

Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: July 2019

Generic Name: esketamine

Generic Name: brexanolone

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

This class update is primarily in response to the approval of two new antidepressants: esketamine (Spravato™) and brexanolone (Zulresso™). New high quality comparative efficacy and safety evidence on antidepressants published since the last update, presented in 2017, will also be evaluated and included.

Research Questions:

1. Is there new high quality evidence demonstrating differences in efficacy or effectiveness between the different antidepressants or classes of antidepressants for major depressive disorder (MDD), generalized anxiety disorder (GAD) or other conditions?
2. Is there evidence demonstrating differences in harms data between the different antidepressants?
3. Are there subgroups of patients, based on demographics (e.g., age, race, sex, socio-economic factors), in which one antidepressant medication would be more effective or associated with less harm?
4. What is the evidence for efficacy and harms associated with esketamine and how does this compare to other antidepressants?
5. What is the evidence for efficacy and harms associated with brexanolone and how does this compare to other antidepressants?

Conclusions:

Depression

- Guidelines by the National Institute of Health and Care Excellence (NICE) recommend fluoxetine first-line in children and young people who require treatment with an antidepressant.¹

Anxiety

- There is moderate strength of evidence that the treatment of children with imipramine or sertraline improve primary anxiety symptoms (which was considered a large treatment effect as assessed by standardized measurement) based on two good quality systematic reviews.^{2,3}

- An Agency for Healthcare Research and Quality (AHRQ) systematic review found moderate to high strength of evidence that serotonin-norepinephrine uptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) were effective in reducing the symptoms of anxiety in children, which was considered a moderate and large treatment effect, respectively.³
- Moderate quality evidence found a reduction in relapse for SSRIs, compared to placebo, in the treatment of social anxiety disorder as described in a 2017 Cochrane Systematic Review.⁴ SNRIs were associated with a larger decrease in anxiety symptom scores compared to placebo, in this same population.⁴

Posttraumatic Stress Disorder

- An AHRQ review found moderate strength of evidence that fluoxetine, paroxetine, and venlafaxine are effective for reducing symptoms of posttraumatic stress disorder (PTSD) in adult patients.⁵ Use of SSRIs and the SNRI, venlafaxine, for PTSD are also supported by NICE guidelines.⁶

Esketamine (Spravato)

- Esketamine nasal spray was found to be more effective than placebo in improving Montgomery-Asberg Depression Rating Scale (MADRS) scores with a mean difference of -4 points (95%CI, -7.3 to -0.64; P<0.05) in patients with treatment resistant depression (TRD) that were also taking oral antidepressants.⁷ Results were considered clinically significant, as demonstrated by a MADRS score change of 2 or more points. Two other trials did not demonstrate superiority of esketamine compared to placebo, in part due to a higher withdrawal rate in the high-dose group of esketamine patients, lower overall effect size than assumed in the protocol, and higher placebo response than anticipated.^{7,8}
- Esketamine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and has a boxed warning due to sedation, dissociation, abuse and misuse and increased suicidal thoughts and behaviors in pediatric patients and adolescents taking antidepressants. Dissociation was experienced in 41% of patients, nausea in 28%, dizziness in 29%, and sedation in 23%. Patients must receive esketamine in a healthcare setting and be monitored for two hours after administration.⁹

Brexanolone (Zulresso)

- Intravenous (IV) brexanolone was more effective than placebo in reducing Hamilton Rating Scale for Depression (HAM-D) scores in women with post-partum depression (PPD) by a mean difference reduction ranging from -2.5 to -5.5 points (p<0.05).¹⁰ Reduction in HAM-D scores are clinically meaningful for reductions of 3-7 points, indicating borderline clinically significant benefits of brexanolone compared to placebo. Results for the secondary outcome, Clinical Global Impression-Improvement (CGI-I) responders, was higher in patients randomized to brexanolone compared to placebo (number needed to treat [NNT] of 3-4).
- Brexanolone has a boxed warning for excessive sedation or sudden loss of consciousness requiring continuous pulse oximetry monitoring. Brexanolone is only available through a REMS program.¹¹

Safety

- A high quality review from AHRQ found an increased risk of adverse events in the acute phase of treatment in older patients (65 years or older) treated with duloxetine and venlafaxine compared to placebo, with a number needed to harm (NNH) of 10 (high strength of evidence).¹² In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (relative risk [RR] 1.85; 95% CI, 1.05 to 3.27; NNH 17).¹² Vortioxetine was associated with less adverse events compared to duloxetine based on high strength of evidence (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).¹² High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).¹²

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of clinical efficacy.
- Recommend prior authorization criteria for brexanolone and esketamine based on safety concerns.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics and cost.
- There were no policy changes based on efficacy or safety evidence presented in the last review.
- Anti-depressants are designated preferred or part of the voluntary PDL.

Background:

Antidepressants are most commonly used for MDD but have demonstrated efficacy in many other disorders, including: obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorders and pain syndromes.¹³ The therapeutic effect of antidepressants is to target serotonin, dopamine and norepinephrine levels.

Major depressive disorder is defined as a chronic disorder in patients experiencing depressed mood or diminished interest or pleasure in activities of daily living. Symptoms of depression are weight changes, changes in appetite and/or sleep, fatigue, feelings of worthlessness, inability to concentrate and feelings of death or suicide that last at least 2 weeks.¹³ The cause of depression is usually a combination of internal, external and traumatic factors that coincide to precipitate MDD. The incidence of MDD has steadily increased with the lifetime incidence in the United States of 17%.¹⁴ Females have almost twice the risk as males for the development of depression. MDD has been associated with the second leading cause of disability.

Antidepressants, in combination with cognitive behavioral therapy, are the main treatment modalities for the treatment of MDD.¹³ Antidepressants are divided into first- and second-generation treatments. First-generation classes are tricyclics and monoamine oxidase inhibitors. Second generation antidepressants include SSRIs, SNRIs, atypicals, and serotonin modulators. The SSRIs increase serotonin and are recommended as first-line agents due to efficacy and tolerability. Commonly used second-line therapies include SNRIs and serotonin modulators.¹³ There is no evidence of clinically meaningful differences in efficacy between the different antidepressants. Adverse effects, safety, comorbidities, drug interactions and cost are common determining characteristics in choosing antidepressant therapy.

Effectiveness of antidepressant treatment is based on symptom improvement, function, and quality of life. Treatment response is measured by a provider administered depression rating scale. Response is considered improvement of 50% or more but less than the threshold for remission. Remission is defined as a score less than or equal to a predefined “normal range” for that scale. Commonly used symptom scales are presented in **Table 1**.

