Table 1. Study characteristics for all trials included in the review. Full reference list for included trials available in the Appendix.

Study ID	Registration number	Country	Sample size	Methods	Participants	Intervention	Control	Duration	Outcomes
Anderson 2017[a1]	ISRCTN 14689382	UK	72	Multicentre, parallel, randomised study comparing ketamine with placebo in the acute treatment of patients with uni- or bi-polar depression.	Adult males and females with a primary diagnosis of uni- or bipolar depression of moderate severity as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a verbal IQ score of 85 or greater, and; (2) an American Society of Anaesthesiol-ogists score of 1, 2, or 3. Patients were excluded if: (1) they spoke a language other than English; (2) were detained under the Mental Health Act; (3) were unable to give informed consent; (4) were diagnosed with psychosis, schizoaffective disorder, obsessive-compulsive disorder, or anorexia; (5) had a history of alcohol or drug dependence as defined by the DSM-IV; (6) had received ECT in the three months prior to trial entry; (7) had known hypersensitivity to ketamine; (8) had a contraindication to ketamine; (9) were diagnosed with an organic brain disease; (10) had a history of using etomidate or other induction agents; (11) were pregnant or not using contraception; (12) were breastfeeding, or; (13) had a score of less than 24 on the Mini Mental Status Examination.	Ketamine: 0·5mg/kg, delivered by intravenous (IV) bolus (duration of administration not reported). Participants received one dose each electroconvulsive therapy (ECT) session, for a maximum of four doses (i.e., once per ECT session).	Control (placebo): saline (dose not reported), delivered by IV bolus (duration of administration not reported). Participants received one dose each ECT session, for a maximum of four doses (i.e., once per session).	Unclear.	Suicidal ideation: MADRS, suicidality item (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
George 2017[a2]	NCT 01441505	Australia	16	Single centre, cross-over, RCT comparing ketamine with midazolam in the acute treatment of older adults (Mean: 65·6 years, SD: 5·7 years) with treatment resistant depression.	Males and females over 60 years of age with a primary diagnosis of major depression as defined by the DSM-IV-TR and clinician-conducted interview. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the MADRS, and (2) insufficient therapeutic response to more than one adequate trial of an antidepressant during the current depressive episode as defined by Anti-depressant Treatment Response Questionnaire. Patients were excluded if they: (1) were judged to	Ketamine: ascending doses from 0·1 mg/kg, 0·2mg/kg, 0·3mg/kg, 0·4mg/kg to 0·5mg/kg, delivered by subcutaneous infusion (duration of administration not reported). Participants received five doses separated by a week.	Control: midazolam, 0·01mg/kg, delivered by subcutaneous infusion (duration of administration not reported). Participants received one dose. Dose was randomly inserted within the first three treatment sessions.	Up to five weeks.	Suicidal ideation: single item from the MADRS (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					be at high suicide risk necessitating urgent management; (2) were pregnant; (3) had a diagnosis of schizophrenia, drug abuse or dependence within the last six months; (3) had current psychotic symptoms; (4) known hypersensitivity or medical contraindication to ketamine; (5) had a history of ketamine abuse.				
Grunebaum 2017[a3]	Not reported.	USA	16	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with bipolar depression.	Males and females between 18 and 65 years of age with a primary diagnosis of bipolar depression as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 16 or greater on the HDRS-17, and; (2) a score of 4 or greater on the Scale for Suicidal Ideation. Patients were excluded if they: (1) had an unstable medical and/or neurological illness; (2) had an electrocardiogram (ECG) abnormality; (3) had current psychosis; (4) had a history of ketamine abuse/dependence; (5) had a history of alcohol and/or drug dependence in the past six months; (6) had drug induced suicidality; (7) had a treatment failure or other adverse reaction to ketamine or midazolam; (8) used opioids daily; (9) had a score of greater than 25 on the Mini Mental Status Examination (MMSE); (10) were unable to provide informed consent, or (11) spoke a primary language other than English.	Ketamine: racemic, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: midazolam, 0·02mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Unclear.	Suicidal ideation: Scale for Suicidal Ideation, clinician-rated version. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Grunebaum 2018[a4]	NCT 01700829 .	USA	80	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with major depression.	Males and females between 18 and 65 years of age with a primary diagnosis of major depression (unclear how defined). Additional inclusion criteria required eligible participants to have: (1) a score of 16 or greater on the HDRS. Participants were excluded if: (1) they were diagnosed with an unstable medical or neurological illness; (2) were pregnant or lactating; (3) had current psychosis; (4) had a history of ketamine use or dependence; (5) had a history of alcohol or drug dependence in the past six	Ketamine: 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received one dose.	Control: midazolam, 0·02mg/kg, delivered by IV infusion over 40 minutes. Participants received one dose.	Unclear.	Suicidal ideation: Scale for Suicidal Ideation, clinician-rated version. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					months; (6) had suicidal ideation due to substance use or withdrawal; (7) had previous ineffective use of ketamine or midazolam, or; (8) a score of greater than 25 on the MMSE (for participants over 60 years of age).				
