

**HEALTH TECHNOLOGY BRIEFING
FEBRUARY 2019****Esketamine (nasal spray) for major depressive disorder with imminent risk of suicide**

NIHRI ID	20542	NICE ID	9977
Developer/Company	Janssen-Cilag Ltd	UKPS ID	647876

Licensing and market availability plans	Currently in phase III clinical trials
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SUMMARY

Esketamine nasal spray is being developed as a treatment that could be given to people with depression with an imminent risk of suicide. Major depressive disorder (often called depression or major depression in UK) is a serious mood disorder that can impact all aspects of daily life. Symptoms can include low mood, weight changes, lack of energy, disturbed sleep, and suicidal intentions and thoughts. The time between suicidal thoughts and attempted suicide is often very short, and so there is a need for urgent intervention and treatment.

Esketamine is currently used as an anaesthetic given as an intravenous infusion but is being developed as a nasal spray in a lower dosage that has demonstrated rapid antidepressant effect with fewer side effects. Esketamine nasal spray has been shown to reduce suicidal thoughts within 2 hours of treatment, whilst standard antidepressants take 4-6 weeks to be fully effective. Esketamine nasal spray may offer an important and rapid treatment to bridge the gap between onset of acute symptoms of depression such as suicidal thoughts and the delay it takes for standard antidepressants to start working.

PROPOSED INDICATION

Adults with major depressive disorder (MDD) with imminent risk of suicide^a

TECHNOLOGY

DESCRIPTION

Esketamine, the S-enantiomer of racemic ketamine, is an antidepressant with a novel mechanism of action. It is a non-competitive, subtype non-selective, activity-dependent glutamate receptor modulator.^b Esketamine's mechanism of action is distinctively different compared to other widely used oral antidepressants, i.e. SSRIs, SNRIs, TCAs and MAOIs, which function through the prevention of reuptake or breakdown of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine), or by alteration of their receptor pharmacodynamics.^{1,2,b}

Putative etiological contributors of depression, including stress and other conditions, are known to cause structural and functional impairment of synapses in brain regions involved with the regulation of mood and emotional behaviour. Evidence within the literature suggests that through N-methyl-D-aspartate (NMDA) receptor antagonism, esketamine produces a transient increase in glutamate release leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation and subsequently to increases in neurotrophic signalling that restore synaptic function in these brain regions. Unlike other antidepressant therapies, the primary antidepressant action of esketamine does not directly involve monoamine, GABA, or opioid receptors.^{1,2,b}

Esketamine nasal spray (JNJ-54135419) is in clinical development for adults with MDD with imminent risk of suicide, in phase III clinical trials (ASPIRE I; NCT03039192 and ASPIRE II; NCT03097133).^{3,4} The proposed esketamine nasal spray dosing regimen for this indication is 84mg (3 devices of 28 mg each) two times per week for four weeks.^c

INNOVATION AND/OR ADVANTAGES

Evidence from post-mortem analyses and imaging studies demonstrate that imbalances in glutamate are associated with disturbances in mood. Glutamate levels have been found to be higher in patients with MDD than their comparators, and the degree of this increase has been correlated with the severity of disease.⁵

Suicidal ideation is a major risk factor for suicide in patients with MDD. The interval between the onset of suicidal ideation and suicide attempt is often very short, and there is therefore a need for urgent intervention and antidepressant therapy with a rapid onset. Standard antidepressant medications have demonstrated efficacy in the treatment of mood symptoms, including suicidal ideation, but they require 4-6 weeks for optimal effect.⁶

Studies have reported that ketamine improved depressive symptoms and reduced suicidal ideation within hours of intravenous (IV) administration, and produced a greater reduction of suicidal ideation within 24 hours compared to midazolam.⁶ For esketamine, rapid onset of antidepressant effects has been observed in patients with treatment-resistant depression as early as 2 hours and 24 hours after

^a Information provided by Janssen-Cilag on UK PharmaScan

^b Information provided by Janssen-Cilag. Wording is as expected to be used in FDA/EMA label

^c Information provided by Janssen-Cilag

single-dose intranasal administration. Esketamine may therefore be an important treatment to bridge the efficacy gap created by the delayed onset of action of standard antidepressants.⁷

Esketamine was formulated for intranasal administration to provide a non-invasive, patient acceptable, rapidly absorbed and readily bioavailable route of delivery. IV administration involves inherent difficulties for both patients and clinicians. Oral administration results in low bioavailability of around 20%, whereas the intranasal route offers a more acceptable bioavailability of up to 45%.⁸

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Esketamine nasal spray does not currently have Marketing Authorisation in the EU/UK for any indication.

