Barriers to Esketamine Nasal Spray Treatment Among Adults With Treatment-Resistant Depression

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Abstract

Background: Under a risk evaluation and mitigation strategy program, esketamine nasal spray CIII requires self-administration at a certified treatment center. Our objective was to identify factors associated with esketamine initiation and continuation.

Methods: A retrospective observational cohort study was conducted among US adults who met treatment-resistant depression (TRD) criteria. Cases (n = 966) initiated esketamine between October 11, 2019, and February 28, 2022, and were compared to controls (n = 39,219) with TRD but no esketamine use. Outcomes included initiation, induction (8 administrations within 45 days), and interruptions (30-day treatment gap). Comorbid psychiatric conditions were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification,* codes.

Results: Cases resided significantly closer to treatment centers (8.9 vs 20.3 miles). Compared to 0–9 miles, initiation rate decreased by 11.9%, 50.8%, 68.1%, 75.9%, and 92.8% for individuals residing 10–19, 20–29, 30–39, 40–49, and 50+ miles from a center. After adjustment, factors associated with increased likelihood of initiation were posttraumatic stress disorder, major depressive disorder with suicidal ideation, and male sex, while increasing distance, substance use disorder, Medicaid, Charlson Comorbidity Index (CCI), and older age were associated with lower likelihood. Factors associated with lower likelihood of completing induction were Medicaid, low socioeconomic status (SES), CCI, and Hispanic communities. Factors associated with increased likelihood of interruption were alcohol use disorder, distance, and minority communities, while generalized anxiety disorder and Medicaid were associated with lower likelihood.

Conclusions: Travel distance, insurance, low SES, and minority communities are potential barriers to treatment. Alternative care models may be needed to ensure adequate access to care.

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Major depressive disorder (MDD) affects 7.1% of individuals living in the United States.[1] While most individuals with MDD are effectively treated with 1 or 2 trials of antidepressants, some individuals demonstrate nonresponse, having persistent symptoms despite multiple trials of therapy. While there are many published definitions of treatment-resistant depression (TRD), a failure to respond to 2 or more trials of medications for MDD is accepted by many as a useful clinical criterion.[2,3] Among individuals diagnosed with MDD, prevalence estimates of TRD range from 6% to 35%.[1,2,4,5] Compared to individuals with MDD who respond to treatment, individuals with TRD have 3-fold longer inpatient hospitalization stays, more than 2-fold lost workdays, greater mortality, and greater self-harm behaviors.[6] Estimates of direct and indirect costs of TRD in the United States exceed $43 billion annually.[7]

In October 2019, the US Food and Drug Administration[8] approved esketamine nasal spray CIII (esketamine) for use in combination with a conventional antidepressant for adults with TRD or for depressive symptoms in adults with major depressive disorder with suicidal ideation (MDSI) or actions. Under a risk evaluation and mitigation strategy program, esketamine is only available in certified treatment centers because of medical monitoring required during treatment. In these health care settings, esketamine is self-administered, followed by a 2-hour clinical observation period. The 4-week induction period includes 2 administrations per week on nonconsecutive days.[9] Following induction, maintenance treatment is weekly or every 2 weeks thereafter.

The current administration model, which requires repeated travel to a certified treatment center, may represent a substantial barrier to care for some patients. Transportation barriers restrict access to care in general[10,11]

Clinical Points

- Since the Food and Drug Administration approval for esketamine under a risk evaluation and mitigation strategy program, esketamine is available to individuals with treatment-resistant depression (TRD) in certified treatment centers.
- Individuals living further from treatment centers and those with lower socioeconomic status (SES) were less likely to initiate and complete therapy compared to individuals with higher SES who are living closer to treatment centers.
- Treatment with esketamine for TRD is substantially influenced by various social determinants of health.

and to mental health care,[12] especially among individuals with lower incomes or inadequate health insurance coverage. In a survey of veterans with serious mental illness, transportation or distance to mental health care and time constraints were identified as barriers in 24% of respondents.[13] In a population-based survey in the United States, perceived barriers to service among respondents who perceived a need for treatment for mental health disorders include the time required to seek care or the inconvenience of seeking care (29%) and lack of knowledge of where to go for help (37%).[14] For the 1 in 5 Americans who live in rural areas,[15] these challenges are magnified. Access to behavioral health providers (ie, psychiatrists, psychologists, and psychiatric nurse practitioners) is reduced in rural areas,[16] and over 60% of rural Americans live in designated mental health provider shortage areas.[17]

Research has documented numerous other barriers to obtaining appropriate mental health services, including cultural differences, social determinants of health (SDoH), lack of perceived need for treatment, stigma, pessimism regarding treatment effectiveness, financial difficulties, and inconvenience or inability to obtain an appointment.[18–20] Of individuals who do seek mental health services, barriers to securing a mental health provider include difficulty finding a mental health professional accepting new patients, difficulty finding a professional who accepts an individual's insurance plan, and treatment not being close enough to home or work.[21]

Based on these documented barriers to in-person health care utilization, we designed the current study to assess for potential barriers to esketamine care for individuals with difficult-to-treat depression living in the United States. In this study, we assessed numerous factors that may present barriers to initiating and continuing esketamine treatment.

