See commentary by Grossman and Hendricks p000

Decreases in Suicidality Following Psychedelic Therapy:
A Meta-Analysis of Individual Patient Data Across Clinical Trials

Richard J. Zeifman, MA[a,b]; Dengdeng Yu, PhD[c]; Nikhita Singhal, MD[d]; Guan Wang, HBSc[e]; Sandeep M. Nayak, MD[f]; and Cory R. Weissman, MD[d,g,*]

ABSTRACT

Objective: Suicide is a global health concern, and innovative interventions that target suicidality are needed. While psychedelic therapy shows promise for a range of mental health concerns, including suicidality, not all psychedelic therapy trials have published their suicidality results and no meta-analysis has been published on the topic. Therefore, we completed the first meta-analysis of patient-level data on the effects of psychedelics on suicidality.

Data Sources: We conducted a systematic search of MEDLINE, PsycINFO, and PubMed for all psychedelic therapy clinical trials (last search: November 5, 2020).

Study Selection: We identified all psychedelic therapy trials that included a measure or measure-item that assesses suicidality.

Data Extraction: Suicidality data were requested from study authors and extracted using a data extraction form developed for this study.

Results: We identified 8, and successfully collected data from 7, relevant trials. Analysis of standardized mean differences (SMDs) indicated that, relative to baseline, psychedelic therapy was associated with large effect sizes for acute (80–240 min) and sustained (1 day, 1–8 weeks, and 3–4 months) decreases in suicidality (SMD range = −1.48 to −2.36; 95% CI range, −4.30 to 0.23). At 6 months, the effect size was medium (SMD = −0.65; 95% CI, −1.14 to −0.16). Reductions in suicidality were significant at all time points except for 7–8 weeks. Acute and post-acute elevations in suicidality were rare (6.5% and 3.0%, respectively).

Conclusions: Limitations include heterogeneous samples and interventions, as well as limited sample size and number of studies. Results provide preliminary support for the safety of psychedelic therapy and its positive effect on suicidality. Controlled trials that specifically evaluate the effect of psychedelic therapy on suicidality may be warranted.

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[a]Department of Medicine, Imperial College London, London, United Kingdom
[b]Department of Psychology, Ryerson University, Toronto, Ontario, Canada
[c]Department of Mathematics, University of Texas at Arlington, Arlington, Texas
[d]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[e]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[f]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland
[g]Dr Weissman is now at the Department of Psychiatry, University of California San Diego, La Jolla, California
*Corresponding author: Cory R. Weissman, MD, Department of Psychiatry, University of California San Diego, 16918 Dove Canyon Road, Suite 100, Mail Code 8322, San Diego, CA 92127 (cweissman@health.ucsd.edu).

Each year, approximately 800,000 individuals die by suicide, accounting for 1.4% of all deaths worldwide.[1] Suicidality (ie, behaviors including suicidal ideation, planning, and attempts) is an important predictor of suicide[2,3] that is far more prevalent than completed suicide. In 2019, among adults in the United States alone, 1.4 million individuals attempted suicide, 3.5 million individuals made suicide plans, and 12 million individuals reported serious suicidal ideation (ie, thinking seriously about trying to kill themselves).[4] Suicidality is prevalent among individuals with major depressive disorder (MDD),[5] but also occurs independent of MDD[6,7]; for instance, it is common among individuals with life-threatening illnesses such as cancer.[8–10]

Currently, no gold-standard intervention exists for targeting suicidality.[11] While several interventions have been shown to lead to decreases in suicidality (eg, cognitive-behavioral therapy [CBT], electroconvulsive therapy [ECT], and pharmacologic interventions [eg, intravenous ketamine]), these interventions are generally limited by a range of factors. CBT is characterized by modest effect sizes[12,13] and generally requires at least 3–10 sessions to be efficacious.[14] ECT is highly effective at eliminating suicidality in patients with treatment-resistant depression, but is also limited by a lack of accessibility, tolerability, and palatability by patients.[15,16] Although selective serotonin reuptake inhibitors are considered a first-line treatment for MDD, some research suggests that they are no more efficacious than placebo in targeting suicidality and may even increase suicidality in certain populations.[17,18] The effect of ketamine on suicidality is rapid-acting but does not appear to last more than 72 hours,[19] and repeated ketamine administration is associated with significant safety concerns, including the potential for abuse, cognitive impairment, genitourinary side effects, and liver damage.[20,21] While additional pharmacologic interventions have been found to lead to reductions in suicidality, these findings are generally specific to certain populations (eg, clozapine and lithium in the context of psychotic and mood disorders, respectively[22,23]). Additionally, research has found mixed results for the effects of buprenorphine on suicidality among individuals with opioid dependence.[24,25] There is especially limited evidence for pharmacologic interventions that effectively target suicidality within specific populations,

Clinical Points

- Psychedelic therapy was associated with large acute and sustained reductions in suicidality.
- Acute and post-acute elevations in suicidality were rare, providing support for the safety of psychedelic therapy within controlled contexts.
- Additional controlled research is necessary to further evaluate the effects of psychedelic therapy on suicidality.

such as individuals with cancer-related distress.[26] Given these important limitations, researchers have called for the development of novel interventions that rapidly and effectively target suicidality.[26–29]