Table 1. Depression Symptom Patient Assessment Tools

Assessment	Description	Remission Score	Clinically Meaningful Important Difference
Hamilton Rating Scale for Depression (HAM-D) ^{15,16}	17 items, each item has a range of 0-2	Less than or equal to 7	3 to 7

Montgomery-Asberg Depression Rating Scale (MADRS) ¹⁷	10 items, clinician-rate scale, range of 0-60, higher scores indicate a higher severity of depression	MADRS total score of less than or equal to 12 for at least 3 of the last 4 weeks	1.6 to 1.9
Patient Health Questionnaire -9 item (PHQ-9) ¹⁸	Nine items with a score of 0-27 based on a 4 point Likert score for each item	Less than 5	Treatment score of less than 9 and 50% improvement in symptoms
Clinical Global Impression-Improvement Score (CGI-I) ¹⁹	7-point scale in which illness is documented as improved or worsened – higher scores represent worsening symptoms/functioning	Response defined as 1 (very much improved) or 2 (much improved)	Not described

Approximately 130,000 fee-for-service (FFS) patients had a diagnosis of MDD in the last year. Antidepressant therapy accounts for a large portion of the Oregon Health Authority (OHP) drug benefit budget. Medications in this class are preferred or on a voluntary PDL. In the last quarter, 64% of the antidepressant claims were for preferred therapies.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Depression

AHRQ- Adverse Effects of Pharmacological Treatments of Major Depression in Older Adults

A systematic review and meta-analysis was done by AHRQ to study the adverse effects of pharmacological treatments for MDD in adults, 65 years and older.¹² Classes of antidepressants included in the review are SSRIs, SNRIs and others (bupropion, mirtazapine, trazodone, vilazodone and vortioxetine). Specific outcomes of interest were: any adverse event, bleeding, blood pressure changes, cognitive measures and electrocardiogram changes, emergency department (ED) visits, falls, fractures, hospitalizations, mortality, seizures, suicidal thoughts/attempts, syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia, weight changes or withdrawals due to adverse events. Thirty-nine publications were included in the review, 37 were randomized controlled trials and two were observational studies. In general, evidence of clinical efficacy in patients 65 years and older is of low quality; however, SSRIs and bupropion XR are most commonly used.¹² Outcomes with moderate to high strength of evidence will be presented.

SSRIs versus Placebo or No Treatment

- There was moderate strength of evidence of no difference in adverse events in the acute phase between SSRIs (fluoxetine and escitalopram) and placebo or no treatment and the strength of evidence for all other outcome comparisons were of low or insufficient quality.¹²

SSRIs versus Tricyclic Antidepressants

- Three trials were identified comparing SSRIs versus TCAs; however, all findings were of low strength of evidence or insufficient findings.¹²

SSRIs versus SSRIs

- A comparison between sertraline and fluoxetine and a comparison between escitalopram and fluoxetine found moderate strength of evidence of no difference in the incidence of any adverse events in the acute phase.
- No difference in any adverse events or serious adverse events in the maintenance phase was found in a comparison between paroxetine and fluoxetine based on moderate evidence.¹²

SNRIs versus Placebo

- In the acute phase of treatment there was high strength of evidence of increased risk of adverse events with duloxetine and venlafaxine compared to placebo with a NNH of 10.¹²
- In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (RR 1.85; 95% CI, 1.05 to 3.27; NNH 17).¹²
- The risk of withdrawals due to adverse events was higher with duloxetine compared to placebo in the acute and continuation phase of treatment based on moderate strength of evidence with a NNH of 12 (RR 2.64; 95% CI, 1.21 to 5.73).¹²
- An increased risk of falls during the acute and maintenance phase was found with duloxetine versus placebo based on moderate strength of evidence (RR 1.69; 95% CI, 1.03 to 2.76; NNH 10).¹²
- There was moderate strength of evidence of no difference between duloxetine and placebo for the outcomes of ECG-QTc changes and serious adverse events in the acute and continuation phase.
- Serum sodium and body weight were reduced in the acute phase of MDD treatment in patients taking duloxetine compared to placebo (specific results not available).

SNRIs versus SSRIs

- There was no difference between the comparison of venlafaxine and citalopram for the outcomes of any adverse events, serious adverse events, or withdrawals due to adverse events in the continuation phase based on moderate evidence.¹²
- There was moderate strength of evidence of no difference between venlafaxine and fluoxetine for any adverse events in the acute phase.

Bupropion XR versus Placebo

- There was no evidence of differences between bupropion XR and placebo for the outcome of any adverse event based on moderate strength of evidence.¹²

Mirtazapine versus Paroxetine

- Moderate evidence found no difference in any adverse events in the acute treatment phase between mirtazapine and paroxetine.

Trazodone versus No Antidepressant Use

- All outcomes were of low strength of evidence.¹²

Vortioxetine

- There was no difference between vortioxetine compared to placebo for the outcomes of any adverse events and serious adverse events, in the acute phase, based on high and moderate strength of evidence, respectively.

- No difference in serious adverse events and withdrawals due to adverse events in the acute phase were found between vortioxetine versus duloxetine based on moderate evidence.
- High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).¹²

Limitations to the review are that none of the randomized controlled trials included in the review were specifically designed to study adverse events and, therefore, resulted in findings of low or insufficient evidence in some comparisons.

Cochrane – Antidepressants for Treating Depression in Dementia

A 2018 systematic review and meta-analysis done by Cochrane analyzed the efficacy and safety of antidepressant therapy in patients with a diagnosis of dementia and coexisting depression.²⁰ A literature search up until August of 2018 identified ten randomized controlled trials which were included in the qualitative synthesis. Eight trials were identified for the meta-analysis. The mean age of included participants was 80 years old and mean dementia severity was 19.65, as determined by the mean Mini Mental State Examination (MMSE) score, which is considered mild dementia.²⁰ Drug classes included in the study were tricyclic antidepressants (TCA), SSRIs, SSRI/SNRIs and one study evaluated a reversible monoamine oxidase inhibitor. All but two studies had unclear risk of bias. The primary outcome was the effect on depression (as determined by a response and remission based on rating scales). Other important outcomes include the number of patients with remission, effect on cognitive function, activities of daily living impact, adverse events and withdrawals.²⁰

There was high quality evidence demonstrating no evidence of effectiveness for patients with dementia treated with antidepressants, compared to placebo, based on depression endpoint score ratings at 6 to 13 weeks (standard mean difference [SMD] -0.10 (95% CI, -0.26 to 0.06)).²⁰ A subgroup analysis of only SSRIs found little or no difference of efficacy, based on score ratings, compared to placebo. The number of patients with remission at 6 to 12 weeks was found to be higher in patients with dementia treated with antidepressants compared to placebo, 217/1000 versus 415/1000 (OR 2.57; 95% CI, 1.44 to 4.59) based on moderate quality evidence.²⁰ Changes based on responder rates were considered low quality evidence and therefore not included. There was moderate quality evidence that antidepressant therapy was associated with more drop outs compared to placebo. Patients taking antidepressants were more likely to experience an adverse event compared to placebo based on moderate quality evidence. In summary, there is no strong evidence for the treatment of depression in patients with dementia.

Cochrane – Antidepressants for the Treatment of People with Co-occurring Depression and Alcohol Dependence

A 2018 Cochrane review was done to determine the efficacy and harms of antidepressant use in patients with alcohol dependence.²¹ There were 33 randomized controlled trials that met inclusion criteria, 18 of the trials were conducted in an outpatient setting. Included patients were a mean age of 42 years and 68% were men. Trials ranged from 3 to 26 weeks and included placebo, psychotherapy and other medications (including other antidepressants).²¹ Medications included in the review were amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, nefazodone, paroxetine, and venlafaxine. The primary outcome was the full remission of depression.