Esketamine nasal spray is in pre-registration with the EMA for treatment-resistant depression.⁹

Esketamine nasal spray has the following regulatory designations/awards:

- A Breakthrough Therapy by the US FDA for MDD with imminent risk of suicide in August 2016⁹

Esketamine solution for injection/infusion is licensed in the UK for hospital use or pre-hospital emergency care in higher dosages for the induction and maintenance of general anaesthesia, as anaesthesia and pain relief in emergency medicine, and as supplementation of regional or local anaesthesia.¹⁰

PATIENT GROUP

DISEASE BACKGROUND

Depressive disorders are typically characterised by persistent low mood, loss of interest and enjoyment, neurovegetative disturbance, and reduced energy, causing varying levels of social and occupational dysfunction. Depressive symptoms include depressed mood, anhedonia, weight changes, libido changes, sleep disturbance, psychomotor problems, low energy, excessive guilt, poor concentration, and suicidal ideation. MDD is characterised by the presence of at least 5 symptoms and can be classified along a spectrum of mild to severe. Severe episodes may include psychotic symptoms such as paranoia, hallucinations, or functional incapacitation.¹¹

Studies suggest that suicidal behaviours occur on a continuum of severity that progresses from less serious and more prevalent behaviours to less prevalent but more harmful and devastating behaviours. This continuum ranges from ideation without specific plans, having a plan, to a completed suicide attempt. Risk factors for suicidal ideation in depression include severity of depression, alcohol abuse and dependence, comorbid anxiety disorder or personality disorder, younger age, female gender, unemployment, poor social support and past suicide attempts.¹²

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, the prevalence of MDD is estimated to be between 5% and 10% of people seen in primary care settings and 10% to 14% of medical inpatients, although it may be underdiagnosed.¹³ At least 60% of people dying by suicide have depression, which may be complicated by other mental health issues, especially alcohol misuse and personality disorders.¹⁴

In 2017 there were 5,821 suicides registered in the UK, an age-standardised rate of 10.1 deaths per 100,000 population. Males accounted for three-quarters of suicides registered in 2017, and the rate of 15.5 deaths per 100,000 was the lowest since 1981. For females the rate for the last 10 years has

been around 4.9 deaths per 100,000. The highest age-specific suicide rate was 24.8 deaths per 100,000 among males aged 45 to 49 years, whilst for females the age group with the highest rate was 50 to 54 years, at 6.8 deaths per 100,000.¹⁵

The total cost of each suicide in England has been estimated £1.7 million (at 2009 prices). This includes intangible costs (loss of life to the individual and the pain and suffering of relatives), as well as lost output (both waged and unwaged), police time and funerals.¹⁶

Data from the Adult Psychiatric Morbidity Survey (APMS) 2014 (a survey of 7,500 adults) found that:¹⁷

- 20.6% of adults reported that they had thought of taking their own life at some point. This was more common in women (22.4%) than men (18.7%), and in people of working-age than those aged 65 or more.
- One person in 15 had made a suicide attempt at some point (6.7%, CI 95%: 6.1% to 7.4%). Despite men being more likely than women to take their own life, women were more likely to report an attempt.
- Of people under 60 years living on their own, 40.2% had suicidal thoughts, compared with 24.8% of people who lived with another adult.
- Half of people who reported they had made a suicide attempt had sought help following their most recent attempt. 25.5% went to a hospital or specialist medical or psychiatric service, 26.5% sought help from a GP, and 21.7% tried to get help from friends or family.
- The proportion of men aged 55 to 64 years who thought about suicide in the past year increased from 1.9% in 2007 to 5.3% in 2014.

Suicidal ideation alone has a substantial negative impact on health-related quality of life (HRQoL) with a disability weight (0.36, 95%CI 0.05-0.67) comparable to disabling physical disorders such as severe asthma and moderate heart failure.¹⁸ Suicide attempts also place a considerable burden on the healthcare system, with more than 70% of costs related to psychiatric inpatient and outpatient care and 14% associated with A&E attendance and medical or surgical care.¹⁹ Suicide prevention is therefore a priority for the English Government with an ambition of achieving a 10% reduction in the national rate for suicide by 2021 and improving support for those affected by suicide.²⁰