Psychedelic therapy is a novel mental health intervention that involves the administration of a classic psychedelic substance (ie, a 5-HT_{2A} receptor agonist), such as psilocybin or ayahuasca, in combination with psychological support.[30] Psychedelic therapy has shown promise for a range of mental health concerns (for a review, see Andersen et al[31]), including several that are associated with suicidality, such as MDD[32–35] and psychological distress associated with life-threatening cancer.[36–39] Early research suggests that psychedelic therapy may lead to reductions in suicidality (for a review, see Zeifman et al[40]). For instance, in the context of a randomized controlled trial,[41] among individuals with treatment-resistant depression, a single dose of ayahuasca was associated with large within-group and moderate (but not statistically significant) between-group effect sizes for decreases in suicidality 1, 2, and 7 days after administration. Similarly, secondary analysis[42] of a randomized controlled psilocybin therapy trial examined the effect of psilocybin therapy on suicidality among individuals with distress associated with life-threatening cancer. Results showed large within-group decreases in suicidality at 8 hours post-psilocybin that persisted as long as 6.5 months later. Among individuals with MDD, a waitlist-controlled trial[33] found large and significant decreases in suicidality 1 and 4 weeks after psilocybin therapy (although there was not a significant between-group difference when comparing the immediate- and delayed-treatment groups). In an open-label trial,[43] among individuals with recurrent MDD, a single dose of ayahuasca was associated with large and rapid reductions in suicidality that were sustained 21 days later. Additionally, within an open-label trial,[32] individuals with treatment-resistant depression showed decreases in suicidality 1 and 2 weeks after psilocybin therapy.

While the aforementioned results provide preliminary support for reductions in suicidality following psychedelic therapy, there nonetheless remain several important limitations. First, not all psychedelic therapy clinical trials have reported on suicidality outcomes,[37] which increases the likelihood of publication bias. Second, research to date examining the effect of psychedelic therapy on suicidality has included small samples. Third, 3 of these studies[32,33,41] did not exclude individuals without suicidality at baseline in their analyses, which increases the potential for a floor effect. Fourth, little research has examined whether psychedelic therapy is associated with elevations in acute and post-acute suicidality, which is essential for examining its safety profile. Finally, to date, there has not yet been a meta-analysis on the effects of psychedelic therapy on suicidality. Therefore, to fill these gaps, we identified all published psychedelic therapy clinical trials (ie, clinical trials that included the administration of a classic psychedelic, such as psilocybin, mescaline, *N*,*N*-dimethyltryptamine [DMT], lysergic acid diethylamide [LSD], ayahuasca, or peyote) that included a suicidality measure and/or suicidality item. We then requested all suicidality-related data from study authors and conducted a patient level meta-analysis on the effects of psychedelic therapy on suicidality. Given previous findings, we hypothesized that psychedelic therapy would be associated with significant acute and sustained reductions in suicidality across clinical trials.

METHODS

This meta-analysis is reported following the PRISMA guidelines.[44] The protocol for this study was registered with PROSPERO (CRD42020158443).

Search Strategy and Study Selection

MEDLINE, PsycINFO, and PubMed databases were searched from their respective inception dates, without time or language restrictions, using the following terms: (psychedelic* OR hallucinogen* OR psilocybin OR ayahuasca OR DMT OR dimethyltryptamine OR mescaline OR peyote OR LSD OR lysergic acid diethylamide) AND (mood* OR distress* OR depress* OR suicid* OR PTSD* OR post-trauma* OR post trauma* OR posttrauma* OR anxiety* OR schizophren* OR bipolar). The search was conducted on March 28, 2020, and repeated on November 5, 2020, to retrieve any articles that had been published since the initial search. Reference lists of eligible studies and review articles were manually searched to identify additional relevant studies. Studies were excluded if they focused on psychedelic microdosing or did not examine the effects of a classic psychedelic (eg, 3,4-methyl enedioxymethamphetamine [MDMA], cannabis). Please refer to our recent systematic review[40] (also derived from this search) for a review of qualitative and quantitative outcomes examining the relationship between classic psychedelics (nonclinical classic psychedelic use and psychedelic therapy) and suicidality.

For the present meta-analysis, all records were screened to determine whether they met the following inclusion criteria: (*a*) clinical trial involving the administration of a classic psychedelic (ie, psilocybin, mescaline, DMT, LSD, ayahuasca, peyote)[45] and (*b*) inclusion of a suicidality measure or a measure that included a suicidality item (ie, an item that specifically measured suicidality) at baseline and post–psychedelic administration. Case studies, experimental non-clinical studies, and observational studies were not included. Given that the majority of studies had not published

results related to individual suicidality items, participant-level data were requested from all study investigators who conducted the clinical trials that met study criteria.

Data Extraction

After removal of duplicates, the titles and abstracts of identified records were independently screened by two authors (R.J.Z. and N.S.) using the aforementioned inclusion and exclusion criteria. The full texts of included articles were then screened according to the same eligibility criteria. These two authors (R.J.Z. and N.S.) discussed conflicts to reach consensus, and a third author (C.R.W.) was consulted to resolve disagreements. One author (R.J.Z.) extracted the following data from included studies: study authors, publication year, study design, sample sizes and descriptions of groups, details on interventions, suicidality-specific exclusion criteria, presence of suicide-related adverse event (eg, suicide completion, suicide attempt) attributed to psychedelic therapy, suicidality-related measure or item used, and suicidality assessment schedule. That author (R.J.Z.) contacted the corresponding author of all studies identified as relevant and requested suicidality-related data. In cases in which more than 1 suicidality-related measure/item was included in a study, the following criteria were used to determine which suicidality measure/item was included in our analyses (in the following order): (1) full suicidality measures were selected over suicidality items; (2) suicidality measures/items with more assessment time points were selected; (3) the suicidality item included in the primary outcome measure was selected; and (4) the suicidality item more frequently used within other studies included in this meta-analysis was selected.

