Trends in Ketamine and Esketamine Dispensing and Administration

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IQVIA

Prepared for: Drug Enforcement Administration (DEA)
600 Army Navy Drive
Arlington, VA 22202

Prepared by: IQVIA Government Solutions, Inc
3110 Fairview Park Drive, Suite 400
Falls Church, VA 22042

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Abbreviations

DEA	Drug Enforcement Agency
Dx	Medical claims data
LRx	Prescription claims data
LTC	Long-Term Care
NP	Nurse Practitioner
OUD	Opioid Use Disorder
PA	Physician Assistant
PTSD	Post-Traumatic Stress Disorder
RN	Registered Nurse
SOB	Source of business
SUD	Substance Use Disorder
US	United States

Executive summary

Current Landscape

In the past 20 years, ketamine has increasingly been used as a therapy for treatment-resistant major depressive disorder (TRD), suicidal ideation, bipolar disorder, and post-traumatic stress disorder PTSD. Currently, ketamine is not approved for the treatment of psychiatric conditions and all use is off-label. Patients will typically seek ketamine treatment through non-traditional healthcare settings, raising concerns about its safety and the potential for misuse. In 2019, esketamine received FDA approval for the treatment of patients with TRD and/or suicidal ideation, in conjunction with an antidepressant. The FDA has issued warnings to patients and providers about potential risks associated with ketamine products, particularly when used without monitoring by a healthcare provider.

New Insights on Ketamine and Esketamine Utilization

We observed increasing use of esketamine in both unprojected office-based administrations and projected retail prescribing since its launch in 2019; office-based administrations and pharmacy dispensing were mostly from psychiatry/neurology specialties, followed by NPs/PAs. While projected retail prescribing of ketamine has increased gradually since 2018 (mostly among NPs/PAs and psychiatry/neurology specialties), unprojected office-based administrations of ketamine increased until 2022 but declined thereafter. Patient profiles of those treated with esketamine and ketamine were mostly similar, with rather limited use in the youngest and oldest patient groups, and male patients. Unlike other groups older patients' ketamine use was still as common as esketamine use in recent years. There were no noteworthy differences in trends across age groups over time, or by sex or other clinical characteristics for both products. Most patients treated with esketamine (office-based administrations and retail prescribing) had depression diagnoses and/or were concurrently treated with antidepressants as indicated, and a notable proportion of those treated with ketamine had PTSD/anxiety diagnoses. Opioids were also concurrently prescribed for a notable proportion of patients treated with ketamine, more so than for those treated with esketamine.

Implications for Ketamine and Esketamine Prescribing and Clinical Practice

Our findings are consistent with the lay press reporting increased interest in ketamine utilization for off-label indications like depression, PTSD/anxiety, and pain, but our data cannot differentiate between appropriate and inappropriate use or quantify the use in non-traditional healthcare settings that lack adequate regulatory controls. More research is needed on the settings and clinical context in which ketamine administration for psychiatric use or pain management occurs, and the clinical factors influencing increased use. While clinical appropriateness of esketamine use cannot be established, these data do suggest esketamine is used primarily among patients with depression in line with its indication and REMS. Because of the potential risks associated with these products, continued monitoring is necessary to better understand their impact on patients at scale and any potentially adverse consequences of their use for off-label indications.

Key findings

Overall trends in esketamine and ketamine utilization

- Unprojected office-based administrations of esketamine increased since launch 2019. Unprojected office-based administrations ketamine increased from 2020 to 2022 and declined from 2022 to 2023.
- Retail prescribing of esketamine and ketamine has increased since 2018; monthly rates of patients initiating ketamine and esketamine treatment via retail prescribing are similar comparing the products.

Characteristics of ketamine and esketamine patients

- The largest age group of patients prescribed esketamine and ketamine are those 45-64 (~40-42%) and most patients (~59-65%) are female.
- A quarter of patients (~24%) administered or dispensed esketamine had a diagnosis of depression. PTSD/anxiety was as common as depression in patients administered or dispensed esketamine.
- Nearly all patients administered or dispensed esketamine have concomitant dispensing of antidepressants; concomitant opioids more common in patients administered or dispensed ketamine, but less so in patients administered or dispensed esketamine.

Provider and clinical practice trends

- Nearly all providers of office-based esketamine administrations were in psychiatry/neurology specialties (~90%). Most of the providers of office-based ketamine administrations were in pain specialties.
- The top two specialties prescribing retail esketamine and ketamine psychiatry/neurology and NPs/PAs. NP/PA prescribing has increased markedly since 2019 for both products.
- Switching between products increased slightly after the introduction of esketamine but was relatively uncommon. Most patients administered or dispensed esketamine and ketamine either did not use either drug in the subsequent six months, or only had follow-up prescriptions for their initial product.

Background

Ketamine is a Schedule III non-narcotic substance used primarily as an anesthetic in human and veterinary medicine. Ketamine is primarily administered via intravenous (IV) infusion, under the supervision of a clinician, although compounded formulations may also come in the form of oral tablets, lozenges, or nasal sprays.[1,2] In the past 20 years, ketamine has increasingly been used as a therapy for treatment-resistant major depressive disorder (TRD), suicidal ideation, bipolar disorder, and post-traumatic stress disorder PTSD. [1,3,4]

In March 2019, esketamine (Spravato) – the *S*-isomer of ketamine – received FDA approval for the treatment of patients with TRD and/or suicidal ideation, in conjunction with an oral antidepressant. Esketamine is self-administered as an intranasal (IN) spray under the supervision of a physician, in conjunction with a course of oral antidepressant. Because esketamine is only available through a restricted distribution system under a Risk Evaluation and Mitigation Strategy (REMS), both prescribers and patients are required to sign additional documentation on patient education and risks during supervised use. [5]

While the FDA has approved Spravato, some patients continue to seek off-label ketamine therapy through sources such as independent ketamine clinics. In addition to in-clinic services, telehealth ketamine services (including in-home, at-risk therapies) have grown in popularity – in part due to waiver of requirements for in-person treatment and medical supervision for ketamine therapy implemented as part of the 2020 public health emergency declaration.[2,7,8] Currently there are an estimated 500 to 750 independent ketamine clinics in the US providing a mix of in-clinic and telehealth services.[6,9] Variability in clinical practice for off-label ketamine use has raised concerns among both clinicians and regulators about safety and the potential for misuse. The number of independent, outpatient ketamine therapy clinics has increased rapidly in recent years, with viral marketing campaigns and celebrity endorsements.[6] In 2023, the FDA issued a warning to patients and healthcare providers about potential risks associated with compounded ketamine products, particularly when used without monitoring by a healthcare provider.[10]

The DEA commissioned IQVIA to investigate US trends in dispensing and use patterns of both medications in office and clinic-based settings, and related implications. This report describes overall trends in ketamine and esketamine pharmacy dispensing and administration in clinics from 2018 to 2023 and patient and provider profiles for ketamine and esketamine use.

Methodology

Objective(s)

The goals of this study are to:

- Assess overall trends in ketamine and esketamine pharmacy dispensing and administration;
- Describe patient and provider profiles for ketamine and esketamine dispensing and administration

To accomplish these goals, we conducted a series of analyses to:

a. Describe overall trends in dispensing of ketamine and esketamine from 2018 to 2023
b. Characterize patterns of initiation and continuing use of ketamine and esketamine
c. Characterize patterns in co-administration of ketamine and esketamine with other controlled substances (e.g., opioids) and psychoactive agents (e.g., antidepressants)
d. Describe trends in dispensing, initiation, and use of ketamine and esketamine, stratified by patient demographics and comorbidities, provider specialties

Data Sources

We used IQVIA's **Longitudinal Prescription Claims (LRx)** data to capture prescriptions dispensed over time and **National Prescription Audit (NPA)** data to project to national estimates. We included prescriptions dispensed in the retail, long-term care, and mail-order channels.

We used IQVIA's **Medical Claims Data (Dx)** to capture professional medical claims generated by office-based physicians and specialist, to assess diagnosis and treatment trends.

Product Markets and Patient Selection

Ketamine and Esketamine Definitions

We defined the ketamine market as all prescriptions dispensed for ketamine, including both injections and bulk powder (which may be used for custom compounding). We defined the esketamine market as all prescriptions dispensed for esketamine nasal solution (Spravato ®). For a complete list of products included, please refer to **Appendix 2**.

Patient Inclusion and Study Period

We selected patients for the study based on prescriptions in the pharmacy (LRx) and from medical claims for administrations in office-based settings (Dx). We analyzed patients identified from prescription data separately from those identified from medical claims due to sample size differences and ability to project the lower counts from the medical claims. We included patients if they had at least one dispensed prescription or administration claim for ketamine or esketamine from January 2018 through December 2023.

Eligibility and Stability Criteria

We applied stability and eligibility rules to maximize the accuracy of longitudinal data and minimize the risk of anomalous results due to natural variation in data contributors over time.

LRx Stability and Eligibility

- *Patient stability* – Patients must have had at least one record of prescription activity (in any market) in the LRx database at any time prior to the look-back period (12 months prior to the index)
- *Pharmacy stability* – To be included in monthly reporting, pharmacies reporting data for included patients must have consistently supplied data to the LRx for the month of interest, for the prior 12 months, and for the following 6 months, totaling 19 months of rolling pharmacy stability.

Dx Stability and Eligibility

- *Physician stability* – To be included in monthly reporting, physicians reporting data for included patients must have consistently and accurately provided 100% of their office-based claims to the Dx dataset for the month of interest, for the prior 12 months, and for the following 6 months totaling 19 months of provider stability.

Analysis

Projected Patient Volume (LRx)

We used IQVIA's proprietary projection methodology, which combines all raw prescription transactions captured in the LRx dataset and NPA information to estimate the number of patients with a prescription for ketamine and esketamine each month, stratified by patient and provider characteristics.

Patient and Provider Characteristics

We report projected estimates by data source (LRx or Dx), age group (<18, 18-24, 25-34, 35-44, 45-64, 65-84, 85+), sex (female, male) on each month's index claim. We calculated patient age using the year of birth and the claim year. We grouped provider specialties into categories using information provider specialty data in NPA.

Treatment Categories

To describe monthly prescribing among new ketamine and esketamine initiators versus continuing users, we sorted patients into treatment categories based on prescription and/or administration activity in the 12 months prior to each month's index claim:

- **New-to-Therapy:** Patient did not have any prescription for the drug market of interest (ketamine or esketamine) during the prior 12 months
- **Continuing:** Patient had at least one prescription for the drug market of interest (ketamine or esketamine) during the prior 12 months

- **Switch:** Patient did not have any prescription for the drug market of interest, but did have a prescription for a different market product during the prior 12 months (e.g. a new-to-therapy esketamine patient with a prescription for ketamine within the prior 12 months)

Exploratory Telehealth Analysis

To assess trends in telehealth administrations we used a telehealth algorithm to identify telehealth index administrations (as compared to in-office administrations). Telehealth was defined primarily using data from Dx and as such the flag was applied to Dx cohorts only.

Continuing Use Definitions

To assess continuing use, we looked for subsequent dispensing or administration of ketamine and/or esketamine within the six months after each month's index claim. Note that for the final two months of data (November and December 2023), look-forward periods of five months and four months respectively were used due to the timing of the latest available data.

