

The Prudent Prescriber

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Spravato (esketamine) Novel Approach to Treatment-Resistant Depression

The February 2019 Prudent Prescriber discussed the use of off-label IV ketamine for depression. In early March, 2019, Janssen brought Spravato (intra-nasal esketamine) to market for treatment-resistant major depression (TRD). This is an important addition to the antidepressant armamentarium. At the same time, Spravato comes with lots of baggage.

Cost: Each Spravato nasal spray device contains esketamine 28mg. The 56mg kit contains two devices (\$590). The 84mg kit contains three devices (\$885). Generic ketamine sells for \$4.62 per vial. Plus clinicians will charge a fee for the two hour observation associated with each dose of Spravato.

Indication: Spravato is indicated for treatment-resistant depression, along with a new oral antidepressant in patients aged 18 to <65 years. The studies that brought Spravato to market defined "treatment resistant" as an inadequate response to at least two different antidepressants, of adequate dose and duration during the current depressive episode. The esketamine study protocols adopted the definition of an adequate trial as used in the STAR*D trials: 10-12 weeks of an adequate dose. (Product information for Spravato. Janssen Pharmaceuticals, March 2019.)

There are no pediatric studies and data among patients over 65 years suggest that Spravato is not more effective than placebo.

Pharm Reps ≠ Rational Prescribing

(PR)



(RP)

Antibiotics do NOT

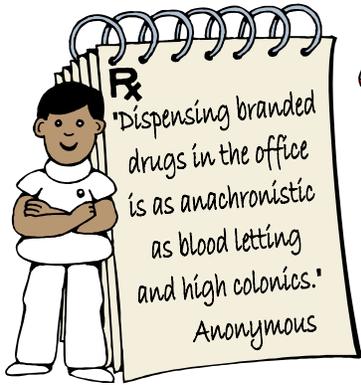


help acute bronchitis

β-blockers in post-MI save lives



Pill splitters save BIG

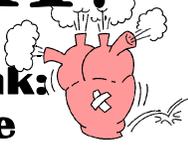


R
"Dispensing branded drugs in the office is as anachronistic as blood letting and high colonics."
Anonymous



CHE?

Think:
Ace
Aldactone
B-blocker
Dig
Diuretic



Avoid these expensive "me-too" drugs:

Intermezzo
Vimovo
Livalo
Gralise
Viibryd
Edarbi
Daliresp



Treat patients > 60 years to 150/90



NOW AVAILABLE ON THE GENERIC MARQUEE

Advair → fluticasone/salmeterol
or Wixela Inhub
Viagra → sildenafil
Uceris → budesonide ER
Suboxone → buprenorphine/naloxone

MOA: Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor and is thought to be 4 times more active than the R-enantiomer. The mechanism by which esketamine exerts its antidepressant effect is unknown.

In a study from Stanford, published in the August 29, 2018 American Journal of Psychiatry, one of the principal authors Alan Schatzberg is quoted, "Now I know the drug (ketamine) works, but it doesn't work like everyone thought it was working." Stanford scientists discovered that ketamine works as an antidepressant at least in part, by activating the brain's opioid system. Researchers found that ketamine reduced depressive symptoms by 90% for three days in more than half of twelve participants, but had virtually no effect on depressive symptoms when it was preceded by naltrexone (an opioid antagonist).

Dosing: Spravato must be prescribed with a new-to-the-patient oral antidepressant medication. Spravato is administered intranasally under the direct observation of a clinician. There are different dosing patterns for the induction phase and the maintenance phase.

- Induction phase, weeks 1 to 4: doses are given twice weekly. The day 1 dose is 56mg. Subsequent doses during induction phase are 56mg or 84mg. At the end of the induction phase, clinicians should assess efficacy and continue to the maintenance phase for those patients who have derived a benefit.
- Maintenance phase, weeks 5 to 8: 56mg or 84mg once weekly.
- Maintenance phase, week 9 and thereafter: 56mg or 84mg once weekly or once every other week.

Each device contains 28mg esketamine in two sprays. Two devices are used for the 56mg dose; three devices are used for 84mg dose.

The inhalation process:

- > Patient blows nose (only before use of the first device).
- > The patient should hold the device with their thumb on the plunger.
- > Recline head at 45° angle
- > Insert the tip of the device into the nostril with the nose rest touching the skin between nostrils.
- > Close the opposite nostril.
- > Inhale through the nose while depressing the plunger until it stops
- > Remove the device and sniff gently.
- > The patient should repeat the steps on the opposite side to deliver the second (and third, if 84mg) doses.
- > A five minute rest is required between use of each device. During this time the patient should rest, preferably semi-reclining.
- > The patient should NOT blow their nose.

Spravato is a C-III drug and can only be given in a clinic or hospital enrolled in the Risk Evaluation and Mitigation Strategy (REMS). Pharmacies must be certified in the REMS in order to dispense Spravato and patients must be enrolled in the REMS in order to receive treatment. Other requirements include that the patient must be observed for at least two hours after each administration, with blood pressure monitoring.