Risk-of-Bias Assessment

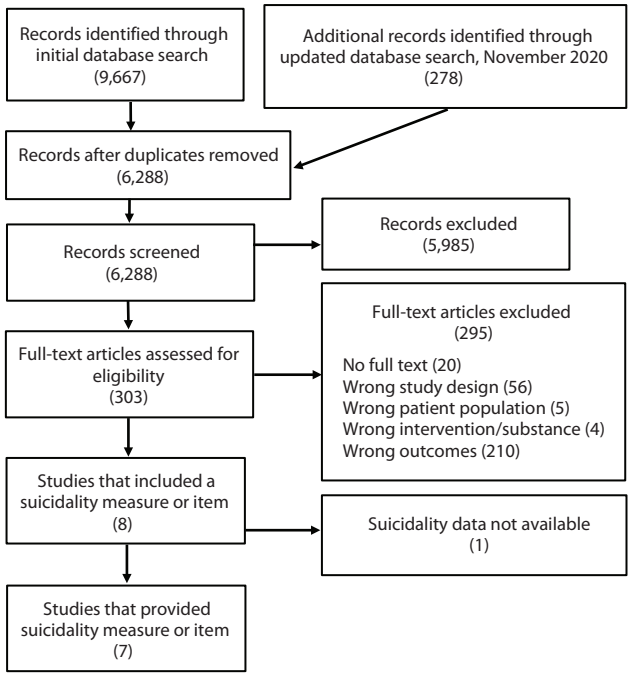
The methodological quality of included studies was assessed using version 2 of the Cochrane risk-of-bias tool[46] for randomized controlled trials and the modified Newcastle-Ottawa scale[47] for non-randomized open-label trials. This assessment was performed by one author (N.S.) and verified by a second (R.J.Z.).

Statistical Analysis

Only individuals with baseline suicidality (ie, suicidality measure or item score > 0) were included in the primary analyses. The method of analysis was based on a similar study[48] focused on change in overall depressive symptoms. Changes in suicidality were analyzed using standardized mean differences (SMDs) with 95% confidence intervals. We compared grouped suicidality scores for each time point to the corresponding baseline scores. All time points with a minimum of 2 studies were included. For studies with variable assessment time points, assessments that occurred within 1–2 days of a respective time point were included. To maximize the number of time points included in the analysis, we created the following extended time points: 7–24 hours (1 day), 4–5 weeks, 7–8 weeks, and 3–4 months. Study heterogeneity was assessed using I^2 testing for each grouped time point. The possibility of publication bias was evaluated using funnel plots in which the SMD of each study was plotted versus its standard error, with a vertical line reflecting the combined SMD of that time point to assess for symmetry.[49]

To examine whether administration of a psychedelic was associated with subsequent elevations in suicidality, we examined the frequency of acute (all time points within 6 hours of the administration of a psychedelic) and post-acute (the first assessment that occurred > 6 hours after the administration of a psychedelic) elevations in suicidality. An elevation in suicidality was operationalized as any increase (ie, ≥ 1-point increase) from an individual's baseline suicidality score. In line with past research,[50] given that an increase of 1 point is a low threshold that may inflate elevations in suicidality, we also examined the frequency at which elevations of ≥ 2 and ≥ 3 points occurred. These analyses were conducted among all participants who were administered a psychedelic (ie, regardless of the presence of baseline suicidality).

Figure 1. Selection of Studies for Inclusion



RESULTS

Study Selection

A total of 9,667 potentially relevant records were identified through our initial literature search, with an additional 278 retrieved upon updating the search in November 2020; 6,288 records remained after duplicates were removed. Following title and abstract screening and subsequent full-text review, a total of 6,280 studies were excluded, as outlined in Figure 1, which depicts an overview of the study selection process. This yielded a total of 8 studies that included a suicidality

Table 1. Primary Outcomes of Studies Included in the Meta-Analysis

Study	Design	Full Sample (Primary Analysis Sample[a])	Suicidality-Specific Exclusion Criteria	Substance/Intervention[b]	Suicide-Related Adverse Event Attributed to Psychedelic Administration	Suicidality Assessment (Range of Possible Scores)	Assessment Schedule
Anderson et al[52]	Open-label	N = 18 (n = 5); long-term AIDS survivors with moderate to severe demoralization	Suicidal ideation with intent in the last 3 months or suicide attempt in last 2 years	Psilocybin (21–25.2 g/70 kg) dosing session plus brief supportive expressive group therapy (8–10 sessions), 1 individual preparation session, and 1 post-psychedelic session	No	Clinician-assessed C-SSRS-SII (0–5)	Baseline; 1-day post-administration; 4–6 additional assessments (variable schedule; range, 3–28 days post-administration)[c]
Carhart-Harris et al[32]	Open-label	N = 20 (n = 17); treatment-resistant depression	History of serious suicide attempts (requiring hospitalization)	Psilocybin (10 mg followed by 25 mg 1 week later) dosing session plus psychological support (6-hour preparation session plus 2 post-psilocybin sessions)	No	Self-reported QIDS-SI (0–3)	Baseline; 1, 2, 3, 5 weeks post dose 2; 3 and 6 months post dose 2
Davis et al[33]	Wait-list–controlled trial; crossover design	N = 24 (n = 16); major depressive disorder	History of a medically significant suicide attempt; high risk for suicidality	Psilocybin (20 g/70 kg followed by 30 mg/70 kg [mean = 1.6 weeks later]) dosing sessions plus individual supportive psychotherapy (approximately 11 hours)	No	Clinician-assessed C-SSRS-SII (0–5)	Baseline; 1 and 4 weeks post dose 2
Griffiths et al[37]	Placebo-controlled trial; crossover design	N = 56 (n = 8); life-threatening cancer + anxiety/mood-related disorder	Depression or anxiety symptoms warranting immediate treatment with antidepressant or daily anxiolytic medication (eg, due to suicidal ideation)	Psilocybin (22 or 30 mg/70 kg) and placebo-like psilocybin (1 or 3 mg/70 kg) dosing session plus individual supportive psychotherapy (mean = 16.1 hours)	No	Self-reported BDI-SI (0–3)	Baseline; 5 weeks post-administration; 2.5 and 6 months post-administration
Palhano-Fontes et al[34]	Placebo-controlled trial	N = 29 (n = 12); treatment-resistant depression	Serious and imminent suicidal risk	Ayahuasca dosing session plus minimal preparation with no psychotherapy	No	Clinician-assessed MADRS-SI (0–6)	Baseline; 100, 160, and 240 minutes post-administration; 1, 2, 7, and 14 days post-administration; 1, 2, 3, 4, 5, and 6 months post-administration[d]
Ross et al[39]	Placebo-controlled trial; crossover design	N = 29 (n = 8); life-threatening cancer + anxiety-related disorder	Active suicidal ideation or suicidal behaviors	Psilocybin (21 mg/70 kg) and placebo (niacin 250 mg) dosing session plus eclectic[e] individual psychotherapy (18 hours)	No	Self-reported BDI-SI (0–3)	Baseline; 7 hours post-dose; 2, 7, and 26–33 weeks post-dose; and 4.5 years post-dose
Sanches et al[35]	Open-label	N = 17 (n = 12); recurrent major depressive disorder	None	Ayahuasca dosing session plus minimal preparation with no psychotherapy	No	Clinician-assessed HDRS-SI (0–6)	Baseline; 40, 80, 140, and 180 minutes post-administration; 1, 7, 14, and 21 days post-administration