METHODS

This study was a retrospective observational comparative cohort study conducted among individuals with evidence of TRD.

Identification and Selection of Study Participants

Eligible study participants were identified using a commercially available open medical and pharmacy insurance claims database, licensed from Clarivate Real-World Data (www.clarivate.com/products/real-world-data/). The Clarivate Real-World dataset includes records of more than 300 million US patients cared for by more than 2 million health care providers and representing coverage from 98% of payers. The case-finding period was from October 11, 2017, to February 28, 2022. To be eligible for the study, all individuals treated with esketamine in the case-finding period were initially considered. Individuals were excluded from the study if they had claims for bipolar disorder (*International Classification of Diseases, Tenth Revision, Clinical Modification* [*ICD-10-CM*]: F06.33, F25.00, F30.x, F31.x, F34.0), schizophrenia (*ICD-10-CM*: F20.x F21.x, F60.1), or schizoaffective disorder (*ICD-10-CM*: F25.x) (Supplementary Table 1). To be eligible as controls, individuals with TRD were required to meet multiple criteria including 2 or more medical claims associated with a diagnosis of MDD (*ICD-10-CM*: F32.x [excluding F32.8] or F33.x [excluding F33.8]) (Supplementary Table 2) at least 30 days apart or 1 inpatient claim with MDD in the primary position. Individuals had to have pharmacy claims consistent with TRD defined by 2 different antidepressant treatment failures of adequate treatment period followed by initiation of a third different antidepressant (suggesting that depressive symptoms persisted after the second antidepressant). The population from which the control cases were selected was required to initiate their third antidepressant agent after October 11, 2019 (date of first esketamine availability). Antidepressant agents in the study included selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic and tetracyclic antidepressants, serotonin modulators, bupropion, α_2 receptor antagonists, and monoamine oxidase inhibitors (Supplementary Table 3). A treatment failure was defined as a minimum duration of 6 weeks of treatment followed by discontinuation (more than 30 days without medication), augmentation with antipsychotic medication, or switch to another antidepressant or antipsychotic agent (Supplementary Table 4). Individuals were excluded from the study if they had claims for bipolar disorder (*ICD-10-CM*: F06.33, F25.00, F30.x, F31.x, F34.0), schizophrenia (*ICD-10-CM*: F20.x F21.x, F60.1), or schizoaffective disorder (*ICD-10-CM*: F25.x). Esketamine users had a paid pharmacy claim for either the 56 mg or 84 mg dose kit or a paid medical claim associated with esketamine administration on or after October 11, 2019. Individuals who met the criteria above but did not initiate esketamine were required to have a paid pharmacy claim indicating a change in antidepressant pharmacotherapy on or after

October 11, 2019. The date of the initial esketamine claim and the date of the new pharmacotherapy were defined as the index date for esketamine users and controls, respectively. Eligible individuals were between 18 and 65 years of age as of the beginning of the baseline period (6 months prior to index) and had continuous eligibility for insurance defined by at least 1 medical or pharmacy claim in each 3-month period from the beginning of baseline through follow-up (6 months following index). The eligible study population included all esketamine users and a 5% random sample of controls.

Covariates

The analysis included (1) demographic characteristics of the patient (sex, age [in years], and insurance [commercial, Medicaid, and other]), (2) comorbidities including both the Charlson Comorbidity Index (CCI)[22,23] and individual measures of psychiatric comorbidities including generalized anxiety disorder (GAD), sleep-wake disorders, substance use and addiction disorders, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), AUD, and MDSI (Supplementary Table 5); SDoH measures; and distance to esketamine treatment center. Comorbid psychiatric conditions (eg, GAD and sleep-wake disorders) were identified using *ICD-10-CM* codes (see Supplementary Table 6).

SDoH was measured at the county level using the Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry Social Vulnerability Index (https://www.atsdr.cdc.gov/placeandhealth/index.html], herein, SVI). The SVI assigns a rank to each county for socioeconomic status (SES), household characteristics, race and ethnicity distributions, and housing type and transportation. The current analysis included the racial and ethnicity distributions and the SES index, which combines measures of poverty, unemployment, housing cost burden, high school education achievement, and health insurance coverage. As the insurance claims dataset only includes the individual's 3-digit zip code (ZIP3) of residence, each individual was assigned to a US county based on the 5-digit zip code (ZIP5) of providers associated with medical claims. Individual ZIP3 was compared to the ZIP5 for providers who provided services during the study period. If the first 3 digits of the ZIP5 matched the individual's ZIP3, priority was given to the ZIP5 of the primary care provider if available or to the provider associated with the preponderance of encounters. The selected ZIP5 was then mapped to county by matching the patient's zip code to the respective county-level Federal Information Processing Standards (FIPS) codes. Finally, each county was assigned the urban, suburban, and rural designation using the National Center for Health Statistics Urban-Rural Classification Scheme for Counties (https://www.cdc.gov/nchs/data_access/urban_rural.htm).

