Evidence profile: Stand-alone treatments

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[1] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Cannabis							
Cannabis for PTSD							
Cameron, Watson, & Robinson (2014)	Retrospective chart review	N = 104	I: Nabilone administered for PTSD symptoms and PTSD-related sleep disturbances C: N/A Nabilone was administered orally, as powder in water.	Nabilone dosage: -Initial dose: M = 1.4mg/day -Final dose: M = 4.0mg/day Length of time on nabilone: -M = 11.2 weeks	Canada Inmates within a Secure Treatment Unit (STU) with a variety of clinically diagnosed serious mental illness M = 32.7 years, range 19-55 years Male 100%	PTSD-related insomnia and nightmares - Insomnia (number of hours slept, sleep quality) (self-report) -Frequency of nightmares (self-report) PTSD symptoms -The PTSD Checklist – Civilian Version (PCL-C) (self-report)	Chronic pain Global Assessment of Functioning (GAF)
This was a retrospective patient chart review examining the dosing, efficacy, and adverse effects of nabilone to treat PTSD-related insomnia and nightmares. Results indicated significant post-treatment improvements compared to pretreatment, in the following self-reported measures: (i) PTSD-associated insomnia improved with a significant increase in number of hours slept ($p < 0.001$), (ii) PTSD-associated nightmares significantly decreased in frequency ($p < 0.001$), and (iii) PTSD symptoms were significantly reduced from 'moderate' to 'borderline-mild' ($p = 0.001$).							

[1] Mean age and SD is given when provided, alternatively age range is provided

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Secondary outcomes were (i) subjective improvements in chronic pain reported by 89.6% of participants using nabilone for chronic pain (n = 68), and (ii) a significant improvement in the clinician-rated post-treatment GAF score (p = 0.001), which reflected a shift from 'serious' to 'moderate' impairments in functioning. Adverse effects occurred relatively more often in cannabis-naïve individuals, and overall, 31 (29.8%) participants reported adverse effects, of which 10 chose to abandon the trial. The most serious adverse effect was psychosis (n=2), and both participants who experienced this effect had pre-existing psychotic illness. Other adverse effects included sedation, dry, feeling 'stoned', orthostatic hypotension, agitation, and headache. Twenty participants abandoned the nabilone trial primarily due to adverse effects and abuse of other medications. Notably, all patients were receiving concurrent treatments with other psychotropic medication/s and a range of psychotherapies which were not controlled for in the analysis.							
Fraser (2009)	Retrospective chart review	N = 47	I: Nabilone administered for PTSD-related nightmares C: N/A Nabilone was administered orally, as capsules.	Nabilone dosage: -The commencing dose was 0.5mg daily, titrated as needed. -The average effective dose was 0.5mg/day, taken one hour before bedtime (range: 0.2mg to 4.0mg/day)	Canada Patients diagnosed with PTSD and having treatment-resistant PTSD-related nightmares M = 44 years [SD = 9] Female 57.4%	PTSD-related nightmare intensity -Self-rated Likert-type scale (1-5, with 5 being the most intense) Hours of sleep -Self-tracking sheet	Subjective reports of sleep time, sleep quality, reduction of daytime flashbacks and night sweats
This was an open-label, retrospective chart review with no control group, designed to evaluate the effects of nabilone on treatment-resistant nightmares in patients (n = 47) with PTSD. Compared to baseline, 34 (72%) of patients receiving nabilone reportedly experienced either total cessation of nightmares (n=28), or a significant reduction in nightmare intensity/severity (n = 6). Improvement in sleep time and a reduction of daytime flashbacks and night sweats were subjectively noted by "some" patients (number not reported). Following four to 12 months of nabilone therapy, four (8.5%) patients were able to discontinue their existing medications (their nightmares did not return, or returned at a reduced level, and did not require medication control). The other 43 patients (91.5%) experienced a recurrence of nightmares upon nabilone withdrawal (usually within the first two nights). Nightmares were controlled again when nabilone treatment was							

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reinitiated, and these participants were asked to attempt withdrawal every six months. This was ongoing at the time of the report, so follow-up results were not available. No adverse effects were reported, but 13 (28%) patients experienced mild-moderate side effects (including light headedness, forgetfulness, dizziness, and headache), leading to discontinuation of nabilone therapy.							
Jetly, Heber, Fraser, & Boisvert (2015)	Double-blind RCT, placebo controlled crossover design	N = 10	I: Nabilone administered for PTSD-related nightmares. Group 1: Nabilone, followed by placebo Group 2: Placebo, followed by nabilone Nabilone was administered orally, as tablets	Nabilone dosage: -The commencing dosage was 0.5mg, titrated weekly to a maximum of 3.0mg. -The dosage achieved at week five was maintained for the final two weeks of the treatment period. Each treatment period was seven weeks, and the two treatments were separated by a two-week washout period	Canada Active duty military personnel with currently diagnosed PTSD M = 43.6 years [SD = 8.2] Male 100%	PTSD-related nightmares -The CAPS Recurring and Distressing Dream Scores (clinician-administered)	- The CAPS Difficulty Falling or Staying Asleep item -Sleep diary log (total sleep time and number of awakenings per night) -The PTSD Dream Rating Scale - The Clinical Global Impression of Change (CGI-C)
Assessments were conducted at the start and end of each seven-week trial period, and no follow-up was reported. Compared to the placebo condition, the nabilone condition demonstrated significantly greater reductions in the frequency and intensity of PTSD-related nightmares (p = 0.03). Separating out the item scores saw a significant reduction for frequency (p = 0.05), but not							