[a]Sample with baseline suicidality that was administered a psychedelic.
[b]Hours of psychotherapy do not include dosing sessions.
[c]Primary analyses used assessments from this study that occurred within 1–2 days of the respective time point.
[d]Data from the following time points that were not included in the primary outcomes report were available and used in the present analyses: 100, 160, and 240 minutes; 14 days; and 1, 2, 3, 4, 5, and 6 months post-administration.
[e]Eclectic = supportive, cognitive-behavioral, existentially oriented, and psychodynamic/psychoanalytic therapy.
Abbreviations: BDI-SI = Beck Depression Inventory–Suicidality Item[53], C-SSRS-SII = Columbia-Suicide Severity Rating Scale–Suicidal Ideation Intensity[54], HDRS-SI = Hamilton Depression Rating Scale–Suicidality Item[55], MADRS-SI = Montgomery-Asberg Depression Rating Scale–Suicidality Item[56], QIDS-SI = Quick Inventory of Depressive Symptomatology–Suicidality Item.[57]

Table 2. Risk-of-Bias Assessment for Randomized Controlled Trials Using Version 2 of the Cochrane Risk-Of-Bias Tool

Study	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Davis et al[33]	Low	Low	Low	Low	Low	Low
Griffiths et al[37]	Low	Low	Low	Low	Low	Low
Palhano-Fontes et al[34]	Low	Low	Low	Low	Low	Low
Ross et al[39]	Low	Low	Low	Low	Low	Low

Table 3. Risk-of-Bias Assessment for Non-Randomized Open-Label Trials Using the Modified Newcastle-Ottawa Scale

	Selection		Outcomes			
Study	Representativeness	Ascertainment of Exposure	Assessment	Was Follow-Up Long Enough for Outcomes to Occur?	Adequacy of Follow-Up	Total (out of 5)
Anderson et al[52]	0	1	1	1	1	4
Carhart-Harris et al[32]	1	1	1	1	1	5
Sanches et al[35]	1	1	1	1	1	5

measure or item and were thus eligible for inclusion. Suicidality data were not available for 1 of these studies[51] (the study author was unable to locate the suicidality item data), resulting in 7 studies ultimately being included in the present meta-analysis. Four randomized controlled trials and 3 open-label studies were included in the final meta-analysis. Please refer to Table 1 for details of studies included, including suicidality-specific exclusion criteria as well as suicidality assessment method and schedule. All studies that contributed individual patient data to this meta-analysis were approved by their local research ethics board. For additional details regarding the design of each particular study, please refer to the respective primary outcomes publications.

Risk of Bias

An overview of the risk of bias for the 4 included randomized controlled trials is provided in Table 2, while the risk-of-bias assessment scores for the 3 included non-randomized open-label trials are provided in Table 3. Overall, the risk of bias was determined to be low for all trials included in the meta-analysis.

