

Off-Label Use of Esketamine

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Abstract: Major depressive disorder (MDD) is a significant psychiatric condition, with many affected individuals not gaining remission from conventional treatments, leading to classification as treatment-resistant depression (TRD). This study aimed to investigate the potential of intravenous (IV) ketamine, particularly the S-enantiomer esketamine in nasal spray form, for treating patients with TRD and associated comorbidities. We report three cases of patients with diverse psychiatric and medical backgrounds whom all reported significant symptomatic relief from depressive episodes and suicidal ideation (SI) following esketamine administration. Additionally, esketamine seemed to proffer benefits beyond the primary depressive symptoms, positively impacting other comorbid conditions, such as agitation, self-injurious behavior (SIB), and chronic pain. The goal of this paper is to highlight that while esketamine's primary utility is in addressing TRD, its therapeutic potential may extend to a variety of associated conditions. However, it is crucial to underscore the heterogeneity of MDD, emphasizing the necessity for individualized therapeutic approaches and further research into esketamine's broader applications.

Keywords: Treatment-Resistant Depression (TRD), Esketamine, Comorbidities

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1. Introduction

Major depressive disorder (MDD) has long been a prominent and debilitating psychiatric condition that impacts countless people of all demographics. MDD has a wide variety of symptoms, but typically presents with persistent sadness, loss of interest and enjoyment in daily life activities (known as anhedonia), sleep and eating abnormalities, and most generally an overall reduction in quality of life. Conventional first line treatments such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are frequently used to improve patients' quality of life. However, approximately 30% of patients fail to be remitted despite proper usage of these pharmaceuticals [1, 2]. Other options for augmentation may include adding another medication, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS); but for some of these patients their struggle against MDD remains, and subsequent steps provide progressively diminishing returns. Unremitted patients often experience a worse quality of life and are at a 21% higher risk for relapse and recurrence when compared to their remitted counterparts [3, 4]. These people are considered to suffer from 'treatment-resistant depression' (TRD), one of the biggest challenges for mental health practitioners. Despite this, there is no consensus definition that exists for TRD, but it is commonly accepted as having MDD and failing to respond to two or more adequate and distinct treatments. The diverse range of symptoms of MDD makes it a difficult condition to treat in the aspect that those with MDD are an extremely heterogeneous group, and various treatments could be better suited for certain symptomatology. This makes the working definition of TRD rather ambiguous, as a patient may not necessarily be "resistant," but instead the treatments they have attempted may not have aligned well with their unique phenotypic psychopathology. These

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considerations brought practitioners and researchers to explore new, non-monoaminergic treatment strategies, with that of intravenous (IV) ketamine seeming to be a promising route.

Although the specific antidepressant mechanism of ketamine isn't fully clear, it is classified as an N-methyl-D aspartate (NMDA) receptor antagonist and has long been used as an anesthetic. Ketamine functions as a noncompetitive inhibitor of the NMDA receptor, one of the targets for the excitatory central nervous system neurotransmitter, glutamate. Antagonism of this receptor is considered to induce neuroplasticity modulation, making it an adequate target for antidepressant therapeutics [5, 6]. Plenty of data have drawn researchers to hypothesize that since NMDA receptor activity is crucial to the pathophysiology of depression, its modulation may help improve patients with severe forms of depression, such as TRD [7, 8]. What is even more promising is how fast acting ketamine may be; even just a single IV infusion has shown to mitigate depressive symptoms [9]. Furthermore, studies have linked strong evidence supporting ketamine's viability in reducing suicidal ideation (SI) in TRD patients [10-12]. From a biochemical perspective, ketamine is a racemic mixture consisting of two enantiomers: (R) and (S). The (S) enantiomer has far superior pharmacokinetic properties than its (R) counterpart, as it bonds to the NMDA receptor with greater affinity. As a result, it has been reported as approximately four times more active and being more tolerable than the (R)-enantiomer, inducing fewer instances of the undesirable adverse effects associated with ketamine usage (e.g., dissociation) [13, 14]. This has made the S enantiomer a recent avenue of exploration for those with TRD, and has led to the 2020 FDA approved nasal spray treatment, esketamine.

This nasal spray is self-administered by the patient in an office-based setting. Each device contains 28mg and the typical dose is 56 or 84mg. Tolerability is assessed to determine proper dosage for each patient. After administration, patients must remain for at least 2 hours to assess any potential adverse reactions and ensure proper safety. Patients are advised not to operate motor vehicles until the following day. The most commonly observed adverse reactions are dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feelings of intoxication. The medication should be taken alongside other oral antidepressants. While esketamine has shown great promise in treating TRD, it has also been anecdotally effective in mitigating other unique comorbidities and their symptoms. This review will present a series of three cases, each of which presents with TRD and other comorbid conditions.