AE: In the clinical trials that brought Spravato to market:

- Sedation: 49%-61%.
- Loss of consciousness: 0.3%.
- Perceptual or dissociative changes: 61%-75%.
- Greater than 40 mmHg increase in systolic blood pressure and/or 25 mmHg increase in diastolic pressure: 8%-17%.
- Nausea: 28% compared to the 5% in the placebo group.
- Vertigo or dizziness 23%-29% vs 3%-8% in the placebo group.

Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with Spravato nasal spray, there was a higher rate of lower urinary tract symptoms (dysuria, micturition urgency, nocturia, and cystitis) in Spravato-treated patients than in placebo-treated patients.

Drug Interactions:

Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation.

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil) may increase blood pressure.

Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure.

CI: Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation

- History of intracerebral hemorrhage
- Hypersensitivity to esketamine or ketamine.

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

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration.
- 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.
- 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.

Select Clinical Studies: Spravato's effectiveness was evaluated in three short-term clinical trials, as well as one longer trial. One of the short-term studies (Study 1), four weeks long, found that the combination of Spravato and an oral antidepressant demonstrated a "statistically significant effect" compared to a placebo, sometimes within two days. **The other two short-term trials did not meet pre-determined statistical tests for effectiveness.**

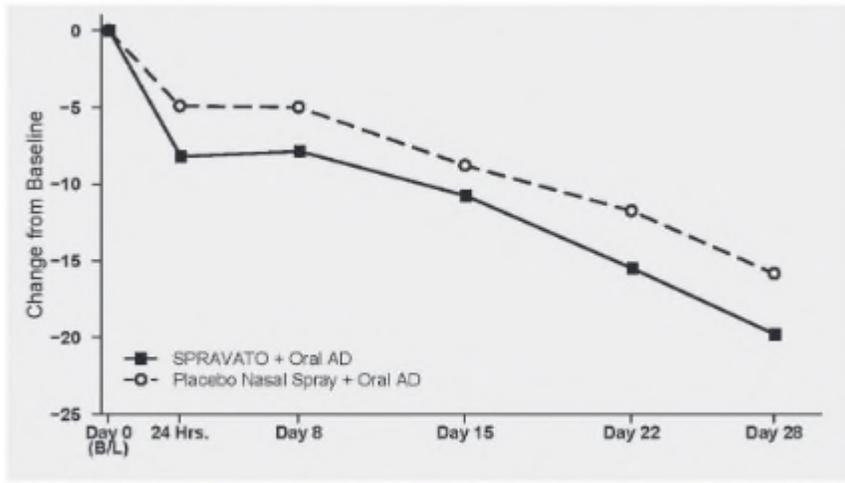
Study 1: Spravato was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), Phase 3 study (Study 1; NCT02418585) in adult patients 18 to <65 years old with treatment-resistant depression. Patients in Study 1 met DSM-5 criteria for major depressive disorder (MDD) and in the current depressive episode had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients in Study 1 were randomized to receive twice weekly doses of intranasal Spravato (flexible dose; 56mg or 84mg) or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (AD) (duloxetine, escitalopram, sertraline, or extended-release venlafaxine) as determined by the investigator based on the patient's prior treatment history). Spravato could be titrated up to 84mg starting with the second dose based on investigator discretion.

The demographic and baseline disease characteristics of patients in Study 1 were similar for the Spravato and placebo nasal spray groups. Patients had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. The newly initiated oral AD was an SSRI in 32% of patients and an SNRI in 68% of patients.

In Study 1, the primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression.

Results of Study 1: Spravato plus a newly initiated oral AD demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral AD. With a mean baseline score of 37, patients' scores in the treatment group decreased by 19.8 points from baseline to week 4, while patients in the placebo group experienced a mean decrease of 15.8 points. Due to esketamine's side effect profile, blinding may have been a problem.

Figure 4: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1* (Full Analysis Set) – MMRM Analysis



* Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

Study 2: Study 2 (NCT02493868) was a long-term randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to Spravato. *Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly- dosed Spravato (56mg or 84mg twice weekly) plus daily oral AD in an initial 4-week phase.*