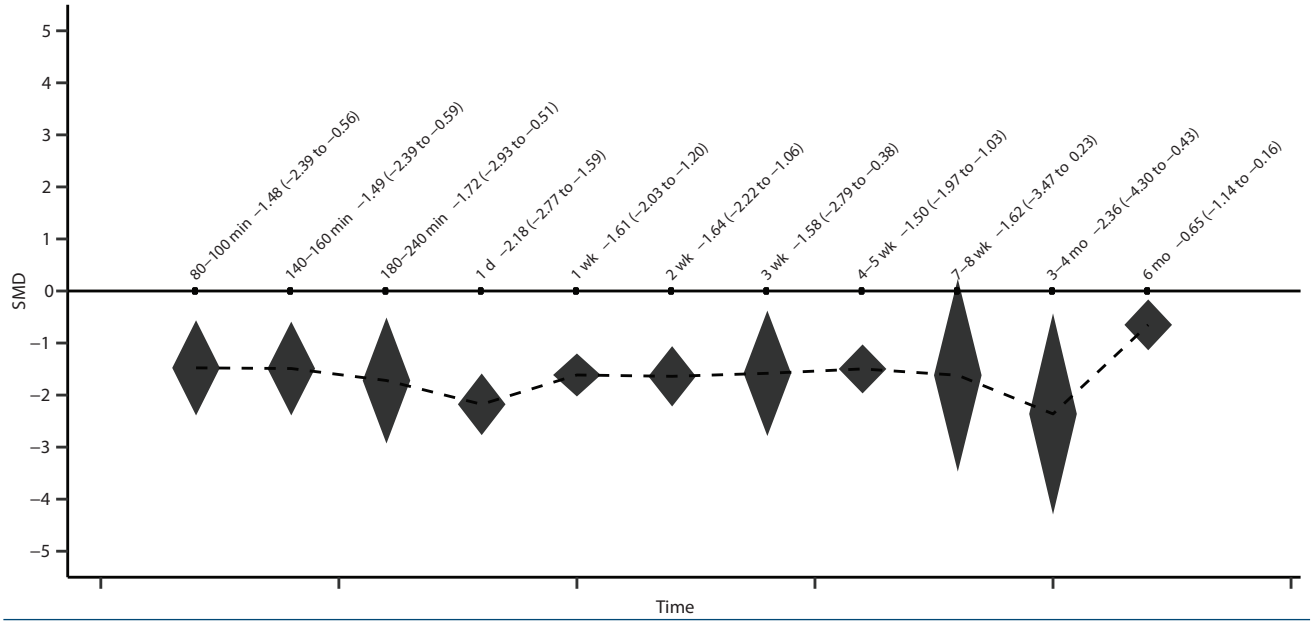
Meta-Analytic Results

We found significant decreases in suicidality at all acute time points (ie, 80–100 minutes, 140–160 minutes, and 180–240 minutes post-administration) and at all post-acute time points except for 7–8 weeks post-administration (ie, 1 day; 1, 2, 3, and 4–5 weeks; and 3–4 and 6 months post-administration). Effect sizes for reductions in suicidality were large at all acute time points and ranged from SMD = −1.48 to SMD = −1.72. Post-acute effect sizes for reductions in suicidality remained large from 1-day to 3–4 months post-administration (including at 7–8 weeks post-treatment), ranging from SMD = −1.50 to SMD = −2.36. At 6 months post-administration, the effect size for reductions in suicidality was medium (SMD = −0.65). For suicidality means, standard deviations, and sample sizes by study at each time point, see Supplementary Table 1. Please refer to Figure 2 for results of the meta-analysis of the 7 included studies, displayed as a kinetic analysis with the SMD for grouped studies comparing baseline to successive time points. There was large variability in heterogeneity of studies by time point. Heterogeneity was 0 at time points of 1 day, 1 week, 5 weeks, and 6 months; mild at 2 weeks ($I^2 = 27.6$); moderate at 80–100 minutes ($I^2 = 41.0$) and 140–160 minutes ($I^2 = 45.8$); and marked at 180–240 minutes ($I^2 = 68.8$), 3 weeks ($I^2 = 74.3$), 7–8 weeks ($I^2 = 75.1$), and 3–4 months ($I^2 = 80.1$). Fail-safe N values ranged from 11 to 101 and were highest at 1 day and 1 week. Fail-safe N values were as follows: 80–100 minutes = 12; 140–160 minutes = 13; 180–240 minutes = 17; 1 day = 72; 1 week = 101; 2 weeks = 77; 3 weeks = 27; 4–5 weeks = 59; 7–8 weeks = 7; 3–4 months = 27; 6 months = 11. Publication bias was examined through funnel plots (see Supplementary Figure 1) and was limited by small sample sizes at all time points, but grossly yielded symmetrical results throughout, suggesting limited to no publication bias.

Elevations in Suicidality

A total of 31 individuals were assessed for suicidality during the acute effects (range, 40–240 minutes post-administration) of a psychedelic (all of whom were administered ayahuasca). Of these, 2 individuals (6.5%) showed a suicidality score increase of +1 (on the HDRS-SI) at a single time point (1 at 40 minutes and 1 at 140 minutes), and both showed decreases to a suicidality score of 0 at all subsequent acute time points and at their post-acute assessment (1 day post-ayahuasca). There were no instances of acute elevations in suicidality that corresponded to a ≥ 2-point or ≥ 3-point increase from baseline. Post-acute suicidality was assessed in a total of 168 individuals (range, 1 day to 26 weeks post-administration). Five individuals (3.0%) showed a suicidality score increase of +1 at their first post-acute assessment. Three of these individuals returned to their baseline level of suicidality at the following assessment, and 1 individual returned to their baseline level of suicidality by the end of treatment. There were no instances of post-acute elevations in suicidality that corresponded to a ≥ 2-point or ≥ 3-point increase from baseline.

Figure 2. Meta-Analysis of Standardized Mean Differences (SMDs) for Pooled Suicidality Scores for Each Time Point Compared to Baseline[a]



[a]The height of diamonds is reflective of 95% CIs for pooled analyses at each time point. Time points are not spaced to scale.

DISCUSSION

Given the need for innovative interventions that target suicidality,[27–29] research has begun to examine the effects of psychedelic therapy on suicidality, with promising early results. However, a meta-analysis has never been conducted. Therefore, we conducted a meta-analysis on the effects of psychedelic therapy on suicidality. We found large effect sizes for acute (80–240 minutes post-administration) and post-acute (1 day, 1 week, 2 weeks, 3 weeks, 4–5 weeks, 7–8 weeks, and 3–4 months) decreases in suicidality following psychedelic therapy, as well as a medium effect size at 6 months post-treatment. Reductions in suicidality were significant at all time points except for 7–8 weeks post-treatment (when the sample size was especially small [ie, n = 14]). No studies reported any suicide-related adverse events due to the administration of a psychedelic. We also observed very few elevations in suicidality during the acute effects of the psychedelic (ie, within 6 hours of psychedelic administration; 6.5%) or during the post-acute assessment that followed psychedelic administration (3.0%). We did not observe any acute or post-acute elevations in suicidality that met the more conservative threshold (ie, an increase of ≥ 2 or ≥ 3 on a respective measure of suicidality). These results provide additional preliminary support for the potentially novel role of psychedelic therapy as a safe intervention that may rapidly and effectively target suicidality.

