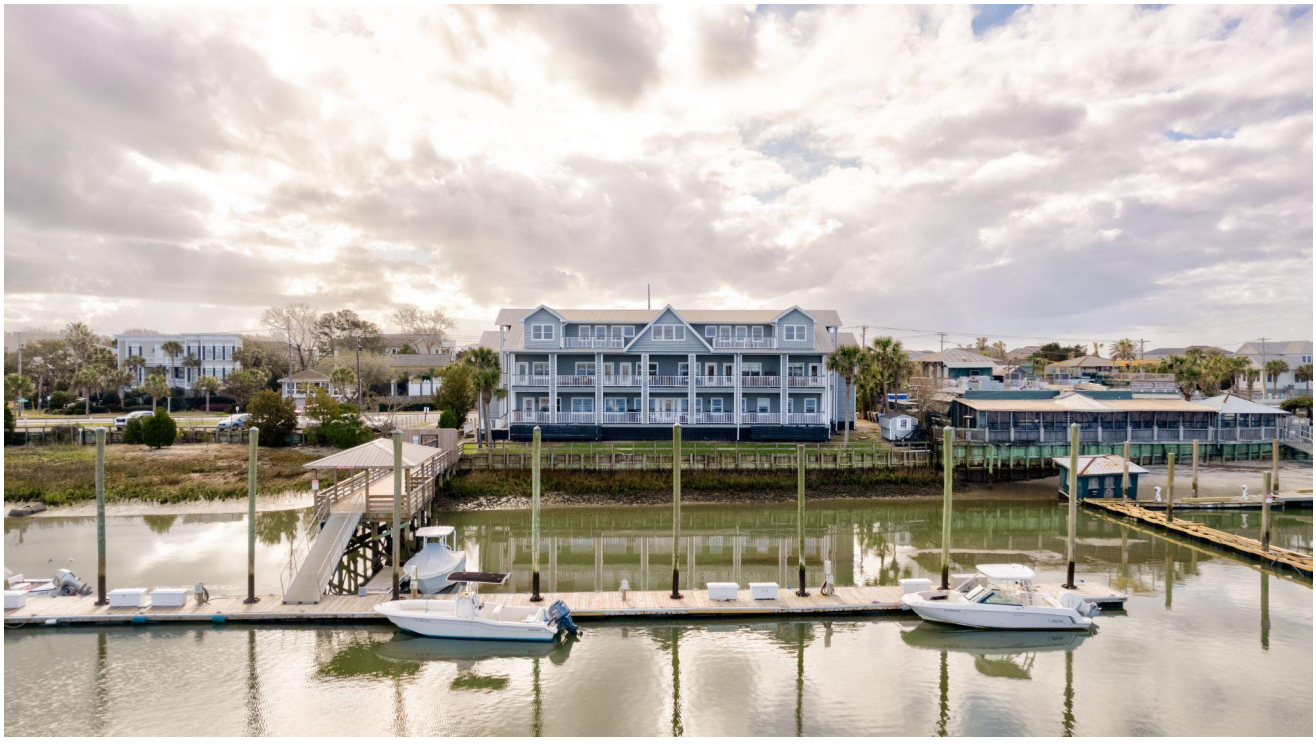
Sweetgrass PSYCHIATRY

Frequently Asked Questions (FAQs) about Esketamine (SPRAVATO)



Updated December 2023

Preface

It is a pleasure for me to meet with you regularly as you undergo therapy with the Food and Drug Administration (FDA)-approved medication SPRAVATO (generic name: esketamine).

You have been diagnosed with treatment resistant depression (TRD), defined as a failure of treatment to produce either a response for patients with a major depressive disorder (MDD) after two or more antidepressants of adequate dose and duration. You are not alone…approximately one in three persons with a MDD suffers from TRD. There is a clear unmet need for rapid-acting and more effective treatments.

You deserve to know as much about this medication and what to expect for your safety and well-being. Each time that we meet, I will ask if you have any questions and seek your perspective as to whether the esketamine is working. As an added benefit, I will review the world medical literature each week about TRD and esketamine and discuss new findings with you if you desire. Our discussions will be at the beginning and end of the required 2-hour session, so that you will have enough time to relax after your dosing.

Described in this handout are my answers to frequently asked questions that our patients have asked about esketamine during the past 4 years. I am not a psychiatrist, but as a physician, I have many decades of experience caring for depressed patients and exposure to ketamine. My responses to your questions come from several sources: my weekly review of the medical literature, observations with more than 2,000 dosing sessions, my correspondence with professionals involved with the Soravati clinical trials, and collaboration from Brittany Albright MD, Taylor Crews, PMHNP and other members of the Sweetgrass Psychiatry team. You will be informed if an answer is not possible and, together, we can reach a logical answer to meet your needs.

William "Bill" Rayburn, MD, MBA

Contents

Responses To Frequently Asked Questions

1. What is important for you to read in the package insert?

A package insert is found in each box containing esketamine (SPRAVATO). The insert is handed to you at the beginning of the first session and any time thereafter if requested. While I encourage you to read this, it contains a lot of medical or chemical words which may be confusing to non-medical professionals. You will find drawings of the nasal spray device and descriptions of how it is to be used in five steps: get ready, prepare the device, prepare patient, patient sprays into each nostril, confirm delivery and rest. I will demonstrate all of this on a model beforehand, so you do not need to be concerned.

The most important portion of the lengthy package insert is the final guide on the back page titled MEDICATION GUIDE. If desired, I have a larger reproduction of this for you on your first visit. Although you will already be prepared with information about esketamine, your homework will be to read this insert between the first and second visit. Questions in the guide address side effects from the medication, what the drug is, who should not take the medicine, and what you should avoid while taking it.

2. How was esketamine (SPRAVATO) discovered?

Esketamine is nearly structurally identical (like a mirror image) to ketamine, a medication approved by the US Food and Drug Administration (FDA) initially in 1970 for anesthesia. Ketamine was found anecdotally to have antidepressant properties for some patients. A review of the medical literature describing the antidepressant effects of ketamine in patients with MDD, and bipolar disorder is beyond the scope of this patient education material. Rather than rebranding ketamine and compounding it for intranasal administration, it was preferred that a new product be developed that would lead to comparable blood levels and be tested carefully using clinical trials.

3. How does esketamine (SPRAVATO) work? Why does it need to be taken with other antidepressants?

Understanding how medications act on the brain can seem speculative and confusing. The predominant hypothesis of the mechanism of action of esketamine is illustrated in a video accessed at:

https://www.janssenmd.com/spravato/multimedia/SPR-001. Simply put, our brains contain nerve cells (or neurons) with specialized receptors and chemicals (called neurotransmitters) which vary in structure and function depending on the region of the brain. In depression, there are structural and functional impairments of synapses in brain regions involved with mood and emotional behavior. The well-established roles of monoamines (e.g., serotonin, norepinephrine, dopamine) and glutamate play important roles in regulating synaptic connectivity between neurons.

Medications prescribed for depression are intended to target specific systems of cell receptors (e.g., glutamatergic, GABAergic, opioidergic). The binding of the drug to certain receptors is believed to influence the neuron function by either stimulating (agonist) or suppressing (antagonist) its function. Selecting target receptors to stimulate or suppress provides many treatment options.

