

Overview for Request

Request ID: cder_iqp_wp010

Request Description: In this request, we described ketamine use and comparator use among patients with psychiatric indications and emergency department (ED) visits in the TriNetX USA Network Database.

Data Source: We ran this query on September 15, 2020. This query contains data from 54 health care organizations (HCOs) provided through the TriNetX USA Network Database from January 1, 2016 through August 31, 2020. TriNetX aggregates electronic health record (EHR) systems data from its partner HCOs to create queryable datasets. TriNetX datasets primarily comprise of clinical patient data such as demographics, diagnoses, procedures, labs, and medications. For more information on the TriNetX Live™ platform and the TriNetX data visit their website here: <https://trinetx.com/>

Study Design: We identified a base population of patients with emergency department visits and two different definitions (broad and specific) of psychiatric indications in the TNX database, by year. We used the treatment pathways analytic module to identify any ketamine use, any ketamine or benzodiazepine use, any ketamine or antipsychotic use, any benzodiazepine use, and any antipsychotic use.

Exposures of Interest: We defined psychiatric indications using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. We defined emergency department visit using TriNetX curated visit term and Please see Appendix A for a list of ICD-10-CM codes and the curated visit term used in this request.

Cohort Eligibility Criteria: Patients of all ages and genders were included in this report.

Characteristics: We described use of the following medications within one day of an emergency department visit: ketamine, benzodiazepines, antipsychotics, and combinations of these medications. Please see Appendix B for a list of RxNorm codes and Healthcare Common Procedure Coding System (HCPCS) codes used to define medications in this report.

Please see Appendices C and D for the overall specifications of parameters used in this report.

Limitations: Algorithms used to define exposures, characteristics, pregnancy, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the US lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that might not participate in the TriNetX USA network. We are unable to determine if absence of evidence of a condition implies a true absence of a condition or if the condition was not observed in the data. Furthermore, not all HCOs provide brand name information for RxNorm terms or laboratory data. Therefore, data should be interpreted with these limitations in mind. All counts provided through the TriNetX Live™ platform are rounded up to the nearest ten to protect patient privacy. This rounding affects error, especially as sample sizes decrease. Error due to rounding can range from <0.09% when sample sizes are >10,000 to nearly 20% as sample sizes drop. Thus, all estimates should be interpreted as ranges, and small sample sizes should be interpreted with caution. Additionally, percentages are calculated based on these rounded numerators and denominators. Thus, due to rounding, the sum of each value in a category may not total to 100%.

Notes: We ran this query on September 15, 2020. A re-run of this query for the same query period in the future may not yield the same results owing to the dynamic nature of the TriNetX Live™ network. Please contact the Sentinel Operations Center (info@sentinelssystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's querying in the TriNetX platform, please refer to the Sentinel Website (<https://www.sentinelinitiative.org/methods-data-tools/methods/trinetx-rapid-querying>).

Overview for Request

Table of Contents

<u>Glossary</u>	List of Terms Found in this Report and their Definitions
<u>Table 1a</u>	Counts of Patients with Psychiatric Indications (Broad Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020
<u>Table 1b</u>	Counts of Patients with Psychiatric Indications (Specific Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020
<u>Figure 1a</u>	Counts of Patients with Psychiatric Indications (Broad Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020
<u>Figure 1b</u>	Counts of Patients with Psychiatric Indications (Specific Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020
<u>Appendix A</u>	List of International Classification of Diseases, Tenth Edition (ICD-10) Diagnosis Codes and Curated Visit Terms Used to Define Exposures in this Request
<u>Appendix B</u>	List of Healthcare Common Procedure Coding System (HCPCS) Procedure Codes and RxNorm Codes Used to Define Characteristics in this Request
<u>Appendix C</u>	Specifications Defining Parameters in this Request
<u>Appendix D</u>	Study Design Diagram for Cohort Entry Requirements

Glossary of Terms for Analyses Using TriNetX Live™ Platform*

Characteristic - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or before the cohort-defining index event.

Explore Cohort - A description module on the TriNetX platform that presents a clinical profile of patients in a given cohort. Patient counts are rounded up to the nearest 10 before percentages are calculated, so the sum each of the values in one category may not total to 100%.

Date Shifting - A data obfuscation technique that some HCOs use to preserve patient privacy. Date shifting entails assigning each patient a random number of days (eg, -365 to +365 days) and consistently adjusting each of their dates by that number of days, thus maintaining temporal relationships between records within a single patient.