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for intensity (p = 0.06). At the end of the nabilone treatment period, four participants reported no distressing dreams in the last week, compared to 0 participants in the placebo condition. Additionally, four placebo participants reported daily or almost daily distressing dreams at the end of their treatment period, while no nabilone participants did. Significantly greater improvements were observed in the nabilone condition compared to the placebo condition for the secondary outcomes including: clinician rated global change (CGI-C) scores (p = 0.05), and general well-being (GWBQ) scores (p = 0.04). However, there was no effect of nabilone on sleep quality and quantity. Common side effects in the nabilone condition were dry mouth and headache, although nabilone was generally well-tolerated.							
Roitman, Mechoulam, Cooper-Kazaz, & Shalev (2014)	Open label pilot study with no control group	N = 10	I: THC administered for chronic PTSD C: N/A THC was self-administered sublingually, after being dissolved in olive oil.	THC dosage: -10mg per day (taken in two 5mg dosages) for three weeks	Jerusalem, Israel. Outpatients with chronic PTSD M = 52.3 years [SD = 8.3] Male 70.0%	PTSD symptoms -CAPS (clinician-administered)	Global improvement and sleep quality -The Clinical Global Impression Scale (CGI) -The Pittsburgh Sleep Quality Index (PSQI) -The Nightmare Frequency Questionnaire (NFQ) -The Nightmare Effects Survey (NES) [*Clinician-administered*]
Results did not demonstrate a significant reduction in total CAPS score posttreatment, however a statistically significant improvement was seen in hyperarousal symptoms (p < .02). Significant improvements were also identified in global symptom severity (CGI-S; p < .02), global symptom improvement (CGI-I; p < .03), PTSD-related sleep quality (PSQI; p < .05), and sleep disturbances (frequency of nightmares (NFQ; p < .04)). Despite short-term reductions in hyperarousal symptoms and PTSD-related sleep disturbances, follow-up data was not collected and therefore the long-term impact of THC could not be assessed. Of note, existing psychotropic medication use was allowable during the trial, and this was not controlled for in analyses.							

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Cannabis for anxiety							
Fabre & McLendon (1981)	STUDY 1: Pre-post, open-label study, with no control group STUDY 2: Double-blind study with a placebo comparison group	STUDY 1 N = 5 STUDY 2 N = 20	I: Nabilone administered for anxiety STUDY 1: I: Nabilone (n = 5) C: N/A STUDY 2: I: Nabilone (n = 10) C: Placebo (n = 10) The method of administration of nabilone was not reported.	BOTH STUDIES: 28-day treatment period, preceded by a four-day washout period STUDY 1: Nabilone dosage: -Dosage commenced at 2mg/day (1mg twice per day), adjusted to a maximum of 10mg/day, M = 2.8mg/day (range: 2 to 8mg/day) STUDY 2: Nabilone dosage: -Fixed dose of 3mg per day (1mg three times per day)	Texas, USA BOTH STUDIES: Psychiatric outpatients suffering from psychoneurotic anxiety STUDY 1: M = 29.4 years, range 22–35 years Male 100% STUDY 2: M = 29.0 years, range 19–41 years Male 75.0%	Anxiety symptoms -Hamilton Anxiety Rating Scale (HAS) (clinician-administered)	-Patient's Global Impressions (SCL-56) -Clinical Global Impression Scale (CGI)
These two studies trialled nabilone for the treatment of anxiety. Study 1 reported a reduction in the total HAS score, and in both factors of the HAS (somatic and psychic anxiety factors), all of which were significant at $p < 0.001$. Additionally, improvements were reported on the clinician-rated CGI-I (n = 5) and CGI-S (n = 3). Statistical tests were not conducted due to small sample size. All five participants reported side effects, and requested that their dosage be lowered when side effects occurred. Side effects were dry mouth, drowsiness, lethargy, headaches, and dry eyes. For study 2, HAS scores (somatic and psychic anxiety factors, and total score) were reported to be significantly lower posttreatment for the nabilone group compared to the placebo group							

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(p < 0.001). The nabilone group demonstrated a 50% reduction in the HAS total score at day 7 which was maintained to day 32, whereas the placebo group showed "only a slight and insignificant reduction" in anxiety. Additionally, the CGI showed a greater improvement for the nabilone group compared to the placebo group (p = 0.002). Patient-reported depression and anxiety (SCL-56) was "greatly reduced" for the nabilone group by day 11, continuing to decline to the end of the trial (significance values were not reported). Side effects were dry mouth, dry eyes, drowsiness, headaches, and insomnia. All participants in the nabilone group (n = 10) completed the study, while five (50%) from the placebo group (n = 10) dropped out before completion of study due to lack of relief of anxiety symptoms.							
Cannabis for depression							
No studies identified							
Ketamine							
Ketamine for PTSD							
Feder et al. (2014)	Randomised, double-blind, crossover trial	N = 41	I: Ketamine hydrochloride administered for PTSD (n = 22) C: Midazolam* (active placebo) (n = 19) Ketamine was delivered intravenously. *Midazolam is a medication which is used for anesthesia	Ketamine hydrochloride dosage: -One dose of 0.5 mg/kg Midazolam dosage: -One dose of 0.045 mg/kg Ketamine and midazolam dosages	NY, USA Patients with chronic PTSD and associated MDD Age range: 18–55 years -Ketamine: M = 36.4 [SD = 10.8] -Midazolam: M = 35.7 [SD = 10.0]	PTSD severity -CAPS (clinician-administered) -Impact of Event Scale–Revised (IES-R) (self-report) (assesses subjective distress caused by traumatic events)	Depression -Montgomery-Asberg Depression Rating Scale (MADRS) -Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR). Global Functioning