2. Materials and Methods

The authors treated the following patients in a typical clinical practice that focuses on Treatment Resistant Depression. Routine depression rating scales are obtained during each patient encounter and dosing of nasal esketamine occurs per usual regulatory guidelines. Three cases were deemed to be unique in that esketamine was used to treat the indicated depressive disorder, but all three cases had unique comorbidities that seem to improve also with depressive disorder treatment. These cases are reviewed and summarized below.

3. Results

3.1. Case Series

3.1.1. Case 1

A 21-year-old woman first presented to the outpatient clinic with a history of TRD. She failed to respond to several medications including SSRIs, SNRIs, atypical antipsychotics as well as psychotherapy, a full course acute ECT, and was now failing on maintenance ECT. She reported symptoms of sadness, loss of interest, hypersomnia,

overeating, excessive crying spells, and to a milder degree; guilt, worthlessness, trouble concentrating, agitation, and occasional passive suicidal ideation. She denied any psychosis or mania history. She also has a past psychiatric history with cerebral palsy. She is also diagnosed with autism spectrum disorder (ASD) and intellectual disability with an IQ of 50. She has a history of self-injurious behavior (SIB) by swallowing non-food items when frustrated or stressed, resulting in hospitalization.

Prior to her first treatment, she reported a Patient Health Questionnaire-9 (PHQ-9) score of 16, indicative of moderate depression. She was started on a twice weekly ultra-low dose of 28mg esketamine to assess tolerability. During initial treatment, she reported mild lightheadedness and nausea with denial of distress, sedation, or dissociation. Dosing increased over the first two weeks from 28mg to 56mg, which it remained at. After the first month, her PHQ-9 scores dropped from 16 to 0. Two months following initial treatment, she denied all depressive symptoms with PHQ-9 remaining at 0, and stated to enjoy spending time again with her family and friends. She also denied any thoughts of SI and no SIB was seen. When treatment was lowered to weekly or longer, it led to anhedonia, elevated PHQ-9 (as high as 16) and SIB of swallowing a magnet that led to hospitalization. The original weekly dosing protocol of 56mg was reinstated and symptomatology resolved. After a year on the treatment, there appears to be continued clinical benefit as above. She continues to deny most depressive symptomatology, SI, and her PHQ-9 scores have not fluctuated above a 2.

3.1.2. Case 2

A 47-year-old female presented to outpatient clinic with chronic TRD and resistant SI. She seemed to have comorbid anxiety disorder, being a mixture of chronic PTSD, generalized anxiety and social anxiety stemming from trauma of a past relationship. She also met criteria for mild borderline personality. In the past she attempted over twenty different medications, including SSRI, SNRI, serotonin partial agonist reuptake inhibitors (SPARI), norepinephrine-dopamine reuptake inhibitors (NDRI), and serotonin antagonist and reuptake inhibitor (SARI). She did not respond to ECT, transcranial magnetic stimulation (TMS), or psychotherapy. Her initial report consisted of anhedonia, severe depressed feelings, insomnia, moderate fatigue and appetite change, and a remarkable sense of guilt and worthlessness without delusion. She had trouble focusing and had moderate levels of daily SI without intention or plan. She exhibited thought and speech hesitancy, with bradykinesia. She denied mania or psychotic history as well as eating or substance use disorders. She has been depressed since her teenage years without any remission. She had an overdose suicide attempt in 2001 and two recent psychiatric hospitalizations. Upon arrival, she had been taking ziprasidone 20mg daily and 80mg nightly, an atypical anti-psychotic, sertraline 50mg daily, an SSRI, lamotrigine 50mg daily, an anticonvulsant, and bupirone 30mg twice daily, an anxiolytic. During her most recent psychiatric hospitalization, she started and underwent 5 esketamine treatments which was effective at alleviating her MDD symptoms, completely ridding her of SI. However, her insurance did not authorize outpatient treatment and esketamine was not continued outpatient and her depression worsened.