In light of limitations with current interventions for suicidality (including modest effect sizes, delayed onset of efficacy, the need for repeated administration, safety concerns, patient acceptability, and lack of efficacy within specific populations [eg, individuals with cancer]),[13,19,20,23,26,27] the present preliminary findings are promising. Of note, similar to the growing body of research on ketamine as an intervention for suicidality,[20] our findings suggest that the effect of psychedelic therapy on suicidality is rapid-acting (ie, decreases in suicidality occur within hours of administration). Importantly, however, while the effect of ketamine on suicidality does not appear to last more than 72 hours,[19] our results suggest that decreases in suicidality following psychedelic therapy may last as long as 6 months post-treatment. Furthermore, while ketamine has a complicated safety profile (eg, potential for abuse and liver damage with repeated administration),[21] psychedelic therapy shows a strong safety profile (including little potential for abuse or harm)[45,58,59] and typically includes only 1 to 3 administrations of a psychedelic (in the present meta-analysis, 2 studies included 2 administrations and all other studies included 1 administration).[60]

The sample included in our analyses included individuals with treatment-resistant MDD, recurrent MDD, AIDS-related demoralization, and distress related to life-threatening cancer. It is of interest to note that we observed large effect sizes for reductions in suicidality across these samples, which suggests that the effect of psychedelic therapy on suicidality may extend across a range of clinical presentations. These findings are of significant interest in light of the high levels of suicidality associated with these clinical populations.[10,61,62] These findings are also promising given that there is little evidence that current interventions effectively target suicidality among individuals with cancer-related distress and call for the development of such interventions.[26] Accordingly, we suggest that additional research on the impact of psychedelic therapy within these clinical populations is especially warranted. It is important to note that these results may not extend to

additional clinical samples associated with increased suicide risk (eg, bipolar disorder, psychotic disorder). Indeed, the presence of a psychotic disorder or mania was considered an exclusion criterion in each of the studies included in our analyses, which is generally recommended in the context of psychedelic therapy.[63]

None of the studies included in the present analyses reported a suicide-related adverse event attributed to the administration of a psychedelic. Additionally, our results also indicated that psychedelic therapy very rarely led to acute or post-acute elevations in suicidality. We observed acute elevations of suicidality in only 6.5% of individuals, and each of these individuals subsequently showed no suicidality at their subsequent acute assessments. Additionally, we observed a post-acute elevation in suicidality among only 3.0% of individuals. These small increases may also be related to natural fluctuations in disease states and cannot be firmly attributed to psychedelic therapy. Importantly, no individuals showed an acute or post-acute elevation in suicidality based on the more conservative threshold (ie, score increase of ≥ 2 or ≥ 3), and none of the included studies reported a suicide-related adverse event due to the administration of a psychedelic. These findings add to the growing body of literature suggesting that psychedelics have a strong safety profile (eg, low risk of harm, abuse, dependence, and suicidality),[40,58,59,64] especially when administered with appropriate attention to context.[63,65] These results also provide additional support for the potential safety of providing psychedelic therapy to individuals with heightened levels of suicidality and suggest that, while maintaining appropriate attention to minimizing safety concerns, such research may be worthwhile, safe, and feasible.[40]

Potential Mechanisms of Change

To date, limited research has evaluated the mechanisms through which psychedelic therapy may lead to reductions in suicidality. Candidate biological mechanisms include psychedelic therapy–modulated potential inflammatory properties,[66,67] as well as neurobiological effects, such as alterations of the serotonergic system; increased brain-derived neurotrophic factor, neuroplasticity, and neurogenesis; altered connectivity or activity; and increased glutamatergic tone (for discussions, see Nobile et al[67] and Dos Santos and Hallak[68]). While there is some support for the role of these biological mechanisms as they relate to psychedelic therapy's positive mood-related effects, they have not yet been examined in relation to the effects of psychedelic therapy on suicidality. Candidate psychological mechanisms include reductions in hopelessness/pessimism,[39,42,69–71] and emotional avoidance.[72–76] Observational results from 3 prospective studies (a study reported by Davis et al[72] and a report by Zeifman et al[76] of 2 studies) have provided preliminary support for decreased emotional avoidance as a putative mechanism. Additionally, findings from a small clinical trial[42] have provided support for the potential role of decreased loss of meaning and hopelessness. Additional research, conducted in the context of psychedelic therapy trials, and at multiple levels of analysis (eg, experiential, psychological, biological), will be necessary to evaluate the mechanisms that underlie the potential effect of psychedelic therapy on suicidality. Further understanding of such mechanisms may help to tailor psychedelic therapy and enhance its positive effects on suicidality through synergistic integration with psychotherapeutic interventions with overlapping and complementary mechanisms of change.[67,75–79]