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				were separated by two weeks.	Female 46.3%		-Clinical Global Impression (CGI) – Severity and – Improvement scales
This study included participants with a CAPS score of at least 50. Crossover analyses revealed significant improvements in PTSD symptom severity (IES-R) in the ketamine condition compared to placebo controls ($p < 0.05$). No residual crossover effects were identified. Comorbid depression symptoms predicted PTSD symptom severity post-infusion, with the ketamine group showing a significantly greater improvement ($p < 0.01$). Seven participants demonstrated maintained symptom reduction at seven days post-infusion, although significant group differences in mean CAPS scores were not observed. Depression symptoms post-infusion did not differ by group. Of note, multiple adverse events were recorded. Transient dissociative symptoms occurred in most participants, although manic or psychotic symptoms were not observed, One participant discontinued ketamine infusion after receiving a higher dose in error, while three participants required acute beta-blocker treatment to reduce blood pressure elevations. Frequently reported side-effects of ketamine use included blurred vision, dry mouth, fatigue, nausea/vomiting and poor coordination. Additionally, it is worth noting that fewer than 50% of participants had previously received psychotropic medication for the treatment of psychiatric conditions.							
Womble et al. (2013)	Case study	N = 1	I: Ketamine administered for MDD associated with PTSD. C: N/A Ketamine was delivered by intravenous (IV) infusion.	Ketamine dosage: -35mg (calculated as 0.5mg/kg)	Alabama, USA Combat veteran diagnosed with PTSD and chronic MDD Male, 26 years	Comorbid depression and PTSD -Subjective self-report of anxiety and depression, sleep improvement, and nightmare reduction	
After obtaining vital signs, the patient was administered a range of substances, beginning with oxygen by nasal cannula, followed by intravenous midazolam (3mg) as a pre-induction medication. Once an anxiolytic effect was observed, he was administered propofol (70mg) plus 30mg of lidocaine. Once a hypnotic state was achieved, a 20-minute infusion by IV piggyback was administered of propofol (30mg) and ketamine (35mg, which was 0.5mg per kg of bodyweight). No adverse effects were observed, however the patient reported difficulty focusing his vision, and of having a slight headache. Improved behaviours, such as smiling and joking, were observed before he was discharged. Follow-up self-reports were of complete resolution of anxiety and							

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depression lasting from between one and 14 days post-infusion. He also experienced normalised and restorative sleep, and the disappearance of all debilitating nightmare events. After 14 days post-infusion however, he began to relapse into his pre-infusion state of depression.							
Ketamine for anxiety							
No studies identified							
Ketamine for depression							
Burger et al. (2016)	Proof-of-concept, randomised, double-blind trial	N = 10	I: Ketamine administered for acute suicidality (n = 3) C: Placebo (saline) (n = 7) Ketamine was delivered intravenously.	Ketamine dosage: -A single dose of 0.2mg/kg	San Diego, USA Active duty military US Marine Corp and Navy personnel who had voluntarily presented to an emergency psychiatric department for suicidality or acute depression M = 27.5 years, range 21-41 years Male 70.0%	Suicidality -Beck Suicidality Scale (BSS) (clinician-administered)	Hopelessness -Beck Hopelessness Scale (BHS) (self-report)
This pilot study trialled intravenous ketamine use primarily for suicidality in military personnel with depressive symptoms. The trial was terminated early due to inaccurate record-keeping, therefore only 10 of the initially enrolled participants (n = 18) were included in the analyses. Participants were assessed 40, 80, 120, and 240 minutes after drug administration, as well as at							

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discharge, and at two-week follow-up. Results were presented graphically, therefore exact scores were not discernible. At the four-hour assessment, the ketamine group scored significantly lower than the placebo group on suicidality (BSS) ($p < 0.05$), however upon discharge and at follow-up, there was no difference between groups. Hopelessness (BHS) scores for the ketamine group were significantly lower than the placebo group at the four-hour assessment ($p < 0.05$) and at discharge ($p < 0.05$), but there was no difference at follow-up. Two of three (67%) participants who received ketamine experienced significant acute decreases in suicidality and hopelessness (within 40 minutes), however the controls remained unchanged during the four-hour observation. Results suggest ketamine was superior to the placebo group in reducing self-reported suicidality and hopelessness, and the effects were rapid, yet transient. No adverse effects occurred during the trial.							
Caddy et al. (2015)	Cochrane Review	25 studies N = 1242	Meta-analysis and review	Varied	Patients with unipolar depression	Varied	
Utilising the Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR), data from single- or double-blind randomised controlled trials was collected to compare adult depression outcomes between glutamate receptor modulators and control conditions, including active and non-active placebo, and electroconvulsive therapy (ECT). In total, 25 studies were included in the review, of which nine refer specifically to the use of ketamine. Among the included studies, intravenous ketamine treatment was the sole glutamate receptor modulator to demonstrate efficacy above that of placebo. Higher numbers of clinical responders were noted in ketamine conditions compared to midazolam at 24 hours (OR 0.36, 95% CI 0.14 to 0.58), 72 hours (OR 0.37, 95% CI 0.16 to 0.59), and one week post-infusion (OR 0.29, 95% CI 0.08 to 0.49). However, the lasting effects of ketamine use were undetermined at two weeks post-infusion. In contrast to active and inactive placebos, ketamine elicited more confusion and emotional blunting and was perceived to be less tolerable than active placebo control (midazolam). A single study demonstrated greater symptom improvement following ketamine infusion in contrast to ECT at 24 hours (OR 28.00, 95% CI 2.07 to 379.25) and 72 hours (OR 12.25, 95% CI 1.33 to 113.06) post treatment. However, these effects were not maintained at one or two week follow-ups. Caddy and colleagues note that long-term efficacy of glutamate receptor modulators, in particular ketamine, is unclear with limited support for symptom improvement at one to two weeks post-infusion. The authors add that the global quality of evidence is limited due to small sample sizes and risk of experimental bias. Adverse events included blood pressure and heart rate changes were noted. Further, many trials did not provide information on all pre-specified outcomes and salient issues such as suicidality, cognitive and dropout rates due to adverse effects and the intravenous nature of ketamine were infrequently acknowledged.							
Jafarinia et al. (2016)	Double blind, parallel-group RCT	N = 40	I: Ketamine administered for depression in chronic pain patients (n = 20) C: Diclofenac* (n = 20)	Ketamine dosage: -50mg three times/day for six weeks	Tehran, Iran Outpatients with chronic pain (headache)	Depressive symptoms	