Outcome Measures

The following outcome measures were included in the analysis: initiation, induction, and interruptions. Initiation was defined as the index esketamine claim. Induction was defined by completing 8 esketamine administrations within 45 days of initiation (index date), and interruptions were defined as a 30-day period without an esketamine claim followed by an esketamine claim (indicating a restart of care).

Statistical Analysis

The analysis included a comparison of demographic, comorbidity, distance, and SDoH measures between the 966 eligible esketamine users and the 39,219 eligible controls. These continuous and categorical variables were tested at a significance level of 0.01. The association between covariates and outcomes of interest was measured by multivariate analyses. Adjusted odds ratios (ORs) and 95% CIs were derived from backwards stepwise logistic regression models, with a P value of .05 required for retention in the model. Regression modeling was conducted using SAS version 9.4 (Cary, NC).

RESULTS

During the study period, there were a total of 1,914 certified esketamine treatment centers in the United States. Treatment centers were available in 42 of the 50 US states, located in 619 of the 3,143 counties nationwide. The study included 966 individuals who initiated esketamine treatment and 39,219 controls.

Compared to controls, esketamine users were younger (41.5 vs 45.1 years), had a lower CCI score (0.3 vs 0.8), and were more likely to be male (36.7% vs 25.1%), to be commercially insured (80.6% vs 62.6%), and to reside in an urban area (72.8% vs 60.3%) (all $P < .01$). Esketamine users were more likely to have diagnosis of GAD (55.3% vs 29.1%), sleep-wake disorders (34.1% vs 26.0%), PTSD (23.4% vs 11.6%), MDSI (14.7% vs 9.0%), and OCD (5.4% vs 2.1%) and less likely to have a diagnosis of substance use disorder (SUD) (14.0% vs 21.2%) and AUD (6.2% vs 7.0%) compared to controls (all $P < .01$) (Table 1).

As reported by the 2020 US Census, the median percentage of individuals residing in US counties is highest for the non-Hispanic white population (67.9%), followed by Hispanic (7.4%), non-Hispanic black (6.7%), Asian (2.8%), multirace (2.7%), and American Indian or Alaska Native (0.6%). The percent of the esketamine user population living in counties that are above the median levels by race include non-Hispanic white population

Table 1.

Demographic, Comorbidity, Social Determinants of Health, and Distance to Esketamine Treatment Center Among Esketamine Users and Controls

	Esketamine users (N = 966)		Nonusers (N = 39,219)		
	n	%	n	%	*P* value
Following indicators are based on individual patients					
Sex					
Female	611	63.3%	29,231	74.5%	<.01
Male	355	36.7%	9,828	25.1%	
Age (mean, SD)	41.5	12.4	45.1	13	<.01
Insurance					
Commercial	779	80.6%	24,564	62.6%	<.01
Medicaid	132	13.7%	12,942	33.0%	
Other/unknown	55	5.7%	1,713	4.4%	
CCI	0.3	0.8	0.8	1.5	<.01
Psychiatric comorbidities					
Generalized anxiety disorder	534	55.3%	11,412	29.1%	<.01
Sleep-wake disorders	329	34.1%	10,197	26.0%	<.01
SUD and addiction disorders	135	14.0%	8,314	21.2%	<.01
PTSD	226	23.4%	4,549	11.6%	<.01
Obsessive-compulsive disorder	52	5.4%	823	2.1%	<.01
Alcohol use disorder	60	6.2%	2,730	7.0%	<.01
MDSI	142	14.7%	3,535	9.0%	<.01
Following indicators are based on patient's zip code					
Race and ethnicity (% of population living in counties above the median level for that racial group nationwide)					
NH white	492	50.9%	19,745	50.3%	NS
NH black	496	51.3%	19,764	50.4%	NS
Asian	508	52.6%	20,325	51.8%	NS
AIAN NHOPI	562	58.2%	22,486	57.3%	NS
Multirace	495	51.2%	20,260	51.7%	NS
Hispanic	485	50.2%	19,729	50.3%	NS
SVI and SES index					
Q1 (lowest risk)	231	23.9%	7,295	18.6%	<.01
Q2	259	26.8%	9,632	24.6%	
Q3	174	18.0%	8,873	22.6%	
Q4	164	17.0%	7,689	19.6%	
Q5 (highest risk)	138	14.3%	5,730	14.6%	
Urban/rural					
Urban	703	72.8%	23,640	60.3%	<.01
Suburban	193	20.0%	8,417	21.5%	
Rural	70	7.2%	7,162	18.3%	
Distance, mi					
Mean (SD)	8.9	11.8	20.4	27.5	<.01
Median (IQR)	4.8	(1.8–11.1)	8.8	(3.4–27.6)	

Abbreviations: AIAN NHOPI = American Indian, Alaska Native, Native Hawaiian, and Other Pacific Islander, CCI = Charlson Comorbidity Index, IQR = interquartile range, MDSI = major depressive disorder with suicidal ideation, NH = non-Hispanic, NS = not significant, PTSD = posttraumatic stress disorder, SES = socioeconomic status, SUD = substance use disorder, SVI = Social Vulnerability Index.