The precise mechanism of action of esketamine nasal spray in MDD is unknown. It is believed to not involve inhibition of serotonin, norepinephrine, or dopamine reuptake or directly involve mu-opioid receptor stimulation. You should understand that esketamine (SPRAVATO) acts differently by being a “non-competitive N-methyl D-aspartate (NMDA)” receptor antagonist. It is believed to act more rapidly

than conventional antidepressants and, therefore, may enhance (or augment) the effect of your antidepressant by acting on a different receptor.

Major depression manifests itself in many ways which is why there needs to be a trial-and-error approach in prescribing, often with more than one medication. Taken alone, esketamine (SPRAVATO) has not been reported as a substitute for a different antidepressant, although a small number of our patients take SPRAVATO alone. Furthermore, while it is encouraging to hear about any relief of suicidal thoughts or anxiety, esketamine is not indicated for either condition.

4. How was the dose determined? Why is it instilled in my nose?

The dose to prompt some effect with the least immediate side effects was determined through phase I clinical trials. This effort included achieving comparable blood levels of ketamine in which an antidepressant effect was observed. Each nasal spray device delivers 28 mg of esketamine. The two standard doses require either two devices (56 mg, medium dose) or three devices (84 mg, maximal dose). No studies have been conducted with one device (28 mg) alone. Research has demonstrated that a higher dose (112 mg) of esketamine is associated with stronger levels of dissociation.

I will monitor you closely to ensure that the medication administration is done properly. The medication is self-administered intranasally. While esketamine can be taken by mouth or intravenously, the nasal route is absorbed rapidly and done safely as an outpatient. The volume of esketamine sprayed in each nostril is 0.1 mL (only a drop or two) which is why I will need to observe closely how well you administer the nasal spray.

We ask that you blow your nose shortly before the first dose to ensure that your upper airway is clear. The initial dosing session requires use of two nasal spray devices (total dose: 56 mg). If you do well (as do most patients), you will be started on a standard and maximal maintenance dose (84 mg: 3 nasal spray devices) on your next visit. Be aware that the spray may be unevenly distributed in each nostril. This is common and, to my knowledge, does not influence the amount of drug getting into your system.

5. How long does it take for the drug to reach a peak blood level? How long is it in my system?

Blood vessels in your nasal airway permit rapid absorption of esketamine. Absorption is within minutes, with peak blood levels being reached at about 20 to 40 minutes after your last dose. Interestingly, only about half of the esketamine in your blood is from absorption in your nose. The remainder is absorbed from your stomach due to postnasal drainage of the medication.

At about 20 to 40 minutes after your dosing, you will begin to sense a mild but temporary alteration in your thinking. Your blood pressure and your heart rate will increase but not to either high or dangerous levels. I intend to be with you to make sure that you are doing well before being left alone to relax.

The blood level of esketamine declines rapidly over 2 and 4 hours, and the half-life (only half of the drug remains in your system) ranges from 7 to 12 hours. It is eliminated primarily in your urine. All medications have by-products or metabolites. In this case, the primary metabolite (noresketamine) is less active and in lower concentration which stays in your system more briefly.

Esketamine does not accumulate over time. You should be relieved to know that tolerance to the drug is not expected.

6. **What should I expect as a usual dosing schedule?**

After your successful initial dosing, the manufacturer recommends twice weekly dosing during the first 4

weeks as the true “induction” period. The second 4 weeks (weeks 5 to 8) consist of administering the same dose either once weekly if you demonstrate a response or twice weekly if there is no response.

If the medication is continued beyond 8 weeks (maintenance period), the dosing regimen will be tailored according to your needs by inhaling the most effective dose (56 mg or 84 mg) and the least frequently to maintain a remission or response. By the beginning of week 9, I will discuss three options with you to consider. Together, we will choose one of the following: 1) take the drug every one or two weeks, 2) take the drug only if you feel symptoms are worsening (“rescue dose”), or 3) discontinue esketamine if there is no response and consider other therapy options with your provider.

In most cases, patients respond to esketamine and continue with regular dosing usually every 2-3 weeks. Infrequently, they will require redosing weekly or monthly. Stopping the medication after a response is uncommon and usual among those who have consistently mild depression.

7. What has been learned from clinical trials that support esketamine’s (SPRAVATO) value?

The gold standard in evaluating any drug therapy is by conducting randomized, double-blind, parallel-group multicenter studies (i.e., for the patient and physician to be blinded as to whether the patient received a medication or placebo in a randomized manner for the same condition). A patient-administered questionnaire, using the Montgomery-Asberg Depression Rating Scale (MADRS), is used to measure the severity of depressive episodes, since it may be more sensitive to changes brought on by antidepressants.

There have now been several published reports with enough patients with TRD who received a new oral antidepressant and either esketamine or placebo intranasally for four weeks (TRANSFORM trials). One of four antidepressants, either a selective serotonin reuptake inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI), was prescribed. These short, phase III clinical trials reported improvement (or a lowering) in their MADRS score. This was apparent as early as within 24 hours after the first dose (56 mg) and with twice weekly dosage (usually 84 mg) by the end of the first 4 weeks. Patients with co-existing anxiety (usually treated with a mild benzodiazepine medication) were also included, even though esketamine is not intended as an antianxiety drug.

As you have experienced, depression symptoms are prone to recur. Studies have also examined continued success with esketamine during the first year for patients who demonstrated a response after the first 4 weeks (SUSTAIN trials). These studies tended to be open-label (unblinded) and direct-enrollment in which the patient usually received either a 56 mg or 84 mg dose every 1, 2 or 3 weeks (phase III trial). The primary study endpoint, according to a rising MADRS score, was the time for depression to relapse for two consecutive weeks or lead to hospitalization. The esketamine group was found to experience a statistically significant longer time (weeks to months) until relapse of depressive symptoms than did patients receiving a placebo.

Intravenous ketamine may rapidly decrease suicide ideation. As a result, another phase 3, double-blind, multicenter study (ASPIRE trial) enrolled adults having severe MDD with active suicidal ideation with intent and need for psychiatric hospitalization. As with the initial TRANSFORM trials, patients received a nasal spray of esketamine (84 mg) or placebo twice weekly. Those who received esketamine demonstrated greater improvement in MADRS total score at 24 hours as well as later points during the 4-week treatment. Common side effects were the same as described before.

Limitations must be acknowledged with these clinical trials. In most cases, the patients were adults 18 to < 65 of age, rather than older. The depression questionnaire survey was the primary tool for assessing depression, but the survey is taken by a patient with much room for subjectivity. Variability in the score

between treatments was sometimes hard to interpret and may be situational (e.g., a child leaving home, job difficulties, loss of a pet, illness of a family member or loved one). Use of a placebo in these trials is commonly shown to be "therapeutic" and show improvement.

Many different antidepressant medications are used by our patients (rather than one of four used in the clinical trials), and many of our patients take two antidepressants. Patients were excluded if they had bipolar disease, obsessive compulsive personality disorder (OCPD), antisocial personality, borderline personality, and alcohol or other substance use. Assessing depression is subjective, and often dependent on the patient's feelings at that time, so clinical research in psychiatry is often subjective or easily quantified.

