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The future of (Es)Ketamine for use in treatment-resistant depression

by

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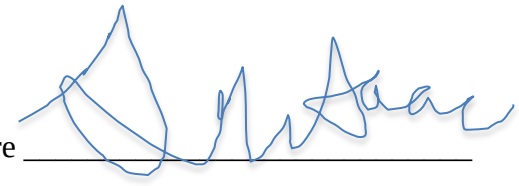
Signature 

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Abstract

E is a 64-year-old white female who has many physical and cognitive comorbidities in addition to her mental health issues. She has struggled most recently (2 years ago) with a diagnosis of vascular dementia following a suspected stroke. She is mostly wheelchair bound for her declining health. E lives alone in an apartment and states she is in constant pain. She was the victim of sexual abuse as a child and has attempted trauma therapy multiple times without successful completion. In addition to her physical impairments she has previously received psychiatric diagnoses of MDD, and PTSD. She states that "nothing" works for her depression and expresses frustration with the "try and see" approach of psychopharmacology. She inquires about the use of ketamine to address her treatment resistant depression as a new, privately owned ketamine clinic has opened in the area.

An overview of the literature supports the use of both IV ketamine and new intranasal esketamine for treatment resistant depression. The plan of care developed for patient E described in the case study below reflects the literature's recommendations and an outside provider's consultation on how to best address treatment resistant depression with esketamine and ketamine.

It would be in the best interest of insurance companies and providers to fully embrace the potential that ketamine and esketamine hold for our patients with treatment resistant depression. The rapid amelioration of symptoms seen with ketamine/esketamine treatments could save our patients (and insurers) large amounts of time, money, and suffering by avoiding a lengthy inpatient stabilization stay. Change can be difficult and takes time, more research is needed to help advance the knowledge and trust in the efficacy of these alternative treatments until they are

no longer considered ‘alternative’ but accepted and reliable treatments for patients who are desperate for an answer.

Background

Treatment-resistant depression (TRD) has no largely and uniformly accepted definition (Wiles, et al., 2014). This makes research surrounding it incredibly difficult to compare and align in larger meta-analyses. In fact, the Centers for Medicare and Medicaid Services, in conjunction with the AHRQ studied the usage of the term TRD and found that it can most commonly be defined as “failure of treatment to produce response or remission for patients after two or more treatment attempts of adequate dose and duration,” but that only 17% of treatment studies on the subject exactly match that definition. Due to this huge gap in commonality they recommended researchers “standardize the number of prior treatment failures and specify the adequacy of both dose and duration” (Gaynes et al., 2018, p. 3). Regardless of definition, it is roughly estimated that overall prevalence of TRD is as follows: more than half of patients do not achieve remission after first-line antidepressant treatment, and one third of patients do not achieve remission even after four courses of treatment (Rush et al., 2006). It is this final third that is considered to be treatment resistant. Once standard first-line treatments fail providers must consider non-standard, more risky, or traditionally less effective medications as the next step in treatment. One of these newer, lesser utilized next steps in the treatment of TRD is IV administered ketamine, and increasingly so, esketamine its intranasally administered counterpart.

Ketamine was first introduced into medical practice in the 1960s in the anesthesia arena (Li & Vlisides, 2016). In 1970 ketamine was approved by the FDA for its use in anesthesia. However, it was not until March 9th, 2019 that the intranasal (IN) version esketamine became FDA approved for the treatment of TRD in conjunction with a traditional oral antidepressant,

whereas IV ketamine itself *still* has not been approved by the FDA and its use remains off-label (Miller, 2019).