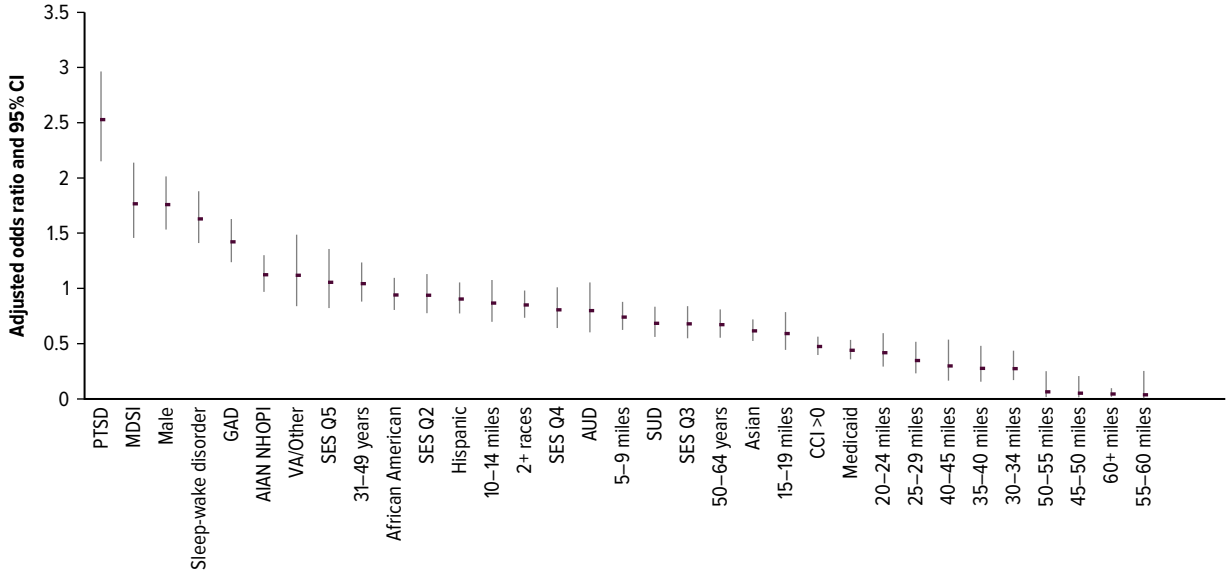
(50.9%), followed by Hispanic (50.2%), non-Hispanic black (51.3%), Asian (52.5%), multirace (51.2%), and American Indian or Alaska native (58.1%). Esketamine users were more likely to live in counties designated as urban (72.8% vs 60.3%) and less likely to reside in counties designated as rural (7.2% vs 18.3%). Esketamine users were more likely to live in counties with low socioeconomic vulnerability (23.9% vs 18.6%) (Table 1).

Esketamine users were more likely to be seen by a psychiatrist (83.1% vs 37.9%), while controls were more likely to visit a primary care physician (64.1% vs 42.2%). Esketamine users were less likely to have an inpatient admission (4.3% vs 8.2%) or emergency department visit (11.1% vs 20.4%) and to have at least 1 prescription filled (72.2% vs 93.1%) compared to controls.

Travel distance: Esketamine users resided significantly closer to an esketamine treatment center (8.9 vs 20.4 miles) compared to controls. Excluding 3 outliers, the maximum distance a case traveled for treatment was 69.5 miles. Overall, 49.9% (n = 19,568) of controls lived more than 8.9 miles from the nearest

Figure 1.

Adjusted Odds Ratios and 95% CIs for Variables Retained in the Backwards Stepwise Regression of Initiating Esketamine Treatment



Abbreviations: AIAN NHOPI = American Indian, Alaska Native, Native Hawaiian, and Other Pacific Islander; AUD = alcohol use disorder; CCI = Charlson Comorbidity Index; GAD = generalized anxiety disorder; MDSI = major depressive disorder with suicidal ideation; PTSD = posttraumatic stress disorder; SES = socioeconomic status; SUD = substance use disorder; VA = Veterans Affairs.

Table 2.

Esketamine Utilization Following Initiation Among the 966 Individuals Who Initiated Treatment

	N	%
Induction (8 treatments)		
Within 30 days	322	33.3%
Within 45 days	400	41.4%
Interruptions		
None	814	84.3%
1 or more	152	15.7%

treatment center, an estimate that increased to 91.6% for rural residents (Table 1).

Treatment Initiation

The adjusted odds of initiating esketamine therapy were highest for individuals with PTSD (OR, 2.52; 95% CI, 2.15–2.96), MDSI (OR, 1.76; 95% CI, 1.45–2.13), sleep-wake disorders (OR, 1.62; 95% CI, 1.41–1.87), and GAD (OR, 1.46; 95% CI, 1.23–1.62). Males were significantly more likely to initiate esketamine than females (OR, 1.75; 95% CI, 1.53–2.01). Compared to individuals residing within 5 miles of a treatment center, the adjusted odds of initiating esketamine therapy declined in a nearly linear fashion for each 5-mile increment, beginning with individuals residing 5–9 miles away (OR, 0.74; 95% CI, 0.62–0.87) and ending with individuals 60+ miles away (OR, 0.04; 95% CI, 0.02–0.10). Individuals with a nonzero CCI score (CCI) were also less likely to initiate esketamine (OR, 0.47; 95% CI, 0.39–0.56) (Figure 1).

