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Published in:
Psychopharmacology

DOI:
10.1007/s00213-021-06027-y

Publication date:
2022

Psychopharmacology
https://doi.org/10.1007/s00213-021-06027-y

REVIEW

Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review

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Received: 8 July 2021 / Accepted: 9 November 2021

Abstract

Background Terminally ill patients may experience existential distress, depression, or anxiety, limiting quality of life in the final stage. Existing psychotherapeutic or pharmacological interventions have (time) limited efficacy. Psychedelic treatment may be a safe and effective alternative treatment option.

Aim Systematically review studies on psychedelic treatment with and without psychotherapy for existential distress, depression, and anxiety in terminally ill patients.

Methods Medline, PsycINFO, and Embase were searched for original-data studies on the treatment of depression, anxiety, and existential distress with classical or a-typical psychedelics in patients with a terminal illness, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results A total of 1850 records were screened, and 33 articles were included in this review: 14 studies on classical psychedelics (DPT, LSD, and psilocybin) and 19 studies on atypical psychedelics (MDMA and ketamine). Results of early pre-post studies are promising but have serious methodological flaws. Recent (controlled) trials with LSD, psilocybin, ketamine, and MDMA are of higher methodological quality and indicate positive effects on existential and spiritual well-being, quality of life, acceptance, and reduction of anxiety and depression with few adverse and no serious adverse effects.

Conclusions Both classical and a-typical psychedelics are promising treatment options in patients with terminal illness. To draw final conclusions on effectiveness and safety of psychedelics, we need larger high-quality studies for classical psychedelics and MDMA. Ketamine studies should pay more attention to existential dimensions of well-being and the psychotherapeutic context of the treatment.

Keywords Anxiety · Depression · Existential distress · Life-threatening disease · Psychedelics

Introduction

Being confronted with a life-threatening illness brings about profound changes in one's physical, emotional, social, and spiritual well-being (LeMay and Wilson, 2008). In some, this confrontation with the finitude of existence may lead to increased self-awareness, psychological growth, and a deepening of close relationships (Carpenter et al., 1999). In others, it can induce depression, anxiety, demoralization, despair, or existential distress (Kissane et al., 2001). Existential distress is a stressor-induced psychological state characterized by hopelessness, loss of meaning and dignity, suicidal ideation, increased pain perception, feeling like a burden to others, and death anxiety (Boston et al., 2011). It is often accompanied by symptoms of anxiety or depression, lower quality of life, and reduced well-being (Wilson et al., 2007; Mitchell et al., 2011). As such, depression, anxiety, and existential distress greatly limit one's possibilities of experiencing a meaningful final stage of life (LeMay and Wilson, 2008).

The prevalence of psychiatric symptoms or disorders in patients with cancer is estimated at 14–21% for anxiety

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Published online: 23 November 2021

disorders (Wilson et al., 2007), 20–25% for minor depression, 15% for major depression (Mitchell et al., 2011), and 6–19% for adjustment disorders (Mitchell et al., 2011; Singer et al., 2013; Hernandez Blazquez and Cruzado, 2016). A cross-sectional study found that 12% of patients with cancer ($n = 377$) had a serious yearning for death, and of those, 52% met criteria for an anxiety and/or depressive disorder (Wilson et al., 2016). Suicide is twice as prevalent in advanced cancer patients compared to the general population of the same age (Chochinov et al., 1998). Existential distress has not been clearly defined. However, prevalence rates of existential distress in patients with terminal cancer vary from 3 to 29%, depending on the operationalization of the concept (Pelletier et al., 2002; De Faye et al., 2006; Wilson et al., 2007; LeMay and Wilson, 2008). There is a significant overlap between symptoms of existential distress and anxiety, depression, and adjustment disorders. The nature of the relationship between existential distress and these disorders remains unclear (Nierop-van Baalen et al., 2020; Bobevski et al., 2018).

The evidence for the pharmacological and psychological treatment of anxiety and depression in patients with a life-threatening illness is ambiguous (Rosenstein, 2011). Evidence for the use of antidepressants is inconclusive (Price and Hotopf, 2009). While antidepressant effects are reported regarding mianserin and the selective serotonin reuptake inhibitors fluoxetine and paroxetine, generally low response rates are reported, and only mianserin was found to be more effective compared to placebo in treating cancer-related depression (Riblet et al., 2014). To our knowledge, there is no published data regarding the effects of anxiolytic treatment in advanced cancer patients (Spencer et al., 2010). The effects of methylphenidate for the treatment of depression in (advanced) cancer were minimal (Andrew et al., 2018). Recently developed psychotherapies for the treatment of existential distress in patients with terminal cancer (Bauereiss et al., 2018) emphasize the importance of meaning and dignity. These therapies yield significant but time-limited (up to 3 months) positive effects on existential well-being, hope, and self-reliance, but no effects on depression and anxiety. Hence, there is a serious need for effective interventions with a sustained effect on existential distress, depression, and anxiety in patients with an incurable illness (Rosenbaum et al., 2019).

The idea of using psychedelics to alleviate end-of-life existential distress was introduced by British writer Aldous Huxley. On his deathbed in 1963, he requested his wife to be injected with two doses of lysergic acid diethylamide (LSD), after which he died peacefully while she coached him 'to the light' (Huxley, 1968). A year later, Kast and Collins (Kast and Collins, 1964) conducted a trial that compared the analgesic effect of LSD with the effect of the opioids pethidine and hydromorphone in 50 patients with a terminal disease and severe pain. They concluded that while LSD-induced pain reduction came about slower, its effects lasted longer. Surprisingly, they also found that patients showed more open and positive attitudes towards their condition after LSD treatment. A subsequent study by Kast with LSD in patients with terminal cancer reported that 89% gained "valuable insights" (1966). In Kast's third study on 128 pre-terminal patients (death foreseen within 1 or 2 months), more emphasis was placed on preparing the patient for the psychedelic session and establishing rapport. After LSD treatment, patients experienced less pain, a better mood, more positive attitudes towards life, and less illness- and death-related distress (1967). It is unclear whether psychiatric comorbidities were present in the studied patients and no formal assessment instruments were used to measure therapeutic effects. In the years that followed, several comparable studies were conducted in which LSD was administered as an adjunct to psychotherapy (Schenberg, 2018) in patients with a terminal illness, again reporting promising results. However, this line of research was abruptly discontinued following the worldwide prohibition of psychedelics in 1968 (Grob et al., 2013). Recently, research has resumed with both classic serotonergic psychedelics (LSD and psilocybin) and atypical psychedelics (ketamine and 3,4-methylenedioxymethamphetamine [MDMA]). Findings of clinical trials on classical psychedelics for the treatment of psychiatric problems secondary to (life-threatening) illness between 1960 and 2018 were reviewed by Ross et al. (Ross, 2018; Reiche et al., 2018) and by Reiche et al. (28), indicating positive effects on anxiety, depression, and existential distress with little side effects. A review on the efficacy of ketamine for depression and pain in palliative care patients found antidepressant effects (Goldman et al., 2019). In all reviews, it was reported that larger and methodologically better studies are needed to draw definite conclusions on effectiveness for this indication. To our knowledge, there is currently no review of psychedelic treatments for end-of-life patients that simultaneously assesses classical and atypical psychedelics. This systematic review aims to summarize the current state of research on typical and atypical psychedelics administered with or without psychotherapy for the treatment of existential distress, depression, and anxiety in patients with a terminal illness.