We defined continuing use as patients with at least one prescription dispensed or administration within the look-forward period and assigned patients to one of the following mutually exclusive categories based on the following criteria after index:

- **Index Product:** Only the index product was observed within the following six months (e.g. ketamine patient with only subsequent dispensing(s) for ketamine)
- **Switch Product:** Only non-index product was observed within the following six months (e.g. ketamine patient with a subsequent esketamine dispensing)
- **Dual Product:** Both ketamine and esketamine dispensing or administration were observed within the following six months
- **Discontinuation:** No dispensing or administration for ketamine or esketamine were observed within the following six months

Co-Treatment Definitions

We looked for co-treatment with an antidepressant, antipsychotic, and/or opioid medication within the three months prior and the three months after the index date. For a complete list of the product groups included in the definition of co-treatment, please refer to **Appendix 3**

Comorbidity Diagnosis Definitions

We looked for select conditions within the three months prior and the three months after the index date using diagnosis codes. Conditions of interest included: substance use disorder (SUD), anxiety disorder, bipolar disorder, major depressive disorder (MDD), schizophrenia, and post-traumatic stress disorder (PTSD). For a complete list of definitions for comorbidity conditions of interest, please refer to **Appendix 4**.

Data Considerations:
Listed below are data considerations to provide context in interpreting the findings of this study:

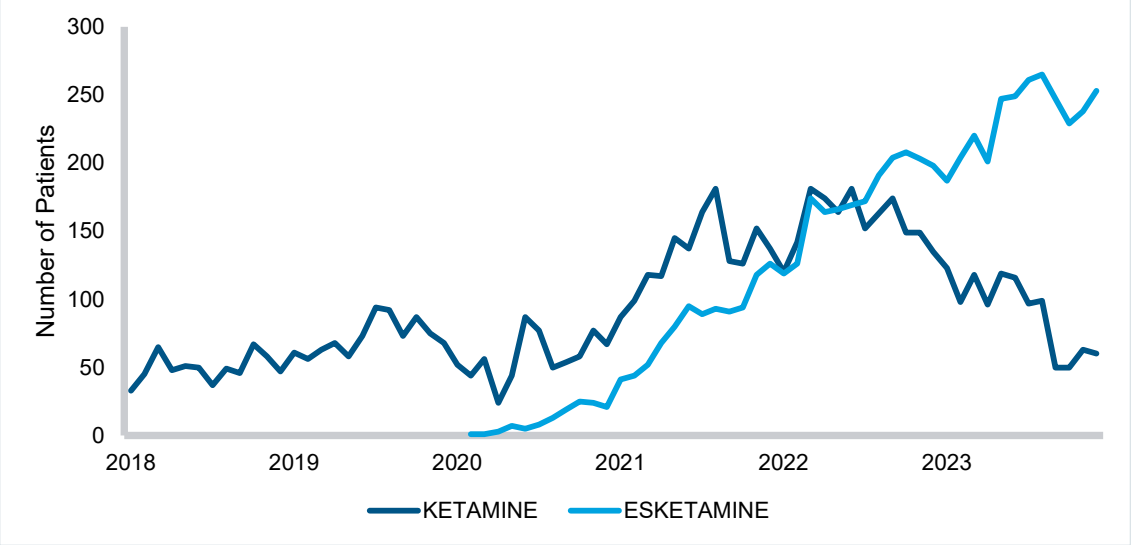
- While this report characterizes prescribing trends of ketamine and esketamine using real-world pharmacy and medical claims information, it cannot differentiate between appropriate use and potential misuse or diversion.
- While some patients may overlap between both data sources (LRx and Dx), looking at the cohorts separately allowed for more complete visibility of all dispensed and administered ketamine and esketamine without limiting the available patient population by requiring that patients be present in both databases at the same time.
- Due to the small number of patients identified, Dx data could not be projected to national estimates; therefore, results are presented at the sample level (i.e., raw counts). Due to the small number of total projected esketamine patients (<400) in the first three months following its introduction to market (March to May 2019), we will report all analyses stratified by patient characteristics beginning in June 2019. The complete LRx data, including March – May 2019, are included in the accompanying pivot tables.
- In all months, fewer than 0.5% of ketamine and esketamine patients had a telehealth claim for their respective drug. Due to the extremely small number of telehealth claims identified, the exploratory telehealth results were not reported.
- The findings of this report are descriptive and contextual, and do not include tests of statistical significance.

Results

Trends in Office-Based Esketamine and Ketamine Administration

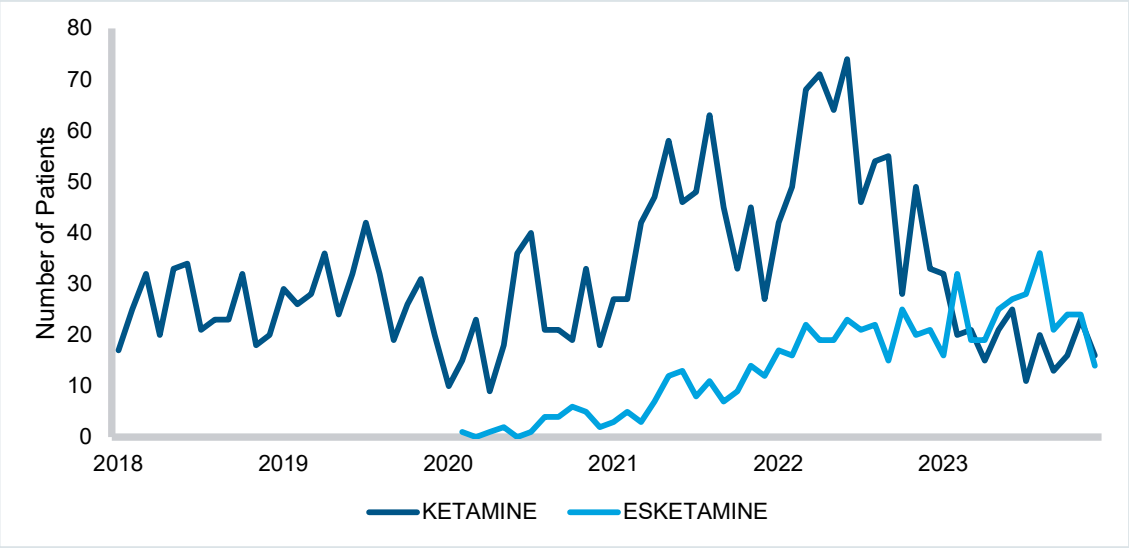
Since its introduction to the market, the total number of patients administered esketamine in office-based settings has generally increased with some minor monthly variation [**Figure 1**]. The total number of patients administered ketamine in office-based settings notably increased in 2021 but declined starting in 2022.

Figure 1. Overall Number of Patients Administered Ketamine and Esketamine in an Office-Based Setting



Trends in the number of new patients (i.e., new-to-market initiators) administered esketamine and ketamine in office-based settings each month were similar to the overall administration trends; however, there were consistently more new patients administered ketamine each month than esketamine until 2023 when new patients per month for both products were roughly equivalent [**Figure 2**].

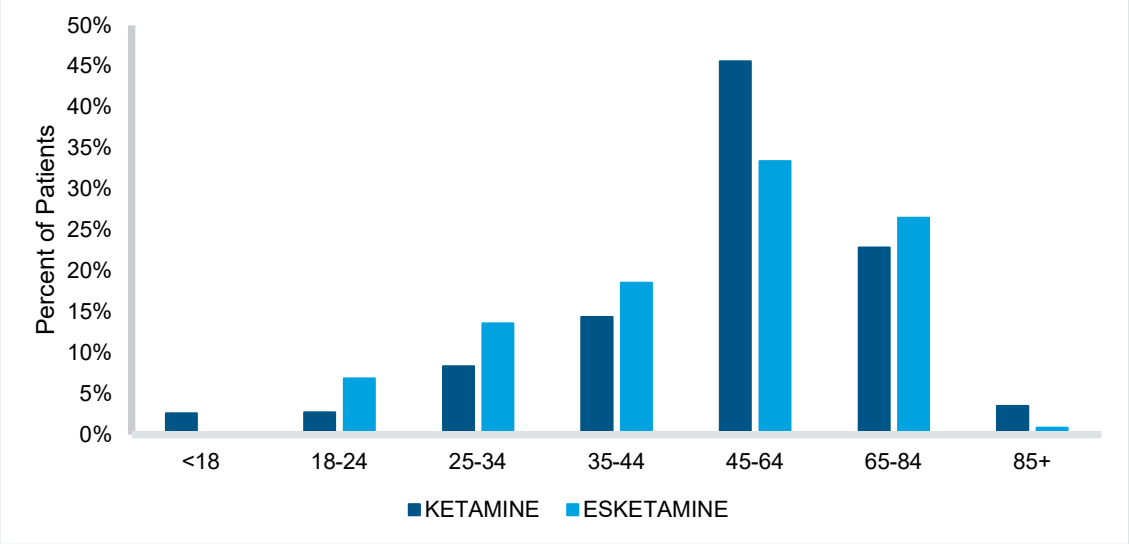
Figure 2. Monthly New-to-Market Patients Administered Ketamine and Esketamine in an Office-Based Setting



Patient demographic and clinical characteristics for office-based administration

Most patients administered either ketamine or esketamine in office-based settings were female. The plurality of office-based administrations of ketamine were for patients aged 45-64 (46%), followed by 65-84 (23%) and 35-44 (14%) [**Figure 3**]. The age distribution of office-based administrations of esketamine was similar, with most patients also aged 45-64 (33%), followed by 65-84 (27%) and 35-44 (19%).