Induction

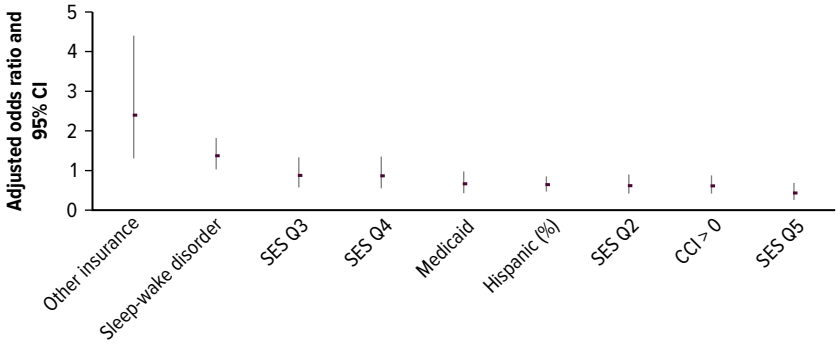
A total of 33.3% of the esketamine users completed the induction phase within 30 days of initiation and 41.4% within 45 days (Table 2). After adjustment, the odds of completing the induction phase within 45 days of initiation were highest for individuals with "other" insurance (OR, 2.39; 95% CI, 1.31–4.40) and individuals with sleep-wake disorder diagnosis (OR, 1.37; 95% CI, 1.03–1.82). The odds of completing the induction phase were lower for individuals with elevated CCI scores (OR, 0.61; 95% CI, 0.42–0.88) and those who resided in the highest risk SES counties (OR, 0.43; 95% CI, 0.26–0.69) or counties with higher proportion of Hispanic populations (OR, 0.64; 95% CI, 0.47–0.85) (Figure 2).

Interruptions

A total of 15.7% of esketamine users experienced an interruption in treatment (Table 2). The highest odds of experiencing an interruption in treatment were noted for individuals with AUD (OR, 3.0; 95% CI, 1.64–5.47), those who reside 30+ miles from the nearest treatment center (OR, 2.32; 95% CI, 1.10–4.88), and those who reside in counties with higher proportion of African Americans (OR, 1.58; 95% CI, 1.04–2.38), multirace

Figure 2.

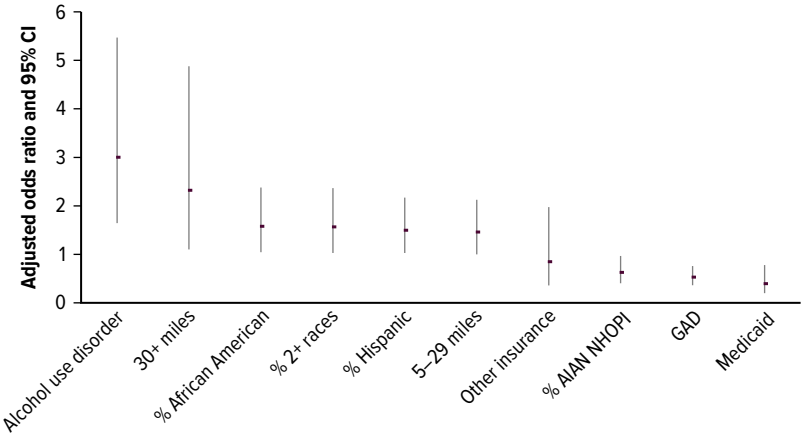
Adjusted Odds Ratios and 95% CIs for Variables Retained in the Backwards Stepwise Regression of Completing the Induction Phase Within 45 Days of Initiation Among the 966 Individuals Who Initiated Esketamine[a]



[a]Race and ethnicity categories are measured at ZIP5 and represent residing in a region with a percentage population above the median US value; SES Q5: highest risk quintile for SES index from the Social Vulnerability Index.
Abbreviations: CCI = Charlson Comorbidity Index, SES = socioeconomic status, ZIP5 = 5-digit zip code.

Figure 3.

Adjusted Odds Ratios and 95% CI for Variables Retained in the Backwards Stepwise Regression of 1 or More Interruptions in Esketamine Care Among the 966 Individuals Who Initiated Esketamine Treatment[a]



[a]Race and ethnicity categories are measured at ZIP5 and represent residing in a region with a percentage population above the median US value.
Abbreviations: AIAN NHOPI = American Indian, Alaska Native, Native Hawaiian, and Other Pacific Islander; GAD = generalized anxiety disorder; ZIP5 = 5-digit zip code.

individuals (OR, 1.56; 95% CI, 1.03–2.37), or Hispanic individuals (OR, 1.49; 95% CI, 1.03–2.17). Individuals with the lowest odds of an interruption in treatment were those insured by Medicaid (OR, 0.39; 95% CI, 0.20–0.78) followed by individuals with GAD (OR, 0.53; 95% CI, 0.0.36–0.76) (Figure 3).