Method

The search and selection strategy was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Medline, PsycINFO, and Embase were systematically searched in October–November 2020 (search query included in the Appendix). Inclusion criteria were

formulated according to the Participants, Intervention, Comparison, Outcome, and Study design (PICOS) approach, as shown in Table 1. Titles and abstracts were independently screened by JJB and NS. References of selected articles were consulted to find additional relevant articles. A PRISMA flowchart of the search process is shown in Fig. 1.

Results

A total of 2129 published records were identified through Pubmed, PsycINFO, and Embase. After removing duplicates, 1842 records remained. Eight records were obtained through other sources including cross-references, resulting in a total of 1850 records. Following independent title/abstract screening by JJB and NS, 1772 records were excluded, and 78 full-text articles were assessed for eligibility. Ultimately, 33 articles were included in this review: 9 RCTs ($n = 11$–417), seven pre-post studies ($n = 14$–50), two retrospective chart reviews ($n = 23$–31), 11 case studies ($n \leq 2$), and four qualitative studies ($n = 4$–13), with a total of 1130 unique patients. An overview of all quantitative $n > 2$ studies is presented in Table 2. Due to the large differences in study designs and outcome measurements, no meta-analyses were performed.

Classical psychedelics

We included 14 articles on classical psychedelics: DPT (one), LSD (six, including one qualitative study), and psilocybin (seven, including three qualitative studies). None of the 1960–1970s studies used control groups, whereas most of the more recent studies were double blind randomized controlled trials (RCTs), many with a crossover design. All classical psychedelic treatment programs included some form of psychotherapy. Below, we describe our findings per substance.

Dipropyltryptamine (DPT)

In a 1979 open-label pre-post study (Richards et al.), 30 cancer patients with depression, anxiety, and/or psychological isolation received DPT (75–127,5 mg, intramuscular [IM]) as an adjunct to brief psychotherapy. Significant therapeutic effects on depression, anxiety, and social isolation were found, which correlated with mystical or peak experiences. No (serious) adverse effects were reported.

Lysergic acid diethylamide (LSD)

Multiple pre-post studies on LSD-assisted psychotherapy for existential distress in severely ill patients were conducted at the Maryland Psychiatric Research Center between 1969 and 1973 (Pahnke et al., 1969, 1970; Richards et al., 1972; Kurland et al., 1972; Grof et al., 1973). Setting, therapeutic context, and the role of 'mystical' or 'peak' experiences were considered as significant mediators of treatment effect and were thus given central roles. The pre-post study by Pahnke et al. (1969) studied the effect of 'psychedelic peak therapy' (PPT) on 22 depressed terminal cancer patients. PPT consisted of 'several weeks' of preparatory psychotherapy in which the therapist got to know the patient, rapport was established, and the patient was prepared for the procedure. Patients received 200–400 µg LSD, either orally (PO), intravenously (IV), or IM. After treatment, 64% showed improvement, of which 27% 'dramatic.' Improvements included decreased depression, anxiety, and fear of death, increased relaxation, and closer relationships. Patients whose somatic state pre-treatment was graver showed fewer positive changes compared to the less severely ill patients. According to the authors, the occurrence of a 'psychedelic peak experience' seemed positively correlated with therapeutic effect. Kurland et al. (1972) extended the previous study sample, describing 50 patients in total, who received oral LSD ($n = 40$; 200–500 mg), parenteral DPT ($n = 7$; 60–105 mg), or both on different occasions ($n = 3$), all as an adjunct to psychedelic psychotherapy. Observer-rated pre-post comparisons showed significant improvements in depression, psychological isolation, anxiety, fear, and acceptance of death. Approximately 36% of the patients improved 'dramatically' and 36% improved 'moderately.' Others remained 'essentially unchanged' (19%), and 8% showed deterioration on a global index of their clinical condition (this was related to illness progression). In separate publications, Richards et al. (1972) and Grof et al. (1973)

Table 1 PICOS inclusion criteria utilized for the selection of articles

Participants	Patients with a terminal illness and depression, anxiety, demoralization, or existential distress
Intervention	Single or multiple administrations in any formulation and of any dose of LSD, DPT, psilocybin, ketamine, or MDMA; as add-on treatment or monotherapy, aimed to reduce depressive, anxiety, demoralization, or existential distress
Comparison	No other intervention, placebo, or another intervention
Outcome	Symptoms of depression, (death) anxiety, existential distress, and demoralization; quality of life, well-being, side effects/(serious) adverse events
Study design	RCT, quasi-RCTs, controlled clinical trials, before-after studies, case series and case reports, qualitative studies