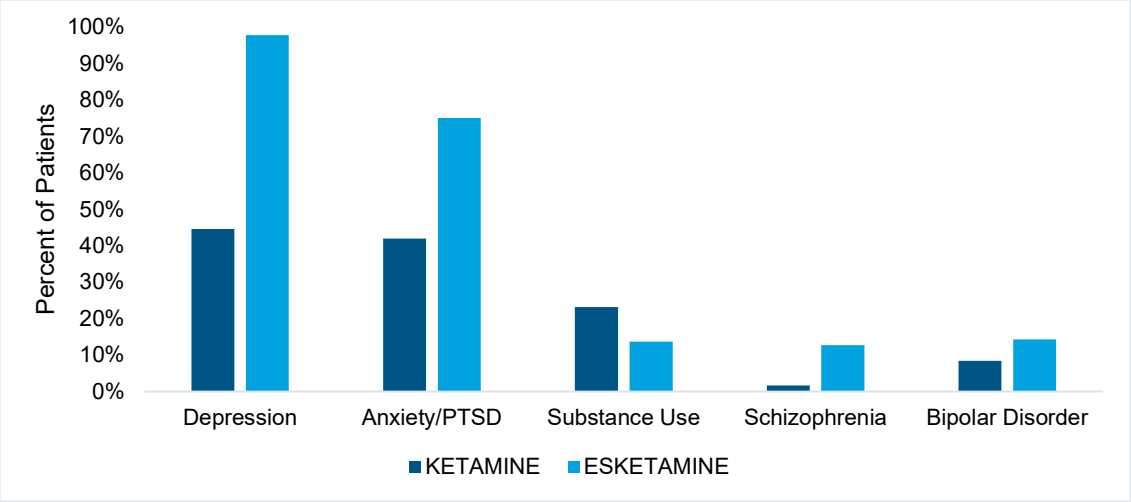
Figure 3. Percent of Patients Administered Ketamine and Esketamine in an Office-Based Setting by Age (2018 – 2023)



On average 45% of patients administered ketamine in-office had a diagnosis of depression, 42% had a diagnosis of anxiety/PTSD, and 23% had a diagnosis of substance use disorder (SUD) [**Figure 5**]. Nearly all (98%) patients administered esketamine in-office had a

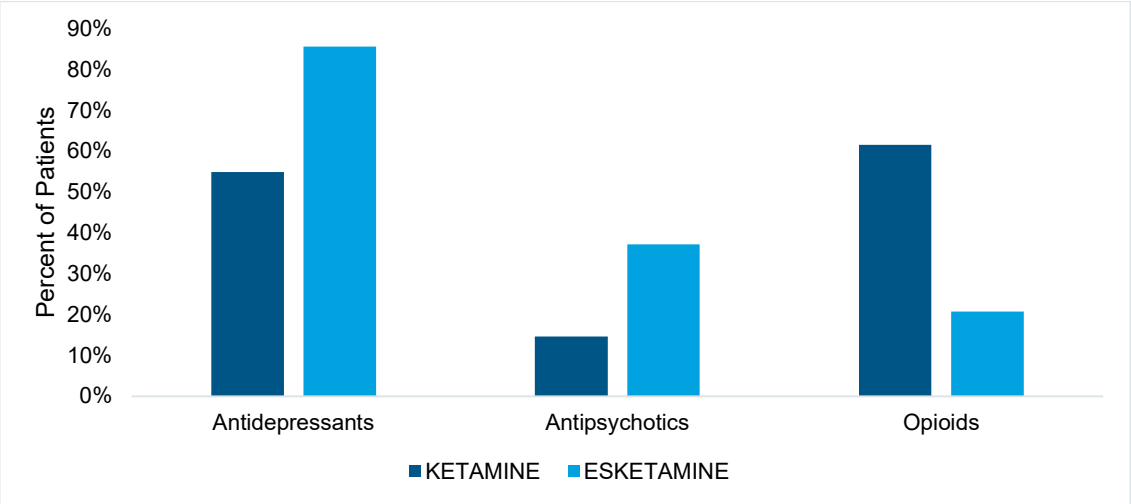
depression diagnosis, 75% had a diagnosis of anxiety/PTSD, and 14% had a diagnosis of SUD.

Figure 4. Percent of Patients Administered Ketamine and Esketamine in an Office-Based Setting by Comorbidity (2018 – 2023)



Overall, 55% of patients administered ketamine in-office were concurrently prescribed an antidepressant, 15% were prescribed an antipsychotic, and 62% were prescribed an opioid [**Figure 5**]. Most patients administered esketamine (86%) were concurrently prescribed an antidepressant, 37% were prescribed an antipsychotic, and 21% were prescribed an opioid.

Figure 5. Percent of Patients Administered Ketamine and Esketamine in an Office-Based Setting by Co-prescription (2018 – 2023)

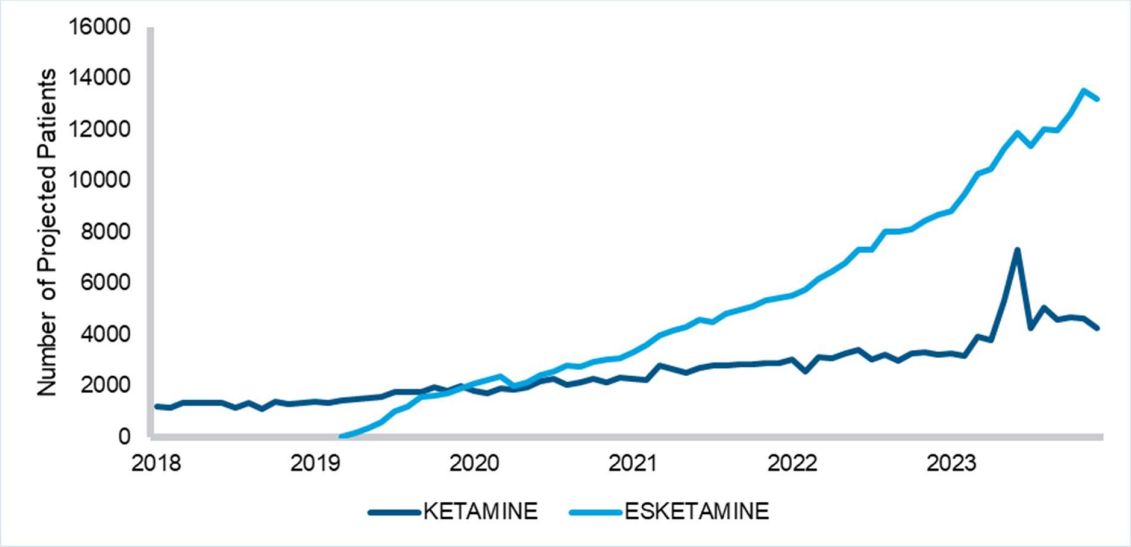


Trends in Retail Ketamine and Esketamine Dispensing

From 2018 to 2023 the projected number of patients dispensed ketamine per month increased by 350%, at an average rate of 43 patients per month [**Figure 6**]. From its

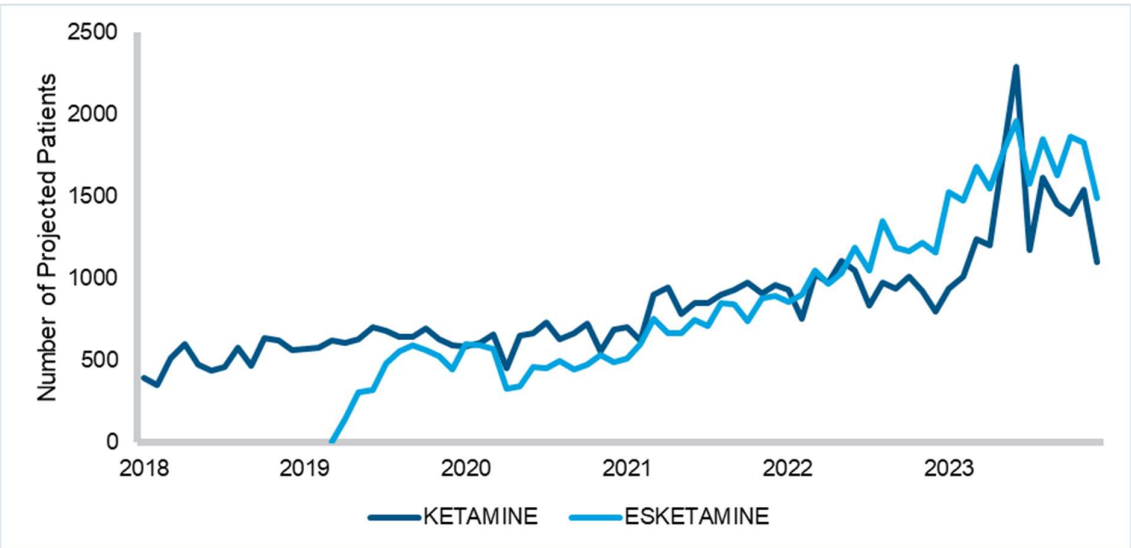
approval in 2019, the projected number of patients dispensed esketamine increased at an average rate of 231 patients per month. By the end of 2023 there were approximately 4,600 ketamine and 13,000 esketamine patients per month.

Figure 6. Number of Monthly Projected Patients Dispensed Ketamine and Esketamine



The number of new patients dispensed ketamine each month increased over time, rising from 392 to 1,110 per month, at an average rate of 10 patients per month [**Figure 7**]. From its introduction to market, the number of new patients dispensed esketamine rose at a rate of 26 patients per month, reaching 1,491 patients per month by the end of 2023.

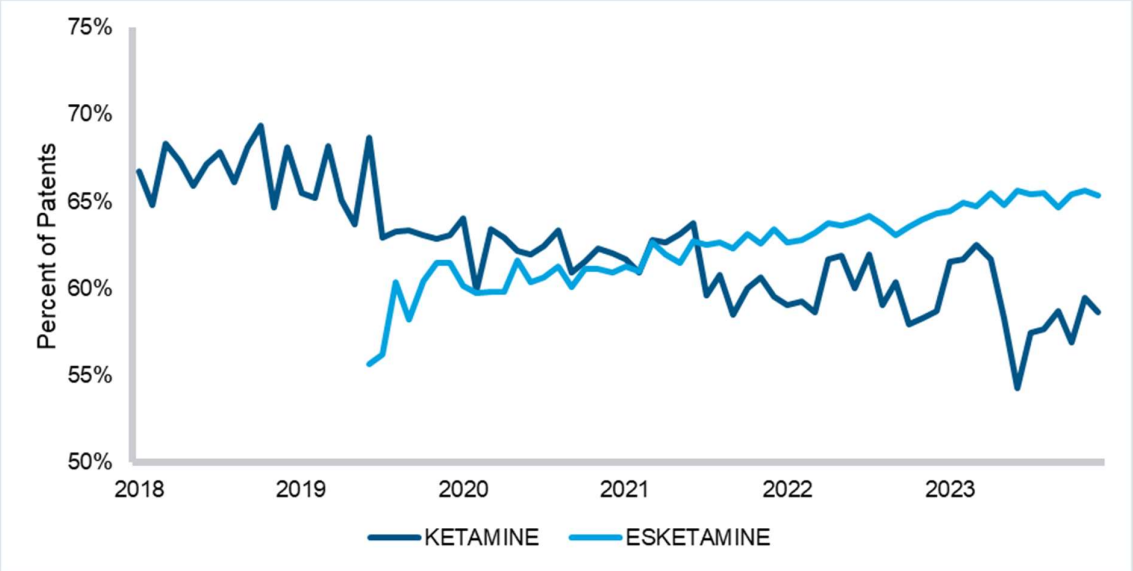
Figure 7. Number of Monthly Projected New-to-Therapy Patients Dispensed Ketamine and Esketamine



Sex and Age Trends in Retail Dispensing

Consistently, most patients dispensed ketamine and esketamine were female. The proportion of patients dispensed ketamine who are female declined (67% to 59%) between 2018 and 2023, while the proportion of patients dispensed esketamine who are female increased (56% to 65%) since its introduction to the market [**Figure 8**].

Figure 8. Proportion of Female Patients Dispensed Ketamine and Esketamine



From 2018 to 2023, the projected number of patients dispensed ketamine in all age groups increased. Overall, most patients dispensed ketamine were between the ages of 45-64 (40%) and 65-84 (22%). Over this same period, the proportion of patients aged 25-34 and 35-44 increased slightly (from 7% to 13% and from 13% to 23% respectively) [**Appendix Figure 1**].

From June 2019 to 2023, the projected number of patients dispensed esketamine in all age groups also increased. Overall, most patients dispensed esketamine were aged 35-44 (23%) and 45-64 (42%). Over time, the proportion of patients dispensed esketamine aged 25-34 and 35-44 increased from 15% to 21% and 16% to 25%, respectively [**Appendix Figure 2**]. Of note, a smaller proportion of esketamine patients were over the age of 65 compared to ketamine patients.