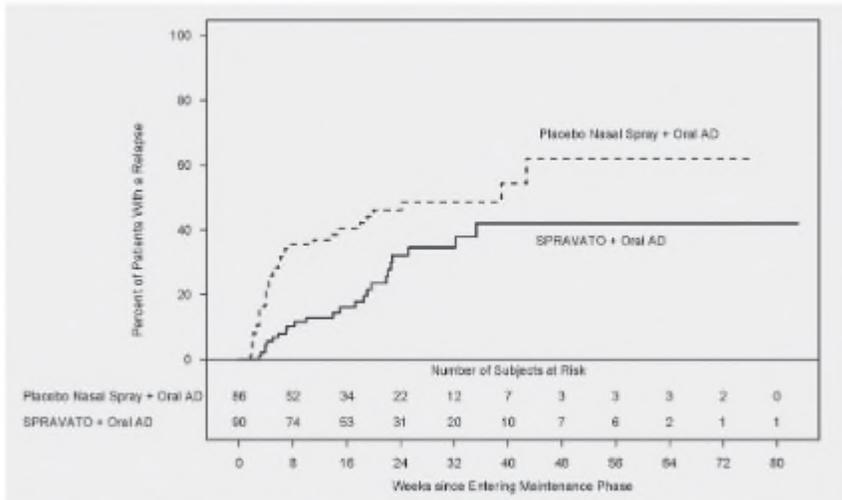
Stable remission was defined as a MADRS total score ≤ 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction $\geq 50\%$ for at least 3 of the last 4 weeks and not in remission. After at least 16 initial weeks of treatment with SPRAVATO and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with SPRAVATO or switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥ 22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

The demographic and baseline disease characteristics of the two groups were similar. Patients had a median age of 48 years (range 19 to 64 years) and were 66% female, 90% Caucasian, and 4% Black. In Study 2, based on depressive symptomatology, the majority of stable remitters (69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remitters received weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to Spravato, 39% received the 56mg dose and 61% received the 84mg dose.

Results of Study 2: Patients in stable remission who continued treatment with Spravato plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD. Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time to relapse of depressive symptoms than patients on placebo nasal spray plus oral AD.

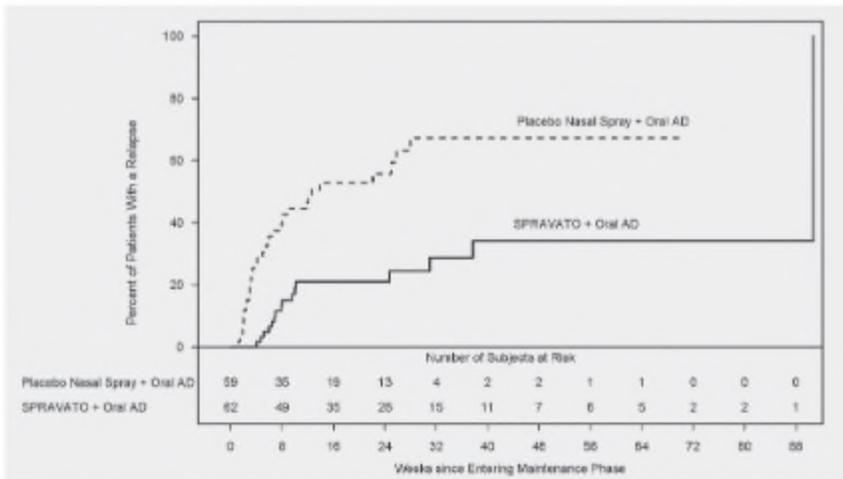
The Number Needed to Treat is 3 or 5 using Spravato and an oral antidepressant to prevent one additional relapse compared with placebo inhaler and oral antidepressant.

Figure 5: Time to Relapse in Patients with TRD in Stable Remission in Study 2* (Full Analysis Set)



* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on weighted estimates was 0.49 (95% CI: 0.29, 0.84). However, the hazard ratio did not appear constant throughout the trial.

Figure 6: Time to Relapse in Patients in Stable Response in TRD Patients in Study 2* (Full Analysis Set)



* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55).

My Take:

Pros:

- First, really novel antidepressant since Prozac.
- Rapid onset of effect
- In the long term study, where enrolled patients had already been shown to be responders, the low NNTs to prevent one relapse look favorable.

Cons:

- Efficacy is modest. A net 4 point improvement over placebo on the 60 point MADRS scale underwhelms me. Yet studies do show that a minimally clinically important difference in the MADRS score is 1.6 – 1.9. This is NOT a wonder drug!
- Cost: Annual medication costs alone would be over \$51,000 for medicine if weekly treatments throughout the year and \$31,000, if able to go to every other week treatments after the first 8 weeks.
- REMS and frequent dosing plan involving a two hour observation will be a depressing ordeal for many patients.
- Side effect profile: Lots of unknowns here. Much of the side effect data we have are very piecemeal experiences with IV ketamine used as an anesthetic in very different doses, as well as IV ketamine as a recreational drug and the small studies that brought Spravato to market.
- The available efficacy data for Spravato are short-term. What does it mean to treat a chronic illness with such an expensive, user-unfriendly drug?
- Treatment-resistant depression was an illness that I always asked for help with. What does it mean to have anesthesiologists and pain management physicians dispensing this drug? Effective use of Spravato will require excellent communication among dispensing clinics, primary care physicians and psychiatrists.
- I believe a psychiatrically trained clinician should be involved in the care of patients receiving Spravato.

You may access previous issues at <https://www.rmhp.org/i-am-a-provider/provider-resources/publications-for-providers>.

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