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			Ketamine was delivered orally, as capsules. *Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain	Diclofenac dosage: -50mg three times/day for six weeks	I: M = 40.7 years [SD = 8.71] C: M = 38.95 years [SD = 9.22] Female 75%	-Hamilton Depression Rating Scale (HDRS) (clinician-administered) -Hospital Anxiety and Depression Scale (HADS) – Depression scale only (self-rated)	
Score reductions in the HADS depression subscale were significantly greater in the ketamine group compared to the diclofenac group at week three (Cohen's *d:* 1.13, *p* = 0.001) and at week six (post-intervention; Cohen's *d:* 0.84, *p* = 0.012). Improvements in HDRS scores were not significantly different between treatment groups at week three. However at week six, mean HDRS score reduction in the ketamine group was significantly greater than the diclofenac group (Cohen's *d:* 0.79, *p* = 0.017). Response rates (where 'response' was defined as at least a 50% reduction in the HDRS score) and remission rates (where 'remission' was defined at an HDRS score of 7 or less) were not significantly different for the two treatment groups at week three, but at week six the ketamine group responded (*p* = 0.008, odds ratio for response: 8.50) and remitted (*p* = 0.031) significantly more than the diclofenac group. Furthermore, ketamine participants responded (*p* = 0.002) and remitted significantly sooner (*p* = 0.013) when compared to diclofenac participants. No serious adverse events were observed, however some participants experienced blurred vision, tremor, restlessness, nervousness, abdominal pain, and a transient loss of appetite. No follow-up beyond six weeks was reported.							
Kishimoto et al. (2016)	Meta-analysis	14 studies N = 588	Meta-analysis and review	Varied	Varied	Major depressive disorder	
Kishimoto and colleagues (2016) meta-analysed 14 parallel-group or cross-over RCTs comparing single intravenous infusion of ketamine (9 studies, n = 234) or a non-ketamine (5 studies, n = 354) NMDA receptor antagonist versus placebo/pseudo-placebo in patients with major depressive disorder (MDD). They concluded that a single infusion of ketamine, but less so non-ketamine NMDA receptor antagonists, has ultra-rapid efficacy for MDD, lasting for up to one week. Ketamine reduced depression significantly more than placebo/pseudo-placebo beginning at 40 minutes, peaking at day 1 (Hedges' *g* = -1.00, 95% CI -1.25 to -0.73, *p* < 0.001), and losing superiority by days 10-12. Non-ketamine NMDA receptor antagonists (e.g. memantine, traxoprodil, lanicemine,							

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and rapastinel) induced smaller effect sizes than ketamine, and were only superior to placebo/pseudo-placebo on days 5-8 (Hedges' *g* = -0.37, 95% CI -0.66 to -0.09, *p* = 0.01), however, the reasons underlying this difference remain unclear.							
Singh et al. (2016)	Double blind RCT	N = 67	I: Ketamine administered for depression (n = 35) C: Intravenous inactive placebo (0.9% sodium chloride) (n = 32) Ketamine was administered intravenously.	Ketamine dosage: -0.5mg/kg either two times/week (n = 18) or three times/week (n = 17) for four weeks	USA Outpatient population with treatment-resistant depression M = 43.9 [SD = 11.0] Female = 67%	Depression – Montgomery-Asberg Depression Rating Scale (MADRS) (clinician-administered)	Clinical Global Impressions (CGI)
Participants assigned to the ketamine condition received doses either two or three times weekly. Change to depression symptom severity (MADRS) was assessed between baseline (pre-infusion), day 15 and day 29 of treatment. Mean MADRS score from baseline to day 15 were significantly improved in both ketamine dosing groups when compared to placebo controls ($p < 0.001$). Mean difference in MADRS scores did not differ between ketamine frequencies. MADRS scores from baseline to day 29 showed a trend for improvement in both ketamine dosing conditions when compared to placebo controls, although significance values were not reported. Significantly higher proportions of clinical responders and remitters were identified in both ketamine dosing groups compared to placebo controls ($p < 0.05$). Additionally, significant decreases were observed in CGI scores for both ketamine dosing groups in contrast to placebo controls ($p = 0.01$). Two adverse events were noted: one patient reported significant anxiety and was subsequently hospitalised, and another patient attempted suicide on day 40 of the trial. Common treatment side-effects included headache, anxiety, nausea and dizziness. Dissociation was observed shortly after infusion and resolved within three hours post-infusion.							

Evidence profile: Adjunct treatments

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
MDMA							
MDMA for PTSD							
Bouso, Doblin, Farre, Alcazar, & Gomez-Jarabo (2008)	Double-blind RCT with placebo control	N = 6	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: MDMA plus psychotherapy (n = 4) C: Placebo plus psychotherapy (n = 2) The method of administration of MDMA was not reported.	Number of non-drug psychotherapy sessions: -Six (90 minutes each) – three preparatory plus three integration sessions Number of experimental drug psychotherapy sessions: -One (8 hours) MDMA dosage: -Single dose of 50mg (n=3) or 75mg (n=1)	Madrid, Spain Women with chronic, treatment-resistant PTSD secondary to a sexual assault M = 35.7 years, range: 29-49 years Female 100%	- PTSD Symptoms (SSSPTSD) (*a Spanish adaptation of the PSS*) -State-Trait Anxiety (STAI-S) -Depression (BDI) -The Hamilton Rating Scale (HAM-D) (clinician-administered)	Self-reported fears of sexual assault victims -The Modified Fear Scale (MFS III) Social and work-related adjustment -The Maladjustment Scale (MS) Global self-esteem -The Rosenberg Self-Esteem scale (SE/R)
This study assessed the efficacy of a single, low dose of MDMA, administered as an adjunct to psychotherapy for the treatment of chronic, treatment-resistant PTSD. The trial was terminated prematurely after treating six of the anticipated 29 participants, due to “political pressures” described as “a series of political decisions as a result of unfavourable media coverage and unrelated to any scientific or ethical considerations”. Due to the small sample size, results were presented descriptively. For the placebo group, the mean pretreatment versus posttreatment score for the SSSPTSD was 44.5 and 40.0 (reduction of 4.5, or 10.1%) respectively, while for the MDMA group, these scores were 37.3 and 28.3 (reduction of 9, or 24.1%), respectively. At one-month follow-							

