and Psilocybin & Other Psychedelics vs. Non-Psilocybin Psychedelics Only	.80 (.69-.93)**	.99 (.94-1.16)	1.08 (.76-1.52)	1.22 (.80-1.87)
Psilocybin Only and Psilocybin & Other Psychedelics vs. No Psychedelics and Non-Psilocybin Psychedelics Only	.77 (.68-.87)[†]	.92 (.80-1.04)	.87 (.63-1.20)	.90 (.63-1.28)

Note. Psilocybin Only: respondents reporting lifetime use of psilocybin but no other classic psychedelic; Psilocybin & Other Psychedelics: respondents reporting lifetime use of psilocybin in addition to other classic psychedelics; Non-Psilocybin Psychedelics Only: respondents reporting lifetime use of any classic psychedelic with the exception of psilocybin; No Psychedelics: respondents reporting no lifetime use of any classic psychedelic substance; Psychological Distress: past month psychological distress; Suicidal Thinking: past year suicidal thinking; Suicidal Planning: past year suicidal planning; Suicide Attempt: past year suicide attempt; OR: weighted odds ratio; CI: confidence interval. Findings in bold are significant.

[§] $p = .05$,

* $p < .05$,

** $p < .01$,

[†] $p < .0001$.