8. Why is FDA approval of esketamine (SPRAVATO) so important?

The FDA ensures that safe and effective drugs are available to improve health. It regulates almost every facet of a prescription drug, including testing, manufacturing, labeling, advertising marketing, efficacy, and safety. New drugs receive extensive, stepwise scrutiny before FDA approval. The average time for drug development from concept to approval was shortened for SPRAVATO, rather than the average 12 years.

The FDA approved esketamine in May 2019 for the treatment of TRD in adults in conjunction with an oral antidepressant. On July 31, 2020, esketamine was approved for a second indication: the treatment of depressive symptoms in adults with MDD with acute suicidal thoughts or behavior.

As part of any approval process, the FDA reviewed data from functional outcome measures in the clinical trials and feedback from patient advocacy groups and individual testimonies. A general theme supporting esketamine was the serious need for additional management options for TRD. Esketamine represented a novel treatment for a severe and life-threatening condition, and its rapid onset of effect was a key benefit. Implementation of a REMS (Risk Evaluation and Mitigation Strategy) program in a medically supervised healthcare setting is mandatory to ensure safe use and minimize abuse potential.

9. Are there any medications that I should either avoid or take before my esketamine (SPRAVATO) dosing?

Our patients usually take many medications. We ask that you maintain your same schedule for taking your antidepressant and any other psychoactive drug except for controlled medications. Drugs that are central nervous system depressants can lead to sedation and respiratory depression, while psychostimulants and monoamine oxidase inhibitor (MAOI) antidepressants can increase blood pressures. We advise that you do not take stimulants on treatment days due to the risk of elevated blood pressure.

We also advise that you do not take benzodiazepines, opioids, alcohol, cannabis, or controlled sleep medications on the day of treatment due to risk of sedation and respiratory depression, and these medications potentially reduce the therapeutic benefits of esketamine. Please consult with your doctor if you are taking opioid pain medications as we do not recommend combining these medications with esketamine. We also ask that you not be on oral at home ketamine while part of our SPRAVATO treatment program for safety reasons. Lastly, try to avoid taking a nasal steroid or decongestant within a few hours before esketamine dosing. Please notify us if there is any change in your medications.

Any elevations in blood pressures are usually minimal and short-lasting, but if you are being treated for hypertension, please follow your BP at home and take your pill a few hours before your esketamine dosing. I will often ask you to provide BP recordings to me.

Few side effects are anticipated during treatment. If you have nausea, we will provide a pill for nausea

(Zofran 4 or 8 mg) and prescribe this medication for you to take two hours before your next dosing. If you have elevated blood pressure, we may provide you with a medication to lower your blood pressure to a safe range (Clonidine 0.1mg po).

10. When should I expect to receive some effect on relieving my depression?

We will ask you to fill out a patient health questionnaire (PHQ-9) and a generalized anxiety disorder (GAD) survey at the beginning of each visit. The PHQ-9 score is an indicator of the severity of depressive episodes which can be used to assess any change of your depression since last seen. An effect is best assessed by combining the score on your survey with the overall impression of your progress since beginning the esketamine.

Some relief or "hitting the reset button" may be felt as early as 24 to 48 hours after your first dosing. While this is hopeful predictor of a response, we consider a 28-day (or 4 week) induction period to often be necessary. This allows us to more reliably see an effect, whether it is a reduction in your survey scores (at least 25% drop from baseline) or you are feeling better in coping. If no effect is found, then we will recommend continuing the medication for another 28-day period for once or twice weekly dosing.

11. What is a positive response to esketamine (SPRAVATO)? a remission?

Using the PHQ-9 and GAD-7 questionnaires in our clinic, we will be able to determine baseline scores to compare later. A response or improvement is a decline in your baseline score (e.g., from 24 to 12). A remission is a decline in score from the baseline to less than 10. Improvement with esketamine and an AD is more common when the patient has "little interest/pleasure in things, "feeling down, depressed, or hopeless," and "feeling tired or having little energy.

Although helpful, these scores are unreliable as a sole predictor of success. I caution all patients that esketamine is not a miracle drug. Instead, it often has a positive effect on "clearing the mind" and "reprioritizing your thoughts with less focus on negativity." It is believed to improve anhedonia which is a common lack of pleasure or capacity to experience it. Two of our patients described esketamine as "removing ankle weights while trying to stay afloat in the middle of the ocean" and "seeing priorities in a different light that helps correct imbalances."

In addition to seeking your feedback, I routinely talk with family members or close friends (with your consent only) where there has been any response that they observe. This information can be very useful as either confirmatory (of a response or not) or conflicting which prompts me to want more clarification of the patient's perception. I will often ask you about any disability at work, home, or social function, since clinical studies often do not evaluate functional improvement in adults.

Using this combined information in defining a response, our experience in the first 60 patients after their first two months of esketamine has shown an 80% response, 5% remission, and 15% failure rate. These proportions are similar to or better than that reported in medical literature.

12. How long will I need to take esketamine (SPRAVATO) after a response?

It is hard to say. There are no clear guidelines, so your impressions will be important as we individualize the use of esketamine. If there is a response by the end of the first month, we recommend continuing the dosing, but on a weekly basis until the end of week 8. Afterwards, we recommend that the drug be taken every other week or up to every four weeks as you "feel things out." There is no reported experience with regular dosing less frequently than every four weeks. Although uncustomary, we are open to discontinuing the drug completely and re-treating (using a rescue dose) if there is a relapse of an MDD

episode.

13. What is the chance of a depression relapse after I stop taking esketamine (SPRAVATO)? What will be done?

Esketamine is effective beyond the first month in patients who have an initial response. As you well know, major depression can be long-standing. Despite success with a certain antidepressant regimen, relapses do occur either without warning or after some traumatic event(s). Reported experience has shown that there is a longer period of remission before the next relapse into major depression in patients who continue esketamine than those with a placebo.

We offer esketamine as "rescue" therapy. Unlike your initial dosing and induction trial over 4 to 8 weeks, this "rescue" therapy is usually short and highly individualized. Either a single dose or often repeat doses for the next few weeks is necessary. We have no reports that provide any stricter guidelines.

While our experience is limited, we may assist you with redosing if you anticipate problems before your next scheduled appointment (using a single "prophylactic" dose), especially if you responded well with the induction trial. Rescue or prophylactic doses are the same as what you received before (56 mg or 84 mg). We may delay use of any third nasal spray device to see how you adjust to the first two, so that there may be less of a pronounced effect with the third dose.

14. What is the chance of failure from esketamine (SPRAVATO)? How soon will you know?

"Patients don't fail drugs…drugs fail patients." With any drug therapy, we should expect some failures which we define as a lack of response. A 2023 clinical trial demonstrated that 75% of patients had a clinical response to Spravato by week 32 of treatment.

We stop the drug usually after a minimum 2-month trial if there is no improvement in symptoms. The trial will continue if there are extenuating circumstances and there is some evidence to suggest that the patient is doing better (e.g., being more active, able to sleep better, more interested in matters). In addition to continuing the esketamine, we may examine the possibility of changing the antidepressant or adding another medication. If there is no response, there is no harm in stopping the treatment abruptly rather than withdrawing gradually.

15. If there is a failure with esketamine (SPRAVATO), what are some other therapies for treating my resistant depression?

There is hope despite a failure with esketamine. I prepared a list of alternative therapies to mention to you to discuss further with your provider. These therapies could be divided into three groups: invasive procedures, other medications, and counseling. There has been no known reported trial combining these alternative therapies with esketamine.