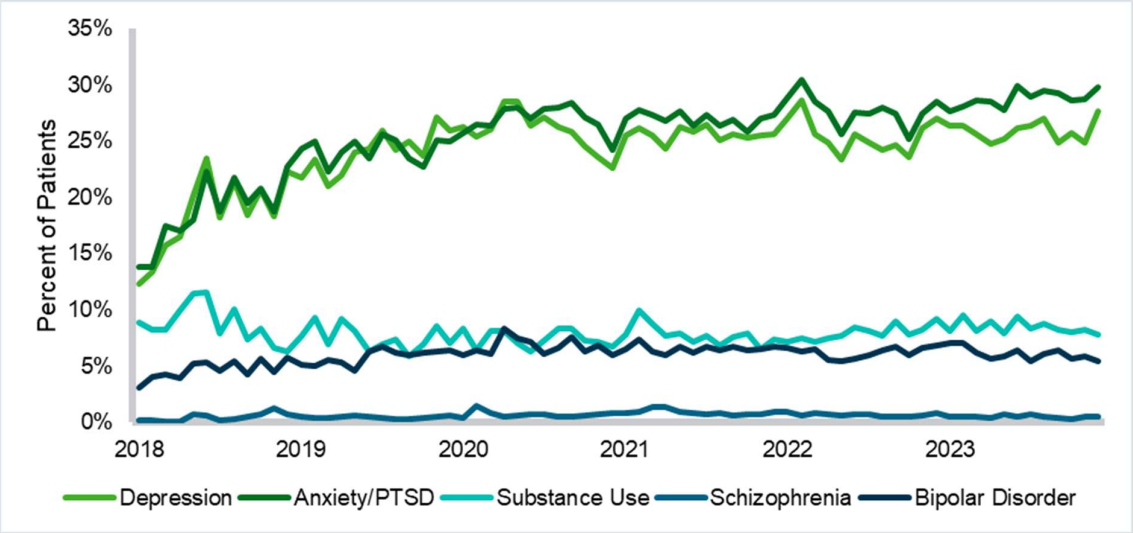
Comorbidities and Co-Prescribing Trends in Retail Dispensing

From 2018 to 2023, a quarter (24%) of patients dispensed ketamine had a diagnosis of depression [

Figure 9] and half of all patients (49%) dispensed ketamine were also dispensed antidepressants [**Figure 10**]. From 2018 to 2020, the annual proportion of patients with a depression diagnosis increased from 18% to 25%, where it remained stable through 2023.

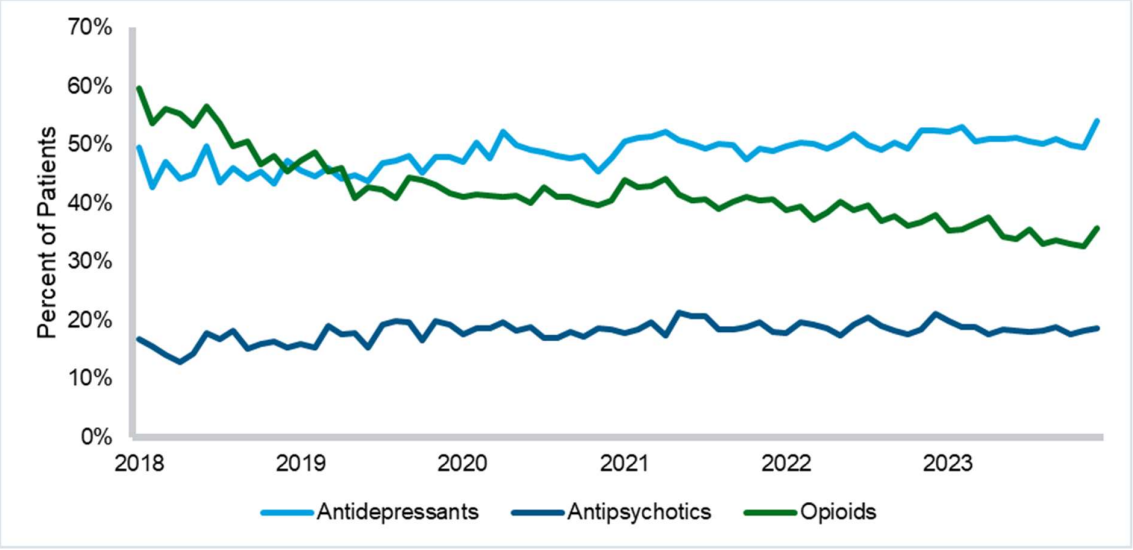
Consistently, 8% of ketamine patients had a diagnosis for a substance use disorder, 6% had a diagnosis for bipolar disorder, and less than 1% had a diagnosis of schizophrenia.

Figure 9. Proportion of Projected Patients Dispensed Ketamine by Comorbidity



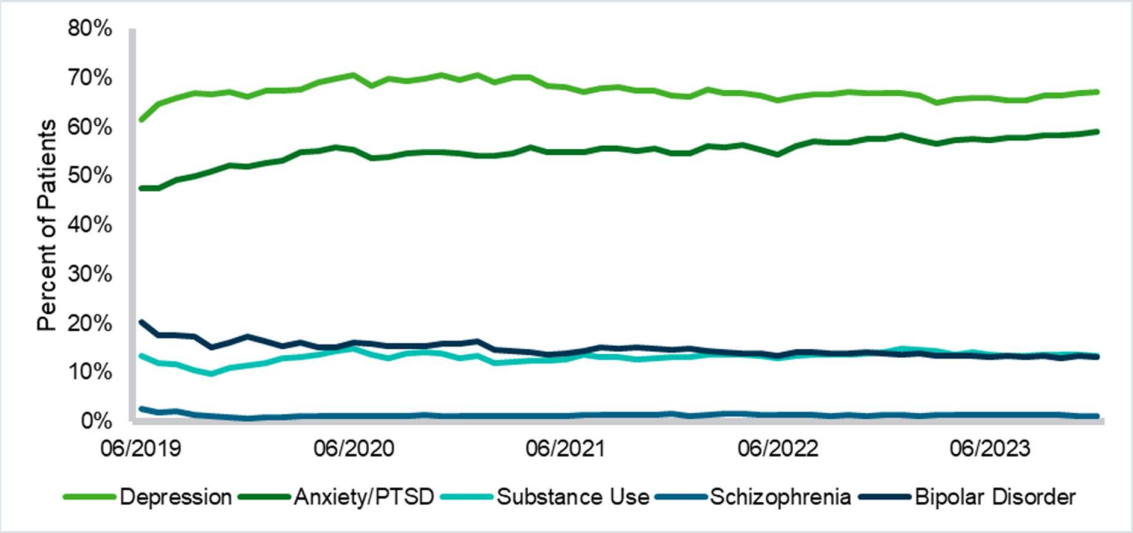
From 2018 to 2023 the proportion of patients co-prescribed opioids declined (60% to 35%), while the proportion of patients co-prescribed antipsychotic medications remained relatively stable (18%) [**Figure 10**].

Figure 10. Proportion of Projected Patients Dispensed Ketamine by Co-prescription



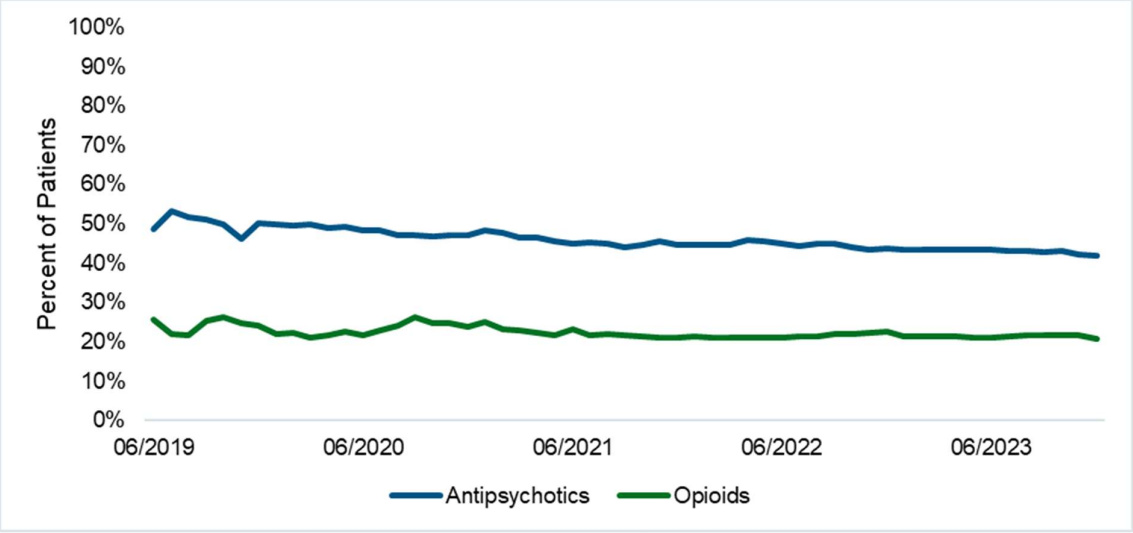
From June 2019 through 2023, more than two thirds (68%) of patients dispensed esketamine had a diagnosis of depression [**Figure 11**] and nearly all patients dispensed esketamine (99%) were also dispensed antidepressants [**Figure 12**]. Consistently 13% of patients dispensed esketamine had a diagnosis for a SUD, 15% had a diagnosis for bipolar disorder, and 1% had a diagnosis of schizophrenia.

Figure 11. Proportion of Projected Patients Dispensed Esketamine by Comorbidity



From 2018 to 2023 the proportion of esketamine patients co-prescribed opioids remained stable (22%), while the proportion of patients co-prescribed antipsychotics declined slightly (50% to 42%) [**Figure 12**]. More than 80% of patients dispensed esketamine were co-prescribed another antidepressant medication [Data Not Shown].