Limitations and Future Directions

Our study includes several limitations. Due to the suicidality measurement tools that have been used within psychedelic therapy research and the limited number of studies on the topic, the present analyses examined suicidality as a broad construct that includes suicidal ideation, intent, risk, behaviors, and attempts. However, given the importance of specificity when examining suicide-related constructs,[80] future research would benefit from using a more fine-grained approach that examines and assesses each of these components individually. Relatedly, several of the studies included in our analyses used a single-item measure of suicidality. Although the use of a single item to measure suicidality is common (eg, see Domany et al,[81]) and considered a valid approach,[82] future research would benefit from including measures specifically designed to assess suicidality, such as the Scale for Suicide Ideation,[83] the Columbia Suicide Severity Rating Scale,[54] and the death/suicide implicit association test.[84] Novel methods for assessing suicidality, such as ecological momentary assessment and digital phenotyping,[85] may also provide rich and informative data. Additionally, due to the limited number of studies, our analyses did not distinguish between various research designs, including the specific diagnosis that individuals had, the specific psychedelic that was administered (psilocybin or ayahuasca), the number of administrations (ie, 1 or 2), and the amount of psychological support that was provided (eg, some studies included no intervention other than brief preparation and administration with minimal psychological support). Much additional research is needed to differentiate between the effects of individual psychedelics, as well as the necessary and optimal number of administrations and amount of psychological support. Use of pragmatic research designs may be especially helpful for examining these remaining questions.[86] Data included in the present meta-analysis were extracted from heterogeneous trials that included a range of psychiatric presentations. Moreover, given that these trials were not specifically designed to evaluate the effect of psychedelic therapy on suicidality, and that several of the trials used an open-label design, our analyses were not powered to control for potential placebo or non-pharmacologic therapeutic effects. Additionally, none of these trials specifically recruited individuals with the presence of suicidality, and most trials actively excluded individuals with serious suicide risk or a history of serious suicide attempts. Accordingly, while the present preliminary

results indicated that psychedelic therapy was generally safe and associated with decreases in suicidality, these results may not necessarily extend to samples that are specifically characterized by high levels of suicidality. Therefore, adequately powered placebo-controlled trials that do not include suicide risk as an exclusion criterion will be necessary to further evaluate the safety and effects of psychedelic therapy on suicidality. Should additional psychedelic therapy trials (eg, see ClinicalTrials.gov identifiers NCT03866174 and NCT03775200) provide additional support for the safety and positive effect of psychedelic therapy on suicidality, trials that specifically recruit individuals with elevated suicidality may be warranted. Within such studies, minimizing safety concerns and optimizing treatment outcomes will be essential, and it is recommended that increased psychological support be provided or that psychedelic therapy be integrated with evidence-based psychotherapeutic interventions for individuals with heightened suicidality.[29,75]

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Supplementary Material

Article Title: Decreases in Suicidality Following Psychedelic Therapy: A Meta-Analysis of Individual Patient Data Across Clinical Trials

Author(s): Richard J. Zeifman, MA; Dengdeng Yu, PhD; Nikhita Singhal, MD; Guan Wang, HBSc; Sandeep M. Nayak, MD; and Cory R. Weissman, MD

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List of Supplementary Material for the article

1. **Table 1** Suicidality Means, Standard Deviations, and Sample Size by Study at Each Time Point

2. **Figure 1** Funnel plots

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Supplementary Material

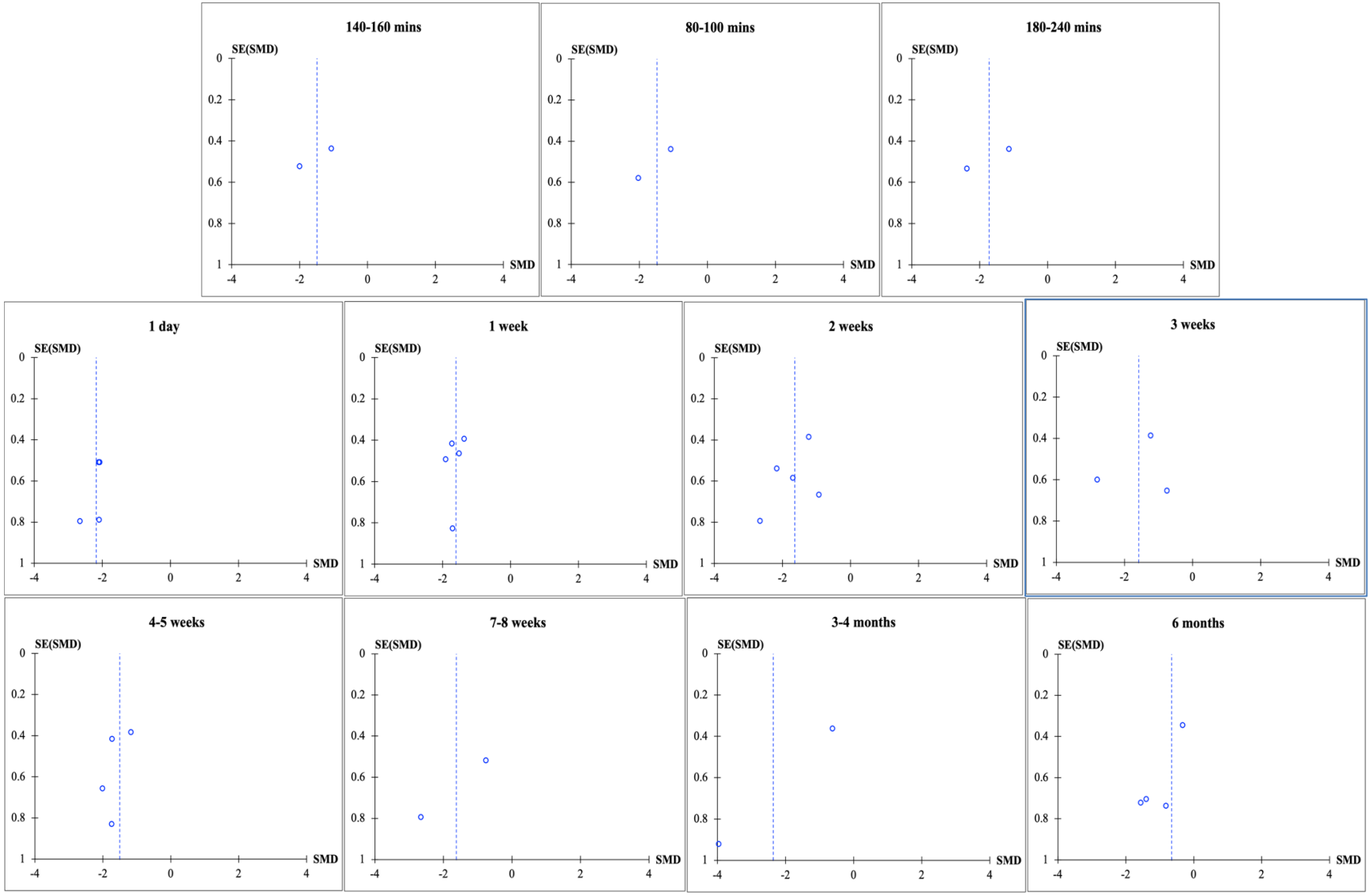
Supplementary Table 1.