Hu 2016[a5]	Not reported.	China	27	Single centre, parallel, randomised study comparing ketamine with escitalopram in the acute treatment of patients with major depression without psychotic features.	Males and females between 18 and 60 years of age with a primary diagnosis of major depression without psychotic features as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 24 or greater on the HDRS; (2) a score of one or greater on item three (suicide risk) of the HDRS, and; (3) sufficient language ability to be able to understand the study aims and to provide informed consent to participate in the study. Patients were excluded if they: (1) had a lifetime history of alcohol or drug dependence; (2) a lifetime diagnosis of psychosis, bipolar disorder, obsessive-compulsive disorder, or any Axis 1 disorder other than major depression; (3) a history of non-response or intolerance to escitalopram; (4) were pregnant or breastfeeding; (5) had attempted suicide in the current depressive episode; (6) had any contraindication to ketamine or escitalopram; (7) had received ECT or any NMDA antagonist medication in the past six months.	Ketamine: 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: placebo (saline solution; dose not specified), delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: QIDS-SR, suicidality item. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Kudoh 2002[a6]	Not reported.	Japan	70	Single centre, parallel, randomised study comparing ketamine with propofol plus fentanyl in the acute treatment of patients with major depression.	Males and females between 35 and 63 years of age with a primary diagnosis of major depression as defined by the DSM-IV. No specific exclusion criteria were reported.	Ketamine: 1·0mg/kg, route of administration not reported, duration of administration not reported. Participants received one dose.	Control: propofol (1·5mg/kg) and fentanyl (2·0 nanograms/kg), route of administration not reported, duration of administration not reported. Participants received one dose.	One day	Suicidal ideation: HDRS, suicidality item. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Loo 2016[a7]	NCT 01441505.	Australia	15	Single centre, cross-over, randomised study	Males and females over 18 years of age with a primary diagnosis of major depression as defined by the SCID-R	Ketamine: ascending doses from 0·1 mg/kg, 0·2mg/kg,	Control: midazolam, 0·01mg/kg, (route of administratio	Up to five weeks.	Suicidal ideation: single item from the MADRS (obtained by correspondence).

				comparing ketamine with midazolam in the acute treatment of patients with treatment resistant depression.	for DSM-IV-TR and as verified by a face-to-face psychiatric interview. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the MADRS, and (2) insufficient therapeutic response to more than one adequate trial of an antidepressant during the current depressive episode as defined by the Maudsley Staging of Treatment Resistance. Patients were excluded if they: (1) were pregnant; (2) had a diagnosis of schizophrenia, bipolar disorder, or drug abuse or dependence within the last six months; (3) had current psychotic symptoms; or (4) had received ECT within the four weeks preceding trial entry.	0·3mg/kg, 0·4 mg/kg to 0·5mg/kg, delivered either by intravenous, intramuscular, or subcutaneous bolus over approximately five minutes. Participants received five doses separated by a week.	n and duration of administratio n not reported). Participants received one dose. Dose was randomly inserted within the first three treatment sessions.		Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Murrough 2013[a8]	NCT 00768430	USA	73	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with major depression.	Males and females between 21 and 80 years of age with a primary diagnosis of major depression as defined by the SCID for DSM-IV-TR. Additional inclusion criteria required eligible participants to have: (1) a history of inadequate response to at least three therapeutic trials of an antidepressant as defined by the criteria of the Antidepressant Treatment History Form; (2) a history of at least one previous episode of major depression before the current episode, or, a chronic episode of at least two years duration, and; (3) a score of 32 or greater on the Inventory of Depressive Symptomatology-Clinician Rated. Patients were excluded if they: (1) had a lifetime diagnosis of psychosis or bipolar disorder; (2) were diagnosed with alcohol or substance dependence in the past two years; (3) were diagnosed with an unstable medical illness; (4) were at serious and imminent risk of suicide or homicide; (5) had a score of less than 27 on the MMSE; (6) were prescribed and were taking any contraindicated medications.	Ketamine: racemic, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: midazolam, 0·045mg/kg, delivered by IV infusion (duration of administratio n not specified). Participants received a maximum of one dose.	One week.	Suicidal ideation: single item from the MADRS (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Murrough 2015[a9]	NCT 01507181	USA	24	Single centre, parallel,	Males and females between 18 and 80 years of age with a primary	Ketamine: racemic, 0·5mg/kg,	Control: midazolam, 0·045mg/kg,	One week.	Suicidal ideation: single item from the MADRS