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up, mean SSSPTSD score for the MDMA group continued to decline to 25.0 (participants in the placebo group did not take part in the one month follow-up). Mean pretreatment and posttreatment scores for the remainder of the outcome measures were: STAI-S, (placebo: 28.5 and 28.0; MDMA: 38.6 and 25.6 (one-month follow-up = 33.0)); the BDI (placebo: 20.0 and 23.5; MDMA: 25.6 and 15.0 (one-month follow-up = 16.6)); and HAM-D (placebo: 35.5 and 22.5; MDMA 39.0 and 22.0 (one-month follow-up = 21.6)). Given the small sample size and limited placebo control condition, inferential statistics were not included. Thus, the generalisability of this study is limited to the descriptive findings of this small cohort.							
Mithoefer et al., (2011[a] & 2013)	2011: Double-blind, inactive placebo, crossover RCT 2013: Prospective long-term follow-up	N = 20	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: Psychotherapy[b] and MDMA (n = 12) C: Psychotherapy[b] and inactive placebo (lactose) (n = 8) MDMA was administered orally, by capsule. Follow-up: Assessments administered 17 to 74 months (M = 45.4 months, SD = 17.3] following initial study close.	Number of non-drug psychotherapy sessions: -Between two and eight introductory sessions; and -Four integration sessions after each enhanced session; and -One final integration session two months after the second enhanced session Number of experimental MDMA- or placebo-enhanced, exposure-based sessions: -Two	USA Psychotherapy patients with chronic, treatment-resistant PTSD symptoms M = 40.4 years [SD = 7.2] Female 85%	- PTSD (CAPS & IES-R)	

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				MDMA dosage: -125mg (+ 62.5mg) prior to each of two experimental sessions			
PTSD symptom severity was assessed at baseline, four days post-intervention, and two months following the final experimental session. MDMA recipients showed a significantly greater decrease in PTSD severity (CAPS) and physical response to stress (IES-R) across post-baseline time points, when compared to placebo controls ($p < 0.01$ and $p < 0.05$ respectively). Additionally, 83% of MDMA recipients demonstrated a clinical response to the experimental condition, in contrast to 25% of the placebo condition. Clinical response was defined as a greater than 30% reduction in baseline CAPS total severity score. In their secondary study, Mithoefer et al. (2013) collected follow-up data on posttreatment symptom outcomes, ranging from 17 to 74 months following study completion. Statistically significant differences in PTSD symptom severity (mean CAPS scores) were not observed between two months post-intervention and long term follow-up. Additionally, psychotherapy and medication management were resumed by some participants following the initial study conclusion and were not controlled for in follow-up analyses. Notably, the authors utilised independent (i.e. non-related) samples methodology to assess changes within a dependent, or related, sample. [a]Mithoefer et al. (2011) released an addendum to their 2011 article, noting that an important reference was omitted in error. [b]Psychotherapy modality comprised principles of LSD psychotherapy, Holotropic Breathwork and music interpretation, which have not been validated for use in populations with PTSD.							
Oehen, Traber, Widmer, & Schnyder (2013)	Double-blind, active placebo RCT	N = 12	MDMA-assisted psychotherapy (MDMA-AP) administered for PTSD I: MDMA (full dose) plus non-drug therapy sessions (n=8)	Number of non-drug psychotherapy sessions: -Twelve (two preparatory sessions and 10 integration sessions)	Switzerland Patients with chronic, treatment-refractory PTSD M = 41.4 years [SD = 11.2] Female 83.3%	- PTSD (CAPS (*German version),* PDS (German version), IES-R	

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			C: Active placebo (low dose MDMA) plus non-drug psychotherapy sessions: (n=4) MDMA was administered orally, by capsule.	Number of experimental sessions: -Three (between eight and 10 hours each) MDMA dosages: -Full-dose: 187.5mg of MDMA in two doses (125mg plus 62.5mg supplemental) administered in each experimental session -Active placebo (low dose): 37.5mg of MDMA in two doses (25mg plus 12.5mg supplemental) administered in each experimental session	PTSD longevity: M = 18.3 years [SD = 12.0]		
Results showed no significant group differences in PTSD symptom reduction (CAPS) for MDMA compared to placebo control (p = 0.066). Changes in CAPS scores from pre to posttreatment were small (15.6 points decrease in the MDMA group and 3.1 points increase in the placebo group), and all participants still fulfilled PTSD diagnostic criteria at posttreatment. A significant reduction in self-reported PTSD symptoms was identified, as measured by the PDS (p = 0.014). Effect sizes were not reported. Three full dose recipients were classified as “non-responders” and received an additional dose. Clinical response at two months posttreatment was observed in four of the eight full-dose group, although all participants continued to meet criteria for PTSD diagnosis. At 12-month follow-up (n = 11), five participants no longer met diagnostic criteria for PTSD and a broad trend toward CAPS score improvement was identified. Psychotropic medication use and external psychotherapy were resumed posttreatment, and were not controlled for in follow-up analyses. No drug-related serious adverse events occurred, although some participants reported moderate insomnia, loss of appetite, headache, dizziness, impaired balance, difficulty concentrating, and anxiety.						