DISCUSSION

Consistent with the published research evidence that social determinants, residing in rural areas, and travel distance negatively affect utilization of mental health services overall, our study reports the negative impact of

travel distance, social determinants, and demographic characteristics on the initiation and continuation of esketamine therapy. Odds of initiating treatment were lower for each 5-mile increase in distance from the nearest certified treatment center, with individuals residing 20–24 miles from a treatment center being more than 50% less likely to receive treatment. Further, individuals insured by Medicaid or who have medical comorbidities were significantly less likely to initiate treatment. In contrast, travel distance was not associated with completing the induction phase of treatment. However, the odds of completing the induction phase were significantly lower among individuals insured through Medicaid, with medical comorbidities, and who resided in counties with a high proportion of Hispanic residents or with the lowest SES. Finally, the odds of an interruption in treatment were higher for individuals with AUD, as distance from treatment center increased, and among individuals who resided in counties with higher proportions of individuals who identified as African American, Hispanic, or multirace.

Travel distance to the nearest esketamine treatment center may be particularly important for individuals living in rural areas. Not only are rural areas disadvantaged in their access to mental health services, but also there is strong evidence that rural residents have a higher prevalence of mental health issues compared to urban residents. Age-adjusted suicide rate among persons 15 and over living in nonmetropolitan counties was 37% higher than the rate among suburban individuals, and rates of depression are higher in rural areas.[24,25] Social stigma related to mental health conditions is prevalent in rural locations and can represent a significant barrier to accessing health care services.[26] In a study of older adults receiving telephone psychotherapy for anxiety, over 80% responded that they "should not need help."[27] Higher rates of individuals living in poverty in rural areas have the potential to impact both the onset of mental health conditions and access to care. In 2019, rates of individuals living in poverty were 15.4% in rural areas compared to 11.9% living in metropolitan areas.[28] After controlling for demographics and poverty, adults living in rural areas were 9% more likely to report having a disability and 24% more likely to report having 3 or more disabilities compared to individuals living in metropolitan centers,[29] which itself can be a risk for depression.[30]

In alignment with a national survey of individuals with mental health illness in 2016 that revealed out-of-pocket costs associated with Medicaid were a substantial deterrent to seeking help from a prescribing professional,[21] our finding that esketamine users were less likely to be insured by Medicaid was not surprising. It is interesting to note, however, that once in treatment, individuals insured through Medicaid were not only significantly less likely to complete the induction phase but also significantly less likely to experience an interruption in care.

The lower likelihood of an interruption in care for individuals insured by Medicaid may reflect the requirement for documented evidence of treatment response before continuing treatment in commercial insurance plans or may be associated with out-of-pocket cost differences.

It is worth highlighting that among those undergoing treatment, individuals covered by Medicaid exhibited a notable pattern: they were not only less likely to successfully finish the initial treatment phase, but they also demonstrated a significantly reduced likelihood of encountering a disruption in their care. This decreased probability of a care interruption might be attributed to several factors. Patients with depression have a decreased likelihood of adherence to treatment plans.[31] Medicaid plans that cover esketamine treatment generally follow Center for Medicare and Medicaid Services (CMS) guidelines for prior authorization and maintenance of therapy that are close to evaluations and treatment models reported in clinical trials. Medicaid plans may have different requirements for documenting treatment response before progressing further in treatment, a benefit plan design with criteria that vary considerably across carriers.[32] Finally, the decreased probability of an interruption could be linked to disparities in out-of-pocket expenses due to the variability in prescription drug coverage per plan by each insurer.

Perhaps less obvious were the findings that individuals with higher physical health comorbidities were less likely to initiate esketamine treatment and, if initiated, less likely to complete the induction phase. These results may be particularly important given the recent evidence that comorbid TRD is associated with substantially higher levels of all-cause health care resource utilization and costs among individuals with underlying physical health challenges.[7]

Esketamine users more commonly suffered from comorbid psychiatric diagnoses including anxiety, sleep-wake disorders, and PTSD, though this may be a result of having greater access to trained psychiatric professionals capable of making advanced diagnoses. The finding that esketamine users were less likely to have a comorbid SUD may suggest that concerns over the addictive potential of esketamine are taken seriously by prescribing physicians.[33] Participants enrolled in esketamine clinical trials were sober for at least 6 months. AUD and MDD often co-occur. The relationship between AUD and depression is complex and bidirectional. Alcohol can impact neurotransmitter systems in the brain that are also implicated in depression. For instance, alcohol affects the serotonin and dopamine systems, which are related to mood regulation.[34–36]

Our findings suggesting that racial and ethnic minorities had more difficulty initiating and receiving uninterrupted esketamine care reflect a much larger

challenge regarding racial and ethnic disparities in US mental health care.[37] Black or African American and Hispanic individuals living in the United States are less likely than whites to receive needed care, less likely to receive prescription medications for serious mental illness, and more likely to terminate care prematurely.[37,38]