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Suicidal behaviour is the most common and most serious psychiatric emergency. Treatment of the suicidal crisis is complicated and requires a series of considerations, and its outcome is ultimately not predictable. Suicidal patients in crisis are often seen by the mental health professional either after a suicide attempt or when tormented by acute, severe suicidal ideation. Patients who are at imminent risk for suicide are usually referred to crisis teams for a comprehensive biopsychosocial assessment and subsequent management.²¹

In the acute phase of MDD with imminent risk for suicide, patients are assessed to determine their level of safety and appropriate level and setting of care for further treatment, after which the acute phase treatment is started immediately with the aim of keeping the patient alive and inducing remission to achieve full return to patient's baseline level of functioning.²²

NICE guidelines recommend that inpatient treatment should be considered for people with depression who are at significant risk of suicide.²³ Pharmacological treatment has a significant role in reducing acute psychological distress. It is advisable to immediately implement a treatment plan focussed on reducing acute psychiatric symptoms such as anxiety, insomnia, depression and eventual

psychotic symptoms. Clinical prevention of suicidal behaviours is obtained through treatment of the underlying psychiatric disorders and through treatment of specific psychiatric symptoms.²¹

Existing evidence supports the efficacy of pharmacological treatment and cognitive behavioural therapy (CBT) in preventing suicidal behaviour. Studies show that antidepressant treatment decreases the risk for suicidality among depressed patients. However, the risk of suicidal behaviour in depressed patients treated with antidepressants exists during the first 10-14 days of treatment, which requires careful monitoring.²¹

CURRENT TREATMENT OPTIONS

NICE guidelines and European guidelines recommend consideration of electroconvulsive therapy (ECT) for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed.^{23,21}

European guidelines recommend the following psychopharmacological and other biological treatments for long-term treatment of suicidal patients:²¹

- Antidepressants should be given. Selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenalin reuptake inhibitors lack sedative potential and may cause agitation. Tricyclic antidepressants and other antidepressants which increase drive should be avoided.
- Short-term supplementary medication with anxiolytics and hypnotics in the case of anxiety and insomnia
- Long-term treatment with lithium has been shown to be effective in preventing both suicide and attempted suicide in patients with unipolar and bipolar depression
- In the case of lithium nonresponse, when the patient displays one or more suicide risk factors, lithium should be combined with another mood stabilizer; valproate and carbamazepine also have an anti-suicidal effect
- Antidepressants have very limited value in the acute treatment of bipolar depression. Some atypical neuroleptics (olanzapine, quetiapine and aripiprazole) have acute antidepressant and long-term mood-stabilizing effect in patients with major depression and bipolar disorders, but their specific anti-suicidal effects need further studies.
- Treatment with clozapine is effective in reducing suicidal behaviour in patients with schizophrenia. Olanzapine may have similar effects.
- CBT is recognized as an evidence-based method in treatment of suicidality

PLACE OF TECHNOLOGY

If licensed, esketamine nasal spray will offer a new treatment option for patients with MDD with imminent risk of suicide, who currently have few fast-acting effective pharmacotherapies available.

CLINICAL TRIAL INFORMATION

Trial	ASPIRE I, NCT03039192 , EudraCT-2016-003990-17; esketamine nasal spray vs placebo, both in addition to standard of care (SoC); phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ³
Location	EU (not UK), USA and other countries
Design	Randomised, placebo-controlled

Participants	n=226; aged 18-64 yrs; MDD without psychotic features, current suicidal ideation with intent, acute psychiatric hospitalisation clinically warranted due to imminent risk of suicide, Montgomery Asberg Depression Rating Scale (MADRS) total score >28 pre-dose on Day 1
Schedule	Randomised to intranasal esketamine nasal spray 84mg two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); or intranasal placebo two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); both in addition to SoC treatment
Follow-up	Active treatment for 25 days, follow-up for 65 days
Primary Outcomes	Change from baseline in MADRS total score at 24 hrs post first dose (Day 2)
Secondary Outcomes	Change from baseline in Clinical Global Impression - Severity of Suicidality - Revised (CGI-SS-R) at 24 hrs post first dose (Day 2)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Jan 2019.