Procedures. Repetitive transcranial magnetic stimulation (rTMS) has become a popular option for TRD and is available at our clinic. Certain key areas of the brain networks and their connectivity can predict immediate and longer-term responsiveness to rTMS. Electroconvulsive therapy (ECT) was a common therapy for TRD for many years. Short-term and perhaps long-term memory loss have limited its use. While its acceptance has been challenged, it may be an alternative in certain circumstances. Your provider will inform you about other procedures and those physician leaders (e.g., subcallosal cingulate deep brain stimulation, trigeminal nerve stimulation).

Ketamine. Ketamine is used less for esketamine failures and more for people without insurance. Off-label and intravenous use of ketamine can be administered by psychiatrists and anesthesiologists. We have had

about a dozen patients who underwent therapy. They described its effects to be more rapid, less predictable, potentially more profound, and more rapid in recovery. This past year, we began administering ketamine, intranasally or intramuscularly, with limited but similar success as esketamine. Preclinical experience suggests that (R)-ketamine (arketamine) holds promise, although it is not yet commercially available. This drug is like esketamine [(S)-ketamine] and may be more potent, exert longer-lasting antidepressant effects, prompt less detrimental effects, lead to more sustained antidepressant effects, and could be safer.

Other medications. I am maintaining a list of other medications which may hold some assistance in select TRD cases. The FDA has approved only one drug for TRD, a fixed-dose combination of olanzapine and fluoxetine, which can lead to metabolic side effects and weight gain. Phase 2 trials of other medications for TRD include brexpiprazole, lithium, psilocybin, nitrous oxide, amisulpride, botulinum toxin (facial injections), ayahuasca, prasterone, Caspian, ethosuximide, monoamine oxidase inhibitor and tricyclic antidepressant combination, and a ketamine-lithium combination. Prescribing these medications alone or in combination with an antidepressant requires the expertise of a qualified psychiatrist.

C*ounseling.* Counseling is often helpful, whether you are taking esketamine or not. It is a mainstay for assisting with anxiety, obsessive compulsive behavior, attention deficit disorder, or a personality disorder (e.g., borderline) which can coexist with depression. Psychotherapy can aid with social withdrawal and stresses that involve being less able to affectively resonate with others (affective empathy). Cognitive behavioral therapy, neurofeedback augmentation, coping skills, and game playing such as video games are worthy of consideration. While often difficult to do with many of our patients, we discuss and encourage some form of regular exercise and proper diet.

16. Are there short-term hazards to taking this drug?

Adverse events during treatment generally become less frequent with ongoing treatment. Fortunately, we have seen only mild, short-lasting effects which have not required us to discontinue the medication. Adverse reactions associated with esketamine are present in the following order: dissociation (41%), dizziness (29%), sedation (29%), nausea (28%), vertigo or “spinning head” (23%), and respiratory depression (very rare). Admittedly, the frequency of these adverse events can be inaccurate due to personal interpretation. Attributing fewer common effects because of esketamine is difficult without its discontinuation.

Dissociation or perceptual changes (distortion of time and space, illusions) derealization, or depersonalization occurs in 60-75% of all dosing sessions. Most commonly, our patients have described themselves as being light-headed, dizzy, head spinning, “feeling high from a few drinks,” feelings of floating, detachment, and being “spaced out” or having an “out of body experience.” Heightened awareness of sounds, ringing in the ears (tinnitus), and numbness of the fingers, toes or lips are sometimes described. These symptoms begin in the first half hour and rarely last beyond one hour. Cumulative perceptual changes seem to be most pronounced after the third dose. Many patients tell me that the frequency and manifestation of dissociation effects is unpredictable, so expect some variation with each dosing. The dissociative and antidepressant effects of esketamine are not significantly correlated. Therefore, if you have no dissociation during a dosing, realize that the medication is still working.

Cognition and mental effort. Many patients are self-conscious of “senior moments” or loss of thought during the first hour post dosing. These are of no consequence, and mental efforts are comparable between esketamine and the placebo groups at 2 hours post dosing. We do instruct our patients to not engage in potentially hazardous activities requiring complete mental alertness or motor coordination. On-road driving or operating machinery is not allowed until, preferably, the next morning after a restful

sleep.

Sedation. A desire to rest and be left alone is common. Sedation occurs in about half of doings, is usually mild or marginal and relieved by remaining stationary or "taking a nap" for a half hour or hour. We are asked to monitor the patient for the first two hours, and it is our custom to escort you to the bathroom or your driver if there is any concern. We may keep you beyond the required 2-hour monitoring period if needed due to safety/side effects. Wishing to lie down and go to bed earlier that night is common, even though sleepiness is comparable after 4 hours post dosing for persons who received either esketamine or a placebo.

Blood pressure (BP) elevations. Elevations in BPs are common when checked shortly after coming to the clinic. I often will leave the room, ask you to meditate for a few minutes, and self-measure the BP. Esketamine can raise the BP of your upper (systolic) and lower (diastolic) measurements in the first hour after administration in about 10% of dosing sessions. A substantial increase could occur after any dose even if small BP elevations are observed without prior dosings. The only contraindication for esketamine is in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, history of intracerebral hemorrhage). Before prescribing esketamine, we screen patients for hypertension and headaches. We may order an electrocardiogram and certain kidney function tests or consult with a primary care physician, cardiologist, or neurologist to determine whether the potential benefits outweigh the risks.

You will be asked about any headaches and will have your BP checked before dosing and at about 30-40 minutes and 1 ½-2 hours post dosing. Your BP can be elevated when you come into the clinic. Often, I will have patients check their BP while alone or after a brief meditation. I will delay esketamine therapy if the BP is elevated (as a general guide: > 140/90). You may be dosed with a pill of clonidine (Catapres, 0.1 mg) as we wait to see if your BP does not decline. About one-third of our patients have some elevated BPs, and I strongly recommend obtaining a BP monitor for self-monitoring as often as twice daily. If the BP reading is declining and not very high, we will allow the patient to go home to rest and let us know the reading at home a few hours later.

17. What is known about long-term risks with esketamine (SPRAVATO)?

The medication has been on the market for 5 years, so risks have been reported for only that period. Under our supervision, our patients have no risk for abuse and misuse of esketamine. A common expression is "This is no high I would ever chase." We monitor for signs and symptoms of abuse and misuse and have not encountered any concern.

Patients taking antidepressants are at increased risk of suicidal thoughts and behaviors. We closely monitor our patients for clinical worsening and emergence of suicidal thoughts and behaviors. A distinct advantage to esketamine is its indication for the reduction of depressive symptoms and acute suicidal ideation.

Long-term knowledge and memory impairment have been reported with repeated ketamine misuse or abuse. However, no adverse effects of esketamine nasal spray on cognitive functioning were observed in several safety studies. It is impossible to discuss any added risk of early dementia or Alzheimer's with esketamine use, and we would not discourage its use because of its common finding in most family histories.

No new safety signal was identified during long-term treatment (up to 4.5 years). Studies have shown that there are no serious heart or vascular sequelae or toxicity to the kidneys with exposure to esketamine.