Our study reinforces the need to explore mechanisms to overcome the substantial barriers to appropriate mental health services faced by individuals with TRD. These results expand upon prior research into factors associated with esketamine initiation and continuation[39] by not restricting the population of nonusers to those who reside within a similar distance to a treatment center; by allowing comparison of users and nonusers on demographic characteristics, insurance, and comorbidities; by expanding the population of esketamine users; and, finally, by including the outcome of interruption in treatment, an outcome that has not been reported on previously. Further research would seek to characterize the efficacy, tolerability, and safety of administration of esketamine in a broader set of clinical environments including physician offices or home-based treatment with appropriate supervision.[9]

Limitations

Interpretation of this study's results should account for several limitations. First, the use of an open claims dataset as the source of clinical conditions and utilization limits the accuracy of the findings due to the potential for missing data. Second, distance to certified treatment center and SDoH measures were derived at the US county level, and individuals were assigned to US county based on an algorithm that links individuals' ZIP3 of residence to a ZIP5 of providers. Distance estimates were based on the centroid of the US county to the exact address of the treatment center while SDoH measures were at the county level rather than individual level. Lastly, identifying individuals suffering from suicidal ideation through analysis of administrative databases has been historically associated with variable sensitivity and specificity.[40] The method employed in this study, requiring both a diagnosis of MDD and at least 1 diagnosis of suicide attempt or self-harm, was felt to be a conservative definition, but there is limited evidence to support the validity of this approach.

Conclusions

Demographic, geographic, and social determinants of health were strongly associated with the initiation and continuation of esketamine treatment. Most counties in the United States are not served by an esketamine treatment center, and many states are underserved by available mental health services, which can lead to avoidable differences in equitable access to care. Consistent with this, increasing distance to the nearest treatment center was a consistent barrier to initiation, with a nearly linear decline in treatment for each 5-mile increase in distance. Further, regardless of travel distance, important populations (individuals with medical comorbidities, communities with high proportions of racial and ethnic minorities, and rural residents) are at increased risk of not initiating esketamine and not continuing esketamine treatment. Because the clinical and economic burden represented by TRD is substantial and treatment with esketamine offers an important treatment option for individuals living with TRD, the exploration of alternative models of care is vital to reduce the burden of the travel distance and other factors that limit esketamine treatment.

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Supplementary Material

Article Title: Barriers to Esketamine Nasal Spray Treatment Among Adults with Treatment-Resistant Depression

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

SUPPLEMENTARY TABLE 1. ICD-10-CM CODES FOR EXCLUSION CRITERIA BIPOLAR DEPRESSION, SCHIZOPHRENIA, AND SCHIZOAFFECTIVE DISORDER

Condition	ICD-10
Bipolar Depression	F30.10 – F30.13, F30.1, F30.2, F30.3, F30.4, F30.8, F30.9, F31.X
Schizophrenia	F20.0, F20.1, F20.2, F20.3, F20.5, F20.8, F20.81, F20.89, F20.9
Schizoaffective disorder	F25.x

SUPPLEMENTARY TABLE 2. ICD-10-CM CODES FOR MAJOR DEPRESSIVE DISORDER

Condition	ICD-10	Definition
Major Depressive Disorder, Single Episode		
	F32	Major Depressive Disorder, single episode
	F32.0	Major Depressive Disorder, single episode, mild
	F32.1	Major Depressive Disorder, single episode, moderate
	F32.2	Major Depressive Disorder, single episode, severe without psychotic features
	F32.3	Major Depressive Disorder, single episode, severe with psychotic features
	F32.4	Major Depressive Disorder, single episode, in partial remission
	F32.5	Major Depressive Disorder, single episode, in full remission
	F32.9	Major Depressive Disorder, single episode, unspecified
Major Depressive Disorder, Recurrent Episode		
	F33	Major Depressive Disorder, recurrent episode
	F33.0	Major Depressive Disorder, recurrent episode, mild
	F33.1	Major Depressive Disorder, recurrent episode, moderate
	F33.2	Major Depressive Disorder, recurrent episode, severe without psychotic features
	F33.3	Major Depressive Disorder, recurrent episode, severe with psychotic features
	F33.4	Major Depressive Disorder, recurrent episode, in remission
	F33.40	Major Depressive Disorder, recurrent episode, unspecified
	F33.41	Major Depressive Disorder, recurrent episode, in partial remission
	F33.42	Major Depressive Disorder, recurrent episode, in full remission
	F33.9	Major Depressive Disorder, recurrent episode, unspecified

SUPPLEMENTARY TABLE 3. LIST OF ANTIDEPRESSANT MEDICATIONS ELIGIBLE FOR INCLUSION AS THE INITIAL ANTIDEPRESSANT MONOTHERAPY

Antidepressant	Starting Dose (mg/day)
Alpha-2 Receptor Antagonists	
Mirtazapine	15
Monoamine Oxidase Inhibitors (MAOIs)	
Isocarboxazid	10-20
Phenelzine	15
Selegiline	6
Tranylcypromine	10
Serotonin Modulators	
Nefazodone	
Trazodone	
Vilazodone	
Vortioxetine	
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Citalopram	
Escitalopram	
Fluoxetine	
Paroxetine	
Paroxetine, extended release	
Sertraline	
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
Desvenlafaxine	
Duloxetine	
Levomilnacipran	
Venlafaxine, immediate or extended release	
Tricyclics and Tetracyclics	
Amitriptyline	
Amoxapine	
Clomipramine	
Desipramine	
Doxepin	
Imipramine	
Nortriptyline	
Protriptyline	
Trimipramine	
Maprotiline	
Antidepressants – Other	
Bupropion, immediate or extended release	
Bupropion, sustained release	