Figure 12. Proportion of Projected Patients Dispensed Esketamine by Co-prescription

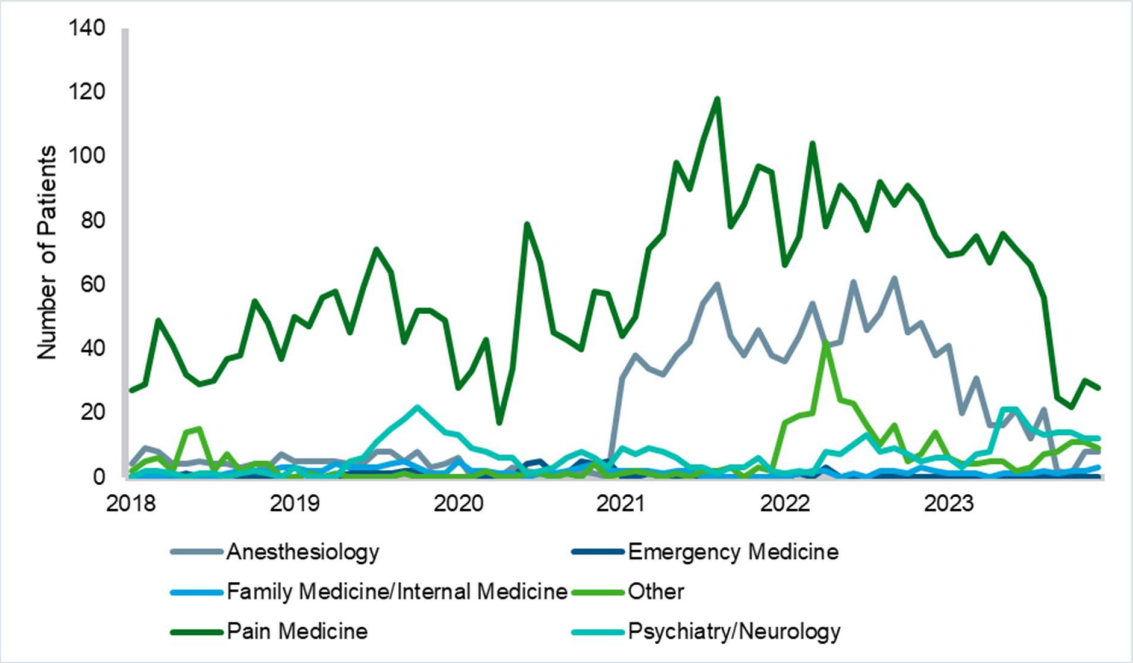


Trends in Ketamine and Esketamine Providers and Clinical Practice

Provider Specialties for Office-based Administration

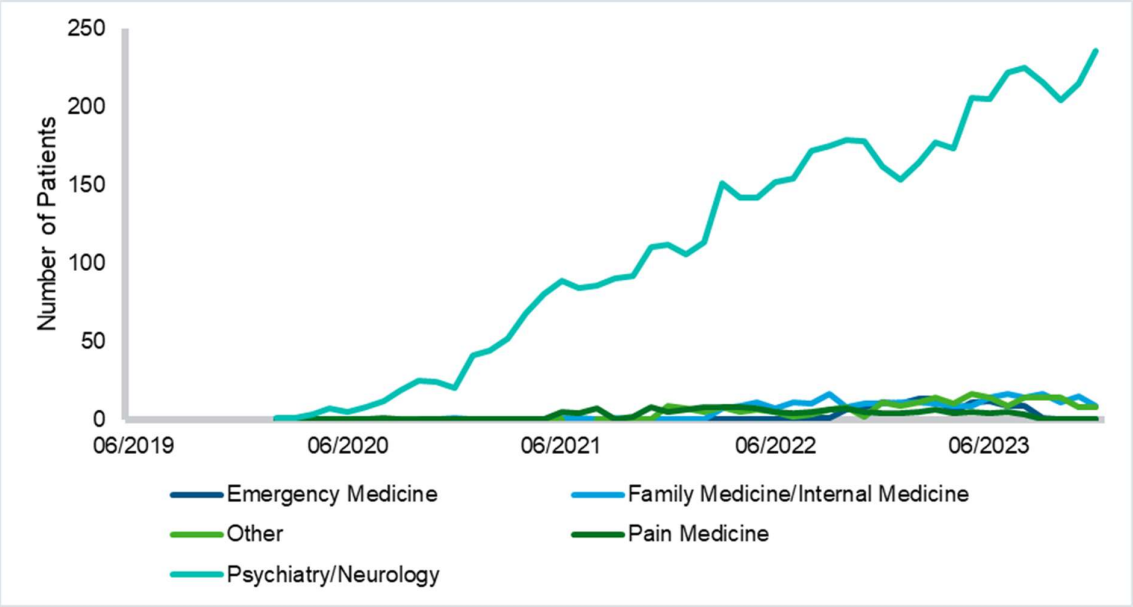
From 2018 to 2023, most patients who received ketamine in office-based settings were seen by pain medicine specialists [**Figure 13**].

Figure 13. Patients Administered Ketamine in an Office-Based Setting by Specialty



Most patients who received esketamine in office-based settings were seen by psychiatrists/ neurologists [**Figure 14**]. For both ketamine and esketamine, office-based administrations by NP/PAs were negligible.

Figure 14. Patients Administered Esketamine in an Office-Based Setting by Specialty

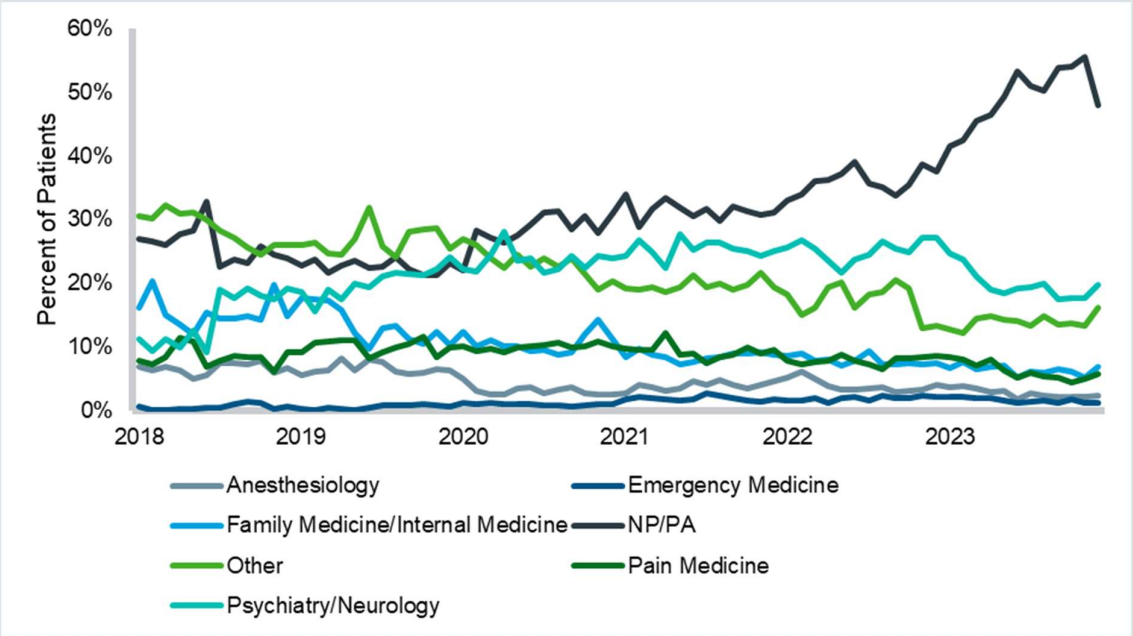


Over the study period, only 0.0-0.7% of claims per month for office-based administration of esketamine and ketamine combined were for telehealth-related healthcare encounters. Due to the low volume of claims, these data were not included in this report.

Provider Specialties for Retail Dispensing

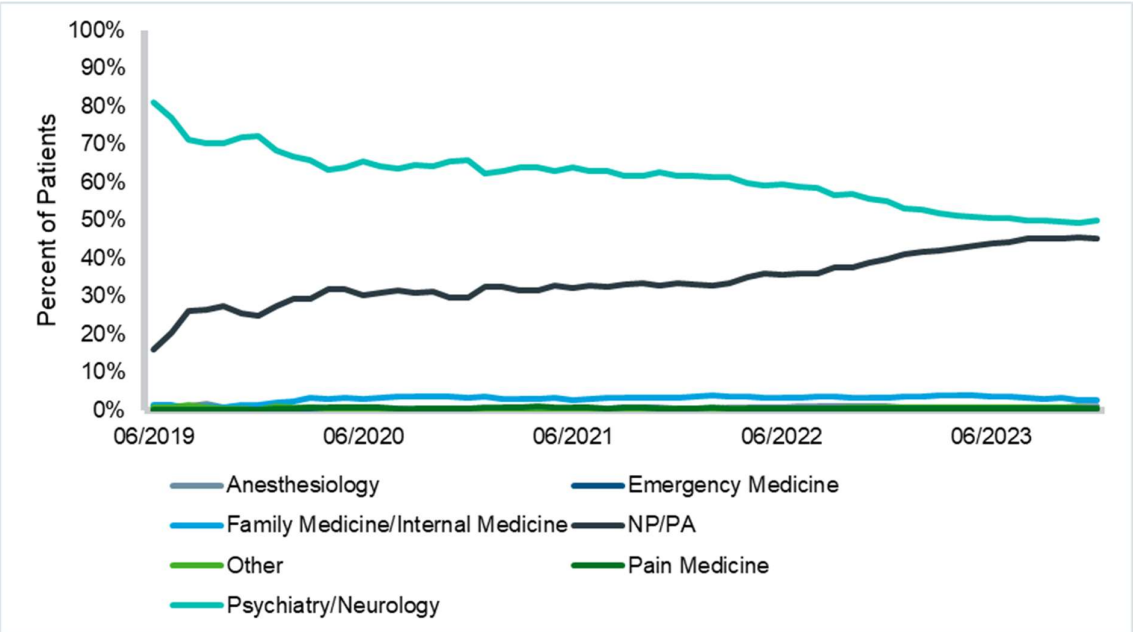
The top two specialties prescribing ketamine through retail settings were psychiatry/ neurology and NPs/PAs [**Figure 15**]. Beginning in 2020, the proportion of retail ketamine prescriptions prescribed by NP/PA increased markedly. By 2023, more than half of all patients dispensed ketamine received their prescriptions from NP/PAs. The proportion of patients prescribed ketamine by psychiatrists/ neurologists rose steadily from 2018 to mid-2022, but then began declining in 2023.

Figure 15. Proportion of Projected Patients Dispensed Ketamine by Specialty



Since its launch, most patients dispensed esketamine received their prescriptions from psychiatrists/neurologists, followed by NPs/PAs [**Figure 16**]. Like ketamine the proportion of patients dispensed esketamine from prescriptions written by NPs/PAs has increased steadily, as the proportion of patients receiving prescriptions from psychiatrists/neurologists has declined. Less than 4% of patients dispensed esketamine receive prescriptions from any other specialty.