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Oehen et al. (2013) utilised a similar study design and an identical treatment protocol to those used in the Mithoefer et al. (2011) RCT. However, in contrast to Mithoefer and colleagues, the results of this study did not replicate the favourability of MDMA treatment over placebo control for PTSD symptom reduction. The study authors attribute this discrepancy to differing sample characteristics, rater and therapist differences, and chance.							
MDMA for anxiety							
No studies identified							
MDMA for depression							
No studies identified							
LSD							
LSD for PTSD							
No studies identified							
LSD for anxiety							
Gasser et al., (2014)	Phase 2 pilot study, double-blind RCT with active placebo	N = 11	LSD-assisted psychotherapy for anxiety I: LSD experimental group (n = 8) C: Active placebo group (n = 3) LSD was administered orally, as free base in capsules.	Number of sessions: -Two experimental sessions (LSD or placebo) two to three weeks apart, plus six psychotherapy sessions LSD dosage: -Experimental 200 µg	Switzerland Patients diagnosed with anxiety associated with life-threatening illnesses. Male 63.6% M = 51.7 years [SD = 9.1]	- Anxiety (STAI)	- Quality of Life (European Cancer Quality of Life Questionnaire) -The SCL-90-R - Anxiety and Depression (HADS)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
				-Active placebo 20 µg; after two-month follow up, all (n = 3) crossed over to receive 200 µg dosage			
To be included, participants were required to have a STAI score greater than 40 on either the state or trait subscale. A significant visit x group interaction was identified for trait anxiety ($p < 0.05$, Cohen's $d = 1.1$); of those in the experimental condition, three of eight showed reductions in trait anxiety below threshold, while all active placebo participants reported increased trait anxiety. No significant differences were observed between two- and 12-month follow-up scores for trait anxiety in those receiving LSD doses (n = 9), suggesting sustained benefits over time. Similarly, a significant visit x group interaction was identified for state anxiety ($p < 0.05$, Cohen's $d = 1.2$), with three of eight in the experimental condition showing reductions below threshold, while two of three controls reported increased state anxiety. These results were maintained at 12-month follow-up for those receiving experimental LSD doses. No severe adverse events were reported, although commonly reported side effects of active LSD treatment included emotional distress, feeling cold, gait disturbance, and illusions.							
McCabe, Savage, Kurland, & Unger (1972)	RCT	N = 85	LSD-assisted psychotherapy (psychedelic therapy) for the treatment of neurotic disorders, including anxiety and depression. Group I: Conventional treatment (group therapy only) (n = 27) Group II: Psychedelic therapy - Low-dose LSD control group (n = 30)	Non-drug group therapy (Group I only): -Three sessions per week in groups of between three and eight; conducted over three to five weeks. Mean hours of formal therapy was 21.2 Psychedelic therapy (Groups II and III):	USA Hospital inpatients with a psychoneurotic diagnosis. Clinically, the patients were depressed, anxious, and typically received a "depressive reaction" diagnosis M = 32.9 years, range 19–53 years	Neuroticism, with anxious and depressive features (MMPI)	- Other personality measures (The Eysenck Personality Inventory, The Personal Orientation Inventory

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Group III: Psychedelic therapy - High-dose LSD experimental group (n = 28) The method of administration of LSD was not reported, other than being referred to as a "drug preparation".	-Preparation period - Mean hours of formal therapy was 19.4 (Group II), and 20.4 (Group III), conducted over three to five weeks; and -One LSD session of 12-14 hours LSD dosages: -Low dose: 50 µg -High dose: 350 µg	Female 65%		
Participants were inpatients diagnosed with "neurotic disorder" between the ages of 18 and 55. Patients presented as anxious and depressed, and typically received a "depressive reaction" diagnosis. The MMPI was administered pre- and post-treatment (conducted 5 to 7 days after treatment). Post-treatment MMPI depression scores differed significantly between the high-dose LSD group and those receiving conventional group therapy (p = 0.039). Significant differences were also identified in post-treatment MMPI anxiety scale scores between the conventional therapy group and both the low-dose and high-dose LSD groups (p = 0.004). There were no differences between high- and low-dose psychedelic therapy groups. Of note, this trial did not include a no-treatment control group.							
Richards, Grof, Goodman, &	Pilot study, pre/post	N = 31	I: LSD-assisted psychotherapy administered for anxiety and	Non-drug psychotherapy sessions:	USA Patients with cancer	Anxiety and depression -Observer* ratings using a specially	- Psychological isolation

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Kurland (1972)[a]	design with no control group		depression associated with having a life-threatening illness C: N/A LSD was administered intramuscularly.	-Preparatory sessions (M = 9.75 hours over two to three weeks); and -"Several subsequent" integration sessions LSD sessions: -28 participants received one LSD session, and three participants received 2, 4, and 6 sessions respectively over several months LSD dosage: -One dosage of between 200 and 500 µg (M = 323 µg)	M = 54.74 years, range 35-81 years Female 74.2%	developed rating scale with a range of values from -6 to +6 reflecting degree of depression and anxiety *Raters included physicians, nurses, family members, therapists, and an independent psychiatric social worker.	- Difficulty in medical management - Fear of death - Preoccupation with pain - Denial of the imminence of death

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Treatment effectiveness was assessed using pre- and post-session observer ratings and changes in narcotic administration. Ratings were made one day before and three days after LSD treatment. Pooled and averaged ratings suggest significant reductions in depression ($p < 0.01$) and anxiety ($p < 0.01$); depression pre (-3.05) and posttreatment (+0.43); anxiety pre (-2.94), posttreatment (+0.33). A trend toward significant reductions in narcotic use was also observed. [a]A secondary paper also reported on this study the following year (Grof, Goodman, Richards, & Kurland, 1973). Using the global rating scale as a marker of therapeutic success, nine patients demonstrated "dramatic" improvement following psychedelic treatment, 13 patients demonstrated "moderate" improvements, while seven patients remained symptomatically "unchanged". Additionally, two patients exhibited an increase in symptomology from pre to posttreatment.							
LSD for depression							
McCabe, Savage, Kurland, & Unger (1972)	RCT	N = 85	LSD-assisted psychotherapy (psychedelic therapy) for the treatment of neurotic disorders, including anxiety and depression.	This study reported on combined anxiety/depression outcomes. Refer to the section 'LSD for anxiety' above.			
Richards, Grof, Goodman, & Kurland (1972)[a]	Pilot study, pre/post design with no control group	N = 31	LSD-assisted psychotherapy administered for anxiety and depression associated with having a life-threatening illness .	This study reported on combined anxiety/depression outcomes. Refer to the section 'LSD for anxiety' above.			