SUPPLEMENTARY TABLE 4. FDA-APPROVED PHARMACOTHERAPY FOR AUGMENTATION/ADJUNCTIVE MDD TREATMENT

Drug class/names
Atypical antipsychotics (second generation)
Aripiprazole (Abilify)
Brexpiprazole (Rexulti)
Olanzapine (Zyprexa)
Risperidone (Risperdal)
Fluoxetine + Olanzapine (Symbyax)
Quetiapine (Seroquel)
Combinations
Chlordiazepoxide-amitriptyline (Limbitrol)
Perphenazine-amitriptyline (Etrafon)
Mood stabilizers
Lithium
Thyroid hormone
Triiodothyronine (T3)

SUPPLEMENTARY TABLE 5. ICD-10-CM CODES FOR SUICIDAL IDEATION AND SELF-HARM BEHAVIOR

Condition	ICD-10
Suicidal ideation	R45.481
Suicide attempt	T14.91
Intentional self-harm by poisoning	T36.[0-9]X2*, T37.[0-9]X2*, T38.[0-7]X2*, T38.8[0-9]2*, T38.9[0-9]2*, T39.0[1-9]2*, T39.1X2*, T39.2X2*, T39.3[1-9]2*, T39.4X2*, T39.8X2, T39.92X*, T40.0[0-5]X2*, T40.6[0-9]2*, T40.7X2*, T40.8X2*, T40.902*, T40.992*, T41.0X2*, T41.1X2*, T41.2[0-9]2*, T41.3X2*, T41.42X*, T41.5X2*, T42.[0-6]X2*, T42.72X*, T42.8X2*, T43.0[1-2]2*, T43.1X2*, T43.2[0-9]2*, T43.[3-4]X2*, T43.5[0-9]2*, T43.6[0-9]2*, T43.8X2*, T43.92X*, T44.[0-8]X2*, T44.9[0-9]2*, T45.[0-4]X2*, T45.5[1-2]2*, T45.6[0-9]2*, T45.7X2*, T45.8X2*, T45.92X*, T46.[0-8]X2*, T46.9[0-9]2*, T47.[0-8]X2*, T47.92X*, T48.[0-1]X2*, T48.2[0-9]2*, T48.[3-6]X2*, T48.9[0-9]2*, T49.[0-8]X2*, T49.82X*, T50.[0-8]X2*, T50.9[0-9]2*, T50.A[1,2,9]2*, T50.B[1,9]2*, T50.Z[1,9]2*
Intentional self-harm by toxic effect	T51.[0-8]X2*, T51.92X*, T52.[0-8]X2*, T52.92X*, T53.[0-7]X2*, T53.92X*, T54.[0-3]X2*, T54.92X*, T55.[0-1]X2*, T56.[0-7]X2*, T56.8[1,9]2*, T56.92X*, T57.[0-8]X2*, T57.92X*, T58.[0,2]2X*, T58.2X2*, T58.8X2*, T58.92X*, T59.[0-7]X2*, T59.8[1,9]2*, T59.92X*, T60.[0-8]X2*, T60.92X*, T61.[0,1]2X*, T61.7[7,8]2*, T61.8X2*, T61.92X*, T62.[0-2,8]X2*, T62.92X*, T63.0[0-4,6-9]2*, T63.1[1,2,9]2*, T63.2X2*, T63.3[0-3,9]2*, T63.4[1-6,8]2*, T63.5[1,9]2*, T63.6[1-3,9]2*, T63.7[1,9]2*, T63.8[1-3,9]2*, T63.92X*, T64.[0,8]2X*, T65.0X2*, T65.1X2*, T65.2[1,2,9]2*, T65.[3-6]X2*, T65.8[1-3,9]2*, T65.92X*
Asphyxiation	T71.1[1-3,5,6,9]2*, T71.2[2,3]2*
Intentional self-harm by drowning	X71.[0-3,8,9]XX*,
Intentional self-harm by gun	X72.XXX*, X73.[0-2,8,9]XX*, X74.0[1,2,9]X*, X74.8XX*, X74.9XX*
Other intentional self-harm	X7[5-6].XXX*, X77.[0-3,8-9]XX*, X78.[0-2,8-9]XX*, X79.XXX*, X80.XXX*, X81.[0-1,8]XX*, X82.[0-2,8]XX*, X83.[0-2,8]XX*

SUPPLEMENTARY TABLE 6. ICD-10-CM CODES FOR PSYCHIATRIC COMORBIDITIES

Condition	ICD-10
Anxiety disorders	F41.x
Adjustment disorders	F43.2x
Obsessive compulsive disorder	F42.x
Post-traumatic stress disorder	F43.1x
Sleep-wake disorders	G47.x
Alcohol, substance, addiction disorders	F10.x – F19.x