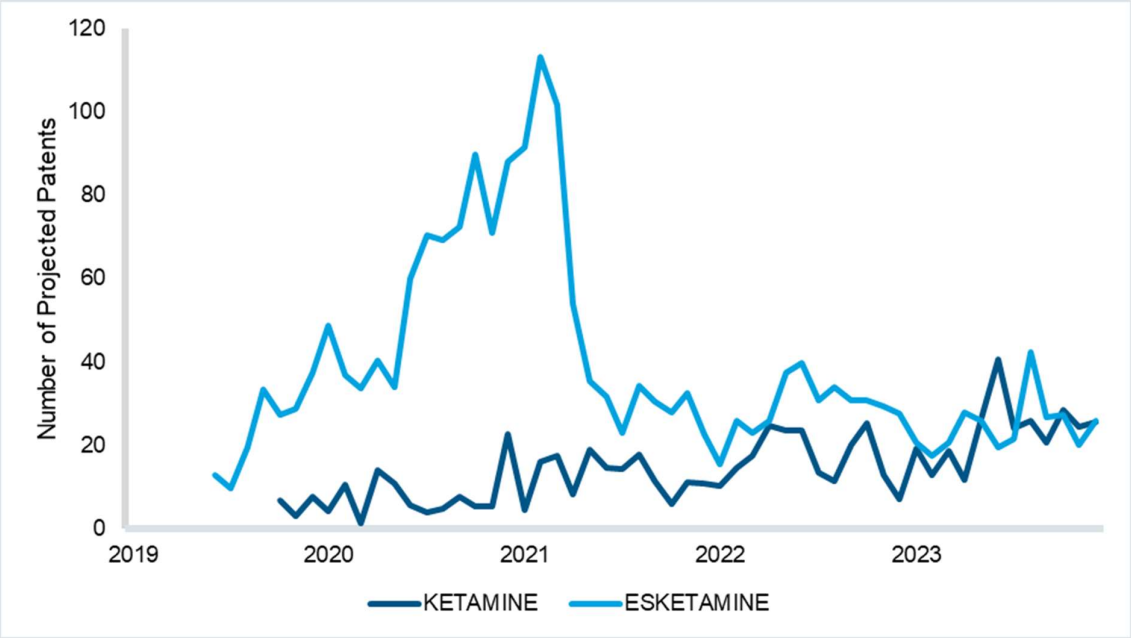
Figure 16. Proportion of Projected Patients Dispensed Esketamine by Specialty



Treatment Patterns for Retail Esketamine and Ketamine

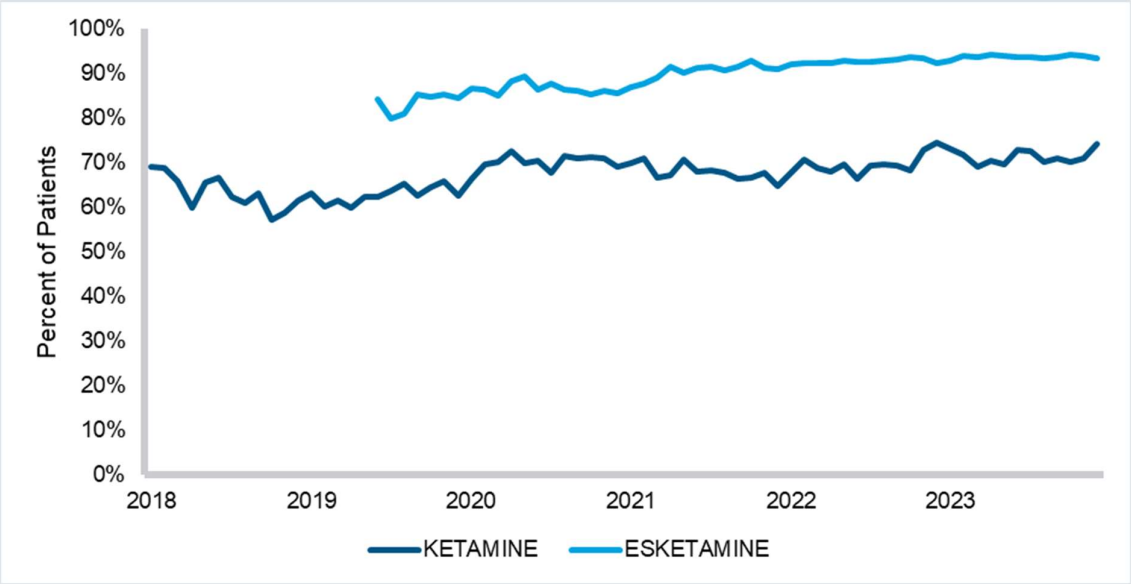
After its introduction the number of patients who switched from ketamine to esketamine each month began to rise, hitting its peak at 113 patients per month in February 2021 before plateauing to an average of 29 patients per month [**Figure 17**]. After October 2019 the number of patients switching from esketamine to ketamine each month remained relatively stable, at an average of 39 patients per month. Switches among patients with office-based administrations were rare.

Figure 17. Number of Projected Patients Dispensed Ketamine and Esketamine Who Subsequently Switch Products



From 2018 to 2023, the proportion of patients dispensed ketamine who had a subsequent prescription for ketamine after their initial (index) prescription remained relatively stable (67%) **[Figure 18]**. The proportion of patients dispensed esketamine who had a subsequent prescription for esketamine remained stable around 90%. Trends in subsequent office-based administrations were similar for both products.

Figure 18. Proportion of Patients Dispensed Ketamine and Esketamine Who are Subsequently Dispensed the Same Product



Discussion

We observed increasing use of esketamine both in unprojected office-based administrations and projected retail prescribing since its launch in 2019; nearly all providers of office-based administrations were in psychiatry/neurology specialties, but retail prescribing was from mostly psychiatry/neurology and NPs/PAs. At the same time, while projected retail prescribing of ketamine has increased gradually since 2018 (mostly among psychiatry/ neurology and NPs/PAs specialties), unprojected office-based administrations of ketamine increased until 2022 but declined thereafter; office-based administrations were most common with pain specialties. Overall, less than 1% of all medical (Dx) claims for ketamine and esketamine office-based administrations had telehealth designations. With respect to ketamine, our findings are consistent with a documented rise in the number of clinics and general interest around ketamine utilization in the lay press; however, it is still unclear in what clinical context and setting ketamine administration occurs, and what factors are driving increasing use. Data on esketamine use suggest continued uptake and market share growth after its approval consistent with other REMS regulated products.

Patient profiles and treatment practice

Patient profiles of those treated with esketamine and ketamine were mostly similar, with rather limited use in the youngest and oldest patient groups, and male patients. There were no noteworthy differences in trends across sex or other clinical characteristics, for both esketamine and ketamine use. A larger proportion (~20%) of ketamine patients were over the age of 65 compared to esketamine patients (~10%), suggesting that there may be age-related factors that influence whether patients access ketamine versus esketamine therapy. Most patients treated with esketamine (office-based administrations and retail prescribing) had depression diagnoses and/or were concurrently treated with antidepressants as indicated, and a notable proportion of those treated with ketamine had PTSD/anxiety diagnoses. Opioids were also concurrently prescribed for patients treated with ketamine, more so than for those treated with esketamine. Our findings are consistent with the lay press reporting increased interest in ketamine utilization for off-label indications like depression, PTSD/anxiety, and pain, but our data cannot differentiate between appropriate and inappropriate use or quantify the use in non-traditional healthcare settings that lack adequate regulatory controls. Similarly, while clinical appropriateness of esketamine use cannot be established, these data do suggest esketamine use is mostly in the context of depression in line with its indication and REMS. It is notable that most patients do not switch between products after their initial dispensing or administration; these subsequent fill data suggest that providers, and patients, are not using these drugs interchangeably.

Implications and next steps

Reports in the lay press of potentially inappropriate esketamine and ketamine use persist, including reports of use in telehealth. Viral marketing campaigns are actively targeting patients with ads suggesting the safe and effective use of these products for depression and other related conditions, but it is unclear what effect any increased awareness of these products has had on its use, appropriate or otherwise. Because of the risks associated with these products, continued monitoring is necessary to understand which groups are

disproportionately impacted by these treatment modalities and the potentially adverse consequences of their use for off-label indications. We observed some decline in ketamine administration in recent years at the same time esketamine use increased which may be due to more coverage by insurance providers and/or greater patient and provider awareness of esketamine, including for potentially other off-label uses. More robust treatment pathway analyses may be useful to better understand the patient profiles (clinical or otherwise) associated with esketamine and ketamine. Of note, while information on cash-paid prescriptions were included, data on office administrations are based on claims submitted for reimbursement and thus did not capture office-based administration paid in cash. As such, if cash payments make up a large proportion of office-based administration, this may result in an underestimation of ketamine and esketamine captured in office-based visits. Additional information is needed on payor-specific reimbursement and authorization practices, and how patients are typically accessing these drugs in clinic/office, retail, or telehealth settings as visibility into various treatment settings providing these therapies may be limited.

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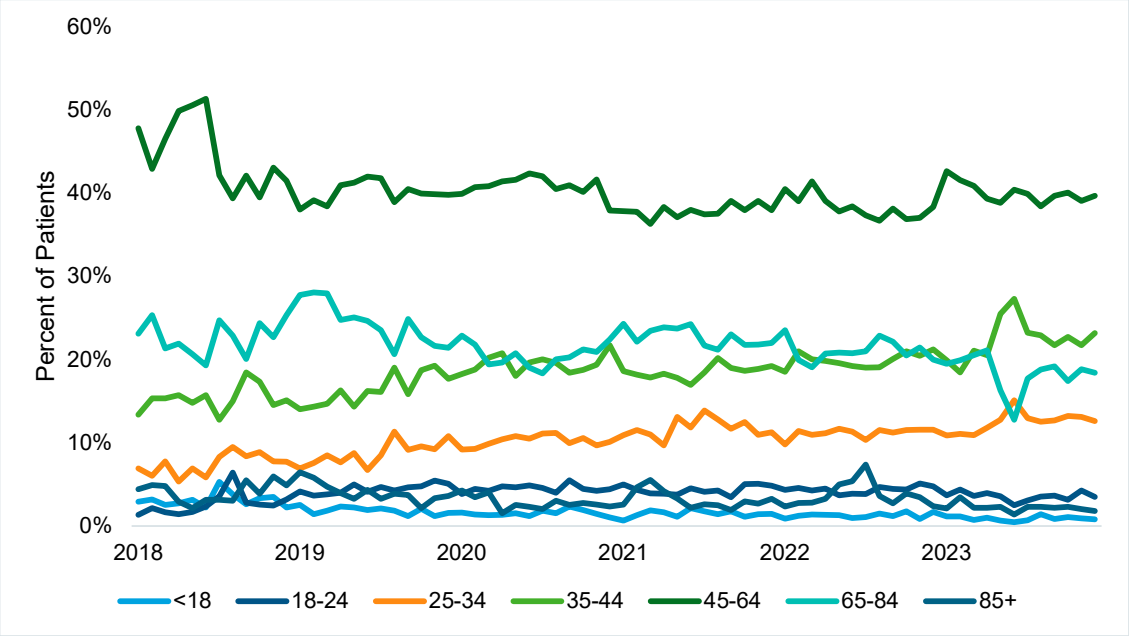
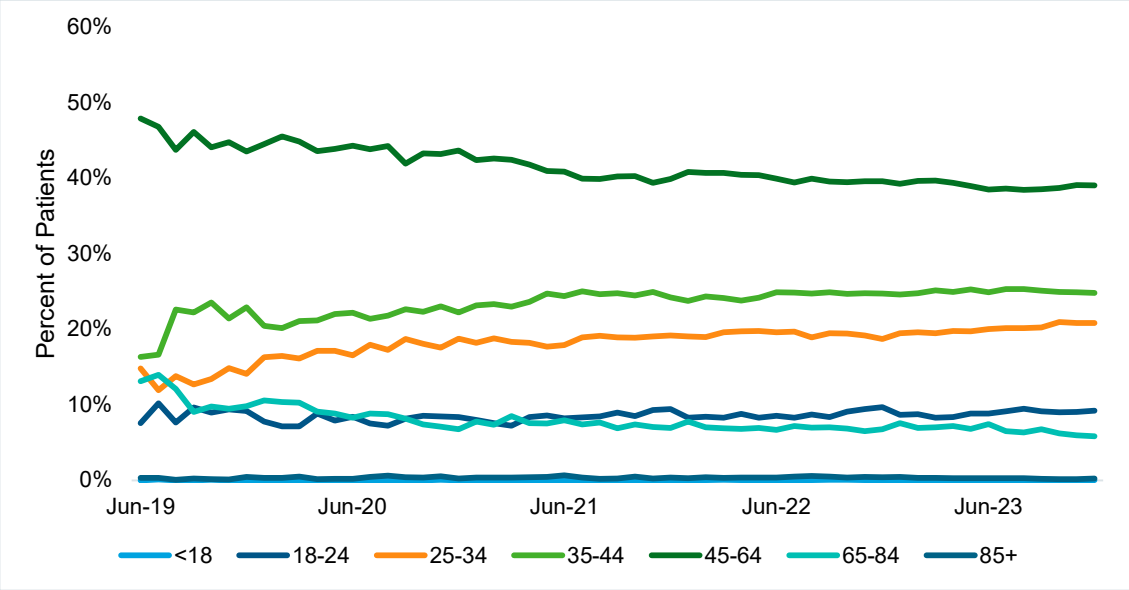
Appendix