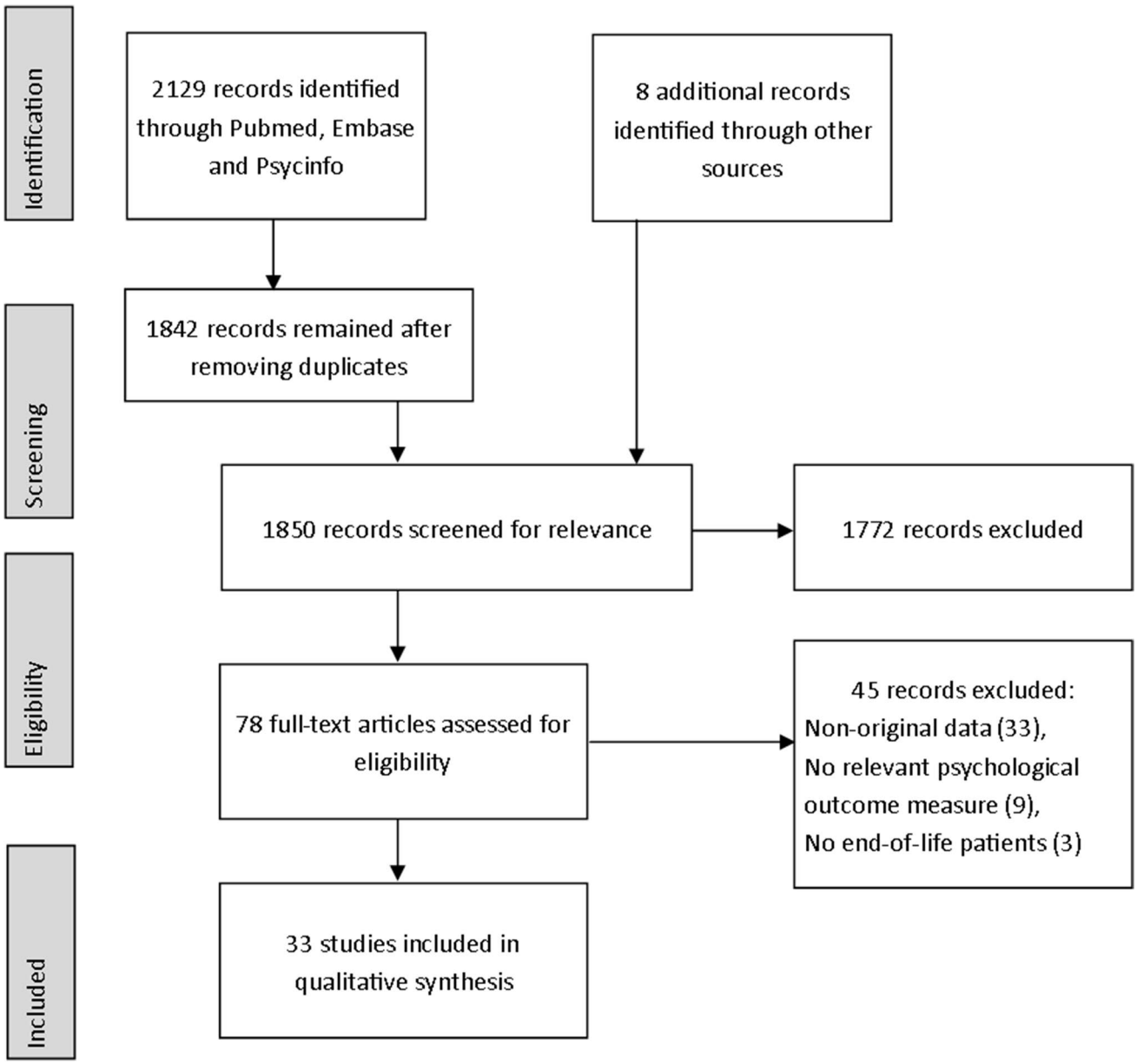

Fig. 1 PRISMA flowchart of the search process

reported on the same 31 (pre)terminal cancer patients with refractory depression, anxiety, physical pain, or psychological isolation secondary to their malignancies. Treatment consisted of oral LSD (200–500 mg) in combination with integrative psychotherapy. Post-treatment, patients showed 'dramatic improvement' (29%) and 'moderate improvement' (42%), or remained 'essentially unchanged' (29%). Overall, improvements were reported on anxiety, depression, and social isolation. Fatigue, as well as other adverse effects such as vomiting or nausea, headache, fatigue, tremors, and/or breathing difficulties were reported during the 12-h LSD sessions. No serious adverse effects were reported.

More recently, a pilot study by Gasser et al. (2014) investigated the efficacy and safety of LSD-assisted psychotherapy comparing two high doses of LSD (200 µg, $n=8$), 2 to 3 weeks apart with a single low dose (20 µg; $n=3$) as an active placebo in 11 patients with a life-threatening disease and illness-related anxiety. After 2 months, the high-dose group showed a significant decrease of anxiety while the low-dose group showed a non-significant increase in anxiety. After crossover, 12 months later ($n=9$), both groups reported a decrease in anxiety. No drug-related severe adverse events were reported. In a qualitative interview, conducted with nine participants (82%) at 12-month follow-up,

Table 2 Overview of clinical studies on the effect of psychedelics for existential distress, depression, and anxiety in patients with terminal illness

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
DPT						
Richards et al. 1979	Terminal cancer, existential distress	$n=30$	Pre-post open label, DPT, 1 × 75–127.5 mg, IM	Integrative psycho-therapy	1 PT: decrease in observer-rated depression and anxiety (ECRS: $p<.03$ and $p<.01$), increase in POI self-regard, self-acceptance, and capacity for intimate contact ($p<.02$, $p<.005$, $p<.02$)	No (S)AEs occurred
LSD						
Pahnke et al. 1969	(Pre) terminal cancer; depression, anxiety, and pain	$n=22$	Pre-post pilot, LSD, 1 × 200–400 µg, PO, IV, or IM	Psychedelic peak therapy	PT: decrease in observer-rated depression, anxiety and fear of death; increased relaxation, ease in medical management, pain tolerance, closeness of family relationships. Meaningful positive change ($n=14$), of which dramatic change ($n=6$)	No (S)AEs occurred
Kurland et al. 1972; Pahnke et al. 1969	Terminal cancer; emotional, and physical distress	$n=50$	Pre-post, LSD, 1 × 200–500 µg, PO ($n=43$) or DPT 1 × 60–105 mg, IM ($n=7$)	Brief intensive psycho-therapy	PT: dramatic and moderate improvement of emotional (36%) and physical (36%) distress. Condition unchanged (19%) or decreased (8%)	No (S)AEs occurred
Richards et al. 1972; Grof et al. 1973	(Pre) terminal cancer; depression, anxiety, psycho-logical isolation, and pain	$n=31$	Pre-post, LSD, 1 × 200–500 µg, IM	Integrative psycho-therapy	PT: improvements on observer-rated depression anxiety, fear of death, isolation, and management of disease (all: $p<.001$)	No (S)AEs occurred. AEs during session: nausea/vomiting, tremors, palpitations, respiratory issues

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Gasser et al. 2014	Advanced cancer, Parkinson's, coeliac, and Bechterew's disease; anxiety	$n=11$	Crossover RCT, LSD, 2×200 µg (20 µg LSD [active placebo]), PO	LSD-assisted psycho-therapy	2 months PT: lower anxiety in LSD-group vs. placebo (STAI-T: 45.2 ± 3.7 vs. 49.0 ± 6.1, $p=0.033$, 65.6% power (NS); STAI-S: 41.5 ± 3.2 vs. 51.7 ± 5.3, $p=0.021$, 72.7% power), and in LSD-group vs. baseline (STAI-T: 53.2 ± 4.3, $d=1.1$; STAI-S: 53.1 ± 4.7, $d=1.2$; HADS-A: 8.1 ± 3.2 vs. 11.7 ± 3.4). NS difference in depression between groups (HADS-D) 12 months PT: lower anxiety and depression in combined group ($n=9$) vs. baseline (STAI-T: 41.1 ± 10.8; STAI-S: 36.1 ± 8.3; HADS-A: 7.6 ± 4.5; HADS-D: 7.6 ± 4.7). Reductions in anxiety and fear of death (77.8 and 77.9%), and improved quality of life (66.7%) reported in semi-structured interviews (Gasser, 2014b)	No SAEs occurred. No AEs persisting beyond 1 day PT
Psilocybin						
Grob et al. 2011	Advanced stage cancer, reactive anxiety	$n=12$	Pilot RCT, Psilocybin, 1×0.2 mg/kg (250 mg niacin), PO	Integrative psycho-therapy	2 weeks PT: NS changes in anxiety and depression (STAI and BDI) 1 month PT: lower anxiety vs. baseline ($p=0.001$; STAI-S NS). NS decrease of depression ($p=.05$) 3 months PT: reduction in anxiety ($p=0.03$; STAI-S NS). NS effect on depression 6 months PT: reduction in depression ($p=0.03$). NS reduction of anxiety	No (S)AEs occurred

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Griffiths et al. 2016	Potentially life-threatening cancer; anxiety, depression, and adjustment disorders	$n=51$	Crossover RCT, Psilocybin, 2 × 0.31–0.43 mg/kg (1–3 mg/70 kg psilocybin; crossover after 5 weeks PT1), PO	Integrative psycho-therapy	5 weeks PT: clinical response and remission on depression in high-dose group vs. placebo (GRID-HAMD: 92 and 60% vs 32 and 16%); clinical response and remission on anxiety in high-dose group vs. placebo (HAM-A: 76 and 52% vs. 14 and 12%) 6 months PT: response and remission (77–79% and 59–71%) on depression, response and remission (82–83% and 50–63%) on HAM-A in both groups	No SAEs occurred. AEs in high-dose session: nausea or vomiting (15%), psychological discomfort (32%), anxiety (26%)
Ross et al. 2016	Advanced cancer, anxiety, and depression	$n=29$	Crossover RCT, Psilocybin, 1 × 0.3 mg/kg (250 mg niacin), PO	Integrative psycho-therapy	1 day PT1: in the psilocybin group vs. placebo lower depression (BDI: $p \leq 0.01$, $d=1.10$; HADS-D ($p \leq 0.001$, $d=1.23$) and anxiety (HADS-A: $p<0.05$, $d=0.80$; STAI-S: $p \leq 0.01$, $d=1.20$; STAI-T: $p \leq 0.01$, $d=0.95$). Larger response and remission rates on depression (BDI and HADS-D: $p \leq 0.01$), and larger response rate on anxiety (HADS-A: $p<0.05$) 7 weeks PT1: in the psilocybin group vs. placebo lower depression (BDI: $p<0.05$, $d=0.82$; HADS-D: $p \leq 0.01$, $d=0.98$) and anxiety (HADS-A: $p \leq 0.01$, $d=1.07$; STAI-S: $p \leq 0.01$, $d=1.18$; STAI-T: $p \leq 0.001$, $d=1.29$). Larger response and remission rates for depression and larger response rate for anxiety (BDI and HADS-A: $p \leq 0.01$). NS differences on HADS-D response and remission rates 6 months PT2: sustained significant reduction of depression and anxiety in both groups. Decreased cancer-related demoralization (DS) and hopelessness (HAI), improved spiritual well-being (FACIT) and quality of life (WHO-brief)	No (S)AEs occurred