There was no difference found in the rate of full remission of depression in antidepressant versus placebo comparisons; however, there were only 4 included studies and there was a high degree of heterogeneity ($I^2=66\%$).²¹ There was moderate quality of evidence that the number of patients that were abstinent from alcohol were higher in the antidepressant group compared to placebo with RR of 1.71 (95% CI, 1.22 to 2.39; $p=0.002$).²¹ In addition, the mean number of alcoholic drinks per day was lower in patient taking antidepressants compared to placebo by 1.13 drinks per drinking days (95% CI, 1.79 to 0.46).²¹ All other studied outcomes were of very low or low quality evidence.

Limitations include a small number of include trials for comparison and one-third of studies were completed in countries outside the US. Overall, there is limited evidence of efficacy of antidepressants for the treatment of patients with co-occurring depression and alcohol dependence.

Anxiety

Cochrane – Pharmacotherapy for Social Anxiety Disorder (SAnD)

A 2017 Cochrane review evaluated treatments used for SAnD in adult patients.⁴ Sixty-six trials met inclusion criteria for the review and approximately half were testing the efficacy of SSRIs. The average trial size was small with the average number of trial participants being 176, and all trials had durations of 24 weeks or less. The primary outcome was treatment response (assessed by CGI-I). Important secondary outcomes were SAnD symptom severity (assessed by the Liebowitz Social Anxiety Scale [LSAS]) and rate of relapse. The CGI-I ranges from 1-7 with higher numbers indicating very ill patients. A change of 1 represents (very much) improved and a change of 2 as (improved). The LSAS is a 24-item scale with higher scores representing a higher level of social anxiety (>95 indicating very severe social phobia).

Clinician rated LSAS total score demonstrated a reduction of anxiety symptoms by 11.91 points (95% CI -16.06 to -7.76; p<0.05) lower in the SNRI group compared to placebo, in patients with low to moderate social phobias. In patients that took SSRIs (paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram), there was moderate evidence of a reduced rate of relapse compared to placebo with a RR of 0.34 (95% CI, 0.22 to 0.5; p<0.00001).⁴ In an overall comparison across all medication classes, there was evidence of higher efficacy with treatment compared to placebo; however, this analysis was associated with a high degree of heterogeneity (I²=69.7%).⁴

AHRQ – Anxiety in Children

An AHRQ review evaluated efficacy and harms of therapies for childhood anxiety disorders (e.g., panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder and separation anxiety).³ A total of 206 studies compared psychotherapy, pharmacotherapy, or combination of treatments in children from the ages of 3 to 18 years. Primary anxiety symptoms were the primary outcome of interest.

In summary, SSRIs (fluoxetine, paroxetine, and sertraline) and SNRIs (atomoxetine, duloxetine and venlafaxine) improved primary anxiety symptoms compared to placebo based on moderate to high evidence.³ SSRIs also demonstrated efficacy in improved remission rates, function, and clinical response compared to placebo (moderate to high strength of evidence). TCAs and benzodiazepines lacked conclusive evidence of benefit. Specific results for comparisons with moderate or high strength of evidence are presented in **Table 2**. Limitations to the data include small number of studies available for the analysis, small sample sizes, and imprecision in the data.

Table 2. Results for Evidence in the Treatment of Children with Anxiety³

Comparison	Outcome	Results*	Strength of Evidence
Drugs +/- Cognitive Behavioral Therapy [CBT] versus CBT			
Imipramine and CBT Vs. CBT	Primary anxiety/patient reported	SMD: -0.74 (95% CI, -1.26 to -0.23) <i>Imipramine and CBT reduced anxiety more than CBT alone</i>	Moderate
	Function	SMD: -1.27 (95% CI, -1.81 to -0.73) <i>Imipramine and CBT improved function more than CBT alone</i>	Moderate
CBT and sertraline Vs.	Primary anxiety/clinician reported	SMD: -0.69 (95% CI, -0.93 to -0.45) <i>Sertraline and CBT reduced anxiety more than CBT alone</i>	Moderate

CBT	Function	SMD: -0.47 (95% CI, -0.70 to -0.23) <i>Sertraline and CBT improved function more than CBT alone</i>	Moderate
Fluoxetine Vs. CBT	Primary anxiety/clinician reported	SMD: 0.78 (95% CI, 0.37 to 1.18) <i>Increased anxiety with fluoxetine</i>	Moderate
	Function	SMD: 0.54 (95% CI, 0.14 to 0.94) <i>Fluoxetine reduced function</i>	Moderate
Sertraline Vs. CBT	Remission	RR 1.51 (95% CI, 1.22 to 1.86) <i>Sertraline improved remission more than CBT</i>	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) <i>Sertraline improved response more than CBT</i>	Moderate
CBT and sertraline Vs. Sertraline	Primary anxiety/clinician report	SMD: -0.46 (95% CI, -0.70 to -0.22) <i>CBT and sertraline reduced anxiety more than sertraline alone</i>	Moderate
	Function	SMD: -0.34 (95% CI, -0.58 to -0.10) <i>CBT and sertraline improved function more than sertraline alone</i>	Moderate
	Remission	RR 1.51 (95% CI, 1.22 to 1.87) <i>CBT and sertraline improved remission rates more than sertraline alone</i>	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) <i>CBT and sertraline improved responses more than sertraline alone</i>	Moderate
Drugs versus Placebo			
SNRI Vs. Placebo	Primary anxiety/clinician report	SMD: -0.45 (95% CI, -0.81 to -0.10) <i>SNRIs reduced anxiety more than placebo</i>	High
SSRI Vs. Placebo	Primary anxiety/parent report	SMD: -0.61 (95% CI, -1.03 to -0.20) <i>SSRIs reduced anxiety more than placebo</i>	Moderate
	Primary anxiety/clinician report	SMD: -0.65 (95% CI, -1.10 to -0.21) <i>SSRIs reduced anxiety more than placebo</i>	Moderate
	Function	SMD: -0.59 (95% CI, -0.85 to -0.34) <i>SSRIs improved function more than placebo</i>	High
	Remission	RR 2.04 (95% CI, 1.37 to 3.04) <i>SSRIs improved remission rates more than placebo</i>	Moderate
	Response	RR 1.96 (95% CI, 1.60 to 2.40) <i>SSRIs improved response rates more than placebo</i>	Moderate
<p>Key: * SMD cutoffs of 0.20, 0.50, and 0.80 are considered to represent small, moderate, and large effect, respectively. Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval; SMD = standard mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor</p>			

Cochrane – Antidepressants versus Placebo for Panic Disorder in Adults

The efficacy and harms of antidepressants for the treatment of panic disorder in adults was the topic of a recent Cochrane systematic review.²² Forty-one randomized, placebo-controlled trials were included with study durations of 8 to 28 weeks. Classes of drugs that were included in the review were: TCAs (17 studies), SSRIs (22 studies), SNRIs (4 studies), MAOIs (1 study), norepinephrine reuptake inhibitor (NRI) (1 study – reboxetine, which is not available in the US). Two studies had active treatment comparisons (nefazodone and ritanserin). Most studies had an unclear risk of selection and performance bias.

