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Esketamine

A Drug to Treat Resistant Depression That Brings More Questions Than Answers

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A novel and rapidly-acting antidepressant, esketamine, was approved by the Food and Drug Administration (FDA) in 2018 for "the treatment of depression in adults who have tried other antidepressant medicines but have not benefited from them (treatment-resistant depression)". The letter of approval goes on to explain that "Patients with major depressive disorder who, despite trying at least two antidepressant treatments given at adequate doses for an adequate duration in the current episode, have not responded to treatment are considered to have treatment-resistant depression." Vagaries in this approval letter, confusion around how to establish a new office-based procedure, and concerns over long term risks versus benefits have stalled implementation of this new treatment.

In August 2020, esketamine was FDA approved "to Treat Depressive Symptoms in Adults with Major Depressive Disorder with Acute Suicidal Ideation or Behavior". How does this treatment fit into the broader repertoire in treating resistant depression and suicidal ideation or behavior, with both concepts ill-defined?

What is treatment-resistant depression?

Currently, there is no consensus on what constitutes treatment resistant depression, with definitions varying from that of Fava in 1996 (1); *"those who fail to respond to standard doses (i.e., significantly superior to placebo in double-blind studies) of antidepressants administered continuously for at least 6 weeks"*, to a technology assessment from the Agency for Healthcare Research and Quality(2); "*the most commonly used definition is a continuing depressive episode following at least two prior antidepressants treatments of at least 4 or 6 weeks of an adequate dose"*. It was noted in that assessment that only 17% of clinical trials ensured that the study population failed antidepressant treatment of adequate number, dose, and duration to meet the common definition of TRD. The number of trials needed to declare treatment resistance is clearly debatable, with "..at least two adequate trials of medications from different classes in the current episode" needed (3). It is also important to note that sustained remission, not simply a response, is the strongly and preferred goal of treatment (3).

As noted by Dyck (4), TRD "is not a diagnosis. It does not describe a depressed person or a syndrome. Rather, TRD describes the expectations or assumptions of a given clinician about a person's response to treatment" (p 34). Some (3), considering all vagaries involved, use the term difficult-to-treat-depression rather than TRD. There are 155 different definitions for TRD in the published literature(5) and exponentially more in unpublished discourse. Perhaps the most relevant definition of TRD comes from the sponsor of the TRANSFORM-1 trial, which defined this cohort of patients: 1)nonresponse to ketamine/esketamine, 2) nonresponse to "All of the oral antidepressant treatment options available in the respective country:, and 3) at least 7 ECT treatments(6). Unfortunately, these were the exclusion criteria, so we don't yet know whether esketamine is safe or effective for this category of TRD.

Acute Suicidal Ideation or Behavior

Settling on a definition of Acute Suicidal Ideation or Behavior may be even more fraught. The DSM-5 (2013) states that *"thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death."* constitute suicidal ideation. The definition of suicidal behavior may simply follow on as being, "Acts of self-harm, with deliberate consideration or planning of possible techniques of causing one's own death". However, a seminal review by Nock (7) titled *Self-Injury*, elucidates, *"It is important to distinguish between directly self-injurious behaviors (e.g., self-injury, suicide) and indirectly harmful behaviors (e.g., alcohol and substance use); however, these different forms of self-harm commonly co-occur, and it may be useful to consider them on a continuum of self-harm behaviors."*

Nock goes on to describe six such forms of thoughts and behaviors associated with suicide and self-injury(7). If the Acute Suicidal Ideation or Behavior that esketamine addresses includes all described forms, one could argue that the effect of esketamine is one of *general distress relief*. In the ASPIRE-1 trial (8) examining the effects of esketamine in major depressive disorder with active suicidal ideation, subjects with DSM-5 (2013) diagnosed borderline personality disorder OR "exhibiting recurrent suicidal gestures, threats, or self-mutilating behaviors" were excluded(8). Subjects with a lifetime history of hallucinogen use disorder, including ketamine, Lysergic acid diethylamide (LSD), 3,4-methylenedioximethamphetamine (MDMA), and phencyclidine (PCP) were excluded, however, "moderate or severe substance or alcohol use disorder" in remission for 6 months or more were permitted. Esketamine was statistically superior to placebo only within four to eight hours after a dose (from supplementary trial data), and subgroup analyses showed that relatively larger improvements in the population of white men from North America were responsible for the overall group effect. Esketamine's indication is for "treatment of depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior" however, the small print on the label states "the effectiveness of SPRAVATO [esketamine] in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated".