Case Report

"E" presented to a routine three month follow-up appointment on her own via a med cab due to her wheelchair transport needs. The wheelchair has been necessary for many years now due to cerebral palsy that affects mainly her ankle joints, but most recently her wrists which were supported bilaterally with braces. She stated that her medical condition causes her chronic pain, for which she is currently prescribed gabapentin. E was also struggling emotionally with her recent diagnosis of vascular dementia stemming more than likely from a stroke. E displays limited insight into her conditions and diagnoses, and tends to blame others for her shortcomings and misunderstandings. She frequently "staff-splits" in that she was talking about how terrible she thought her numerous previous psychiatric providers and neurologists were while praising her current provider, clearly displaying some Borderline personality traits. This does beg the differential diagnosis of Borderline personality disorder vs MDD. Borderline personality disorder is a strong contender as a differential diagnosis, not just because it is a usual consideration to make when viewing treatment resistant depression, but as therapy and skill work are really the best approach to treatment in that population and E has traditionally done poorly in therapy- she shows resistance to even the idea of it. She was open to having a student in the room present during her appointment with her provider. She had a diagnostic history of MDD, and PTSD related to childhood sexual abuse.

During this appointment, E endorsed "8 to 10 out of 10" depression with passive SI thoughts. She denied any self-harm or suicidal thoughts, but stated that she often wished that she would not wake up. She has never admitted to any previous suicide attempts. She denied all

other mental health issues. When asked if she was currently seeing a therapist, as suggested at the last appointment, she stated that she had not spent any time trying to find one as she has tried multiple times in the past to work through issues (including her childhood sexual abuse) without success. She has never been able to follow therapy through to the end.

Her medications currently include: Lamictal 150 mg, Buspar 10 mg TID, Fetzima 120 mg, and the newest TRD medication trail of Vilazodone 20 mg. In E's lifetime she has been on virtually all the antidepressants without any relief, including ECT treatments in the past, and at this appointment it was decided to discontinue the Vilazodone and start Brexpiprazole titrating up to 1 mg, and possibly up to 2 mg if there is still no benefit. At the end of the appointment E brought up the idea of a ketamine trial for her treatment resistant depression. She stated that she had recently seen advertisements on the television and in the newspaper endorsing a newly opened ketamine clinic run by two CRNAs. The private practice was attempting to bridge the gap left when one of the local "hub" hospitals had their ketamine/ECT provider retire without a replacement. The provider later placed a call to the local clinic to inquire about their services, costs, and process. He was told by the providers at the ketamine clinic that it would cost around $400 per session for E. When the provider informed E of the conversation she stated that as she is on SSI she would not be able to afford the treatments, but was thankful to the provider for checking for her.

Treatment goals for E ultimately include the hope that she is able to verbalize at least moderate relief from her depressive symptoms, including her passive SI sentiments. Functional goals for E would include leaving her apartment more frequently with her PCA for outings and engaging more socially.

Literature Review

What is frustrating from a provider's standpoint is that a meta-analysis of RCTs found that even single doses of IV ketamine has been shown to be rapidly efficacious as a medication for TRD, and yet is not recognized with FDA approval (McGirr et al., 2015). While it has questionable efficacy as a long-term treatment, more research needs to be done with this drug to assess this (McGirr et al., 2015). In speaking with Patrick Bailey, CRNA, part owner of Ketamine North Infusion Clinic in Duluth, he echoes this sentiment stating, "No big drug companies are out there pushing for ketamine trials and for FDA approval because they wouldn't make any money off of it. Even though we know they probably won't get anything out of it, we encourage our patients to submit their claims with insurance to show that this is a worthwhile treatment for depression," (P.Bailey, personal communication, December 3rd, 2019).

Bailey may have a considerable point, of the 32 registered clinical trials recently completed on the ClinicalTrials.gov website regarding the esketamine version, 29 of them were funded by Janssen Pharmaceuticals, the company who makes the Spravato™ IN esketamine (Bahr, Lopez, & Rey, 2019). However, if their data is to be believed, they may be onto something. One RCT with 67 participants diagnosed with MDD/TRD, showed that IN esketamine decreased the Montgomery-Åsberg Depression Rating Scale (MADRS) total score of participants and that this decrease in depressive symptoms was both dose dependent and sustainable through longer periods of treatment of up to 2 months with lower dose maintenance treatments (Daly et al., 2018). Bahr, Lopez, and Rey's (2019) RCT meta-analysis of IN esketamine also revealed strong results and conclusions, as well as suggestions for additional research opportunities, including more head-to-head studies and long-term research.