Appendix Figure 1. Proportion of Projected Patients Dispensed Ketamine by Age



Appendix Figure 2. Proportion of Projected Patients Dispensed Esketamine by Age



Appendix 1. Data Sources

Prescription Claims Data (LRx)

Longitudinal Prescription (LRx) data track individual patients' prescriptions over time. IQVIA receives approximately 3.7 billion prescription claims for 250 million patients per year. LRx captures approximately 94% of all raw prescription transactions from retail pharmacies across the US, 74% for traditional and specialty mail order pharmacies, and 76% for long-term care pharmacies. LRx data are received electronically from pharmacies, payers, software providers, and transactional clearinghouses. LRx data contain granular prescription-level information on the pharmaceutical product dispensed, prescription specifications (e.g., dose, duration, etc.), prescriber, payer, and geographical location of the patient. Using an anonymous patient identifier, LRx data are longitudinally linked to other IQVIA patient-level data. For this analysis, prescriptions dispensed in the retail, long-term care, and mail-order channels were included.

Prescription patients were projected to national estimates using National Prescription Audit (NPA) projected prescription audits. NPA delivers prescriber-level prescription trends for retail, mail, and long-term care channels of distribution, and covers 93% of retail, 72% of mail, and 72% of long-term care prescriptions. Projection factors were calculated using product, channel, and month, and computed using the ratio of LRx prescriptions to NPA projections each month.

Office-Based Medical Claims Data (Dx)

Medical claims (Dx) data represent pre-adjudicated professional claims generated by office-based physicians and specialists and collected through practice management software and claims clearinghouses, or "switches." These data are sourced from CMS-1500 form-based or EDI 837p claim transactions, the standard reimbursement form for all non-cash claims. Medical claims contain patient level diagnoses, procedures performed, tests ordered, and drugs prescribed during visits to United States (US) office-based healthcare professionals, ambulatory and general healthcare sites. IQVIA receives more than 1.5 billion office-based medical claims per year, for more than 200 million patients per year. These claims represent transactions for services performed by physicians in office, ambulatory, or general healthcare sites, capturing over 96% of AMA providers.

Appendix 2. Ketamine and Esketamine Products

Market	Products	Formulations
ESKETAMINE	SPRAVATO 56MG DOSE	ESKETAMINE HCL NASAL SOLN 28 MG/DEVICE X 2 (56 MG DOSE PACK)
	SPRAVATO 84MG DOSE	ESKETAMINE HCL NASAL SOLN 28 MG/DEVICE X 3 (84 MG DOSE PACK)
KETAMINE		KETAMINE HCL INJ 10 MG/ML
		KETAMINE HCL INJ 100 MG/ML
	KETALAR	KETAMINE HCL INJ 50 MG/ML
	KETAMINE HCL	KETAMINE HCL INJ 50 MG/ML
	KETAMINE HCL-0.9% NACL	KETAMINE HCL
		KETAMINE HCL INJ 0.6 MG/ML
		KETAMINE HCL INJ 1 MG/ML
		KETAMINE HCL INJ 10 MG/ML
		KETAMINE HCL INJ 100 MG/ML
		KETAMINE HCL INJ 50 MG/ML
		KETAMINE HCL IV SOLN 100 MG/100ML
		KETAMINE HCL IV SOLN PREF SYR 30 MG/3ML (10 MG/ML)
		KETAMINE HCL IV SOLN PREF SYR 50 MG/5ML (10 MG/ML)
		KETAMINE HCL SOLN INJ PREF SYRINGE 100 MG/2ML
		KETAMINE HCL SOLN INJ PREF SYRINGE 300 MG/30ML
		KETAMINE HCL SOLN INJ PREF SYRINGE 50 MG/ML
		KETAMINE HCL SOLN PREF SYR 100 MG/10ML (10 MG/ML)
		KETAMINE HCL SOLN PREF SYR 100 MG/2ML
	KETAMINE HYDROCHLORIDE	KETAMINE HCL SOLN PREF SYR 20 MG/2ML (10 MG/ML)

Appendix 2. Ketamine and Esketamine Products

Market	Products	Formulations
		KETAMINE HCL SOLN PREF SYR 30 MG/3ML (10 MG/ML)
		KETAMINE HCL SOLN PREF SYR 50 MG/5ML (10 MG/ML)
		KETAMINE HCL SOLN PREF SYR 50 MG/ML
		KETAMINE HCL SOLN PREF SYR 60 MG/20ML (3 MG/ML)
		KETAMINE HCL TROCHE 100 MG
	KETAMINE HCL (BULK)	KETAMINE HCL (BULK) POWDER
	KETAMINE HYDROCHLORIDE (BULK)	KETAMINE HCL (BULK) POWDER
		KETAMINE HCL-NACL INJ PREF SYR 100 MG/10ML-0.9% (10MG/ML)
		KETAMINE HCL-NACL INJ SOLN PREF SY 50 MG/5ML-0.9% (10MG/ML)
		KETAMINE HCL-NACL IV SOLN 1000 MG/100ML-0.9% (10MG/ML)
		KETAMINE HCL-NACL SOLN PREF SY 10 MG/ML-0.9% (10MG/ML)
		KETAMINE HCL-NACL SOLN PREF SY 100 MG/10ML-0.9% (10MG/ML)
		KETAMINE HCL-NACL SOLN PREF SY 20 MG/2ML-0.9% (10MG/ML)
	KETAMINE HYDROCHLORIDE/SO	KETAMINE HCL-NACL SOLN PREF SY 50 MG/5ML-0.9% (10MG/ML)

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
ANTIDEPRESSANTS	ANTIDEPRESSANTS IN COMBINATION	CHLORDIAZEPOXIDE-AMITRIPTYLINE
		PERPHENAZINE-AMITRIPTYLINE
	ANTIDEPRESSANTS, OTHER	BREXANOLONE
		ESKETAMINE HCL
		ZURANOLONE
	MAO INHIBITORS	ISOCARBOXAZID
		PHENELZINE SULFATE
		SELEGILINE
		TRANYLCYPROMINE SULFATE
	NEWER GENERATION ANTIDEPRESSANT	BUPROPION HCL
		BUPROPION HCL-DIETARY MANAGEMENT PRODUCT
		BUPROPION HYDROBROMIDE
		DEXTROMETHORPHAN HYDROBROMIDE-BUPROPION HYDROCHLORIDE
		NEFAZODONE HCL
		TRAZODONE HCL
		TRAZODONE HCL-DIETARY MANAGEMENT PRODUCT
	SSRI	CITALOPRAM HYDROBROMIDE
		ESCITALOPRAM OXALATE
		FLUOXETINE HCL
		FLUVOXAMINE MALEATE
		PAROXETINE HCL

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		PAROXETINE MESYLATE
		SERTRALINE HCL
	SSRI/5HT PARTIAL AGONIST	VILAZODONE HCL
		VORTIOXETINE HBR
	SSRIs (SARAFEM/FLUOXETINE PMDD)	FLUOXETINE HCL (PMDD)
	TRICYCLICS & TETRACYCLICS	AMITRIPTYLINE HCL
		AMOXAPINE
		CLOMIPRAMINE HCL
		DESIPRAMINE HCL
		DOXEPIN HCL
		IMIPRAMINE HCL
		IMIPRAMINE PAMOATE
		MAPROTILINE HCL
		MIRTAZAPINE
		NORTRIPTYLINE HCL
		PROTRIPTYLINE HCL
		TRIMIPRAMINE MALEATE
ANTIPSYCHOTICS	ANTIDOPA PHENOTHIAZINE	PROCHLORPERAZINE
		PROCHLORPERAZINE EDISYLATE
		PROCHLORPERAZINE MALEATE
	ANTI-MANIA	CARBAMAZEPINE (MOOD)

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		LITHIUM
		LITHIUM CARBONATE
	ANTIPSYCHOTIC COMBINATION	OLANZAPINE-FLUOXETINE HCL
		OLANZAPINE-SAMIDORPHAN L-MALATE
	ANTIPSYCHOTICS, OTHER	ARIPIPRAZOLE
		ARIPIPRAZOLE LAUROXIL
		ARIPIPRAZOLE WITH SENSOR
		ARIPIPRAZOLE WITH SENSOR, STRIPS, & POD
		ASENAPINE
		ASENAPINE MALEATE
		BREXPIPRAZOLE
		CARIPRAZINE HCL
		CLOZAPINE
		HALOPERIDOL
		HALOPERIDOL DECANOATE
		HALOPERIDOL LACTATE
		ILOPERIDONE
		LOXAPINE
		LOXAPINE SUCCINATE
		LUMATEPERONE TOSYLATE
		LURASIDONE HCL

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		MOLINDONE HCL
		OLANZAPINE
		OLANZAPINE PAMOATE
		PALIPERIDONE
		PALIPERIDONE PALMITATE
		PIMAVANSERIN TARTRATE
		PIMOZIDE
		QUETIAPINE FUMARATE
		RISPERIDONE
		RISPERIDONE MICROSPHERES
		THIOTHIXENE
		ZIPRASIDONE HCL
		ZIPRASIDONE MESYLATE
	PHENOTHIAZINE DERIVATIVES	CHLORPROMAZINE
		CHLORPROMAZINE HCL
		FLUPHENAZINE DECANOATE
		FLUPHENAZINE HCL
		PERPHENAZINE
		THIORIDAZINE HCL
		TRIFLUOPERAZINE HCL
OPIOIDS	ANESTH GENERAL, INJECTABLE	ALFENTANIL

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		ALFENTANIL HCL
		REMIFENTANIL HCL
		REMIFENTANIL HCL-SODIUM CHLORIDE
		SUFENTANIL CITRATE
	CODEINE & COMB, NON-INJECTABLE	ACETAMINOPHEN W/ CODEINE
		ACETAMINOPHEN-CAFF-DIHYDROCOD
		ASPIRIN-CAFFEINE-DIHYDROCODEINE BITARTRATE
		BENZHYDROCODONE HCL-ACETAMINOPHEN
		BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE
		BUTALBITAL-ASPIRIN-CAFFEINE W/COD
		CODEINE SULFATE
		HYDROCODONE BITARTRATE
		HYDROCODONE-ACETAMINOPHEN
		HYDROCODONE-IBUPROFEN
		OXYCODONE
		OXYCODONE HCL
		OXYCODONE W/ ACETAMINOPHEN
		OXYCODONE-ASPIRIN
		OXYCODONE-IBUPROFEN
	DRUG DEPENDENCE	BUPRENORPHINE
		BUPRENORPHINE HCL