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Anderson et al. 2020	Long-term AIDS survivors, demoralization	Open-label pre-post pilot, $n=18$	Psilocybin, 1 × 0.3 mg/kg (cohort 1), 1 × 0.36 mg/kg (cohort 2 and 3), PO	Individual and group psycho-therapy	PT: lower demoralization vs. baseline (DS:-6.67 ± 6.51; ≥ 50% reduction in 50%) 3 months PT: lower demoralization (−5.78 ± 6.01, $\eta_p^2=0.47$; ≥ 50% reduction 33.3%), PTSD (PCL-5: − 7.11 ± 13.81, $\eta_p^2=0.27$) and complicated grief (ICG-R: − 7.06 ± 7.61, $\eta_p^2=0.45$), improved quality of life (MQOL: 0.94 ± 2.44, $\eta_p^2=0.34$)	No SAEs occurred. Expected AEs in 14 patients. During session: anxiety (44%), paranoia (22%), and thought disorder (5%)
Ketamine						
Irwin et al. 2013	Terminal disease, depression, and anxiety	Pre-post, $n=14$	Ketamine, 28 daily doses 0.5 mg/kg, PO	-	3 days PT: lower anxiety vs. baseline (HADS-A: $p=0.004$, $d=0.67$). NS change in depression (HADS-D) 1 week PT: lower anxiety ($p<0.001$, $d=1.1$). NS change in depression 2 weeks PT: lower anxiety ($p<0.012$, $d=1.13$) and depression ($p=0.01$, $d=1.14$) 3 weeks PT: lower anxiety ($p<0.001$, $d=1.36$) and depression ($p=0.002$, $d=1.36$) 4 weeks PT: lower anxiety ($p<0,001$, $d=1.34$) and depression ($p=0.001$, $d=1.34$). Effect of time on anxiety ($p<0,001$, $\eta^2=0.67$) and depression ($p=0,002$, $\eta^2=0.534$) NS effects on suicide risk and quality of life	No SAEs occurred. AEs in 12.5%: diarrhea, trouble sleeping, and sitting still (all $n=1$)
Iglewicz et al. 2015	Hospice patients, depression	Retrospective chart review, $n=31$	Ketamine, 0.5 mg/kg, PO ($n=29$), SC ($n=1$), oral + SC ($n=1$); 1 ($n=22$), 2 ($n=5$), or 3 doses/day ($n=4$)	-	1–3 days PT: observer-rated therapeutic effect on depression (CGI) in 93%, global improvement in 49%. Treatment response occurred mostly on day 1 PT ($p<0.05$) 4–7 "days PT: therapeutic effect on depression in 80%, global improvement in 55% 8–21 days PT: therapeutic effect on depression in 60% global improvement in 80%	No SAEs occurred. AEs: disorientation (22.6%), hallucinations (12,9%), sedation, insomnia, delusions, and anxiety (all 3.2%). No AEs: 59.1%; 1 AE: 13.6%; 2–3 AEs: 27.3%

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Fan et al. 2017	Newly diagnosed cancer patients, suicidality	$n=37$	RCT, Ketamine, 1×0.5 mg/kg, (0.05 mg/kg midazolam), IV	-	1 day PT: lower suicidality and depression in ketamine group vs. placebo (BSI: 9.53 ± 9.53 vs. 16.79 ± 7.07, $p=0{,}049$; MADRS-SI: 1.69 ± 1.93 vs. 3.42 ± 1.75, $p=0{,}012$; MADRS: 24.46 ± 8.04 vs. 31.89 ± 7.39, $p=0.036$) 3 days PT: lower suicidality and depression in ketamine group (BSI: 9.07 ± 8.21 vs. 16.93 ± 8.27, $p=0{,}027$; MADRS-SI: 1.77 ± 1.84 vs. 3.52 ± 1.89, $p=0{,}011$; MADRS: 25.09 ± 7.07 vs. 31.89 ± 7.21, $p=0.055$) 7 days PT: NS effects	No (S)AEs occurred
Xu et al. 2017	Breast cancer patients, postoperative depression	$n=50$	RCT, Ketamine, 1×0.5 mg/kg (saline), IV	-	1 day PT: lower depression in ketamine group vs. placebo (HAMD: 12.55 ± 4.50 vs. 18.64 ± 3.83, $p<0{,}05$) and baseline (18.82 ± 2.82, $p<0.05$) 3 days PT: lower depression vs. placebo (10.64 ± 4.33 vs. 16.27 ± 4.45, $p<0.05$) and baseline ($p<0.05$) 7 days PT: lower depression vs. baseline ($p<0.05$). NS difference between groups	No SAEs occurred. AEs: nausea ($n=1$), irritability ($n=2$), and mild respiratory depression ($n=1$)
Wang et al. 2020	Cervical carcinoma patients receiving hysterectomy, depression, and pain	$n=417$	RCT, S-ketamine 1×0.5 mg/kg ($n=104$), S-ketamine 1×0.25 mg/kg ($n=104$), racemic ketamine 1×0.5 mg/kg ($n=104$) (saline, $n=105$), IV	-	1, 2, and 3 days PT: lower depression in all treatment groups vs. placebo (HAMD: all $p<0.05$), lowest depression at all time points in high-dose S-ketamine group ($p<0.05$). NS difference between racemic and low-dose ketamine group 5 days PT: NS differences between groups 7 days PT: NS differences between groups and vs. baseline	No (S)AEs occurred

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Liu et al. 2020	Breast cancer patients receiving mastectomy, postoperative depression	$n=303$	RCT, Racemic ketamine 1×0.125 mg/kg ($n=102$), S-ketamine 1×0.125 mg/kg ($n=101$), (saline, $n=100$), IV	-	3 days PT: lower depression in racemic and S-ketamine groups vs. placebo (HAMD: 13.2 ± 2.5 and 11.4 ± 2.2 vs. 16.4 ± 2.0; $p<0.001$), lower depression in S-ketamine vs. racemic ketamine ($p<0.05$) 1 week PT: lower depression in racemic and S-ketamine groups vs. placebo (10.5 ± 2.9 and 9.4 ± 3.0 vs. 11.2 ± 3.6; $p<0.001$), lower depression in S-ketamine vs. racemic ketamine ($p<0.05$) 1 month PT: lower depression in racemic and S-ketamine vs. placebo (9.5 ± 2.9 and 6.9 ± 2.8 vs. 11.0 ± 3.8; $p<0.001$), lower depression in S-ketamine vs. racemic ketamine ($p<0.05$) 3 months PT: NS differences among racemic and S-ketamine groups vs. placebo (7.5 ± 3.2 and 6.5 ± 3.3 vs. 7.5 ± 3.0)	No (S)AEs occurred
Falk et al. 2020	Palliative care patients, anxiety, and depression	$n=16$	Retrospective pilot, Ketamine 1×0.25 mg/kg, IV (treatment as usual)	-	1–4 days PT: decrease in anxiety in the ketamine group vs. baseline (STADI 55.63 ± 11.73 vs. 68.88 ± 11.01; $p=0.007$, $r=0.65$), multivariate effect on anxiety and depression (STADI: $p=0.046$, $r=0.50$). NS effect on depression	No (S)AEs occurred
MDMA						