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
[a]A secondary paper also reported on this study the following year (Grof, Goodman, Richards, & Kurland, 1973).							
Psilocybin							
Psilocybin for PTSD							
No studies identified							
Psilocybin for anxiety							
Moreno, Wiegand, Taitano, & Delgado (2006)	Modified double-blind exploratory study	N = 9	I: Psilocybin for OCD C: N/A Psilocybin was administered orally.	Psilocybin dosage: -Up to four single-dose exposures per person -Very low dose (VLD) = 25 µg/kg (n = 7) -Low dose (LD) = 100 µg/kg (n = 9) -Medium dose (MD) = 200 µg/kg (n = 7) -High dose (HD) = 300 µg/kg (n = 6) Dose escalation protocol: Each participant received dosages in the order of	USA Patients with treatment resistant OCD M = 40.9 years [SD = 13.2] Male 77.8%	OCD symptoms (Yale-Brown Obsessive Compulsive Scale (YBOCS) (self-report) Overall obsessive compulsive symptom severity -Visual analogue scale (VAS) (self-report)	Hallucinogen experience -The Hallucinogen Rating Scale (HRS) (self-report)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
				LD, MD, and HD, with VLD inserted randomly at any time after the LD			
The YBOCS and VAS were administered immediately before psilocybin ingestion (baseline) and at four, eight, and 24 hours post-ingestion while the HRS was administered at eight hours post-ingestion. Decreases in OCD symptoms, as measured by the YBOCS, were observed in all participants during one or more sessions (23% - 100% reduction in YBOCS score). A significant contrast comparison of baseline versus post-ingestion OCD symptoms was identified across all doses (YBOCS; p = .028). Although this study reports only a transient reduction of OCD symptoms, one participant achieved long-term remission at the end of the four test sessions, as measured at six month follow-up. No significant correlations were identified between HRS total and changes in OCD severity. Other than transient hypertension without relation to anxiety or somatic symptoms (n = 1), no other significant adverse effects were observed.							
Griffiths et al. (2016)	Double-blind RCT cross-over design with placebo control	N = 51	Psilocybin for anxiety and depression associated with having a life-threatening disease I: High dose psilocybin group: -High dose (n = 26) followed by low dose (n = 25) C: Very low (placebo-like) dose group: -Low dose (n = 25) followed by high dose (n = 24)	Number of treatment sessions per person: -Two sessions, spaced five weeks apart Psilocybin dosage: -High dose: The first participant received 30mg/70kg, and the remainder (n = 49) received 22mg/70kg -Very low dose: The first 12 participants	Maryland, USA Psychologically distressed cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. M = 56.3 years [SD = 1.4] Male 51%	- Anxiety and depression (GRID-HAMD-17; HAM-A; SIGH-A; BDI; HADS; (STAI) -Profile of Mood States (POMS) (self-report)	Subjective drug effect measures -Hallucinogen Rating Scale (HRS); 5-Dimension Altered States of Consciousness (5D-ASC); Mysticism Scale; States of Consciousness Questionnaire (SOCQ) Psychiatric symptoms -Brief Symptom Inventory (BSI)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Psilocybin was administered orally	received 3mg/70kg, and the remainder (n = 38) received 1mg/70kg			Other secondary measures: Quality of life and life meaning, optimism, death anxiety, and spirituality
At post-session assessment (five weeks after session one), participants who received the high dose prior to the low dose demonstrated significant decreases in anxiety and depression, when compared to the low dose first condition. Specifically, 92% and 60% of the high-dose first group experienced a clinically significant response and symptom remission for depression, respectively (GRID-HAMD-17; $p < 0.05$). Both of these percentages were significantly greater than those reported in the low-dose first group ($p < 0.01$), which were 32% and 16%, respectively. Similarly, 76% and 52% of the high-dose first group experienced a clinically significant response and symptom remission for anxiety, respectively (HAM-A; $p < 0.05$). Both of these percentages were significantly greater than those reported in the low-dose first group ($p < 0.01$), which were 24% and 12%, respectively. Significant differences between high dose first and low dose first groups were not identified in these domains following session two, after both groups had received high doses of psilocybin. Additionally, no significant differences were observed in response and remission rates between session two and six month follow-up, suggesting relatively sustained symptom improvement. No severe adverse events were reported, however side effects of psilocybin doses included increased blood pressure and pulse, nausea, vomiting, transient anxiety and psychotic symptoms.							
Grob et al. (2011)	Double-blind, placebo controlled pilot study.	N = 12	I: Psilocybin for anxiety and depression associated with having a life-threatening illness. C: Placebo (Niacin). Participants acted as their own control and received both conditions.	Each participant received two experimental treatment sessions. Dosages: -Psilocybin: 0.2mg/kg -Niacin: 250mg	USA Advanced stage cancer patients with anxiety and/or acute stress disorder.	- Anxiety (STAI) - Depression (BDI) -Profile of Mood States (POMS) (self-report)	Psychiatric Symptoms -Brief Psychiatric Rating Scale Consciousness -5-Dimension Altered States of Consciousness Profile