Prior to her first outpatient session, she reported a PHQ-9 of 20 suggesting severe depression. She was started on 84mg biweekly, with no adverse effects other than mild depersonalization and psychomotor slowing. A month after starting treatment, her depressive symptoms still proved fairly resistant to treatment, but she did report remission in SI. She was also able to take her daughter out to practice driving, which prior she reported feeling too overwhelmed and anxious to do. Three months into treatment, her subjective report and PHQ-9 scores lowered to the 15-18 range indicating her depression decreased some and she noted less insomnia with less fatigue. However, she still endorsed anhedonia and feelings of guilt and worthlessness. Six months later she reported less anxiety and paranoid ideation at work surrounding her responsibilities and

coworkers, respectively, and now expressed hope for the future with less pessimism. Her PHQ-9 scores seem to fluctuate from visit to visit but her answers to depression and anhedonia items remain at 1. Her core MDD symptoms seem to be better but trauma and personality symptoms not as much. That being said, there was some global improvement in these areas: improved quality of life and no longer any high utilization of emergency or inpatient services. She switched to one session every three weeks. Two years since starting treatment, her PHQ-9 scores have dropped significantly, with the past 3 months all now within the 7-12 range, indicating mild to moderate depression. Treatments have gradually increased her ability to function, continue to work, and not be psychiatrically hospitalized, making this a clinically significant response across all comorbidities.

3.1.3. Case 3

A 67-year-old man reported to the clinic with MDD for the last ten years. It had recently worsened with his diagnosis of thyroid cancer with bone metastasis, which led to numerous orthopedic surgeries and incredible amounts of pain. He had tried 3 SSRIs, an NDRI, and augmentation with two atypical antipsychotics with no success. Despite these surgeries and ample pain medications, he has lived with significant pain from his bone metastases and at times has impaired ability to complete his activities of daily living. He was dysphoric, finding no joy in life and no interest in doing anything, with guilt about his life and past decisions. He had reported trouble sleeping and no appetite. He said that in the past six months he had begun worrying about everything in his life and finding it difficult to control his ruminations. He reported being more irritable, fatigued and had difficulty concentrating. He endorsed SI, but without active intent or plan. He was receiving the SNRI venlafaxine 300 mg, and the sedative alprazolam 1 mg twice daily.

A PHQ-9 score of 22 was reported prior to first treatment session, indicating moderate to severe depression. He began receiving the typical twice weekly treatment at a dose of 56mg. other than somnolence, no adverse effects were reported. By the third session, he reported significantly reduced SI frequency, and PHQ-9 score was 11. He also reported improvements in his ability to ambulate and the quality of his sleep. Just over 4 months into treatment, he reported ongoing 50% reduction in his depressive symptoms and remarkable reduction in suicidal ideation. He admitted that at admission he had active SI with intent and minimized it until he felt confident enough to share this information and says as he no longer has any active intent. PHQ-9 scores have ranged anywhere between 11 and 15 during this time, suggesting an improvement in his depression from severe to mild intensity. He feels esketamine has also greatly helped with his pain, reporting a 50% reduction in severity, and remarkable increasing engagement in instrumental activity. He has been able to walk without his cane, reporting better stamina and quality of life. He feels this medication was a life-changing treatment for him, and considered it medically needed to control both pain and depression at his end-stage of life.

4. Discussion

Many treatments start out with a different intended purpose and are modified over time based on research and clinical experiences. Ketamine started first as a dissociative anesthetic, later being utilized for treatment of depression. Esketamine currently has two FDA approved uses, being approved for use in treatment resistant depression and for treatment of major depressive disorder with suicidality. There is currently ongoing research to explore its possible effect on PTSD symptoms [15, 16]. Esketamine is administered in a controlled setting due to potential of adverse effects and to control the access to this controlled medication, due to its addictive potential.

Given that patients seldom come into an encounter with only MDD, it allowed us the opportunity to examine how other issues may appear to respond to esketamine treatment. We suspect that TRD is often driven by other psychiatric and medical comorbidities. In

addition to reductions in MDD symptoms and suicidal ideation, it appears there may be other benefits such as reducing agitation, self-injurious behavior, or providing analgesia. Esketamine's ability to benefit comorbid conditions should not overlook its primary effectiveness at treating TRD, as we suspect the two are not exclusive. In a recent trial, patients receiving esketamine nasal spray were 1.54 times as likely as patients receiving extended-release quetiapine, another guideline-supported antipsychotic augmentation agent approved for the use in TRD, to have remission at week 8. Furthermore, patients in the esketamine group were 1.55 times as likely as patients in the quetiapine group to have no relapse through week 32 after remission at week 8 [17, 18]. The primary effectiveness of esketamine allows for more opportunity of further consideration of off-label uses of this psychopharmacologic approach, and prompt further research into its application for other conditions.

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