There was moderate quality evidence demonstrating less dropouts in patients taking antidepressants compared to placebo with a mean difference of 38 fewer dropout per 1000 patients (RR 0.88; 95% CI, 0.81 to 0.97; number needed to benefit [NNTB] 27).²² The benefit was driven by TCAs, as there was no difference from placebo for SSRIs and SNRIs. Risk associated with failure to obtain remission was lower with antidepressant treatment compared to placebo based on moderate evidence (RR 0.83; 95% CI, 0.78 to 0.88), and a mean difference of 101 patients per 1000 treated fewer patients failed to remit in the antidepressant group.²² There was an increased risk of dropouts due to adverse events in the antidepressant group compared to placebo with a RR of 1.49 (95% CI, 1.25 to 1.78), based on moderate evidence.²² This was most common with TCAs and SSRIs.

Limitations to this review include unclear risk of bias in some domains and insufficient long-term data. Overall, there is not robust evidence to support the treatment of panic disorder in adults with antidepressants.

Wang, et al. – Comparative Effectiveness and Safety of Cognitive Behavioral Therapy and Pharmacotherapy for Childhood Anxiety Disorders

A recent good quality systematic review and meta-analysis included 7719 children and adolescents (mean age of 9 and 56% female) with a diagnosis of panic disorder (31%), social anxiety disorder (71%), specific phobias, generalized anxiety disorder (63%) or separation anxiety (61%) that were receiving cognitive behavioral therapy (CBT), pharmacotherapy or both.² Patients who were using pharmacotherapy were on SSRIs, SNRIs, tricyclic antidepressants (TCAs), and benzodiazepines. Most studies were up to 12 weeks in duration with the longest study lasting 32 weeks. The overall risk of bias was considered moderate to high due to lack of blinding of patients, providers, and outcome assessors, in addition to an unclear risk of conflicts of interest. Determination of publication bias, related to pharmacotherapy, was not done due to lack of studies. The primary outcome of the review was the occurrence of primary anxiety symptoms (as measured by a standardized measure of child anxiety symptoms), clinical remission, treatment response and adverse events.²

There was moderate quality of evidence that SSRIs were more effective at reducing anxiety symptoms compared to placebo, as reported by parents (SMD -0.61; 95% CI, -1.03 to -0.20) and clinicians (SMD -0.65; 95% CI, -1.10 to -0.21).² There was high heterogeneity with both findings, ranging from 55% to 73%. SSRIs were also associated with higher remission rates compared to placebo (RR 2.04; 95% CI, 1.37 to 3.04) and response (RR 1.96; 95% CI, 1.60 to 2.40), both based on moderate quality of evidence.² The efficacy of SNRIs on primary anxiety symptom reduction, as reported by clinicians, was higher than placebo based on high quality of evidence and a standard mean difference of -0.45 (95% CI, -0.81 to -0.10).² Active treatment was more commonly associated with adverse events but none were considered serious.

CBT was more effective than wait listing/no treatment in reducing primary anxiety symptoms based on child, parent and clinician assessments, SMD -0.77, -0.88 and -1.38, respectively (moderate quality evidence).² Clinician-assessed treatment response was also improved based on moderate quality evidence (RR 4.72; 95% CI, 2.39 to 9.32).² All estimates had a high degree of heterogeneity. Moderate quality evidence found the combination therapy of imipramine and CBT, compared to CBT alone, reduced primary anxiety symptoms based on child assessment, SMD of -0.74 (95% CI, -1.26 to -0.23).² Sertraline combined with CBT reduced primary anxiety symptoms (SMD 0.69; 95% CI, -0.93 to -0.45), improved treatment response (RR 1.35; 95% CI, 1.15 to 1.58), and remission (RR 1.51; 95% CI, 1.22 to 1.86) when compared to CBT alone based on clinician assessment.² In a comparison of sertraline to CBT, there was no difference in the reduction of primary anxiety

symptoms. There was moderate quality evidence that CBT was more effective than fluoxetine at reducing primary anxiety symptoms based on clinician assessment (SMD -0.78; 95% CI, -1.18 to -0.37).²

Posttraumatic Stress Disorder

AHRQ- Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder

A systematic review and meta-analysis was done by AHRQ to evaluate the efficacy and harms of treatments for PTSD.⁵ This 2018 report updates a previous 2013 version. The report analyzes the psychological as well as pharmacotherapy recommendations; however, the focus of this summary will be on the evidence for medications which included the following classes: SSRIs, SNRIs, TCAs, and other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone). Paroxetine and sertraline are the only therapies approved for the treatment of PTSD; however, the other therapies are often used off-label for the treatment of PTSD. Patients 18 years old and older with PTSD (diagnosed by any DSM criteria) were included.⁵ The primary outcome was the reduction in PTSD symptoms.

There was moderate quality of evidence that treatment with fluoxetine, paroxetine and venlafaxine were more effective than placebo (**Table 3**).⁵ All studies of fluoxetine, paroxetine and venlafaxine demonstrated medium risk of bias. Overall, SSRIs were associated with a reduction in clinician administered PTSD symptom scores, with a SMD of -0.30 (95% CI, -0.40 to -0.20; p=0.041).⁵ Depression symptoms were reduced with SSRIs compared to placebo in patients with PTSD by a SMD of -0.24 (95% CI, -0.38 to -0.11; p<0.001).⁵ Two trials provided direct evidence comparisons; venlafaxine extended release (ER) versus sertraline and paroxetine + placebo versus desipramine + placebo. Both trials found similar decreases in PTSD symptoms; however, comparisons were considered insufficient or low strength of evidence. A head to head comparison of venlafaxine ER to sertraline found moderate strength of evidence of no difference for changes in depression symptoms.

Table 3. Outcomes for Pharmacological Treatment used in PTSD with Moderate to High Strength of Evidence (placebo comparisons)⁵

Treatment	Outcome	Result	Interpretation	Strength of Evidence
Fluoxetine	PTSD symptoms	SMD -0.28 (95% CI, -0.42 to -0.14)	Fluoxetine reduced PTSD symptoms	Moderate
Paroxetine	PTSD symptoms	SMD -0.44 to -0.56 (CI not provided)	Paroxetine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD 0.13 to 0.19 (CI not provided)	Paroxetine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -0.60 to -0.34 (CI not provided)	Paroxetine reduced depression symptoms	Moderate
Venlafaxine	PTSD symptoms	SMD -0.35 to -0.26 (CI not provided)	Venlafaxine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD of 0.12 to 0.15 (CI not provided)	Venlafaxine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -2.6 to -1.6 (CI not provided)	Venlafaxine was associated with reduced depression symptoms	Moderate

Abbreviations: CI = confidence interval; PTSD =posttraumatic stress disorder; RD =risk difference; SMD = standardized mean difference

Direct comparative effectiveness evidence was insufficient for most pharmacotherapy comparisons for PTSD and for commonly used treatments such as escitalopram, fluvoxamine, desvenlafaxine, duloxetine, TCAs and other second generation antidepressants.