Nock makes an important distinction of substance use as a form of harmful behavior (7). This sets up a possible ethical

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conflict with the physician prescribing rapidly acting anti-distress medications in the cases where frequent re-treatment is necessary and long-term use carries risk. Persistent physical effects of esketamine 84mg used twice per week for 8 weeks are likely not to exist, but the effects of chronic retreatment at this dose for variable periods of time are not known. The effects, and risks, of ketamine enantiomers differ in preclinical models(9), where repeated administration of s-ketamine leads to neuron loss, and clinical reports (10), where open-label r-ketamine infusions produced the desired antidepressant effect without psychotomimetic side effects. In addition, we commonly fail to account for non-physical risks of medication, like the hopelessness that can be induced when a patient realizes the medicine is not working, or worse, when it has worked well but suddenly "worn off" and doesn't work again. Repeated-dose ketamine has not outperformed placebo in every study, for example, in patients with chronic TRD and suicidal ideation(11). How are distinctions between type and severity of suicidal ideation or TRD made in thousands of different private offices?

Outpatient Providers: local example

A search on the Janssen Neuroscience (company of Johnson & Johnson) website in September 2020 reveals over 30 providers, nearly all outpatient centers, within 100 miles of our office in Detroit, Michigan, that are registered and "now treating" patients with esketamine. None of these centers are affiliated with a university and only one is affiliated with a large health system. Some are directed by non-psychiatrist specialists (e.g., emergency medicine, anesthesiology). What are the conditions patients are being treated under, and what form of continuity care is occurring in these contexts? These are unstandardized; dictated loosely and entirely by the Risk Evaluation and Mitigation Strategy (REMS) developed by Janssen Neuroscience as required by the FDA. There is implementation in "good-faith" but inconsistencies are likely to arise. The strict guidance that esketamine is to be delivered in a REMS "certified treatment center" with 2 hours of monitoring in the facility seems contrary to the permissive indication. What evidence is there regarding how to manage a patient receiving esketamine in the medium term and long term?

The following clinical vignettes illustrate the complexity of esketamine use in clinical practice in the two FDA approved indications of this drug.

Clinical vignettes

A. A middle-aged patient with acute major depressive disorder, and opioid use disorder in remission is treated in the emergency department with esketamine intranasal 56mg and reports immediate relief of plan to kill themselves by driving into oncoming traffic. He is discharged due to no longer meeting criteria for admission to inpatient psychiatry. Two days later he re-presents with original suicidal ideation.
B. A young patient with intrusive suicidal thoughts of stabbing themselves in the chest, a history of treatment resistant major depressive disorder, and posttraumatic stress disorder, is treated in the outpatient setting with esketamine intranasal 56mg and reports immediate relief of depression and intrusive thoughts that recur 24 hours later. Biweekly treatment with esketamine 84mg through 4 weeks produces relief of depression for another 8 weeks before recurring.

It is difficult to weigh the long-term risks against benefits of esketamine treatment in these preceding cases because these risks are largely unknown. In case A, there is a history of opioid use disorder and the general effect of ketamine (and presumably esketamine) is suggested to be mediated in part by opioid reward pathways (12). Obviously, patients should be screened out for active drug use, but does a history of opioid use negatively affect long term chances of remission with esketamine?

In case B, it seems like esketamine produced a reasonable response of 8 weeks. If this pattern persists, is it acceptable to be receiving biweekly esketamine treatment for one-third of every year, or acceptable to taper but treat once weekly, bimonthly, or monthly for an undetermined period of time? This is a wholly appropriate and commonly used maintenance treatment pattern used in patients that respond to ECT. The SUSTAIN-2 (13) open label trial examined long-term esketamine in >300 patients over 6 months and >100 patients over 12 months. "Responders" to esketamine twice weekly were continued with weekly or every-other-week esketamine, depending on symptom recurrence, for the duration of the trial. The authors (13) made no recommendations of how to proceed after the 12-month study period, nor did they report what they planned to do with their cohort. The Janssen Neuroscience website only offers information on drug indications, interactions, and side effects.

In cases A and B we have the issue of what to do after a treatment failure. In the ASPIRE-1 trial, patients were included only if they agreed to voluntarily undergo psychiatric hospitalization for 5 or more days (8). Surely, this part of the treatment as usual was responsible for the bulk of the placebo effect. Psychiatric hospitalization is not an ubiquitous or fast option from emergency departments or outpatient clinics across the country (in this case, the United States), and esketamine does not work 100% of the time, so is it by definition inappropriate to treat with esketamine unless the option of hospitalization is assured?

Conclusion

We could have asked whether we were prepared to experiment with esketamine in the messy, uncontrolled real world that abounds with legal and illegal drugs, external stress, and unstable relationships at the time of its introduction, considering esketamine's properties and possible risks. We may not be. It is not clear whether the requirements of REMS and personnel are enough to assure not only safety, but also proper selection of patients, correct indications (which are quite vague) and long-term use. Whose responsibility it is, whether of the esketamine maker, FDA, or the field, is not clear. Maybe of all. But one thing is sure: We have let the genie out of the bottle. The question is whether he brings us problems and disease or good luck and abundance.

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