				randomised study comparing ketamine with midazolam in the acute treatment of patients with any mood and/or anxiety disorder.	diagnosis of any mood and/or anxiety disorder as defined by the DSM-IV-TR. Additional inclusion criteria required eligible participants to have: (1) clinically significant suicidal ideation as defined by a score of four or greater on the suicidal ideation item of the MADRS. Patients were excluded if they: (1) scored five or greater on the C-SSRS (for outpatients only); (2) had a lifetime diagnosis of schizophrenia or any other psychosis; (3) had current psychosis symptoms; (4) had current mania symptoms; (5) had a diagnosis of substance use disorder in the past one month; (6) had a positive urine screen for any drug; (7) had a lifetime history of abuse of ketamine or phencyclidine, or (8) were diagnosed with an unstable medical illness.	delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.		(obtained from correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Ray-Griffith 2017[a10]	Not reported.	USA	16	Single centre, parallel, randomised study comparing ketamine with methohexital in the acute treatment of patients with uni- or bi-polar depression.	Adult males and females with a primary diagnosis of uni- or bi-polar depression as defined by the SCID for DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the HDRS. Patients were excluded if they: (1) spoke a primary language other than English; (2) had a history of any adverse event whilst receiving ketamine or methohexital anaesthesia; (3) were pregnant, or; (4) had a Body Mass Index of greater than 40.	Ketamine: 1·0mg/kg, delivered by IV bolus. Participants received a maximum of five doses (once per ECT session).	Control: methohexital, 1·0 mg/kg, delivered by IV bolus. Participants received a maximum of five doses (once per ECT session).	One week.	Suicidal ideation: HDRS, suicidality item and BDI, suicidality item (from authors). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Sos 2013[a11]	EudraCT 2009-010625-39.	Czech Republic	27	Single centre, parallel, randomised study comparing ketamine with placebo in the acute treatment of patients with major depression.	Males and females between 18 and 65 years of age, primary diagnosis of major depression as defined by the MINI (DSM-IV). Additional inclusion criteria: (1) a score of 20 or greater on the MADRS; (2) be on a stable dose of antidepressant(s) for three or more weeks prior to study entry, and; (3) be right handed. Patients were excluded if: (1) at imminent risk of suicide (according to clinical examination); (2) diagnosed with an Axis 1 or 2 co-morbidity; (3) diagnosed with a serious, unstable medical illness	Ketamine: racemic, 0·27mg/kg, delivered by IV infusion over 30 minutes. Participants received a maximum of one dose.	Control (placebo): saline, 0·09mg/kg, delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.	One week.	Suicidal ideation: MADRS, suicidality item (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					or neurological disorder (e.g., epilepsy, head trauma with loss of consciousness); (4) lifetime diagnosis of psychosis or psychosis symptoms (including in any first- or second-degree relative), and; (5) had received ECT within three months prior to study entry.				
Su 2017a[a12]	Not reported.	Taiwan	71	Single centre, parallel, randomised study comparing ketamine at two different dosages (0·2mg/kg and 0·5mg/kg) with placebo in the acute treatment of patients with major depression.	Adult males and females with a primary diagnosis of major depression as defined by the MINI. Additional inclusion criteria required eligible participants to have: (1) previous failure to respond to at least two trials of antidepressants. Patients were excluded if they: (1) were diagnosed with bipolar depression, psychosis, substance dependence (other than nicotine); (2) had mild depressive symptoms (defined as a score of less than 18 on the HDRS), or (3) were diagnosed with hypertension or hyperglycaemia.	Ketamine (0·2mg/kg): ketlar, 0·2mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: single item from the HDRS (from authors). Suicide attempt: not reported. Suicide: measure used not reported. All-cause mortality: not evaluated.
Su 2017b[a12]	Not reported.	Taiwan	71	Single centre, parallel, randomised study comparing ketamine at two different dosages (0·2mg/kg and 0·5mg/kg) with placebo in the acute treatment of patients with major depression.	Adult males and females with a primary diagnosis of major depression as defined by the MINI. Additional inclusion criteria required eligible participants to have: (1) previous failure to respond to at least two trials of antidepressants. Patients were excluded if they: (1) were diagnosed with bipolar depression, psychosis, substance dependence (other than nicotine); (2) had mild depressive symptoms (defined as a score of less than 18 on the HDRS), or (3) were diagnosed with hypertension or hyperglycaemia.	Ketamine (0·5mg/kg): ketlar, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: single item from the HDRS (from authors). Suicide attempt: not reported. Suicide: not reported. All-cause mortality: not evaluated.