Trial	ASPIRE II, NCT03097133 , EudraCT-2016-003992-23; esketamine nasal spray vs placebo, both in addition to SoC antidepressant treatment; phase III
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry ⁴
Location	EU (not UK), USA, Canada, Argentina and Brazil
Design	Randomised, placebo-controlled
Participants	n=224 (planned); aged 18-64 yrs; MDD without psychotic features, current suicidal ideation with intent, acute psychiatric hospitalisation clinically warranted due to imminent risk of suicide, MADRS total score >28 pre-dose on Day 1
Schedule	Randomised to intranasal esketamine nasal spray 84mg two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); or intranasal placebo two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); both in addition to SoC antidepressant treatment
Follow-up	Active treatment for 25 days, follow-up for 65 days
Primary Outcomes	Change from baseline in MADRS total score at 24 hrs post first dose (Day 2)
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in CGI-SS-R at 24 hrs post first dose (Day 2) <p>Time frame: at 4, 24 hrs post first dose and through to end of double-blind treatment phase (Day 25)</p> <ul style="list-style-type: none"> • % of pts with remission (MADRS <= 12) • % of pts achieving resolution of suicidality (CGI-SS-R score of 0 or 1) <p>Time frame: Baseline, 4 hrs post first dose (Day 1) and through to end of double-blind treatment phase (Day 25)</p> <ul style="list-style-type: none"> • Change from baseline in MADRS total score on Days 1 and 25 • Change from baseline in CGI-SS-R score on Days 1 and 25

	<p>Time frame: Baseline, 4 hrs (Day 1) and 24 hrs (Day 2) post first dose and through to end of double-blind treatment phase (Day 25)</p> <ul style="list-style-type: none"> Change from baseline in Clinical Global Impression of Imminent Suicide Risk (CGI-SR-I) on Days 1 and 25 <p>Time frame: Baseline through to end of double-blind treatment phase (Day 25)</p> <ul style="list-style-type: none"> Change from baseline in Beck Hopelessness Scale (BHS) score Change from baseline in European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L) Change from baseline in Quality of Life in Depression Scale (QLDS) score Treatment Satisfaction Questionnaire for Medication (TSQM-9) score Change from baseline in Suicide Ideation and Behaviour Assessment Tool (SIBAT) Module 5 (My Risk) Question 3 (Participant-reported frequency of suicidal thinking) Clinician Administered Dissociative States Scale (CADSS) <p>Time frame: up to end of double-blind treatment phase (Day 25)</p> <ul style="list-style-type: none"> Number of pts with abnormal clinical laboratory findings as a measure of safety and tolerability Number of pts with nasal examination findings as a measure of safety and tolerability Modified Observer's Assessment of Alertness/Sedation (MOAAS) Scale score Arterial oxygen saturation (SpO2) <p>Time frame: up to final visit (Day 90)</p> <ul style="list-style-type: none"> Number of pts with treatment emergent adverse events (AEs) as a measure of safety and tolerability SIBAT <p>Other time frames (as stated):</p> <ul style="list-style-type: none"> Plasma concentrations of esketamine nasal spray and noresketamine nasal spray [Time frame: Days 1 and 4: 30-50min, 1.5 hr to 2.5 hrs, and 4 hrs to 12 hrs post dose] Number of pts with electrocardiogram (ECG) abnormalities findings as a measure of safety and tolerability [Time frame: Days 1, 8 and 25] Number of pts with vital sign abnormalities as a measure of safety and tolerability [Time frame: Days 1, 4, 8, 11, 15, 18, 22, 25 and 90]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as July 2019.

Trial	PeRSEVERe, NCT02133001 ; esketamine nasal spray vs placebo, both in addition to SoC; phase II
Sponsor	Janssen Research & Development, LLC