After review, 22 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

NICE – Depression in Adults: Recognition and Management

A 2009 review that was updated in April 2018 provided guidance for adults who present with depression as the primary diagnosis.¹⁵ If antidepressants are indicated, a choice should be made based on adverse events, drug interactions, patient comorbidities and perception and tolerability of previous treatments.

Recommendations:

- Generic SSRIs are recommended first-line based on efficacy and tolerability.
 - SSRIs have an increased risk of bleeding and caution is advised in older patients or in patients taking other medications that are known to damage the mucosa of the gastrointestinal tract or interfere with clotting.
 - Drug interactions are most common with fluoxetine, fluvoxamine, and paroxetine.
 - Paroxetine is associated with a high risk of discontinuation.
- For patients at increased risk of suicide:
 - Venlafaxine is associated with a higher risk of death due to overdose than other equally effective antidepressants used for routine use in primary care.
 - TCAs are associated with the greatest risk of overdose.
- The following considerations are warranted with antidepressant use other than SSRIs
 - Higher discontinuation rates with TCAs
 - Some antidepressants may require monitoring, have specific cautions or contraindications which need to be considered with each individual patient.
- If symptoms have not improved in 3-4 weeks of antidepressant therapy consider increasing the antidepressant dose or switching to another antidepressant.

NICE – Post-traumatic Stress Disorder

NICE updated their guidance on post-traumatic stress disorder in 2018. Medication therapy is not recommended for prevention of PTSD.⁶ If medication is appropriate for treatment, venlafaxine or a SSRI (e.g., sertraline) is recommended for adult patients. Treatment effectiveness should be assessed frequently and monitored for adverse reactions. Antipsychotics, such as risperidone, should be considered only with the following qualifying factors: presence of disabling symptoms and behaviors (e.g., severe hyperarousal or psychotic symptoms) and when symptoms have not responded to other drug or psychological treatments.

NICE – Depression in Children and Young People: Identification and Management

The treatment of depression in children and young people was the focus of a September 2017 update.¹ In patients with mild depression, antidepressant therapy is not recommended for initial treatment in children and young people. All antidepressant treatment should be offered in conjunction with psychotherapy and follow an assessment and diagnosis by a child and adolescent psychiatrist. In individuals with moderate to severe depression who continue to have symptoms despite the care of a multidisciplinary team, fluoxetine should be offered if patients are 12-18 years old. In younger children, ages 5 to 11, fluoxetine could be cautiously considered if they are unresponsive to psychological therapy (minimum of 4 sessions), although evidence is limited. Guidance for the use of antidepressants in children and young people is outlined in **Table 4**.¹ Venlafaxine, paroxetine and TCAs should not be used in children and young people for the treatment of depression.

Table 4. Recommendations for Medication Use in Children and Young Persons¹

First-line Therapy - Fluoxetine
<ul style="list-style-type: none">• Starting fluoxetine dose should be 10 mg daily• Fluoxetine dose can be increased to 20 mg daily after 1 week if clinically indicated• Medication should be continued for at least 6 months after remission
Second-line Therapies
<ul style="list-style-type: none">• Sertraline or citalopram are the recommended second-line therapies• Medication should be continued for at least 6 months after remission• Starting dose should be half the adult dose• Dose can be titrated over the next 2 to 4 weeks up to the adult dose, if clinically indicated

US Preventative Services Task Force – Interventions to Prevent Perinatal Depression

A systematic review and meta-analysis was completed in 2019 to determine the benefits and harms of interventions offered in primary care to prevent perinatal depression (major or minor depressive episode during pregnancy or up to 1 year after childbirth).²³ Randomized and non-randomized controlled trials were included. Behavior-based interventions, antidepressants, and dietary supplements were studied for prevention in perinatal depression in pregnant and postpartum women or those at increased risk of perinatal depression. There was insufficient evidence to determine the benefits or harms of antidepressants in this population.

After review, four guidelines were excluded due to poor quality.^{24–27}

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 155 citations were manually reviewed from the initial literature search. After further review, 154 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Jacobsen, et al ²⁸ RCT, DB, MC	Vortioxetine Vs. Escitalopram (8 weeks)	Adults (40% male) with well-treated MDD experiencing treatment-emergent sexual dysfunction (n=447)	Change from baseline in the CSFQ-14 total score after 8 weeks	Vortioxetine: 8.8 Escitalopram: 6.6 MD: 2.2 (CI not provided) P = 0.013 <i>Vortioxetine improved sexual dysfunction scores more than escitalopram</i>
Key: CSFQ-14 – 14 item scale with 36 items with higher scores indicating higher sexual frequency ²⁹ Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire Short Form; DB =double-blind; RCT=randomized controlled trial				

NEW DRUG EVALUATION: Esketamine (Spravato™)

See **Appendix 4 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Esketamine is a Schedule III nasal spray which is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for use in conjunction with oral antidepressants for the treatment of TRD in adults.⁹ Esketamine should be administered under the supervision of a medical provider and is made available only through a restricted program called the Spravato REMS. The dose of esketamine ranges from 56-84 mg and is given twice weekly during the induction phase and once weekly during the maintenance phase (**Table 6**). Patient should be monitored for 2 hours after administration. Baseline blood pressure monitoring and blood pressure reassessment at 40 minutes post-dose, and subsequently if warranted, is recommended.⁹

Table 6. Esketamine Intranasal Dosing Recommendations⁹

Phase	Dose
Induction Phase – weeks 1-4 Twice weekly dosing	56 mg for initial dose; subsequent doses are 56-84 mg. At the end of the induction phase, the maintenance phase dose should be continuation of the initial dose.
Maintenance Phase – weeks 5-8	56 or 84 mg once weekly
Maintenance Phase – week 9 and thereafter	56 or 84 mg once weekly or once every other week (i.e., every 2 weeks)
* Each device contains 28 mg of esketamine in two sprays; 2 devices for the 56 mg dose and 3 devices for the 84 mg dose	

Five, phase 3, randomized, placebo controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUTSTAIN-2) were used to determine the clinically efficacy and safety of esketamine in adult patients with TRD. TRANSFORM-2 is the only published study so the efficacy and safety results of the other trials will be based on data from prescribing information and the esketamine dossier.^{7,8}

TRANSFORM-2 included patients (n=223), mean age of 47 years, with MDD (mean MADRS score of 37) who had not responded adequately to at least two different antidepressants appropriately titrated and treatment of adequate duration (**Table 9**).⁷ All patients received open-label oral antidepressant therapy, 32% SSRI (duloxetine, escitalopram, sertraline) and SNRI in 68% (extended-release venlafaxine). The primary outcome measure was change from baseline MADRS total score at the end of week 4. Important secondary endpoints were the number of responders (MADRS score decrease of 50% or more), number of patients obtaining remission (MADRS score of equal to or less than 12) and change in CGI-S. Esketamine decreased MADRS scores more than placebo, -19.8 and -15.8 (MD -4.0; 95% CI, -7.3 to -0.64; P<0.05) at day 28, which was clinically and statistically significant.⁷ Response rates (based on MADRS) and CGI-S scores were not statistically different.

