Dear Patients and Clients,

The following is from the front page of the New York Times health section, February 12, 2019.

**F.D.A. Panel Recommends New Depression Treatment**

The active ingredients of ketamine, a popular club drug, show promise in battling deep despair.

The new drug is a nasal spray that delivers the active ingredients of ketamine, widely used as an anesthetic. Credit Teresa Crawford/Associated Press

- By Benedict Carey
  - Feb. 12, 2019

In a move that may clear the way for the first new treatment in years for depression, an expert panel recommended on Tuesday (February 11, 2019) that federal regulators approve a nasal spray that delivers the active ingredients of ketamine, a popular club drug in the 1980s and 1990s.

The new drug, called Esketamine and developed by Johnson & Johnson, is aimed at people with severe depression, particularly those with suicidal thinking. The panel, with 17 voting members, including psychiatrists and consumer representatives, was nearly unanimous in deciding that the drug’s benefits outweighed its risks. The Food and Drug Administration typically follows the recommendations of its expert panels.

In recent years, scores of clinics have opened around the country, offering to administer intravenous ketamine for depression, on a schedule similar to that of electroshock therapy: as a series of treatments, over a
period of days or weeks, and sometimes including follow-up or "booster" visits months later. These treatments, at an average cost of $3,000, are officially "off-label," and usually are not covered by insurance. Their effectiveness is not well studied, although people who have received the course of treatment have reported rapid, if not always lasting, relief.

If approved, Esketamine would be covered by most insurers.

The interest in ketamine as a potential treatment dates back to 2006, when researchers at the National Institute of Mental Health, led by Dr. Carlos A. Zarate, reported that 18 people who received the drugs intravenously reported that their despair lifted within hours. The drugs currently on the market for depression typically take two weeks or more to provide any noticeable relief, if they do so at all.

The discovery of ketamine’s effects on depression was serendipitous; the underlying biology of the disorder remains unknown. Some researchers have since turned away from investigating serotonin — the brain transmitter on which most popular antidepressants work — to instead study the effect of ketamine on brain chemistry, to see if the drug provides any clues to the biology of depression.

The federal agency has until March 4 to decide whether to approve the drug.

Brook Johnson, 38, a piano teacher in Westminster, Md., has been waiting on approval for months. Ms. Johnson, who is married and has a 9-year-old daughter, doesn’t know if Esketamine will help her, but said that existing antidepressants have failed. She said she had been in and out of psychiatric hospitals six times and has attempted suicide twice.

"It was back and forth, and then I’d relapse and they’d put me back in," Ms. Johnson said in an interview last month. “None of the medicines ever seemed to work. At best, they would either numb me out completely, and you just feel nothing and you can’t think.”

--Benedict Carey, NYT

Dr. Satinover: “Here is some additional background to our longstanding use of Ketamine here at the Sterling Institute.

“Ketamine was developed in the 1940’s as a rapid-on, rapid-off field-hospital anaesthetic for combat injuries. Medics treating soldiers on active battlefields discovered that it could be administered in the mud, so to speak, as a nasal spray, where IV insertion was impractical and too slow. This improvisation was only rediscovered decades later. It works because nasal absorption of ketamine is a very high 50%.

“Generic ketamine vials for injection are available in standard pharmacies but as yet inconsistently, and from specialized pharmacies in customizable form, including as a nasal spray in any concentration. (This is how we order it.) It could be helpful for you to understand the following details about ketamine when Janssen Esketamine hits the market. (Janssen is the pharmaceutical branch of Johnson & Johnson.)

“Generic ketamine is a ‘racemic mixture’—50:50—of right-handed ketamine [a.k.a. R-ketamine or "Arketamine"] and of left-handed ketamine, [S-ketamine or "Esketamine"]. The presumptive anti-depressant effect of ketamine is blockade of the NMDA-type glutamate receptor. Glutamate is another neurotransmitter chemical
alongside the more familiar serotonin, norepinephrine and dopamine, but more foundational to brain regulation mechanisms than these.

"Esketamine and Arketamine are very similar in their effects and side effects, with small, counter-balancing advantages and disadvantages. For example, Esketamine is 3.5 times more potent as an NMDA antagonist than Arketamine. Greater potency implies lower doses for the same effect (or side effects). But this does not mean that Esketamine is 3.5 times stronger than ketamine because ketamine is itself $\frac{1}{2}$ Esketamine. Esketamine is therefore only 1.6 times more potent. This difference has no practical effect. A spray of 75 mg/ml ketamine (7.5 mg per spray) is as potent as a spray of 50 mg/ml Esketamine (5.0 mg/spray). Concentrations of up to 200 mg/ml of ketamine are available and well-tolerated (20.0 mg/spray). Indeed the counter-balance of benefits and side effects makes a racemic mixture possibly superior to either individual molecule. (Times' article above, referring to "the active ingredients" of ketamine, is poorly worded).

"It is generally much easier to synthesize mixture of left- and right-handed molecules than to synthesize just one form or to purify a racemic mixture. That's why ketamine has been around for over fifty years. Jansen has patented a more sophisticated method that yields pure Esketamine. This means that when its spray is approved on March 4th, it will be marketed as a branded medication, not a generic.

"Its patent will permit Esketamine spray to be sold at a high retail price. At some later point it obtain partial coverage by Medicare (probably with a step program for approval), then by commercial insurers and Medicaid. The usual discount cards, prior authorizations, and assistance programs will bring its cost to within reach for many people, but not all. Because both ketamine and Esketamine are controlled medications, the FDA will not permit samples.

"Sterling has engaged a specialty pharmacy in Massachusetts that has long been producing customized intranasal ketamine for our patients. It is not covered by
insurance so the retail cost to our patients averages about $100 monthly. For those for whom this is too steep a burden, we prescribe ketamine in glass vials from local pharmacies and instruct patients in how to transfer the fluid to plastic nasal sprayers inexpensively available locally or from Amazon.com. Two to four vials provide a month’s supply of ketamine and with discount coupons cost it might be possible to bring the cost down to between $15 and $30 per vial, or $30 to $60 per month. Dissolvable lozenges are also available although the absorption in this form is less consistent.

"In research studies, ketamine has shown significant positive effects not only for the treatment of depression, but for the treatment of anxiety, OCD and PTSD.

"Once Jansen Esketamine becomes available, we will prescribe from whichever source and in whatever form you prefer, at the lowest cost.""

*Sterling and its physicians are not involved in any way in the production, preparation or marketing of ketamine and as with any medication we prescribe, garner no financial benefit from, nor are in any way financial intermediaries with, the pharmacies that provide medications for our patients. Other than samples of non-controlled medications, we do not store medications on site nor dispense any. When ketamine is administered on site under supervision, it is pre-purchased by our patients, shipped directly to them by the dispensing pharmacy, and brought here by them. Our role is strictly limited to prescribing and directing the optimal use of medications, including ketamine.