Status	Published
Source of Information	Publication, ⁷ trial registry ²⁴
Location	USA
Design	Randomised, placebo-controlled
Participants	n=68; aged 18-64 yrs; MDD, current suicidal ideation with intent, acute psychiatric hospitalisation clinically warranted due to imminent risk of suicide, MADRS total score >=22 pre-dose on Day 1
Schedule	Randomised to intranasal esketamine nasal spray 84mg two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); or intranasal placebo two times per wk for 4 wks (Days 1, 4, 8, 11, 15, 18, 22 and 25); both in addition to SoC treatment. Esketamine nasal spray dose may be reduced to 56mg per day at investigator's discretion.
Follow-up	Active treatment for 25 days, follow-up for 56 days
Primary Outcomes	Change from baseline in MADRS total score at 4 hrs post first dose (Day 1)
Secondary Outcomes	<ul style="list-style-type: none"> • Change from baseline in clinician's assessment of SIBAT at 4 hrs post first dose (Day 1) • Change from baseline in Beck Scale for Suicidal Ideation (BSS) total score at 4 hrs post first dose (Day 1) • % of pts with response based on MADRS total score [Time frame: Day 1 up to Day 25] • Change from baseline in depressive symptoms based on MADRS total score at Day 25 [Time frame: Day 1 and Day 25] • Change from baseline in clinician's assessment of SIBAT at Days 25 and 81 [Time frame: Day 1, Day 25 and Day 81] • Change from baseline in BSS total score at days 25 and 81 [Time frame: Day 1, Day 25 and Day 81] • Change from baseline in BHS score at Day 25 [Time frame: Day 1 and Day 25] • Change from baseline in pt's assessment of suicide risk at Day 25 [Time frame: Day 1 and Day 25]
Key Results	A significantly greater improvement in MADRS score was observed in the esketamine nasal spray group compared with the placebo group at 4 hrs (least-square mean difference=-5.3, SE=2.10; effect size=0.61) and at ~24 hrs (least-square mean difference=-7.2, SE=2.85; effect size=0.65), but not at day 25 (least-square mean difference=-4.5, SE=3.14; effect size=0.35). Significantly greater improvement was also observed in the esketamine nasal spray group on the MADRS suicidal thoughts item score at 4 hrs (effect size=0.67), but not at 24 hrs (effect size=0.35) or at day 25 (effect size=0.29). Between-group reductions in clinician global judgment of suicide risk scores were not statistically different at any time point.
Adverse effects (AEs)	The most common adverse events among participants in the esketamine nasal spray group were nausea, dizziness, dissociation, unpleasant taste, and headache.

ESTIMATED COST

The cost of esketamine nasal spray is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Guidance on the use of electroconvulsive therapy (TA59). April 2003, updated October 2009.
- NICE clinical guideline. Depression in adults: recognition and management (CG90). October 2009, updated April 2018.
- NICE clinical guideline. Common mental health problems: identification and pathways to care (CG123). May 2011.
- NICE clinical guideline. Depression in adults with a chronic physical health problem: recognition and management (CG91). October 2009.
- NICE quality standard in development. Suicide prevention (GID-QS10121). Publication anticipated September 2019.
- NICE quality standard. Depression in adults (QS8). March 2011.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No guidance identified.

OTHER GUIDANCE

- European Psychiatric Association. Guidance on suicide treatment and prevention. 2012.²¹

REFERENCES

¹ Iadarola ND, Niciu MJ, Richards EM, Vande Voort JL, Ballard ED, Lundin NB et al. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Ther Adv Chronic Dis*. 2015 May; 6(3): 97-114. Available from: <https://doi.org/10.1177/2040622315579059>

² Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. *Philos Trans R Soc Lond B Biol Sci*. 2012 Sep 5; 367(1601): 2485-2494. Available from: <https://doi.org/10.1098/rstb.2012.0212>

³ ClinicalTrials.gov. A Study of the Efficacy and Safety of Intranasal Esketamine in the Rapid Reduction of Symptoms of Major Depressive Disorder, in Adult at Imminent Risk for Suicide (Aspire I): NCT03039192. Available from: <https://clinicaltrials.gov/ct2/show/NCT03039192> [Accessed 14 January 2019]

⁴ ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Participants Assessed to be at Imminent Risk for Suicide (Aspire II): NCT03097133. Available from: <https://clinicaltrials.gov/ct2/show/NCT03097133> [Accessed 14 January 2019]

⁵ Covvey JR, Crawford AN, Lowe DK. Intravenous Ketamine for Treatment-Resistant Major Depressive Disorder. *Annals of Pharmacotherapy*. 2012; 46(1): 117–123. Available from: <https://doi.org/10.1345/aph.1Q371>

⁶ Grunebaum MF, Galfalvy HC, Choo T-H, Keilp JG, Moitra VK, Parris MS et al. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. *Am Jn Psych*. 2017 Dec. Available from: <https://doi.org/10.1176/appi.ajp.2017.17060647>