Table 2 (continued)

First author, year	Illness, treatment aim	Study type, *n*	Substance, dose (placebo), administration	Psycho-therapy	Results	Adverse effects (AEs/SAEs)
Wolfson et al. 2020	Cancer or non-dementia neurological disease, anxiety	RCT with open-label crossover, $n=18$	MDMA, 3 × 125 mg (125 mg lactose), optionally followed by 62.5 mg MDMA-dose (lactose), PO	Psycho-therapy	1 month PT: NS lower anxiety and greater post-traumatic growth in the MDMA group vs. placebo (STAI-T: -23.5 ± 13.2 vs. -8.8 ± 14.7, $p=0.056$; PTGI: 12.9 ± 23.3 vs. -2.6 ± 6.1, $p=0.04$; $g=0.50$). State anxiety (STAI-S), depression (BDI, MADRS), and global functioning (GAF) NS 6 months PT: lower state and trait anxiety (-27.5, $p<0.0001$; -27.1, $p<0.0001$) and depression (BDI: -27, $p<0.0001$; MADRS: -15.8, $p<0.0001$), greater in post-traumatic growth (PTGI: $+29.4$; $p<0.0001$), self-compassion (SCS: $p=0.008$), and emotional and functional well-being (FACIT: $p<0.0001$, and $p=0.0005$) for combined group ($n=17$) vs. baseline. NS change in fear of death (DAP) and physical and social well-being (FACIT) 12 months PT: reduction in anxiety (STAI-T: -26.9, $p<0.0001$; STAI-S: -24.6, $p<0.0001$) and depression (BDI: -25.9; $p<0.0001$; MADRS -15.9, $p<0.0001$), greater post-traumatic growth ($+27.3$; $p<0.0001$), self-compassion ($p=0.025$), physical-, emotional-, and functional well-being ($p=0.032$, $p<0.0001$, and $p=0.0008$). NS change in fear of death and social well-being	No SAEs occurred. AEs during session: thirst, jaw clenching/tightness, dry mouth, headache, and perspiration 1 week PT: fatigue, insomnia, and low mood

ECRS Emotional Condition Rating Scale, *POI* Personal Orientation Inventory, *STAI-T/S* State-Trait/State Anxiety Inventory, *HADS-A/D* Hospital Anxiety and Depression Scale, *BDI* Beck Depression Inventory, *GRID-HAMD-17* GRID-Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale, *DS* Demoralization Scale, *HAI* Hopelessness Assessment and Illness Scale, *FACIT* Functional Assessment of Chronic Illness Therapy Scale, *WHO-Brief* World Health Organization Quality of Life Scale, *PCL-5* PTSD Checklist Scale-5, *ICG-R* Inventory of Complicated Grief-Revised, *MQoL* McGill Quality of Life, *PTGI* Post-Traumatic Growth Inventory, *MADRS* Montgomery-Asberg Depression Rating Scale (for Suicidal Ideation), *HAMD* Hamilton Depression Rating Scale, *GAF* Global Assessment of Functioning, *SCS* Self-Compassion Scale, *DAP* Death Attitudes Profile, *CGI* Clinical Global Impression, *BSI* Beck Scale for Suicidal Ideation, *STADI* State Trait Anxiety Depression Inventory, *DPT* dipropyltryptamine, *IM* intramuscular, *PT* post-treatment, *(S)AE* (serious) adverse event, *LSD* d-lysergic acid diethylamide, *PO* per os, *IV* intravenous, *RCT* randomized controlled trial, *NS* non-significant, *SC* subcutaneous, *MDMA* 3,4-methyleendioxymethamfetamine

all stated to have profited from the treatment and felt more relaxed and patient (Gasser et al., 2015). Seven of these participants were less anxious (about death), and six reported improved quality of life. Positive psychological changes included increased relaxation, equanimity, self-assurance, and mental strength. Some patients experienced intense emotions during the session, which were later regarded as a 'breakthrough.'

Psilocybin

Grob et al. (2011) conducted the first pilot study on psilocybin in advanced cancer patients ($n = 12$) with existential distress and acute stress disorder, generalized anxiety disorder (GAD), cancer-related anxiety disorder, or adjustment disorder with anxiety (according to DSM-IV). Patients randomly received a moderate dose of psilocybin (0.2 mg/kg) or niacin (vitamin B_3, active placebo), with a crossover after 2 weeks. Before crossover, the psilocybin group ($n = 6$) reported a larger, yet statistically non-significant reduction of depression and anxiety symptoms compared to the placebo group ($n = 6$). After 3 months, trait anxiety was significantly decreased in both groups compared to baseline. After 6 months, this was also the case for symptoms of depression. Participants further reported improved social interactions, new insights regarding the influence of the illness on their lives, and a more positive attitude towards their limited life expectancy. Psilocybin treatment did not reduce pain or the need for analgesic medication. No (serious) adverse effects were reported.

More recently, Griffiths et al. (2016) and Ross et al. (Ross et al., 2016) studied the effects of a moderately high dose (22–30 mg/70 kg and 0.3 mg/kg, respectively) of psilocybin compared to (active) placebo combined with preparatory and integrative psychotherapeutic sessions in two similar randomized crossover studies. Participants ($n = 51$ and $n = 29$, respectively) had life-threatening cancer and a related depressive disorder with or without GAD, adjustment disorder with or without anxiety and/or depression, or GAD with and without dysthymia. Crossover took place 5 or 7 weeks after initial dosing session, respectively. Griffiths et al. (2016) ($n = 51$) reported significantly larger response (92% versus 32%) and remission (60% versus 1%) on depression and anxiety (76% vs. 24%; 52% vs. 12%, respectively) in the high-dose group compared to active placebo after 5 weeks. Six months after crossover, 78% and 83% of all participants showed clinical responses on depression and anxiety compared to baseline. Both participants and their friends and family reported positive effects on attitude towards life and the self, spiritual well-being, social contacts, quality of life, acceptance of death, and optimism (Ross et al., 2016). In the second crossover RCT ($n = 29$) (2018), significant differences in response were found between the high-dose first and the low-dose group. After 7 weeks (before crossover), anxiety response was 58% versus 14%, and depression response was 83% versus 14%. Six months after crossover, there were significant decreases in anxiety (60%) and depression (80%). Moreover, treatment reduced demoralization and hopelessness, and improved spiritual well-being and quality of life, both short term (after 2 weeks) and longer term (after 6 months). Death anxiety did not significantly decrease on the short term, but in the high-dose group a significant improvement in attitude towards death was found after 26 weeks. After 3 and 4 years, two additional follow-ups were conducted in 14 participants (13 patients of the original group were deceased). After 3 years, there were still reductions in anxiety, depression, hopelessness, and demoralization, death anxiety was significantly lower, and spiritual well-being was improved compared to baseline. After 4 years, 60–80% of the patients still showed significant reductions in depression and anxiety compared to baseline (Agin-Liebes et al., 2020). In both studies, mystical experiences correlated significantly with therapeutic outcomes. Findings from qualitative studies show that patients also experienced other important outcomes, such as better insights in existing relationships, improved access to one's feelings, increased self-acceptance and -esteem, and acceptance of their illness (Belser et al., 2017; Swift et al., 2017).