TRANSFORM-1 was a randomized, double-blind, multi-center trial in 346 patients. Patients were randomized to fixed dose esketamine 56 or 84 mg or placebo with both groups also taking an oral antidepressant. After 4 weeks of treatment, mean change in MADRS scores were: -19.0 for esketamine 84 mg, -18.8 for esketamine 56 mg and -14.8 for the placebo group. Changes were not found to be statistically significant (p=0.088). A similarly designed trial (TRANSFORM-3) was done in elderly patients, 65 years and older (n=138). At four weeks, a mean change from placebo of -3.7 points on the MADRS scale was demonstrated, which was not statistically significant (p=0.059). A long-term induction and stabilization trial (SUSTAIN-1) was conducted in 705 patients, that were stable remitters during the maintenance phase, comparing 28-84 mg esketamine + antidepressant compared to placebo + antidepressant to evaluate delayed relapse.⁹ Esketamine was found to delay relapse, with 26.7% of the esketamine group experiencing a relapse compared to 45.3% in the placebo group with a relapse (p=0.003).⁹ The mean time to relapse was not able to be determined according to manufacturer data.

Limitations to the study include small sample size and short treatment duration all efficacy studies. There is low external validity due to extensive exclusion criteria and the allowance of only four different oral antidepressants. The relapse prevention study biased trial results towards patients that were esketamine responders or remitters to treatment during the optimization phase. Patients were also started on a new oral antidepressant, in both groups, which could influence efficacy results in both groups.

Clinical Safety:

Common adverse events associated with esketamine are presented in **Table 7**.⁹ Adverse events experienced in patients taking esketamine, with an incidence of at least 5% or more, and twice placebo rates in patients also taking antidepressants, where dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting and feeling drunk.⁹ The most common psychological effects were dissociation, perceptual changes, derealization and depersonalization in 61% to 75% of patients given esketamine. Precautions include cognitive impairment, embryo-fetal toxicity and increased blood pressure.

Table 7. Some of the Adverse Reactions Reported in Greater than or equal to 2% of Esketamine Treated Patients and More than Placebo⁹

Adverse Reaction	Esketamine (N=346)	Placebo (N=222)
Dissociation	41%	9%
Dizziness	29%	8%
Nausea	28%	9%
Sedation	23%	9%
Vertigo	23%	3%

Anxiety	13%	6%
Increased blood pressure	10%	3%
Vomiting	9%	2%
Feeling Drunk	5%	0.5%
Feeling abnormal	3%	0%

Esketamine REMS Program Requirements⁹

- Pharmacists must be certified in the REMS in order to dispense.
- Healthcare setting must be certified in the REMS in order to treat patients with esketamine nasal spray.
- Patient must be enrolled in the esketamine REMs to receive treatment.
- Provider must supervise administration, post-administration monitoring and provide patient education about potential serious outcomes associated with sedation and dissociation.
- Patients must be observed as least 2 hours administration for resolution of dissociation effects and sedation.
- Blood pressure should also be monitored for transient blood pressure increases lasting around 4 hours.

A 52-week safety study (SUSTAIN-2) was done in 802 patients with treatment resistant depression, mean age of 52 years, and 63% females.⁸ Patients were entered into a 4-week induction phase followed by a 43 day optimization and maintenance phase. The primary outcome was to evaluate safety with the change in MADRS score being a secondary outcome. Approximately 9.5% of patients in the esketamine group discontinued due to adverse events by the end of the maintenance phase. Concerning adverse events of acute hypertension, severe dissociation and severe sedation were seen in 2.3%, 1.4% and 0.5% of patients, respectively.⁸

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Remission of depressive symptoms
- 2) Relapse of depressive episode
- 3) Symptom reduction (as determined by a validated scale)
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change in MADRS score at day 28

Table 8. Pharmacology and Pharmacokinetic Properties of Esketamine.

Parameter	
Mechanism of Action	non-competitive N-methyl D-aspartate (NMDA) receptor antagonist with the exact antidepressant mechanism unknown
Nasal Bioavailability	48%
Distribution and Protein Binding	709 Liters; protein binding 43-45%
Elimination	1% unchanged in the urine
Half-Life	7-12 hours
Metabolism	P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19

Table 9. Esketamine Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Popova, et al ⁷ Phase 3, DB, PC, RCT	1. Esketamine nasal spray (28 -84 mg) + antidepressant twice weekly† (E) 2. Placebo nasal spray + antidepressant twice weekly† (P) 28 days	<p>Demographics: Age: 45 years Male: 38% SNRI at baseline: 68% HAM-D score: 37</p> <p>Key Inclusion Criteria: - 18-64 years - single episode (greater than or equal to 2 years) or recurrent major depressive disorder without psychotic features - score of 34 or greater on the IDS-C - diagnosis of treatment resistant depression*</p> <p>Key Exclusion Criteria: - current or recent homicidal suicidal ideation/intent or suicidal behavior within the last year - psychotic disorder, MDD with psychotic features, bipolar or related disorders, antisocial, histrionic or narcissistic personality disorder, OCD or intellectual disability - seizures, uncontrolled hypertension - substance use disorder</p>	<p>mITT: 1. 114 2. 109</p> <p>PP: 1. 98 2. 99</p> <p>Attrition: 1. 16% 2. 11%</p>	<p>Change in baseline of MADRS score at day 28: E: -21.4 points P: -17.0 points</p> <p>E vs. P LSMD -4.0 (95% CI, -7.31 to -0.64) p-value: 0.020</p> <p>Secondary Endpoints: MADRS response: E: 9 (7.9%) P: 5 (4.6%) p-value: 0.0321</p>	<p>NA</p> <p>3.3% /30</p>	<p>Discontinuations due to Adverse Events: E: 8 (7.0%) P: 1 (0.9%)</p> <p>Dissociation: E: 30 (26%) P: 4 (3.7%)</p>	<p>NA for all</p>	<p>Risk of Bias (low/high/unclear): Selection Bias: (low) Randomized 1:1, computer generated. Baseline characteristics similar except for a higher number of females in the esketamine group compared to placebo, 66% versus 58%. Performance Bias: (low) Double-blind design, investigators, patients, study team, site staff, principle investigator were all blinded to treatment allocation. Identical packaging was used to maintain blinding. Detection Bias: (low) Data analysis was blinded and MADRS assessments were done by independent (remote) blinded evaluators. Attrition Bias: (high) attrition was high both groups. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer and pre-specified secondary outcome of remission rates was not reported.</p> <p>Applicability: Patient: Applies to patients with severe depression taking oral antidepressants that do not have other personality disorders (low external validity) and have had an inadequate response to at least two antidepressants. Studies in patients 65 and older found no benefit compared to placebo. Intervention: Appropriate dose based on pharmacokinetic studies Comparator: Placebo appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: MADRS is a validated tool to assess therapeutic efficacy of antidepressants. Setting: Thirty-nine centers in the USA.</p>
<p>Key: * Treatment-resistant depression: nonresponse to an adequate trial (dosage, duration, and adherence) of at least 2 antidepressants in the current episode (of which one was observed prospectively); † Newly initiated open-label oral antidepressant (escitalopram, sertraline, duloxetine or venlafaxine) administered daily Abbreviations: ARR = absolute risk reduction; CGI = Clinical Global Impression-Improvement response; CI = confidence interval; IDS-C =Inventory of Depressive Symptomatology- Clinician Rating; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OCD = obsessive compulsive disorder; PC = placebo-controlled; PP = per protocol; PPD = post-partum depression; SNRI = serotonin norepinephrine reuptake inhibitor</p>								