Zarate 2012[a13]	NCT 00088699	USA	15	Single centre, cross-over, randomised study comparing ketamine with placebo in the acute treatment of patients with bipolar disorder, types I or II.	Adult males and females, between 18 and 65 years of age, with a primary diagnosis of bipolar disorder, types I or II, as defined by the SCID-P for DSM-IV, and as verified by clinical interview. Additional inclusion criteria: (1) a current duration of a major depressive episode of at least four weeks; (2) a MADRS score of 20 or greater; (3) history of inadequate treatment response to at least one adequate antidepressant	Ketamine (0·5mg/kg): ketamine hydrochloride, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	40 minutes	Suicidal ideation: MADRS item (estimated from graphics in the original trial report). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					trial as defined by the Antidepressant Treatment History Form, modified, and (4) history of inadequate treatment response following a prospective open trial of a mood stabiliser (lithium or valproate) for at least four weeks at minimum therapeutic levels (serum lithium: 0·6—1·2mEq/L; valproic acid: 50—125 nannograms/mL). Patients were excluded if: (1) diagnosed with comorbid substance abuse or dependence for at least three months prior to trial entry; (2) any serious unstable medical condition; (3) previous treatment with ketamine; (4) concomitant treatment with psychotropic medications other than lithium or valproate in the two weeks preceding trial entry (or five weeks for fluoxetine); or (4) pregnant or breast-feeding.			
Canuso, 2018[a14]	NCT 02133001	USA	68	Multicentre, parallel, randomised controlled trial comparing esketamine with placebo in the acute treatment of patients with major depression.	Adult males and females, between 19 and 64 years of age, with a primary diagnosis of major depression without psychotic features as defined by the DSM-IV-TR and as verified by the MINI. Additional inclusion criteria: (1) current suicidal ideation as defined by an affirmative response to the MINI question B5 ("Think about suicide?") and question B9 ("Intend to act on thoughts of killing yourself within the next 24 hours?"); (2) in need of immediate psychiatric hospitalisation due to imminent risk of suicide; and (3) a score of ≥22 on the MADRS. Patients were excluded if they: (1) were diagnosed with bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial or borderline personality disorder; or (2) had a current or past diagnosis of any psychosis.	Esketamine (up to 84mg): esketamine dissolved in 100µL of saline solution delivered by intranasal spray. Participants received a maximum of six sprays (i.e., three 'devices' per session, separated by 5 mins) delivering a maximum of 84mg of esketamine over the 4-week study period.	Control (placebo): saline with added embittering agent, delivered by intranasal spray. Participants received a maximum of six sprays (i.e., three per session, separated by 5 mins) over the 4-week study period.	15 minutes	Suicidal ideation: single item from the MADRS and the 21-item Beck Scale of Suicidal Ideation. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Ionescu, 2019[a15]	NCT 01582945	USA	26	Single centre, parallel, randomised controlled trial comparing ketamine	Adult males and females, between 18 and 65 years of age, with a primary diagnosis of major depression as defined by the SCID for DSM-IV. Additional inclusion criteria required eligible	Ketamine (0.5mg/kg): ketamine, 0.5mg/kg, delivered by IV infusion over 45 minutes.	Control (placebo): saline, delivered by IV infusion over 45 minutes. Participants	45 minutes.	Suicidal ideation: Columbia Suicide Severity Rating Scale (C-SSRS) total score. Suicide attempt: not evaluated.

		with placebo in the acute treatment of patients with major depression.	participants to have: (1) a score of ≥20 on the HDRS; (2) history of ≥3 failed trials of antidepressant treatment of adequate dosage and duration during the current episode of depression as measured by the Antidepressant Treatment History Questionnaire; (3) suicidal ideation for ≥3 months as measured by a score of ≥1 on the C-SSRS; (4) a score of ≥2 on the suicide item of the HDRS on at least three assessments; (5) ability to remain on an adequate, stable antidepressant regimen for ≥4 weeks prior to trial entry; (6) access to a secure, reliable adult chaperone after each ketamine infusion; (8) able to maintain treatment by a psychiatrist aware of the safety plan of the trial protocol, and; (9) physically healthy as determined by a physical exam, blood laboratory testing, electro-cardiogram, and medical history obtained from a board-certified physician. Patients were excluded if they: (1) were pregnant; (2) were diagnosed with an unstable medical illness; (3) were diagnosed with bipolar disorder or psychosis; (3) had been diagnosed with a substance use disorder within the past year; (5) had positive urine toxicology; (6) had past multiple adverse drug reactions; (7) had a history of ketamine abuse, (8) had suicidal ideation requiring immediate hospitalisation and/or indicating immediate suicide risk, or use of any of the following within the 6 months prior to trial entry: St John's wort, theophylline, tramadol.	Participants could receive up to six doses over the three-week study period.	could receive up to six doses over the three-week study period.	Suicide: not evaluated. All-cause mortality: not evaluated.

REFERENCES