18. Will it ever be possible for esketamine (SPRAVATO) to be administered as a pill or given outside the office?

Unlikely, because of the strict monitoring after two or three doses required by the FDA for the drug to be approved. Currently, there are no FDA approved commercially available dosage forms given topically, orally (like lozenges), or as an injectable. Intravenous, subcutaneous (under the skin), and possibly oral esketamine may offer an effective and safe addition to the depression treatment armamentarium. However, the few studies outside the U.S. often lacked a control group and had small sample sizes.

19. How can the cost of esketamine (SPRAVATO) be justified?

TRD accounts for about 1% of the total health care. It represents a significant burden-of-disease and a high level of lost productivity. Esketamine has undergone much research. Its novel delivery system and need for two hours of monitoring in a clinic can be costly. Novel treatments such as esketamine have the potential to improve both patient mood, symptoms, and economic productivity, reducing the human capital costs associated with MDD.

We understand and regret that some persons with MDD are unable to obtain esketamine due to a lack of insurance coverage, high cost of hospital admissions and emergency room visits, and long distances to receive it. Post marketing experience and additional studies of esketamine, including evaluation of longer dosing intervals and potential home therapy with a professional, may lead to new approaches that enhance access, although I am not aware of any reports.

We are offering intranasal ketamine gel compounded at a nearby pharmacy and intramuscular ketamine for those who are unable to obtain insurance coverage for esketamine. The monitoring routine and the dose equivalency are similar. We are limited in comparing the therapeutic equivalency between ketamine and esketamine with our limited experience.

20. Does the time of day or day of the week matter when esketamine (SPRAVTO) is administered?

No, yet this was not monitored in the clinical trials. Our impression is that it does not make any difference. We administer treatment every weekday, although I am available only in the afternoon on Monday, Wednesday, and Friday. The advantage of afternoon dosing is for people who need to work earlier that day. When the medication is given twice weekly, we prefer that there be at least one day separation between dosing. Treatment with a one-day rest period (e.g., Monday and Wednesday, Wednesday, and Friday) is done often, and more side effects are not apparent.

21. Are there any foods or beverages that should be encouraged or avoided with esketamine (SPRAVATO) use?

Modest benefit in MDD has been demonstrated with folic acid supplementation in foods, pills, or vitamins. We ask that you avoid eating any food for at least 2 hours before dosing and drinking liquids at least 30 minutes before. Alcohol consumption is always a concern for patients with depression. We recommend avoiding the use of alcohol during esketamine treatment, especially on actual treatment days.

22. What are medical conditions that contraindicate esketamine (SPRAVATO)?

TRD patients compared with no-TRD MDD patients have a substantially higher prevalence of various psychiatric and medical comorbidities and higher health care utilization (HCU). This highlights the challenges of developing interventions and care coordination strategies to meet the complex clinical needs of TRD patients.

The safety margin of esketamine is high, yet we take precautions in anyone with a history of liver impairment, vascular disease, prior brain hemorrhage, aneurysms, kidney disease, potential of pregnancy, or substance abuse including alcohol. Each of these conditions will be sought on your first visit. I will also review your medical records about medications and any history of psychosis. With each visit, I will ask about your medications and whether you wish to talk with me about any medical illnesses which may be aggravating your depression. A headache is not a contraindication to therapy, and migraine-like headache may improve when you are dosed with esketamine.

23. Are there any special populations that cannot take this medication?

Yes, but very few adults. The medication has not been reported in clinical trials involving children, adolescents, pregnant women, or breastfeeding women. Any fetal harm is unknown, and I will screen for the possibility of pregnancy among our select patients. I will provide counseling about TRD and esketamine in relation to pregnancy planning and prevention, any altered sperm analysis, impaired fertility, menstrual abnormalities, and menopause, as necessary. Studies have shown that there is no difference between men and women in the effectiveness and safety of esketamine intranasal spray in short-term trials. Older patients represent another special population, and special considerations are discussed below in more detail.

24. Would someone who is 65 or older be at greater risk with esketamine (SPRAVATO)?

We see patients who are older with TRD, yet fewer research reports with smaller samples exist exclusively about older persons. Although we consider esketamine to be safe, older persons are at greater risk for dissociation symptoms with a slower reaction time and elevated systolic BPs. The maximal blood concentration of the drug in the brain circulation and the average concentration over time are higher in older than younger adults.

Despite this, age does not require treatment suspension Therefore, most of our patients > 65 years better tolerate the lower therapeutic dose (56 mg versus 84 mg) of esketamine. They may require more assistance while going home, since the medication is cleared less rapidly. Furthermore, signs of a response to esketamine can be more challenging, and more research is needed.

25. Can this medication disturb my sleep between dosings?

No. Depression is strongly associated with difficulty falling asleep or remaining asleep. Many patients require a sleeping aid. Esketamine alone can be mildly sedating, but its effect beyond the first 24 hours is not thought to increase the risk of insomnia or unrest. Vivid dreams are very infrequently reported to me on the first night, but we have no information to suggest any greater likelihood of nightmares.

26. Have you ever seen any allergic reaction to esketamine (SPRAVATO)?

No. We have neither seen any reaction nor has the literature or manufacturer reported any confirmed hypersensitivity to esketamine. Reporting any allergic reaction (e.g., hives, swelling, breathing difficulties) is a requirement for drug companies to maintain approval of their medication. While any reaction is possible (likely shortly after administration), it must be exceedingly rare. We will monitor you carefully while in the clinic. While this happens rarely, any desire to notify us by email or phone is encouraged if there is any undesired reaction or question.

27. Are there medications available if I have any problems after dosing?

Yes. We stock medications in the clinic if you have any headache (acetaminophen or Tylenol), unacceptably high BP (clonidine or Catapres 0.1 mg), or nausea (ondansetron or Zofran 4or 8 mg) during

the treatment session. This need is uncommon, and if it occurs, we may also prescribe BP or nausea medication for you to take about two hours before your next clinic visit. Agitated behavior or a panic attack is rare and not directly related to esketamine. We can provide a relaxant if necessary. We typically recommend cariprazine 1.5mg po (which we have in office) to help with acute dissociation symptoms as we have found it safe, quick acting, and effective for patients experiencing dissociation on Sparano.

28. What if I miss a treatment session?

If you anticipate missing a treatment session, let us know promptly and we will get you scheduled in the next day or so. We really dislike charging anyone for nonmedical reasons for not attending the clinic that same day, but a clinic room is reserved for you for two hours and two professional employees. If there is a worsening of your depression symptoms, we will see you earlier for your next dosing. Furthermore, we will consider shortening your dosing interval (e.g., from every two weeks to once weekly).

29. Does my mood immediately before the dosing make any difference in the effectiveness of esketamine (SPRAVATO)?

Likely not. I have often wondered about this, since patients have said that they experience less or little effect when they are angry, anxious, tearful, or feel sadder than usual. There are no reports about this in the medical literature. Ideally, you should be relaxed and comfortable before and during your dosing. I attempt to listen to any immediate problems you may have. However, we will still offer the medication regardless of your mood.