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		BUPRENORPHINE HCL-NALOXONE HCL DIHYDRATE
		METHADONE HCL
	MORPHINE/OPIUM, INJECTABLE	BUPRENORPHINE HCL
		FENTANYL CITRATE
		FENTANYL CITRATE-BUPIVACAINE HCL-SODIUM CHLORIDE
		FENTANYL CITRATE-ROPIVACAINE HCL-SODIUM CHLORIDE
		FENTANYL CITRATE-SODIUM CHLORIDE
		HYDROMORPHONE HCL
		HYDROMORPHONE HCL-BUPIVACAINE HCL-SODIUM CHLORIDE
		HYDROMORPHONE HCL-ROPIVACAINE HCL-SODIUM CHLORIDE
		HYDROMORPHONE HCL-SODIUM CHLORIDE
		MEPERIDINE HCL-SODIUM CHLORIDE
		MORPHINE SULFATE
		MORPHINE SULFATE FOR CONTINUOUS MICROINFUSION
		MORPHINE SULFATE IN DEXTROSE
		MORPHINE SULFATE-SODIUM CHLORIDE
		NALBUPHINE HCL
	MORPHINE/OPIUM, NON-INJECTABLE	BUPRENORPHINE
		BUPRENORPHINE HCL
		FENTANYL
		FENTANYL CITRATE

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		FENTANYL HCL
		HYDROMORPHONE HCL
		MORPHINE SULFATE
		MORPHINE SULFATE BEADS
		MORPHINE-NALTREXONE
		OXYMORPHONE HCL
		SUFENTANIL CITRATE
	PROPOXYPHENE	PROPOXYPHENE HCL
		PROPOXYPHENE HCL W/ ACETAMINOPHEN
		PROPOXYPHENE-N W/ ACETAMINOPHEN
	SYNTH NARCOTIC, INJECTABLE	BUTORPHANOL TARTRATE
		FENTANYL CITRATE-BUPIVACAINE HCL-SODIUM CHLORIDE
		MEPERIDINE HCL
		MEPERIDINE HCL-SODIUM CHLORIDE
		METHADONE HCL
		METHADONE HCL-SODIUM CHLORIDE
		OLICERIDINE FUMARATE
	SYNTH NARCOTIC, NON-INJECTABLE	BUTORPHANOL TARTRATE
		CELECOXIB-TRAMADOL HCL
		LEVORPHANOL TARTRATE
		MEPERIDINE HCL

Appendix 3. Co-Treatment Definition

Market	Products	Formulations
		MEPERIDINE W/ PROMETHAZINE
		METHADONE HCL
		PENTAZOCINE W/ NALOXONE HCL
		PENTAZOCINE-ACETAMINOPHEN
		TAPENTADOL HCL
		TRAMADOL HCL
		TRAMADOL-ACETAMINOPHEN
	SYNTH NON-NARC, NON-INJECTABLE	TRAMADOL HCL

Appendix 4. Comorbidity Definition

Diagnosis	ICD-10 Codes
ANXIETY	F06.4, F40, F40.0, F40.00, F40.01, F40.02, F40.1, F40.10, F40.11, F40.2, F40.21, F40.210, F40.218, F40.22, F40.220, F40.228, F40.23, F40.230, F40.231, F40.232, F40.233, F40.24, F40.240, F40.241, F40.242, F40.243, F40.248, F40.29, F40.290, F40.291, F40.298, F40.8, F40.9, F41, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F42.2, F42.3, F42.4, F42.8, F42.9, F43.1, F43.10, F43.11, F43.12, F43.22, F43.23, F93.0, F93.8
BIPOLAR	F30, F30.1, F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F30.9, F31, F31.0, F31.1, F31.10, F31.11, F31.12, F31.13, F31.2, F31.3, F31.30, F31.31, F31.32, F31.4, F31.5, F31.6, F31.60, F31.61, F31.62, F31.63, F31.64, F31.7, F31.70, F31.71, F31.72, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.8, F31.81, F31.89, F31.9
DEPRESSION	F32, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.8, F32.81, F32.89, F32.9, F32.A, F33, F33.0, F33.1, F33.2, F33.3, F33.4, F33.40, F33.41, F33.42, F33.8, F33.9, F34.1, F43.23, F53.0
SCHIZOPHRENIA	F20, F20.0, F20.1, F20.2, F20.3, F20.5, F20.8, F20.81, F20.89, F20.9, F25, F25.0, F25.1, F25.8, F25.9
SUBSTANCE/ALCOHOL ABUSE	F10, F10.1, F10.10, F10.11, F10.12, F10.120, F10.121, F10.129, F10.13, F10.130, F10.131, F10.132, F10.139, F10.14, F10.15, F10.150, F10.151, F10.159, F10.18, F10.180, F10.181, F10.182, F10.188, F10.19, F10.2, F10.20, F10.21, F10.22, F10.220, F10.221, F10.229, F10.23, F10.230, F10.231, F10.232, F10.239, F10.24, F10.25, F10.250, F10.251, F10.259, F10.26, F10.27, F10.28, F10.280, F10.281, F10.282, F10.288, F10.29, F10.9, F10.90, F10.91, F10.92, F10.920, F10.921, F10.929, F10.93, F10.930, F10.931, F10.932, F10.939, F10.94, F10.95, F10.950, F10.951, F10.959, F10.96, F10.97, F10.98, F10.980, F10.981, F10.982, F10.988, F10.99, F11, F11.1, F11.10, F11.11, F11.12, F11.120, F11.121, F11.122, F11.129, F11.13, F11.14, F11.15, F11.150, F11.151, F11.159, F11.18, F11.181, F11.182, F11.188, F11.19, F11.2, F11.20, F11.21, F11.22, F11.220, F11.221, F11.222, F11.229, F11.23, F11.24, F11.25, F11.250, F11.251, F11.259, F11.28, F11.281, F11.282, F11.288, F11.29, F11.9, F11.90, F11.91, F11.92, F11.920, F11.921, F11.922, F11.929, F11.93, F11.94, F11.95, F11.950, F11.951, F11.959, F11.98, F11.981, F11.982, F11.988, F11.99, F12, F12.1, F12.10, F12.11, F12.12, F12.120, F12.121, F12.122, F12.129, F12.13, F12.15, F12.150, F12.151, F12.159, F12.18, F12.180, F12.188, F12.19, F12.2, F12.20, F12.21, F12.22, F12.220, F12.221, F12.222, F12.229, F12.23, F12.25, F12.250, F12.251, F12.259, F12.28, F12.280, F12.288, F12.29, F12.9, F12.90, F12.91, F12.92, F12.920, F12.921, F12.922, F12.929, F12.93, F12.95, F12.950, F12.951, F12.959, F12.98, F12.980, F12.988, F12.99, F13, F13.1, F13.10, F13.11, F13.12, F13.120, F13.121, F13.129, F13.13, F13.130, F13.131, F13.132, F13.139, F13.14, F13.15, F13.150, F13.151, F13.159, F13.18, F13.180, F13.181, F13.182, F13.188, F13.19, F13.2, F13.20, F13.21, F13.22, F13.220,

Appendix 4. Comorbidity Definition

Diagnosis	ICD-10 Codes
	F13.221, F13.229, F13.23, F13.230, F13.231, F13.232, F13.239, F13.24, F13.25, F13.250, F13.251, F13.259, F13.26, F13.27, F13.28, F13.280, F13.281, F13.282, F13.288, F13.29, F13.9, F13.90, F13.91, F13.92, F13.920, F13.921, F13.929, F13.93, F13.930, F13.931, F13.932, F13.939, F13.94, F13.95, F13.950, F13.951, F13.959, F13.96, F13.97, F13.98, F13.980, F13.981, F13.982, F13.988, F13.99, F14, F14.1, F14.10, F14.11, F14.12, F14.120, F14.121, F14.122, F14.129, F14.13, F14.14, F14.15, F14.150, F14.151, F14.159, F14.18, F14.180, F14.181, F14.182, F14.188, F14.19, F14.2, F14.20, F14.21, F14.22, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.25, F14.250, F14.251, F14.259, F14.28, F14.280, F14.281, F14.282, F14.288, F14.29, F14.9, F14.90, F14.91, F14.92, F14.920, F14.921, F14.922, F14.929, F14.93, F14.94, F14.95, F14.950, F14.951, F14.959, F14.98, F14.980, F14.981, F14.982, F14.988, F14.99, F15, F15.1, F15.10, F15.11, F15.12, F15.120, F15.121, F15.122, F15.129, F15.13, F15.14, F15.15, F15.150, F15.151, F15.159, F15.18, F15.180, F15.181, F15.182, F15.188, F15.19, F15.2, F15.20, F15.21, F15.22, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.25, F15.250, F15.251, F15.259, F15.28, F15.280, F15.281, F15.282, F15.288, F15.29, F15.9, F15.90, F15.91, F15.92, F15.920, F15.921, F15.922, F15.929, F15.93, F15.94, F15.95, F15.950, F15.951, F15.959, F15.98, F15.980, F15.981, F15.982, F15.988, F15.99, F16, F16.1, F16.10, F16.11, F16.12, F16.120, F16.121, F16.122, F16.129, F16.14, F16.15, F16.150, F16.151, F16.159, F16.18, F16.180, F16.183, F16.188, F16.19, F16.2, F16.20, F16.21, F16.22, F16.220, F16.221, F16.229, F16.24, F16.25, F16.250, F16.251, F16.259, F16.28, F16.280, F16.283, F16.288, F16.29, F16.9, F18, F18.1, F18.10, F18.11, F18.12, F18.120, F18.121, F18.129, F18.14, F18.15, F18.150, F18.151, F18.159, F18.17, F18.18, F18.180, F18.188, F18.19, F18.2, F18.20, F18.21, F18.22, F18.220, F18.221, F18.229, F18.24, F18.25, F18.250, F18.251, F18.259, F18.27, F18.28, F18.280, F18.288, F18.29, F18.9, F18.90, F18.91, F18.92, F18.920, F18.921, F18.929, F18.94, F18.95, F18.950, F18.951, F18.959, F18.97, F18.98, F18.980, F18.988, F18.99, F19, F19.1, F19.10, F19.11, F19.12, F19.120, F19.121, F19.122, F19.129, F19.13, F19.130, F19.131, F19.132, F19.139, F19.14, F19.15, F19.150, F19.151, F19.159, F19.16, F19.17, F19.18, F19.180, F19.181, F19.182, F19.188, F19.19, F19.2, F19.20, F19.21, F19.22, F19.220, F19.221, F19.222, F19.229, F19.23, F19.230, F19.231, F19.232, F19.239, F19.24, F19.25, F19.250, F19.251, F19.259, F19.26, F19.27, F19.28, F19.280, F19.281, F19.282, F19.288, F19.29, F19.9, G62.1, I42.6, K29.2, K70, K70.0, K70.1, K70.10, K70.11, K70.2, K70.3, K70.30, K70.31, K70.4, K70.40, K70.41, K70.9, Z71.41, Z71.51