While IV delivered ketamine has virtually 100% bioavailability, IN esketamine bioavailability remains much lower at an average of 45-50% (Zanos et al., 2018). While this does put esketamine at a disadvantage in some aspects, it would still be the preferred route for many based on this route being considered less invasive (no needle pokes), it's even more rapid systemic absorption, and esketamine not being subjected to first-pass hepatic metabolism (Zanos et al., 2018). Another perceived benefit to the IN route is that it can be self-administered on a weekly, or bi-weekly basis under medical supervision (Köhler-Forsberg, Cusin, & Nierenberg, 2019). However, similarly to IV ketamine which also requires routine monitoring, due to the risk of transient blood pressure anomalies (8.2-13.9%) and the risk of dissociation (12.5-25.6%) vitals and mental status must be monitored for 2 hours after IN administration and the patient cannot drive until the next day (Wilkinson, Howard, & Busch, 2019).

While IN esketamine (Spravato™) now basks in the light of FDA approval, several barriers to use still exist. To start with, many providers and institutions have yet to start offering up treatment centers for vitals/mental status monitoring during treatment. A zip code search for a treatment center/participating provider on the Spravato™ website for the Duluth area code 55812 yielded a closest result of 141 miles away in Minneapolis. When asked if there were plans to incorporate IN esketamine into their Ketamine North practice, Patrick Bailey, CRNA stated they were hoping to avoid doing so. He said that, anecdotally, he has patients who have now tried both the IN esketamine and the IV ketamine and have told him that the ketamine was much more effective for the management of their TRD. He also stated that he is hoping that with the FDA approval of IN esketamine that FDA approval for IV ketamine will be coming soon as well (P.Bailey, personal communication, December 3rd, 2019). Something else that may still prove to be a barrier to any form of ketamine/esketamine treatments is the cost. The average cost per

treatment for IV ketamine (which is not routinely covered by insurance) is $500-1000 per treatment at an average of 6 initial treatments over 2 weeks with a monthly maintenance treatment thereafter (Bahr, Lopez, & Rey, 2019). This may seem entirely reasonable to patients without insurance in comparison to the cost of IN esketamine which again carries a high cost of initial dosing with a lower cost of maintenance dosing; estimated costs are $5,664 to $8,142 in the first month, $2,832 to $4,248 in the second month, and up to $1,416 to $4,248 each month thereafter, weekly or biweekly dose dependent (Bahr, Lopez, & Rey, 2019).

Implications

From the data that we have, there is a clear benefit to the utilization of ketamine and esketamine for use in treatment resistant depression. In order to ketamine/esketamine to reach its fullest potential many things need to happen and align. The first recommendation would be for research to not only continue, but to broaden the studies and increase their numbers so that the body of evidence in support of ketamine/esketamine becomes overwhelming and harder to deny. In particular, head-to-head studies comparing/contrasting ketamine/esketamine to not just to each other and other non-traditional treatments, but to our classic first-line pharmacologic treatments is needed. Secondly, there is a large educational gap in providers as to when/where/how to refer a patient to ketamine services as they do require additional support services to administer. Thirdly, it must be fully embraced and covered by insurance companies and Medicaid/Medicare as a treatment that is vital to the health of their patients.

Conclusion

E has suffered the majority of her life with treatment resistant depression, as she is now getting older it would be nice to finally have an answer for her. The research clearly shows that ketamine and esketamine have the potential ability to make a difference in E's life. It is unfortunate that because of her life-long struggle with depression and her inability to work that she is of a lower social-economic status and unable to afford the higher cost of the out-of-pocket ketamine treatments. Continued advocacy from providers and patients alike for further research is necessary to ensure that the full potential of ketamine is realized, mainstreamed, and ultimately recognized and covered by insurance companies. What has been tantalizingly out of reach for many of our patients for so long needs to become as accessible as the rest of our treatment options.

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