In the most recent pre-post open label study, Anderson et al. (2020) investigated the effects of one 0.3 mg/kg (cohort 1) or 0.36 mg/kg (cohorts 2 and 3) psilocybin session with individual and group therapy in demoralized older long-term AIDS survivors with and without complex medical and psychiatric histories ($n = 18$). They found robust reductions in self-reported demoralization, grief, and psychological trauma from baseline to end-of-treatment and after 3 months. Two unexpected events were reported: one patient vividly re-experienced a traumatic event (not psilocybin-related) 2 days after treatment, and another reported severe anxiety due to feeling rejected by the group after 1 week.

Atypical psychedelics

We included a total of 19 studies on atypical psychedelics, mostly on ketamine ($n = 18$, including 11 case studies) and one recent study on MDMA. With one exception (Kolp et al., 2007), none of these studies included psychotherapy.

Ketamine

Since 2008, 11 case studies were published in which ketamine was administered in varying dosages to a total of 12 palliative- or hospice care patients to treat anxiety, depression, and suicidality (Stefanczyk-Sapieha et al., 2008; Irwin and Iglewicz, 2010; Zanicotti et al., 2012; Grott Zanicotti et al., 2013; Moitra et al., 2016;

Swiatek et al., 2016; McNulty and Hahn, 2012; Sexton et al., 2018; Rodríguez-Mayoral et al., 2020; Rajagukguk and Lee, 2020; Kolp et al., 2007; Barbosa et al., 2020). Across the board, large effects were found on depression and anxiety. These effects tended to wear off after some time (several hours to 1 week) if the ketamine administration was not repeated. Kolp et al. (2007) described two cases of hospice patients with death anxiety who received ketamine-enhanced psychotherapy (150 mg IM). In one patient, decreased pain and panic attacks were reported after 1 week and lasted for the remaining months of the patients' life. The other patient, who was reported to be a heavy polysubstance user, had a'very negative experience,' noted no positive results, and declined further (psychotherapeutic) treatment.

Irwin et al. (2013) studied the antidepressant and anxiolytic effect of 28 continuous daily administrations of oral ketamine (0,5 mg/kg) in depressed and/or anxious patients receiving hospice care ($n = 14$). In this pre-post study, all patients showed statistically significant responses on anxiety. Four patients withdrew after 2 weeks due to lack of effect, and two withdrew for non-ketamine related reasons. All eight remaining patients showed significant responses on depression. Significant treatment effects emerged after 3 days for anxiety and after 14 days for depression, which remained significant until the final treatment day. There was no significant effect on pain (not all participants had pain pre-treatment), functional status, cognition, suicidal ideation, and quality of life. No serious adverse effects were noted, but patients did report diarrhea, trouble sleeping, and trouble sitting still during the treatment period. No longer term follow-ups were conducted.

Iglewicz et al. (Iglewicz et al., 2015) retrospectively described the effects of ketamine (0.5 mg/kg) in depressed hospice care patients ($n = 31$). Treatment consisted of one daily dose ($n = 22$), two daily doses ($n = 5$), or three daily doses for 7 days ($n = 4$), administered orally ($n = 29$), subcutaneously ($n = 1$), or both ($n = 1$). In the first 3 days after the initial dose, 93% had a positive effect on the Global Clinical Impression Scale (GCI). This effect was maintained in 80% of the patients after 4 to 7 days, and in 60% after 8 days to 3 weeks. In most cases, treatment effects occurred within a day after the first dose. Between-group comparisons were not conducted. No (serious) adverse effects were reported.

Fan et al. (2017) compared the effects of a single dose of IV-ketamine (0.5 mg/kg; $n = 20$) to midazolam (0.5 mg/kg; $n = 17$) on suicidality and depression in newly diagnosed cancer patients. On day one, a significant effect of ketamine compared to midazolam was found on suicidality and depression. On day three, the effect on suicidality remained significant, whereas no difference was found on depression. On day seven, both effects were no longer significant. No (serious) adverse effects were reported.

In a RCT, Xu et al. (2017) studied the effect of one intraoperative IV-dose of ketamine (0.5 mg/kg; $n = 25$) or placebo (isotonic saline 0.5 mg/kg; $n = 25$) on depression in breast cancer patients undergoing mastectomy. At the first and third postoperative day, depression scores in the ketamine group were significantly lower compared to the control group. This effect was no longer significant at day seven. No (serious) adverse effects were reported.

Wang et al. (2020) studied the effect of an intraoperative IV-ketamine administration in mild to moderately depressed patients with cervical cancer who received hysterectomy in a large RCT ($n = 417$). Patients were randomized into four groups: a control group (saline, $n = 105$), a racemic ketamine group (0.5 mg/kg, $n = 104$), a high-dose S-ketamine group (0.5 mg/kg, $n = 104$), and a low-dose S-ketamine group (0.25 mg/kg, $n = 104$). Depression scores after 1, 2, and 3 days decreased significantly more in all treatment groups than in the control group. This decrease was highest for the high-dose S-ketamine group, while no significant difference was found between the racemic and low-dose S-ketamine groups. After 5 and 7 days, depression scores were low in all four groups with no significant between-group differences. No (serious) adverse effects were reported.

Liu et al. (2020) tested the antidepressant effect of an intraoperative IV infusion of ketamine in mild to moderately depressed breast cancer patients who received mastectomy. In this RCT, patients randomly received placebo (saline; $n = 100$), racemic ketamine (0.125 mg/kg, $n = 102$), or S-ketamine (0.125 mg/kg, $n = 101$). After 3 days, 1 week, and 1 month, depression scores were significantly lower in the ketamine groups compared to control, with significantly larger effects for S-ketamine than racemic ketamine. Group differences were no longer significant after 3 months. No (serious) adverse effects were reported.

Finally, Falk et al. (2020) retrospectively analyzed mental distress in palliative care patients ($n = 8$) who received a single IV ketamine injection (0.5 mg/kg), compared to a matched control group who received the same palliative care treatment without ketamine ($n = 8$). They found a significant group effect on anxiety with a larger reduction of anxiety in the ketamine group, but no significant group effects on depression or pain. No (serious) adverse events were reported.

4-Methylenedioxymethamphetamine (MDMA)

One RCT (Wolfson et al., 2020) compared the effect of two psychotherapy sessions with MDMA (125–187.5 mg; $n = 13$) or placebo ($n = 5$) in patients with anxiety secondary to a life-threatening illness. One month after the second session, the MDMA group had a borderline significant larger reduction in trait anxiety compared to the placebo group. Positive changes in the MDMA group were also reported

on depression, sleep quality, state anxiety, and global functioning. Then, the MDMA group received an additional open-label MDMA session, and the placebo-group received three open-label MDMA sessions. Statistically significant improvements were found in anxiety, depression, sleep, global functioning, well-being, self-compassion, mindfulness, and attitudes regarding death, compared to baseline. Improvements remained stable after 6 months and 1 year. Frequently reported acute adverse reactions included fatigue, needing more sleep or insomnia, and low mood. These reactions decreased over the course of 1 week.