NEW DRUG EVALUATION: Brexanolone (Zupresso)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Brexanolone is a GABA_A receptor positive modulator (similar to progesterone, which is reduced after pregnancy) indicated for the treatment of moderate to severe PDD in adults.¹¹ Brexanolone is administered by IV and titrated from a starting dose of 30 mcg/kg/hour up to a maximum dose of 90 mcg/kg/hour and back down again, over 60 hours. FDA approval was based on 2, double-blind, randomized, identical phase 3 trials (n= 226). Women were eligible if they were 18-45 years and had a HAM-D score indicating severe to very severe depression. In the first study, the mean age was 27 years, 25% had current antidepressant use at baseline, and the average HAM-D score was 29.¹¹ In the second study, the mean age was 28 with antidepressant use in 18% at baseline and average HAM-D score of 23.¹⁰ Patients were followed for a total of 30 days. The mean time of brexanolone administration was approximately 4 months after delivery. The primary endpoint was change in the 17-item HAM-D total score from baseline at 60 hours. An important secondary endpoint was CGI-I response at 60 hours, which was a change of 1-2 points on the CGI-I scale.

In the first study, patients were randomized 1:1:1 to brexanolone 60 mcg/kg/hr (BX60), brexanolone 90 mcg/kg/hour (BX90) or placebo infusion over 60 hours (**Table 12**).¹⁰ The changes in HAM-D scores were statistically significant compared to placebo for the BX60 and BX90 dose, -5.5 and -3.7 points, respectively.¹⁰ Changes in the CGI-I response compared to placebo were statistically significant with 26-31% of patients responding to treatment (NNT of 4 for both doses). In the second study, BX90 decreased HAM-D scores by -2.5 points (p=0.016) more than placebo, which is not considered a clinically meaningful change. The change in CGI-I response was greater than placebo by 39% (NNT of 3).¹⁰

Trial limitations include small sample sizes and short-term durations. Adverse events associated with brexanolone may have alerted investigators to treatment randomization, potentially causing investigator bias. Background antidepressants were allowed and used in approximately 30% of the study participants.

Clinical Safety:

Common adverse reactions which occurred at least 5% more often and at least twice the rate of placebo were sedation/somnolence, dry mouth, loss of consciousness and flushing/hot flush (**Table 10**).¹¹ Dose interruption or reduction due to sedation and somnolence occurred more frequently in patients receiving brexanolone compared to placebo, 5% versus 0%, respectively. Loss of consciousness also occurred in 4% of brexanolone treated patients compared to none in the placebo group. Sedative effects should be evaluated every 2 hours during the infusion. Consequently, there is a boxed warning, due to risk of excessive sedation or sudden loss of consciousness. For these reasons, while administering brexanolone patients should have continuous pulse oximetry monitoring and brexanolone is only available through a REMS program.

Requirement of the REMS program are:

- healthcare facilities must be enrolled in the program and brexanolone must only be administered to patients who are enrolled in the program,
- pharmacies must be certified with the program and must only dispense brexanolone to healthcare facilities who are certified in the brexanolone REMS,
- patients must be enrolled in the brexanolone REMS prior to administration, and
- wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies.¹¹

Breast feeding was not permitted during the trials. It is estimated that 2% or less of the maternal dose would be excreted into breast milk.

Table 10. Adverse Reactions Reported in Greater than or equal to 2% of Brexanolone Treated Patients and More than Placebo¹¹

Adverse Reaction	Placebo	Brexanolone 60 mcg/kg/hour	Brexanolone 90 mcg/kg/hour
Sedation, somnolence	6%	21%	13%
Dizziness, presyncope, vertigo	7%	13%	12%
Dry mouth	1%	11%	3%
Loss of consciousness	0	5%	3%
Flushing, hot flush	0	5%	2%
Diarrhea	1%	3%	2%
Oropharyngeal pain	0	3%	2%
Tachycardia	0	0	3%
Dyspepsia	0	0	2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Remission of depressive symptoms
- 2) Relapse of depressive episode
- 3) Symptom reduction (as determined by a validated scale)
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 2) Change in 17-item HAM-D total score at 60 hours

Table 11. Pharmacology and Pharmacokinetic Properties of Brexanolone

Parameter	
Mechanism of Action	Thought to be due to its positive allosteric modulation of GABA _A receptors
Oral bioavailability	NA
Distribution and Protein Binding	3 Liters/kg >99%
Elimination	47% in the feces and 42% in the urine
Half-Life	9 hours
Metabolism	Non-CYP based pathways via three main routes (keto-reduction, glucuronidation, and sulfation).

Abbreviations: Not applicable

		- 6 months or less post-partum at screening with PPD - qualifying 17-item HAM-D score (20-25) <u>Key Exclusion Criteria:</u> - see above	2. 2%	BX90: 39 (80%) P: 29 (56%) BX90 vs. P: OR 5.0 (95% CI, 2.0 to 12.5) p-value: 0.0005	39/3		<u>Reporting Bias:</u> See above <u>Applicability:</u> <u>Patient:</u> Applies to women with severe depression, with or without current antidepressant use. <u>Intervention:</u> See above <u>Comparator:</u> See above <u>Outcomes:</u> See above <u>Setting:</u> See above
<u>Abbreviations:</u> ARR = absolute risk reduction; CGI =Clinical Global Impression-Improvement response; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; LSMD= least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PP = per protocol; PPD = post-partum depression							

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Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL status</u>
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	NORPRAMIN	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluoxetine HCl	SARAFEM	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
imipramine HCl	TOFRANIL	TABLET	Y
maprotiline HCl	MAPROTILINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y

protriptyline HCl	PROTRIPTYLINE HCL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
trimipramine maleate	SURMONTIL	CAPSULE	Y
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24	V
desvenlafaxine	KHEDEZLA	TAB ER 24	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
desvenlafaxine fumarate	DESVENLAFAXINE FUMARATE ER	TAB ER 24	V
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	V
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	V
duloxetine HCl	CYMBALTA	CAPSULE DR	V
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
nefazodone HCl	NEFAZODONE HCL	TABLET	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V

paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
selegiline	EMSAM	PATCH TD24	V
tranylcypromine sulfate	TRANLYCYPROMINE SULFATE	TABLET	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
amoxapine	AMOXAPINE	TABLET	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

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Appendix 2: Abstracts of Comparative Clinical Trials

Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, and Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction.