30. What is the REMS program? Why is it important?

Because of recognized side effects for sedation, dissociation, and the potential for abuse and misuse, esketamine is only available through a restricted program called the Risk Evaluation and Mitigation Strategy (REMS) Program. We are pleased to report that Sweetgrass Psychiatry is a healthcare setting certified as a REMS Program. We are required to fill in data sheets that are reported to the manufacturer (Janssen Neuroscience, a pharmaceutical company of Johnson and Johnson), so you will often see me filling out some data sheets. Furthermore, the pharmacy which we use (Sweetgrass Pharmacy) is certified in the REMS program and must only dispense esketamine to healthcare facilities that are certified in the program.

31. Can a patient become dependent on or suffer from withdrawal of esketamine (SPRAVATO)?

No. Risks of abuse and misuse are well known about ketamine being taken in higher doses and illegally. Esketamine is a controlled substance, and its use needs to be closely monitored. Given in our practice setting, esketamine will be used safely, and you should not be concerned about any dependence potential. I have not heard any patient complain of withdrawal when they discontinue therapy or go many weeks without esketamine. An overdose is not possible in our prescribing practice, and the drug clears the system rapidly. One report revealed that use of esketamine was not associated with a change in the risk perception of recreational ketamine use and not associated with increased use.

32. Is there any disturbing information from animal studies about this medication?

Not really. These studies are often intended to understand molecular or cellular mechanisms of depression to determine what medications may be useful in correcting these imbalances. Every new drug needs to undergo animal studies to determine any toxic effect. Observations in rats and mice have shown no increased risk of tumors, genetic mutations, gene toxicity, microscopic nerve damage, or impaired fertility. Any relation between esketamine and detrimental effects in offspring of exposed mice, including ADHD and depression-like behaviors, requires caution with any interpretation for humans.

33. Will esketamine (SPRAVATO) affect my appetite?

Probably not. Any nausea is not expected to persist beyond the first few hours. We have had several patients say that their appetite may be less during the day of dosing. However, a lack of desire to eat for several days is highly unlikely to result from esketamine. Any worsening of depression, another illness, or another medication is likely the explanation and needs to be evaluated further.

34. What has been learned about the success of this medication with the recent COVID-19 pandemic?

Symptoms of depression and anxiety and thoughts of suicide are more commonly reported in the recent medical literature with COVID-19. We are seeing less sense of relief in our patients during this era due to less activity, less interpersonal interaction with family and friends, and more feelings of "being down." If the combination of esketamine and an antidepressant is not thought to be helpful, we need to keep this pandemic in mind as we continue the medication combination, alter the esketamine dosing schedule, or consider any alternative therapies.

We continue to follow precautions in our clinic (cleaning, asking about symptoms). If a patient has either a positive test or symptoms suggesting COVID-19, we will discourage you from coming into the clinic. We have also treated patients in their car as you wait with your driver. While there has been no literature about esketamine and COVID-19, we anticipate that the patient response will be the same.

35. Is esketamine (SPRAVATO) more effective with certain antidepressants?

You have been treated without success with at least two antidepressants (AD). We see patients on the same AD for as short as 3 months or as long as many years. Furthermore, about half of our patients are on one or two ADs and another centrally acting medication.

Physicians prescribe the medication which they feel provides the best balance between effectiveness and safety. Listed in the appendix are the most prescribed ADs and their class or presumed mechanism of action. The four ADs used in the initial clinical trials with esketamine were either SSRI or SNRI drugs. None was preferred for patient use or found to work better with esketamine in demonstrating a better response.

You will be asked whether you have undergone any genetic testing to determine whether metabolism (or "break down") of the drug is more or less rapid, thereby affecting its effectiveness. There are no such metabolism tests for esketamine because of its rapid "first pass effect." If your AD has changed for any reason, we like to continue the esketamine while another medication is "taking effect" that may require 3-6 weeks.

Many ADs have other properties that may add benefit for other conditions (e.g., seasonal depression, anxiety, sexual dysfunction, insomnia, fibromyalgia, excess fatigue, BP, OCPD). If your AD is changed for any reason, we usually maintain the same dosing schedule of esketamine.

36. Is esketamine (SPRAVATO) effective if my problem relates more to anxiety than depression alone?

Not necessarily. About half of our patients have accompanying moderate or severe anxiety. Esketamine is not thought to cause or correct fidgeting or feeling the onset of a panic attack. For this reason, you will be asked to fill out an anxiety (GAD) survey with each visit. Esketamine is not intended to treat anxiety, and few antianxiety drugs are effective for long-term regular use.

Patients enrolled in the earlier clinical trials frequently had anxiety and were taking mild benzodiazepines. Improvement in the depression scores were not different between patients with anxiety/depression or

depression alone. We have no experience or data in the medical literature for those persons with severe anxiety.

37. What do you look for when you search the medical literature each week to help me?

A feature at Sweetgrass Psychiatry is the effort to inform you of the newest medical information about esketamine, ketamine, and TRD. My position is unique in that I devote time each Sunday to regularly search the literature with a well-qualified librarian. My background in clinical research and continuing medical education are put to good use. The med-line search from the *National Library of Medicine* is intended to search for the best new information to either answer your questions or bring relevant information to your attention.

My searches exclude animal reports, clinical commentaries, case studies, pilot or preliminary studies, and nonmedical journals, since they have no direct relevance to you. Many clinical trials have the limitations of small numbers of eligible patients, enrollment of patients in a nonrandomized manner, or being retrospective (look back) which represent limitations. A high proportion of the literature is from Asia which can be a challenge for me to interpret.

The most encouraging article reviewed was a review of etamine by the Cochrane review. This independent organization critically reviews all prescribed medications. Esketamine was reported to improve response, remission, and depressive symptoms as early as 24 hours post-first dose among patients with TRD and patients with MDD and active suicidal ideation with intent.

38. What can be done if I may not be improving, but esketamine (SPRAVATO) may have some effect and I wish to continue?

You must want to improve and sometimes medications alone are inadequate. Daily reflections on your mood can often be revealing and more objective. Input from a close friend or family member is often invaluable. Some of our patients have found success using free depression streaming apps. For example, a few questions are to be answered at three specific times daily using the free app *Moodpath.com*. These questions are not the same as on your PHQ-9 survey. Results of responses become available after 14 days and can clarify what can lead to or improve your depressive symptoms. We always encourage our patients to be engaged in regular psychotherapy with a licensed mental health counselor.

39. Is there an extended-release form of esketamine (SPRAVATO) being considered?

No. A major advantage of esketamine is its rapid action, compared with other antidepressants, and its ability to “hit the reset button.” Extended-release forms of medications are exceedingly popular and require less frequent dosing. According to the manufacturer, there are no plans in the foreseeable future for an extended-release preparation.

40. Why do you wish to talk with a family member or partner about my depression?

While you know best about your condition, others close to you have their own perceptions. This additional information provides more insight as to whether your condition is improving or how your condition is affecting others. Often, the family member or partner has a similar impression about your well-being but, unless there is discussion and openness, then the extent or depth of your depression may not be fully realized by yourself.

It is encouraging to me when after the initial month that others feel that you are doing better. This either reinforces your impression or offers some encouragement to continue with the treatment. Lastly, when a patient does not consider esketamine as being helpful, this confirmation by others reinforces the need to

consider therapeutic alternatives.