⁷ Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results

- of a Double-Blind, Randomized, Placebo-Controlled Study. *Am J Psych*. Jul 2018; 175(7):620-630. Available from: <https://doi.org/10.1176/appi.ajp.2018.17060720>
- ⁸ Molero P, Ramos-Quiroga JA, Martin-Santos E, Calvo-Sánchez E, Gutiérrez-Rojas, Meana JJ. Antidepressant Efficacy and Tolerability of Ketamine and Esketamine: A Critical Review. *CNS Drugs*. May 2018; 32(5): 411-420. Available from: <https://doi.org/10.1007/s40263-018-0519-3>
- ⁹ Johnson & Johnson. *Janssen Submits European Marketing Authorisation Application for Esketamine Nasal Spray for Treatment-Resistant Depression*. [press release] (10 Oct 2018). Available from: <https://www.jnj.com/janssen-submits-european-marketing-authorisation-application-for-esketamine-nasal-spray-for-treatment-resistant-depression> [Accessed 15 January 2019]
- ¹⁰ electronic Medicines Compendium. *Vesierra 25 mg/ml solution for injection/infusion*. Available from: <https://www.medicines.org.uk/emc/product/9413/smpc> [Accessed 17 January 2019]
- ¹¹ British Medical Journal Best Practice. *Depression in adults*. Dec 2018. Available from: <https://bestpractice.bmjjournals.com/topics/en-gb/55> [Accessed 24 January 2019]
- ¹² Subramaniam M, Abdin E, Seow ELS, Picco L, Vaingankar JA, Chong SA. Suicidal Ideation, Suicidal Plan and Suicidal Attempts Among Those with Major Depressive Disorder. *Ann Acad Med Singapore*. 2014; 43:412-21. Available from: <http://www.annals.edu.sg/pdf/43Vo1No8Aug2014/MemberOnly/V43N8p412.pdf> [Accessed 24 January 2019]
- ¹³ National Institute for Health and Care Excellence. *Vortioxetine for treating major depressive disorder: Final scope*. Available from: <https://www.nice.org.uk/guidance/ta367/documents/major-depressive-disorder-vortioxetine-id583-final-scope2> [Accessed 24 January 2019]
- ¹⁴ Centre for Suicide Research. *Assessment of suicide risk in people with depression*. Available from: <http://cebmh.warne.ox.ac.uk/csr/clinicalguide/docs/Assessment-of-suicide-risk--clinical-guide.pdf> [Accessed 24 January 2019]
- ¹⁵ Office for National Statistics. *Suicides in the UK: 2017 registrations*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2017registrations> [Accessed 21 January 2019]
- ¹⁶ Knapp M, McDaid D, Parsonage M (eds). *Mental health promotion and mental illness prevention: The economic case*. April 2011. Available from: http://eprints.lse.ac.uk/32311/1/Knapp_et_al_MHPP_The_Economic_Case.pdf [Accessed 21 February 2019]
- ¹⁷ McManus S, Hassiotis A, Jenkins R, Dennis M, Aznar C, Appleby L. Chapter 12: suicidal thoughts, suicide attempts and self-harm,' in McManus S, Bebbington P, Jenkins R, Brugha T. (eds) *Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014*. Available from: <https://files.digital.nhs.uk/publicationimport/pub21xxx/pub21748/apms-2014-suicide.pdf> [Accessed 21 January 2019]
- ¹⁸ Van Spijker BAJ, van Straten A, Kerkhof AJFM, Hoeymans N, Smit F. Disability weights for suicidal thoughts and non-fatal suicide attempts. *J Affect Disord*. 2011; 134(1-3): 341-347. Available from: <https://doi.org/10.1016/j.jad.2011.05.020>
- ¹⁹ Sinclair JMA, Gray A, Rivero-Arias O, Saunders KEA, Hawton K. Healthcare and social services resource use and costs of self-harm patients. *Soc Psychiatry Psychiatr Epidemiol*. 2011; 46: 263. Available from: <https://doi.org/10.1007/s00127-010-0183-5>
- ²⁰ Mackley A. *Suicide Prevention: Policy and Strategy*. House of Commons Briefing Paper CBP08221. Sep 2018. Available from: <https://researchbriefings.files.parliament.uk/documents/CBP-8221/CBP-8221.pdf> [Accessed 21 February 2019]
- ²¹ Wasserman D, Rihmer Z, Rujescu D, Sarchiapone M, Sokolowski M, Titelman D et al. The European Psychiatric Association (EPA) guidance on suicide treatment and prevention. *Euro Psych*. Fe 2012; 27(2): 129-141. Available from: <https://doi.org/10.1016/j.eurpsy.2011.06.003>
- ²² American Psychiatric Association. *Practice Guidelines for the Treatment of Patients with Major Depressive Order*. 3rd ed. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf [Accessed 21 February 2019]
- ²³ National Institute for Health and Care Excellence. *Depression in adults: recognition and management (CG90)*. April 2018. Available from: <https://www.nice.org.uk/guidance/cg90/resources/depression-in-adults-recognition-and-management-pdf-975742638037> [Accessed 21 January 2019]
- ²⁴ ClinicalTrials.gov. *A Double-blind Study to Assess the Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Participants Who Are Assessed to be at Imminent Risk for Suicide: NCT02133001*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02133001> [Accessed 16 January 2019]

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