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
			Psilocybin was delivered orally.				
Broadly, trends approaching significance were observed on measures of depression and anxiety in the psilocybin condition compared with placebo controls. Observable changes in depression symptoms were not noted pre- and post-psilocybin administration. However, self-reported depression severity decreased by almost 30% between session one and 1-month follow up (BDI; p = 0.05), a decrease that was sustained at six-month follow-up (p = 0.03). Significant changes in anxiety level were not observed at two weeks post-treatment. However, self-reported trait anxiety (STAI) was significantly decreased at one-month (p = 0.001) and 3-month follow up (p = 0.03). Psychiatric symptoms did not vary between experimental and control conditions, although marked differences in state of consciousness were observed between psilocybin and niacin administrations.							
Ross et al. (2016)	Double-blind RCT, placebo controlled, crossover design	N = 29	Psilocybin-assisted psychotherapy for anxiety and depression associated with having a life-threatening illness I: Psilocybin first, followed by niacin (n = 14) C: Niacin first, followed by psilocybin (n = 15) Psilocybin was delivered orally, by capsules.	Each participant received two dosing sessions. Treatment cross-over occurred at seven weeks post-session one. Psychotherapy: -Three preparatory and three integration sessions following each dosing session Dosages: -Psilocybin – a single 0.3mg/kg dose -Niacin – a single 250mg dose	NY, USA Patients with life-threatening cancer, and cancer-related, clinically significant anxiety and depression M = 56.28 years [SD = 12.93] Female 62.1%	- Anxiety and depression (HADS; BDI; STAI) -The Profile of Mood States (POMS) (self-report) -The Brief Symptom Inventory (BSI) (self-report)	Subjective drug effects and mystical experience -The Mystical Experience Questionnaire (MEQ 30) -The Hallucinogen Rating Scale (HRS) -The 5 Dimension Altered States of Consciousness Profile (5D-ASC) Persisting effects of psilocybin -The Persisting Effects Questionnaire (PEQ)
Prior to crossover, significant differences were observed in anxiety and depression symptoms for the psilocybin group verses the control condition. Specifically, significant differences were observed in clinical response and remission rates for self-reported depression (BDI; p < 0.01) and anxiety (HADS-A; p < 0.01) symptoms at seven weeks post-session one. Significant group							

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
differences were not observed for the clinician administered measure of depression symptom changes (HADS-D). Within-group anxiety and depression reductions for the psilocybin first group were significant across all time points (baseline to each post-baseline time point), including eight month follow-up. At six month follow-up, 60 – 80% of all participants maintained clinical reductions in depression and/or anxiety. Participants' mystical or spiritual experiences (measured using MEQ 30) were highly correlated with clinical improvements and mediated a significant proportion of the treatment effects of psilocybin on depression and anxiety measures. Although severe adverse events were not recorded, symptoms including increased blood pressure, nausea, vomiting, anxiety and psychotic symptoms were reported.							
Psilocybin for depression							
Carhart-Harris et al. (2016)	Open-label, feasibility (pilot) study with no control group	N = 12	I: Psilocybin plus psychological support for depression (n = 12) C: N/A Psilocybin was delivered orally, via capsules	Psilocybin dosage: -Doses were administered in two separate sessions, seven days apart. -The first session was low-dose (10mg). -The second session was high-dose (25mg). Psychological support using a non-directive, supportive approach was provided during dosing.	London, UK Patients with moderate to severe unipolar treatment-resistant major depression (mean duration of depression 17.8 years, SD = 8). M = 42.7 years, range 30-64 years Male 50%	Depressive symptoms and severity (QIDS; BDI) (self-report) -Snaith-Hamilton Pleasure Scale (SHAPS) (self-report) -The 21-item Hamilton Depression Rating Scale (HAM-D) (clinician-rated) -Montgomery-Asberg Depression Rating Scale (MADRS) (clinician-rated)	Clinician assessment of global functioning -Global Assessment of Functioning (GAF) Additional patient-rated scales -State-Trait Anxiety Inventory (trait version only) (STAI-T) -Patient-rated subjective intensity of psilocybin's effects reported on a 0-1 scale (a feasibility measure)

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
Mean self-rated intensity of psilocybin experience (on a 0-1 scale) was 0.51 [SD = 0.36] for the low-dose (10mg) session, and 0.75 [SD = 0.27] for the high-dose (25mg) session. Relative to baseline, significant reductions were reported in mean QIDS scores at week one (p = 0.002), week two (p = 0.002), week three (p = 0.002), week five (p = 0.003), and three months (p = 0.003) after the high-dose sessions. The greatest reduction occurred at week two, and significant reductions were maintained at the end of three months. There were also significant reductions in depressive symptoms measured using the BMI at week one (p = 0.002), and at three months (p = 0.002), compared to baseline. Remission of depressive symptoms, as indicated by a score of nine or less on the BDI, was achieved by eight (67%) patients at week one, five (42%) of whom remained in remission at three months. Anhedonia was also significantly reduced at week one (SHAPS; p = 0.002), and at three months (SHAPS; p = 0.002), compared to baseline. Clinician assessments (HADS and MADRS) were conducted at week one and showed significant improvements at that time**.** Adverse events included transient anxiety during drug onset, transient confusion or thought disorder, nausea, headache, and mild paranoia.						
Griffiths et al. (2016)	Double-blind RCT cross-over design with placebo control	N = 51	Psilocybin for anxiety and depression associated with having a life-threatening disease	This study reported on combined anxiety/depression outcomes. Refer to the section ‘psilocybin for anxiety’ above.			
Grob et al. (2011)	Double-blind, placebo controlled pilot study.	N = 12	Psilocybin for anxiety and depression associated with having a life-threatening illness.	This study reported on combined anxiety/depression outcomes. Refer to the section ‘psilocybin for anxiety’ above.			
Ross et al. (2016)	Double-blind RCT, placebo controlled,	N = 29	Psilocybin-assisted psychotherapy for anxiety and	This study reported on combined anxiety/depression outcomes. Refer to the section ‘psilocybin for anxiety’ above.			

Authors & year	Design	Total sample size	Intervention (I) and Comparison (C) and participants for I and C	Dosage (total drugs administered & number of sessions)	Population Mean age (SD)[2] Gender (%)	Primary Outcome domain (Measure(s))	Secondary Outcome domain (Measure(s))
	crossover design		depression associated with having a life-threatening illness				
Gamma-Hydroxybutyric Acid (GHB)							
GHB for PTSD							
No studies identified							
GHB for anxiety							
No studies identified							
GHB for depression							
No studies identified							