Introduction: Sexual dysfunction is common with serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), and does not resolve in most patients. Vortioxetine, an antidepressant with a multimodal mechanism of action, has shown low rates of sexual dysfunction in previous major depressive disorder (MDD) trials.

Aim: This study compared the effects of vortioxetine and escitalopram on sexual functioning in adults with well-treated MDD experiencing treatment-emergent sexual dysfunction (TESD).

Methods: Participants treated with, and responding to, citalopram, paroxetine, or sertraline were randomized to switch to either vortioxetine (10/20 mg; n = 225) or escitalopram (10/20 mg; n = 222) for 8 weeks. Sexual function was assessed using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), and antidepressant efficacy was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions (CGI) scale, and Profile of Mood States brief form (POMS-brief). Safety and tolerability were also assessed.

Main Outcome Measures: The primary endpoint was change from baseline in the CSFQ-14 total score after 8 weeks of treatment. The MADRS, CGI, and POMS-brief were used to assess antidepressant efficacy. Safety was assessed via adverse events, vital signs, electrocardiograms, laboratory values, weight, and physical examination findings.

Results: Vortioxetine showed significantly greater improvements in CSFQ-14 total score (8.8 ± 0.64 , mean \pm standard error) vs. escitalopram (6.6 ± 0.64 ; $P = 0.013$). Benefits vs. escitalopram were significant on four of five dimensions and all three phases of sexual functioning assessed by the CSFQ-14 ($P < 0.05$). Antidepressant efficacy continued in both groups, with similar, but slight, improvements in MADRS and CGI scores. Vortioxetine and escitalopram had similar clinical efficacy profiles in this study, with safety profiles similar to previous trials. Nausea (n = 9, 4.0%) was the most common treatment-emergent adverse event leading to discontinuation of vortioxetine.

Conclusion: Switching antidepressant therapy to vortioxetine may be beneficial for patients experiencing sexual dysfunction during antidepressant therapy with SSRIs.

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to April Week 1 2019

Search Strategy:

#	Searches	Results
1	amitriptyline.mp. or Amitriptyline/	8629
2	bupropion.mp. or Bupropion/	4249
3	citalopram.mp. or Citalopram/	6187
4	desipramine.mp. or Desipramine/	7653
5	doxepine.mp.	86
6	escitalopram.mp. or Citalopram/	5085
7	fluoxetine.mp. or Fluoxetine/	12328
8	fluvoxamine.mp. or Fluvoxamine/	2686
9	imipramine.mp. or Imipramine/	12752
10	maprotiline.mp. or Maprotiline/	1259
11	mirtazapine.mp. or Mirtazapine/	1873
12	nortriptyline.mp. or Nortriptyline/	2930
13	paroxetine.mp. or Paroxetine/	5672
14	protriptyline.mp. or Protriptyline/	399
15	sertraline.mp. or Sertraline/	4304
16	trimipramine.mp. or Trimipramine/	494
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
18	clomipramine.mp. or Clomipramine/	3766
19	desvenlafaxine.mp. or Desvenlafaxine Succinate/	348
20	duloxetine.mp. or Duloxetine Hydrochloride/	2051
21	isocarboxazid.mp. or Isocarboxazid/	404
22	levomilnacipran.mp.	54
23	nefazodone.mp.	727
24	phenelzine.mp. or Phenelzine/	1595
25	selegiline.mp. or Selegiline/	2723
26	tranylcypromine.mp. or Tranylcypromine/	2172

27 venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
28 vilazodone.mp. or Vilazodone Hydrochloride/	148
29 vortioxetine.mp. or Vortioxetine/	249
30 amoxapine.mp. or Amoxapine/	436
31 trazodone.mp. or Trazodone/	1845
32 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	66706
33 limit 32 to (english language and humans)	39890
34 limit 33 to yr="2017 -Current"	1640
35 limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	155

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Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRAVATO™ safely and effectively. See full prescribing information for SPRAVATO™.

SPRAVATO™ (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)
- Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)
- SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)

-----INDICATIONS AND USAGE-----

SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. (1)

Limitations of Use: SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

-----DOSAGE AND ADMINISTRATION-----

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)
- Assess blood pressure prior to and after administration. (2.1)
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment. (2.2)
- See Full Prescribing Information for recommended dosage during the induction and maintenance phases. (2.2)

- See Full Prescribing Information for important administration instructions. (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

-----CONTRAINDICATIONS-----

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

-----WARNINGS AND PRECAUTIONS-----

- *Increases in Blood Pressure:* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment:* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity:* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

-----ADVERSE REACTIONS-----

The most commonly observed adverse reactions (incidence $\geq 5\%$ and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZULRESSO safely and effectively. See full prescribing information for ZULRESSO.

ZULRESSO™ (brexanolone) injection, for intravenous use, [controlled substance schedule pending]

Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

See full prescribing information for complete boxed warning.

- Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO. (5.1)
- Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). (5.1)
- ZULRESSO is available only through a restricted program called the ZULRESSO REMS. (5.1, 5.2)

INDICATIONS AND USAGE

ZULRESSO is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

- A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion (2.1).
- Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows (2.2):
 - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
 - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour

- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
 - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
 - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour
- Dilution required prior to administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors: Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Avoid use in patients with end stage renal disease (ESRD). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with major depressive disorder, anxiety disorder or post-traumatic stress disorder
Intervention	Antidepressant
Comparator	Placebo or active treatment comparison
Outcomes	Symptom improvement, response or remission of depression
Timing	At onset of symptoms
Setting	Outpatient and inpatient (brexanolone)

Appendix 6: Proposed Safety Edits

Brexanolone (Zulresso)

Goal(s):

- To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:

One time use only.

Requires PA:

- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
4. Does the patient have severe to very severe post-partum depression?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness
5. Has the patient had an adequate trial of an oral antidepressant?	Yes: Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	No: Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 7/19 (KS)
Implementation: TBD

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an FDA approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class.	No: Go to #5
5. Is the request for maintenance dosing of esketamine?	Yes: Go to #10	No: Go to #6
6. Is the patient 65 years or older?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #7
7. Has the patient failed two antidepressants during the current depressive episode?	Yes: Go to #8	No: Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (4-6 weeks) of 2 or more antidepressants.
8. Is the patient currently on an adequate dose of an oral antidepressant?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.

Approval Criteria

9. Does the patient have any of the following: <ul style="list-style-type: none">• Aneurysmal vascular disease or arterial venous malformation OR• Intracerebral hemorrhage OR• Pregnancy OR• Uncontrolled hypertension	Yes: Pass to RPh. Deny; medical appropriateness.	No: Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)
10. Has the patient demonstrated an adequate response during the induction phase (stable remission or response*)?	Yes: Approve for up to 6 months (maximum of 12 per month)	No: Pass to RPh. Deny; medical appropriateness.

* In clinical trials remission was defined as MADRS total score of less than or equal to 12 for at least 3 of the last 4 weeks and stable response was defined as a MADRS total score reduction of 50% or greater for at least 3 of the last 4 weeks and not in remission.

P&T/DUR Review: 7/19 (KS)
Implementation: TBD