41. Are there other uses of ketamine or esketamine (SPRAVATO)?

I often see reports of clinical trials using either ketamine or esketamine for persons with the following conditions: postpartum depression, post-traumatic stress disorder, terminally ill cancer, bipolar depression, chronic opioid refractory pain, alcohol use disorder, MDD with psychotic features. Being used in anesthesia, esketamine and ketamine are often reported during or after procedures (e.g., Cesarean deliveries, thoracic surgery, abortion, gastrointestinal procedures to relieve discomfort and reduce analgesic needs. This may apply particularly to those with preexisting depression.

42. What can be done about the terrible taste after the nasal spray?

All patients complain at some time about the "horrible" or "lousy" taste of the esketamine spray. The taste is difficult to describe but has been characterized as "chemical, "burning," "salty," and "bitter." There is no plan for the spray to be berry flavored. Improvement in the taste is often seen by chewing any gum (any brand), ginger ale, Sprite Zero, lemon-lime seltzer water, throat lozenge, candy (e.g., Life Savers, lowly pop), ginger mints, and pretzels. We have many of these options, so let us know your preference. If the taste is accompanied with nausea, we also have ondansetron (Zofran) available. We request that you avoid taking any candy or lozenge until after your treatment to prevent choking.

43. Should I be concerned if I must undergo a urine drug test?

No. Ketamine is not routinely sought in urine drug screens. Ketamine remains in your urine for a short time. If there should be any positive test within a day or so after your esketamine dose, we can provide written documentation about verification about your use and need to be treated with this ketamine-like medication.

44. Should I talk about feeling better off dead or hurting myself?

By all means. we realize that this subject may be awkward and uncomfortable to discuss this subject with me, another provider or professional, and even with your family. Esketamine holds a promise about diminishing acute suicide thoughts for several hours or days but not indefinitely. We respect your privacy, potential fear of hospital admission, or decision to not report to suicide hotlines. If you feel suicidal but have no active plan or intent to harm yourself, I try first to reach your provider or a member of the Sweetgrass Psychiatry team to discuss these issues further with you.

45. Which is better for my depression: ketamine or esketamine (SPRAVATO)?

Both drugs are essentially the same. It really depends on the dose and the route of delivery. Some nonrandomized trials have shown that ketamine may act more quickly but the end results are the same. I attempt to avoid taking too much liberty in loosely translating results from clinical trials with ketamine to esketamine. We prefer esketamine, since it is FDA approved for TRD and MDD with suicide intent after and continues to undergo close monitoring worldwide.

46. Will this medication affect my memory or cognition?

Both may improve memory for the first few days or weeks after dosing. It may improve cognition before depression relief. Long-term studies are now only about 4 years old, but impairment in memory or cognition is not believed to be present with esketamine. While quality of life can be subjective, greater improvements are generally observed among patients treated with esketamine.

47. Can esketamine (SPRAVATO) be taken alone without an antidepressant?

Commercially available esketamine is to be used with another antidepressant. However, we do have a few patients who strongly desire esketamine alone because of a past lack of success with many other antidepressants. We do caution those patients that we have not seen any reported experience with esketamine alone and may not justify its long-term use if questioned by the insurance carrier. Depression is a risk factor of Alzheimer's but, like other centrally acting drugs, we cannot say whether there is additional harm or benefit with esketamine.

48. Have any TRD patients at Sweetgrass Psychiatry been hospitalized during or after esketamine (SPRAVATO)?

Ideally, esketamine use is intended to treat patients with TRD to avoid absences from work and admissions to hospitals. The few patients who have been hospitalized have either had problems unrelated to the side effects of esketamine or had other mental or medical comorbidities. While esketamine is useful with acute suicide ideation, it is not known to be effective in reducing long-term successful suicide intent.

49. Can this medication be continued during transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT)?

I have not found any comparative clinical trials. Our clinic does offer TMS to patients who took esketamine. We have a few patients who continue to take esketamine during TMS. I have not seen any reports of esketamine, or ketamine taken with ECT.

50. If these medications are controlled substances, how can they be advertised online for use at home?

Our patients occasionally ask about at-home ketamine therapy that is now becoming advertised as having positive outcomes for persons who have lived with thoughts of self-harm and suicide. Supervision is “in spirit and in video” using personalized programs after an evaluation from a clinician.

At-home ketamine treatment, initiated by an online provider presents many legal, clinical, and ethical challenges to providers and potential risks to patients. We strongly recommend against unsupervised at home use of ketamine in any dose. Esketamine is not offered with any of these treatment options and unfortunately you will not be able to continue esketamine at our practice combined with at home ketamine use.

51. Is there anything that can be measured in my blood or in imaging studies that can predict whether esketamine (SPRAVATO) is helping with my depression?

Attempting to assess the effectiveness of any therapy is essential for any medical condition. For example, there are many biomarkers used in cancer to assess individual effectiveness or safety of chemotherapy. Unfortunately, I have not yet read about any association between biomarkers and clinical responses to ketamine or esketamine for unipolar TRD. While there is potential, there are no known blood or imaging studies today that are specific or sensitive for widespread use for clinical utility.

52. What can I expect at my first session?

You will be greeted by our friendly team and escorted to a private room with either a zero-gravity massage chair or a waterfront view. We also have beautiful waterfront balconies, but we request that you not use them unsupervised/unaccompanied for safety reasons. We will check your blood pressure and have you fill out rating scales. You will self-administer the nasal sprays while we monitor your use. We will

stay in the room at your request if you need additional emotional support. We also encourage you to create a playlist of relaxing music to listen to on your phone. This is your personal time to relax and focus on your inner healing wisdom. We invite any supportive friends/loved ones to be present with you. We will check your blood pressure at least three times during your 2-hour session and a provider will always be available for any concerns/side effects that may arise.

53. Will anyone touch me under the influence of private?

We respect your right to safety and take your physical space very seriously. While under the influence of esketamine, you should only be touched by a provider or staff if absolutely necessary for blood pressure measurements and/or for your safety in appropriate areas if you experienced an adverse reaction to the medication (ex: touching you on the shoulder to ground you if you experience a panic attack; helping to steady you/prevent a fall if you appear unsteady while getting up from the couch). Upon your request, we can assist you in the restroom and/or down the stairs at the office after the 2-hour monitoring. Your safety and security are our top priority.

53. What about after my session - how will I feel?

We require you to have a safe and arranged ride home and not to drive or operate heavy machinery until you have had a full night's rest after your treatment. Out of abundance of precaution, we recommend that you have childcare arranged if you are typically alone with young children. We also recommend avoiding alcohol and controlled/sedating medications the evening of your treatment. Most individuals feel normal/back to their baseline after treatment, but we recommend not working or making any commitments the evening of Sparano treatments. Occasionally, individuals may feel tired or flu like the day after their initial esketamine treatments.

54. Why do you place a pulse oximeter on my index finger during esketamine (SPRAVATO) treatment?

A pulse oximeter (or Pulse Ox) is a small electronic device which measures the percent oxygen saturation carried in your red blood cells. A normal resting level is between 95% and 100% at sea level. Routine use of this device is conducted on all our SPRAVTO patients to minimize any risk of respiratory depression, a very rare adverse event reported by the manufacturer in 96 cases. In thirty cases, the time from treatment until onset of breathing difficulties was not reported. Only eight patients had no clinical symptoms and/or an oxygen saturation above 93%. The remainder reported serious symptoms that required emergency medical service, oxygen, medication, stimulation, or CPR. Most cases were in patients using CNS depressants (e.g., opioids, alcohol) or had other conditions such as obesity, anxiety, cardiovascular, or respiratory conditions. No deaths have been reported.