Discussion

We systematically reviewed studies investigating the effect of classic and atypical psychedelics with or without psychotherapy for the treatment of depression, anxiety, and existential distress in patients with a life-threatening illness. Classical psychedelics, administered in a psychotherapeutic context, appear to be well-tolerated and effective in both the short and longer term, with beneficial effects on depression, anxiety, existential distress, and a variety of psychological domains such as quality of life and well-being. A study on psilocybin combined with group and individual therapy for demoralization in older AIDS survivors indicates that it can have a positive effect on demoralization, grief, and psychological trauma as well. No adverse effects were reported in the studies that used classical psychedelics. Adverse events, such as nausea, psychological discomfort, and anxiety, were transient and did not persist beyond 1 day after treatment. Overall, results of trials that investigated the use of classical psychedelics in patients with a life-threatening illness are promising. However, it is important to note that most of the study designs were limited by small sample sizes and lack of a control group. Regarding atypical psychedelics, it is interesting that none of the RCTs combined ketamine treatment with psychotherapy. Ketamine seems to be mainly offered as a stand-alone pharmacological treatment, like conventional antidepressants (Greenway et al., 2020). Several case studies suggest rapid effects of ketamine on anxiety and depression in patients with a (potentially) terminal illness, but this effect is transient in single-dose treatment regimens (Smith-Apeldoorn et al., 2020). Two studies from the same research group (Liu et al., 2020; Wang et al., 2020) compared racemic and S-ketamine and found S-ketamine to be superior to racemic ketamine in treating pain and depression, although the 0.125 mg-kg dose of racemic ketamine in the study by Liu et al. might have been too low for optimal treatment efficacy. Findings on ketamine's effectiveness in treating depression in terminally ill patients are in line with the relatively robust evidence of ketamine's effectiveness in patients with treatment-resistant depression (Smith-Apeldoorn et al., 2020; Breeksema et al., 2020b; Zheng et al., 2019) and with preliminary evidence of ketamine for anxiety disorders (Glue et al., 2018, 2017; Breeksema et al., 2020b). Finally, a recent exploratory pilot study that used MDMA-assisted psychotherapy to treat existential distress in patients with a life-threatening illness found lasting positive change on anxiety, depression, and attitudes towards death (Wolfson et al., 2020). While adverse effects such as jaw-clenching, thirst, and perspiration were reported in the treatment group during the experimental session, these reactions were mostly short-lived and subsided by the end of the session or in the week following treatment. Results of this study should be interpreted with caution due to study limitations such as a small sample size and lack of a control group after crossover. To our knowledge, MDMA treatment efficacy is so far mainly assessed in PTSD patients, indicating moderate to large effects (Krediet et al., 2020; Bahji et al., 2020). MDMA has been reported to induce cardiovascular effects such as increased blood pressure and heart rate (Fonseca et al., 2021). Given the medical frailty of this patient population, it is advisable to carefully weigh the risk/benefit ratio, especially in patients with known cardiovascular disease.

In contrast with classic psychedelics, we found that the effects of ketamine on mood emerge but also diminish rapidly if not repeatedly administered. One possible explanation for this difference is the lack of psychological guidance in most ketamine treatments. Like classical psychedelics, ketamine can induce short-term changes in consciousness and perception that may have therapeutic relevance. Whether ketamine-induced changes in consciousness can improve or broaden its therapeutic effect is not clear. These psychedelic effects are usually either not addressed (Grabski et al., 2020; Mathai et al., 2020) or regarded as unwanted 'psychotic' side adverse effects in clinical trials (Romeo et al., 2015). In contrast, it has also been suggested that ketamine-induced psychedelic peak experiences may contribute to its antidepressant effect (Sumner et al., 2021). Interestingly, studies that administered ketamine to anesthetized patients—thereby canceling out acute psychedelic effects—reported short-term effects on depression, indicating that the psychedelic experience is not *necessary* for its effect on depression. Still, integrating the acute psychedelic effects of ketamine within a psychotherapeutic (integrative) framework may facilitate a therapeutic process in which not only the core symptoms of depression and anxiety are addressed, but also the existential and spiritual issues that can arise in the face of severe illness and death, possibly resulting in a longer lasting positive change and broader treatment effect (LeMay and Wilson, 2008). 'Ketamine-assisted psychotherapy' may have positive effects on depression, anxiety, and quality of life (Dore et al., 2019). Repeated dosing and a therapeutic setting could facilitate the emergence of meaningful themes which can be addressed in psychotherapy and thereby prolong

the therapeutic effects of ketamine. Providing psychological guidance during and after ketamine administration may reduce the occurrence of psychologically challenging experiences during treatment, thereby improving patient care. No (serious) adverse events were reported in the ketamine studies included in this review. However, side effects such as ketamine-induced ulcerative cystitis and dependence may pose a concern, especially when ketamine use is frequent and of prolonged duration (Short et al., 2018; Morgan et al., 2012). However, studies indicate that ketamine dependence is not frequently observed in either chronic pain patients and depressed patients who receive daily ketamine dosages (Blonk et al., 2010; Schoevers et al., 2016). Bladder dysfunction and lower urinary tract impairment have been described in long-term (> 2 years and > 6 years, respectively) recreational ketamine use (Mak et al., 2011; Chen et al., 2018). This should be monitored carefully by attending clinicians, although the risk in this specific patient population is arguably relatively low due to the limited life expectancy and lower dosages used in treatment for these patients. Furthermore, adverse effects reported in clinical trials with ketamine are mild and usually resolve within an hour of administration (Van Amsterdam and Van den Brink 2021).

In most ketamine studies, treatment was aimed at (symptoms of) depression or anxiety, while the other psychedelic treatments were usually offered to patients with varying types of psychological distress in the face of life-threatening illness. Population differences therefore may have contributed to some of the observed differences. Furthermore, it is important to note that besides Falk et. al. (2020), none of the ketamine studies included an active placebo other than lower doses of ketamine. Additionally, while we found some qualitative studies detailing patient experiences with classical psychedelics (Grof et al., 1973; Agin-Liebes et al., 2020; Belser et al., 2017), no qualitative studies on ketamine treatment in terminally ill patients were encountered in the literature. This may explain why no non-clinical psychological measures such as quality of life, meaningfulness, and existential issues were reported for ketamine. Indeed, there appears to be little qualitative research on patient experiences with ketamine for the treatment of any mental disorder (Breeksema et al., 2020a). Qualitative research methods provide opportunities to further understand the phenomenology of ketamine treatment, how it may contribute to personal and therapeutically relevant outcomes, and the ideal setting of this treatment from the patients' perspective (Breeksema et al., 2020a).

Although the results of the presented studies are promising, it is imperative to conduct larger and methodologically stronger studies. While placebo-controlled designs without crossover may produce results that have a stronger scientific value, we believe that the substantial ethical issue of withholding a possibly effective treatment from patients with high symptom burden and a limited life expectancy outweighs this consideration. Utilizing (active) placebo-controlled crossover designs with more objective effect parameters and including larger groups of participants are examples of how to improve research quality. Furthermore, one should be wary of selection bias and limited generalizability, since it is conceivable that mainly people who are open to treatment with psychedelics are keen to participate in this type of research. About half of the participants in the studies by Griffiths et al. (2016) and Ross et al. (2016) reported to have former experience with psychedelics. Also, existential distress needs to be more clearly defined and assessed, and more knowledge is needed on how this type of distress is related to (symptoms of) anxiety and depression (Nieropvan Baalen et al., 2020). Given the stressor-related nature of the phenomenon, pathological disease-related distress may be seen as an adjustment disorder (Vehling and Kissane, 2018). However, in the context of a life-threatening illness, it is hard to determine if and when the level of suffering is no longer in proportion to the gravity of the stressor. Future research may also be aimed at the treatment of existential distress in patients with chronic, non-life-threatening conditions or in patients with successful cancer-treatments. As severely ill patients often use a variety of medications, possible interactions of psychedelics with commonly used medications within this population should be assessed. Qualitative research may constitute an added value to the current state of knowledge on ketamine treatment, aiding in further improving the (range of) its effectiveness in patients with a terminal illness.