Suicidality Means, Standard Deviations, and Sample Size by Study at Each Time Point

Study	Measure		Baseline	40 mins	80-100 mins	140-160 mins	180-240 mins	1 day	2 days	1 week	2 weeks	3 weeks	4-5 weeks	7-8 weeks	3-4 months	6 months	3.2 years	4.5 years
Anderson et al.[41]	CSSRS-SII	Mean	1.80	--	--	--	--	0	--	0.25	0.80	0.80	0.50	--	--	--	--	--
		(SD)	(1.10)	--	--	--	--	(0)	--	(0.50)	(0.84)	(1.30)	(0.71)	--	--	--	--	--
		n	5	--	--	--	--	5	--	4	5	5	2	--	--	--	--	--
Carhart-Harris et al.[21]	QIDS-SI	Mean	1.71	--	--	--	--	--	--	0.63	0.69	0.69	0.81	--	1.12	1.41	--	--
		(SD)	(0.59)	--	--	--	--	--	--	(0.89)	(0.95)	(0.95)	(0.83)	--	(1.09)	1.06	--	--
		n	17	--	--	--	--	--	--	16	16	16	16	--	16	17	--	--
Davis et al.[22]	CSSRS-SII	Mean	1.88	--	--	--	--	--	--	0.31	--	--	0.31	--	--	--	--	--
		(SD)	(0.96)	--	--	--	--	--	--	(0.79)	--	--	(0.79)	--	--	--	--	--
		n	16	--	--	--	--	--	--	16	--	--	16	--	--	--	--	--
Griffiths et al.(a)[26]	BDI-SI	Mean	1.20	--	--	--	--	--	--	--	--	--	0.25	--	0	0.50	--	--
		(SD)	(0.45)	--	--	--	--	--	--	--	--	--	(0.50)	--	(0)	(1.00)	--	--
		n	5	--	--	--	--	--	--	--	--	--	4	--	4	4	--	--
Griffiths et al.(b)[26]	BDI-SI	Mean	1.00	--	--	--	--	--	--	--	--	--	--	--	0	1.5	--	--
		(SD)	(0)	--	--	--	--	--	--	--	--	--	--	--	(0)	(2.12)	--	--
		n	3	--	--	--	--	--	--	--	--	--	--	--	3	2	--	--

Palhano-Fontes et al.[23]	MADRS-SI	Mean	3.92	--	1.44	1.09	1.00	1.33	0.82	1.17	1.88	--	1.71	3.00	0.86	1.80	--	--
		(SD)	(0.90)	--	(1.67)	(1.64)	(1.41)	(1.44)	(1.40)	(1.75)	(1.73)	--	(1.70)	(2.07)	(1.07)	2.05	--	--
		n	12	--	9	11	12	12	11	12	8	--	7	8	7	5	--	--
Ross et al.(a)[28]	BDI-SI	Mean	1.00	--	--	--	--	0.17	--	--	0.17	--	--	0.17	--	0.40	0.33	0.33
		(SD)	(0)	--	--	--	--	(0.41)	--	--	(0.41)	--	--	(0.41)	--	(0.55)	(0.58)	(0.58)
		n	6	--	--	--	--	6	--	--	6	--	--	6	--	5	3	3
Ross et al.(b)[28]	BDI-SI	Mean	1.00	--	--	--	--	--	--	--	--	--	--	--	--	0.5	--	--
		(SD)	(0)	--	--	--	--	--	--	--	--	--	--	--	--	(0.71)	--	--
		n	2	--	--	--	--	--	--	--	--	--	--	--	--	2	--	--
Sanches et al.[24]	HAM-D-SI	Mean	1.92	0.83	0.83	0.92	0.83	0.33	--	0.58	0.36	0.09	--	--	--	--	--	--
		(SD)	(0.79)	(1.12)	(1.12)	(1.00)	(1.03)	(0.65)	--	(0.90)	(0.67)	(0.30)	--	--	--	--	--	--
		n	12	12	12	12	12	12	--	12	11	11	--	--	--	--	--	--

Note. BDI-SI = Beck Depression Inventory-Suicidality Item[42]; C-SSRS = Columbia-Suicide Severity Rating Scale-Suicidal Ideation Intensity[43]; Griffiths et al.(a) = psilocybin first condition; Griffiths et al.(b) = psilocybin second condition; HAM-D-SI = Hamilton Depression Rating Scale-Suicidality Item[44]; MADRS-SI = Montgomery-Åsberg Depression Rating Scale-Suicidality Item[45]; QIDS-SI = Quick Inventory of Depressive Symptomology-Suicidality Item[46]; Ross et al.(a) = psilocybin first condition; Ross et al.(b) = psilocybin second condition.



Supplementary Figure 1. Funnel plots

Note. SMD = Standardized mean difference; SE = Standard error