55. Is a new antidepressant (Auvelity) thought to act similarly as esketamine (SPRAVATO)?

Antidepressants in clinical trials were mostly SSRI and SNRI medications. We cannot say whether any was more effective than another. In 2022, the FDA approved the combination drug dextromethorphan-bupropion (Auvelity) for major depression. Dextromethorphan is a common cough suppressant and, like private, reduces symptoms of depression quickly, within 1 to 2 weeks and reaches maximum effectiveness in 4 to 6 weeks. Unlike esketamine, this antidepressant can be taken at home without direct supervision.

56. Why do you routinely ask about sedation and dissociation before I leave the clinic?

We are routinely required to search for high BP and ask about sedation and dissociation, since each is an adverse event from the SPRAVATO. Fortunately, we have not encountered any of these events as serious. In contrast, some patients are disappointed without some mild feelings of dissociation. The medical

literature documents no evidence of a clinically significant positive or negative association between dissociation and antidepressant effect for esketamine.

57. If I have a substance use disorder, would I still be a candidate for esketamine (SPRAVATO) therapy?

Many of our patient, both men and women, have “tried drugs” in the past, and some use marijuana occasionally. Approximately one-fifth of our patients have or are currently seeking rehabilitation for a history of alcohol abuse. We are always watching for patients with long-term benzodiazepine use, and esketamine may facilitate the deprescription of those medications. We do not care for persons who are active substance users, although retrospective multicenter studies have shown that side effects from SPRVATO were time-dependent and not more frequent and may be effective with more patients and a longer follow-up period.

58. If I responded to esketamine (SPRAVATO) in the past and wished to take the medication again, what would I expect?

Most of our patients who respond to esketamine wish to remain on the medication to lengthen the time before remission. Some of our patients have been treated elsewhere and moved here. For those who wish to be restarted, the same protocol is given, and we anticipate that the success rate and dosing schedule to be similar with no new safety signals.

APPENDIX

Acronyms

Medicine is full of acronyms or abbreviations. This can lead to frustration in patients and more reluctance to ask questions. Here are several that are standard mentioned in this report and tossed around by providers.

AD	antidepressants
ADHD	attention deficit/hyperactivity disorder
BP	either blood pressure or bipolar disorder
ECT	electroconvulsive therapy
FDA	Food and Drug Administration
GAD	Generalized anxiety disorder; a survey we use to assess anxiety
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
OCPD	obsessive compulsive personality disorder
PHQ-9	personal health questionnaire to assess the severity of depression
PTSD	post-traumatic stress disorder
rTMS	repetitive transcranial magnetic stimulation
REMS	risk evaluation and mitigation strategy
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TMS	transcranial magnetic stimulation
TRD	treatment resistant depression

Types of Clinical Trials

Phase 1	Aim to find the best dose of a new drug with the fewest side effects usually 15 to 30 patients.
Phase 2	Test an experimental drug; often combine with phase 1; usually 2 years with often two groups (receive drug or placebo)
Phase 3	Confirm and expand on safety and effectiveness from phases 1 and 2 trials; often compare drug to standard therapies to compare risks and benefits; on the average 3 years.

Commonly Prescribed Antidepressants and Their Drug Class

mirtazapine (Remeron)	noradrenergic and specific serotonergic
escitalopram (Lexapro)	SSRI
venlafaxine (Effexor)	SNRI
sertraline (Zoloft)	SSRI
citalopram (Celexa)	SSRI
bupropion (Wellbutrin)	dopamine reuptake inhibitors
paroxetine (Paxil)	SSRI
milnacipran (Savella)	SNRI
fluoxetine (Prozac)	SSRI
duloxetine (Cymbalta)	SNRI
fluvoxamine (Luvox)	SSRI
reboxetine (Edronax)	norepinephrine reuptake inhibitor
lamotrigine (Lamictal)	
vilazodone (Viably)	
vortioxetine (Trintellix)	
aripiprazole (Abilify)	
brexpiprazole (Exult)	
dextromethorphan-bupropion (Auvelity)	
desvenlagaxine (Pristiq)	

Other Commonly Prescribed Psychoactive Medications

Anti-anxiety drugs
- benzodiazepines
  - lorazepam (Ativan)
  - alprazolam (Xanax)
  - clonazepam (Klonipin)
  - diazepam (Valium)
- non-benzodiazepine sedative hypnotics
  - clonidine (Catapres)
  - hydroxyzine (Vistaril)
  - buspirone (Buspar)

Psychostimulants
- dexamphetamine (Vyvanse)
- amphetamine and dextroamphetamine (Adderall)
- methylphenidate (Dayanara, Quillivant XR, Aptensio XR)
- dexmethylphenidate (Focalin)

Monoamine oxidase (MAO-B) inhibitors
- Selegiline (Emsam)

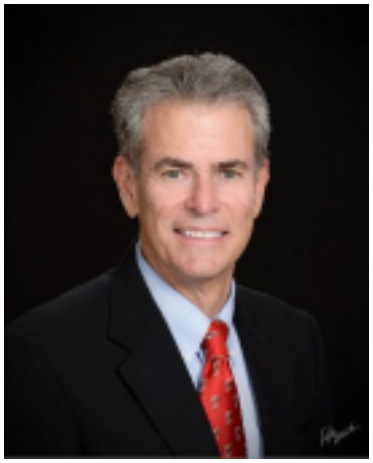
Sleep aids
- trazodone (Desyrel)
- temazepam (Restoril)
- doxepin (Silenor)
- zolpidem (Ambien)
- gabapentin (Neurontin)
- buspirone (Buspar)

Obsessive compulsive disorder
- clomipramine (Anafranil)
- fluvoxamine (Luvox)

Attention deficit/hyperactivity disorder
- amphetamine
- bupropion (Wellbutrin)
- clonidine (Catapres)
- guanfacine (Tenex)
- lisdexamfetamine (Vyvanse)
- methylphenidate (Floraline, Methylin)
- modafinil (Provigil)

Libido enhancer
- flibanserin (Addyl)

About The Author



William (Bill) Rayburn, MD, MBA joined Sweetgrass Psychiatry in February 2020 with experience in educating and monitoring patients undertaking esketamine (SPRAVATO) drug therapy. Dr. Rayburn is a former distinguished professor, associate dean, chair of obstetrics and gynecology, and chief of staff at the University of New Mexico in Albuquerque. With a faculty appointment at MUSC, he attends clinics for underserved women and was named a distinguished teacher. His background and interests in new drug development, care for patients with depression, patient education, and clinical research make him a valuable addition to the Sweetgrass practice. Studies in his former research laboratory dealt with long-term effects from exposure to antidepressants and antianxiety drugs on the fetal brain. Dr. Rayburn is the recipient of several awards for his teaching, research, and publications including twenty-five books and nearly 800 medical articles or research abstracts. Current and recent physician leadership positions have been in several national medical specialty, research, and education organizations.

"*Depression can be difficult to treat because it involves complex workings of the brain. What's effective for one person may not work for another."*

" My goals in serving our patients being treated with SPRAVATO are to fully educate, maximally administer, and closely monitor progress in a safe and supportive environment."