It is important that alternative treatments for depression, anxiety, and existential distress in patients with a life-threatening illness are developed. Evidence of enduring effects of conventional psycho- or pharmacotherapy is limited or ambiguous (Akechi et al., 2008; Ostuzzi et al., 2018). It may take weeks to months before patients respond to treatment with an antidepressant, and half of the patients do not achieve symptom remission, taking time that these patients may not have or cannot bear (Trivedi et al., 2006). Faster acting treatment options need to become available, especially given the increased risk of suicide in this population (Ross, 2018). Conventional pharmacological interventions may decrease symptoms of anxiety and depression, which can improve patients' quality of life to an important degree. However, they do not address important existential domains of distress, such as lack of meaning and dignity, death anxiety, and coping with overwhelming changes. Since all psychedelics exert effects rapidly and are known to induce mystical-type, peak, or transcendental effects that are correlated with therapeutic outcomes (Dore et al., 2019; Johnson et al., 2019; Barrett and Griffiths, 2018), these treatments may be especially helpful in the context of existential distress (Rosenbaum et al., 2019). Furthermore,

psychedelic treatment may be a suitable option in palliative care given the importance that is placed upon existential and spiritual themes. Findings from clinical studies on ketamine for the treatment of addiction support the notion that spiritual (Krupitsky and Grinenko, 1997) or mystical-type experiences (Rothberg et al., 2021; Dakwar et al., 2018) may also mediate its therapeutic effect. Given the importance of spiritual and existential well-being in palliative care, psychedelics may play a unique role in enabling patients to address these critical issues in the last stage of their lives (Bauereiss et al., 2018; Rosa et al., 2019).

Appendix Search terms

Database	Search query
Pubmed	("Hallucinogens"[Mesh] OR "Hallucinogens" [Pharmacological Action] OR "Ketamine"[Mesh] OR "Esketamine" [Supplementary Concept] OR "Esketamine" OR "N-methylketamine" [Supplementary Concept] OR "N-methylketamine" OR "2-Oxo-PCE" [Supplementary Concept] OR "2-Oxo-PCE " OR "Lysergic Acid Diethylamide"[Mesh] OR lsd[tiab] OR Dipropyltryptamine[tiab] OR Hallucinogen*[tiab] OR psychedelic*[tiab] OR ketamine[tiab] OR MDMA[tiab] OR "N-Methyl-3,4-methylenedioxyamphetamine"[Mesh] OR "methylenedoxyamphetamine demethylenase" [Supplementary Concept]) **AND** ("Depression"[Mesh] OR "Adjustment Disorders"[Mesh] OR "Major Depressive Disorder 1" [Supplementary Concept] OR "Anxiety"[Mesh] OR depress*[tiab] OR anxiet*[tiab] OR existential*[tiab] OR psychol*[tiab] OR stress*[tiab] OR distress*[tiab] OR "fear of death"[tiab] OR "Demoralization"[Mesh] OR "Psychological Distress"[Mesh] OR "Mental Disorders"[Mesh]) **AND** ("Palliative Care"[Mesh] OR "Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Neoplasms"[Mesh] OR "Terminal Care"[Mesh] OR palliative[tiab] OR terminal*[tiab] OR life-threaten*[tiab] OR end-of-life[tiab] OR cancer*[tiab] OR dying[tiab] OR tumor[tiab] OR advanced malignanc*[tiab] OR hospice[tiab]) NOT ("animals"[MeSH] NOT "humans"[MeSH])
EMbase	('psychedelic agent'/exp OR 'ketamine'/exp OR 'esketamine'/exp OR 'lysergide'/exp OR 'midomafetamine'/exp OR (Hallucinogen* OR psychedelic* OR ketamine OR MDMA OR lsd OR Dipropyltryptamine):ab,kw,ti) AND ('depression'/exp OR 'adjustment disorder'/exp OR 'anxiety'/exp OR 'demoralization'/exp OR (depress* OR anxiet* OR existential* OR psychol* OR distress* OR 'fear of death'):ab,kw,ti) AND ('hospice'/exp OR 'neoplasm'/exp OR 'terminal care'/exp OR (palliative OR terminal OR 'life-threaten*' OR 'end-of-life' OR cancer* OR dying OR 'advanced malignan*'):ab,kw,ti) NOT ('animal'/exp NOT 'human'/exp)
PsycInfo	(DE "Hallucinogenic Drugs" OR DE "Bufotenine" OR DE "Lysergic Acid Diethylamide" OR DE "Mescaline" OR DE "Peyote" OR DE "Phencyclidine" OR DE "Psilocybin" OR DE "Ketamine" OR DE "Lysergic Acid Diethylamide" OR DE "Methylenedioxymethamphetamine" OR **TI** (Hallucinogen* OR psychedelic* OR ketamine OR MDMA OR OR lsd OR Dipropyltryptamine OR "methylenedioxyamphetamine demethylase" OR "2-Oxo-PCE" OR "N-methylketamine") OR **AB** (Hallucinogen* OR psychedelic* OR ketamine OR MDMA OR lsd OR Dipropyltryptamine OR "methylenedioxyamphetamine demethylase" OR "2-Oxo-PCE" OR "N-methylketamine")) **AND** (DE "Depression (Emotion)" OR DE "Emotional States" OR DE "Sadness" OR E "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression" OR DE "Adjustment Disorders" OR DE "Anxiety" OR DE "Anxiety Sensitivity" OR DE "Computer Anxiety" OR DE "Death Anxiety" OR DE "Health Anxiety" OR DE "Mathematics Anxiety" OR DE "Performance Anxiety" OR DE "Social Anxiety" OR DE "Speech Anxiety" OR DE "Test Anxiety" OR DE "Demoralization" OR DE "Psychological Needs" OR DE "Psychological Stress" OR DE "Affective Disorders" OR DE "Disruptive Mood Dysregulation Disorder" OR DE "Major Depression" OR DE "Seasonal Affective Disorder" OR DE "Anxiety Disorders" OR DE "Generalized Anxiety Disorder" OR DE "Panic Attack" OR DE "Panic Disorder" OR **TI** (depress* OR anxiet* OR existential* OR psychol* OR stress* OR distress* OR "fear of death") OR **AB** (depress* OR anxiet* OR existential* OR psychol* OR stress* OR distress* OR "fear of death")) **AND** (DE "Hospice" OR DE "Palliative Care" OR DE "Assisted Suicide" OR DE "Euthanasia" OR DE "Neoplasms" OR DE "Benign Neoplasms" OR DE "Breast Neoplasms" OR DE "Endocrine Neoplasms" OR DE "Leukemias" OR DE "Melanoma" OR DE "Metastasis" OR DE "Nervous System Neoplasms" OR DE "Terminal Cancer" OR DE "Terminally Ill Patients" OR DE "Death and Dying" OR DE "Death Anxiety" OR DE "Death Attitudes" OR **TI** (palliative OR terminal* OR hospice OR "life-threaten*" OR "end-of-life" OR cancer* OR dying OR tumor OR "advanced malignanc*") OR **AB** (palliative OR terminal* OR hospice OR "life-threaten*" OR "end-of-life" OR cancer* OR dying OR tumor OR "advanced malignanc*"))

Author contribution All authors conceived the project and collaborated on the methodology. NS developed the search queries, performed the searches, and drafted the manuscript; NS and JB collected and selected the data. All authors analyzed the data and revised the manuscript.

Declarations

Ethics approval Ethic approval was not required for this systematic review of existing literature.

Conflict of interest NS, JB, SM, and WB have no conflicts of interest to declare. JV received a speakers fee from Janssen Pharmaceuticals, outside the submitted work. RS received research funding for two randomized clinical trials with generic oral esketamine from the Netherlands Organisation for Health Research and Development and the National Health Care Institute, a speakers fee from Janssen Pharmaceuticals, and consultancy fee from Clexio biosciences, both outside the submitted work.

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