Fact - (Medical Fact) A unit of utilization that represents a medical observation on a patient (e.g., diagnosis, procedure, clinical observation).

Filter - A method of limiting terms included in queries to a specific subset of data. Filters include age at time of event, data source (electronic health record or natural language processing); brand name, route, and strength for medication terms; occurrence (first or most recent) for lab terms; and priority for diagnosis and procedure terms.

Group - A series of codes and terms defined with Boolean logic that are used to create a query cohort. For each group, users have the ability to specified time periods of interest, and the number of instances that the group must occur for cohort entry.

Subgroup - Within a group, additional subgroups can be specified to define temporal relationships between the terms in the subgroup (e.g., terms in subgroup B must occur within 5 days after terms in subgroup A). Users can require that these temporal constraints be applied to the 1) first, 2) last, or 3) any instance of each subgroup.

Health Care Organization (HCO) - Organizations that contribute electronic healthcare record data to the TriNetX data networks. HCOs include academic institutions and community health provider systems and a single HCO may contain one or more individual sites or facilities.

Index - The first date when a patient meets all of the cohort-defining criteria. In Analytics modules, the index can be defined as the date when a patient meets all of the cohort criteria, or only one specific group's criteria.

Module - A subsection of the TriNetX platform that performs a distinct functionality. Cohorts are created using the Query Builder module. Descriptive modules include Healthcare Organizations, Explore Cohorts, Rate of Arrival, Summary Statistics, and Analyze Criteria. Advanced analytic modules include Analyze Outcomes, Compare Outcomes, Compare Cohorts, Treatment Pathways, and Incidence and Prevalence.

Network - An aggregation of HCOs contributing data to the platform. Multiple networks are available for querying on the platform; the different networks represent subsets of HCOs organized by date-shifting practices or availability of downloadable datasets.

Outcome - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or after the cohort-defining index event.

Query - In the TriNetX platform, a query is a distinct cohort with a unique set of terms and logic. Query cohorts are created using the Query Builder platform module.

Risk - In Advanced Analytics modules, risk refers to the percentage of patients in each cohort with the specified outcome of interest.

Priority - An indication whether the code was the condition that the provider spent the most time evaluating or treating during a visit. Possible values include primary, secondary, or unknown.

Term - The codes used to specify patient cohort criteria in a query. Code options include diagnoses, procedures, medications, labs, demographics, genomics, and visits. Terms can be linked together using and/or Boolean logic. TriNetX also creates terms that group together multiple medical codes into single clinical concepts.

Cannot Have Term - A category of terms within a query group that patients must not have evidence of to be included in the cohort.

Must Have Term - A category of terms within a query group that patients must have evidence of to be included in the cohort.

Time Constraint - used to define time periods of interest for each group within a query. Time constraints can be defined relative to the date the query was run (e.g., any time before today), or defined based on specific dates (e.g., January 1, 2015 to September 30, 2020).

Treatment Pathway - In Advanced Analytics modules, the Treatment Pathways module returns the order in which patients received treatment and the prevalence of treatments, including combination of medications, following an index event.

Glossary of Terms for Analyses Using TriNetX Live™ Platform*

TriNetX Codes - For commonly used laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes at a clinically significant level to new queryable TNX:LAB terms.

Visit - A type of term used to specify the type of medical encounter or facility where the encounter was recorded. Visit terms are derived by TriNetX from the source data. Visits are recorded separately from the codes or labs that occurred during the encounter; care settings are not attached to individual codes. Values for visit terms include: ambulatory, emergency, field, home health, inpatient encounter, inpatient acute, inpatient non-acute, laboratory, observation, pharmacy, pre-admission, short stay, virtual, and unknown.

*all terms may not be used in this report

Table 1a. Counts of Patients with Psychiatric Indications (Broad Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020

	2016		2017		2018		2019		YTD2020	
	Patients	HCOs	Patients	HCOs	Patients	HCOs	Patients	HCOs	Patients	HCOs
<i>ED visit and broad ICD-10 codes</i>	388,310	54	455,600	54	502,750	54	522,790	53	302,710	54
<i>Any ketamine</i>	1,822		2,402		2,580		3,113		2,190	
<i>Ketamine alone</i>	549		699		812		1,042		739	
<i>Any benzodiazepine</i>	57,932		69,265		74,774		78,746		51,949	
<i>Benzodiazepine alone</i>	42,886		50,012		52,718		54,650		33,442	
<i>Any antipsychotic</i>	28,974		37,454		44,468		47,778		33,744	
<i>Antipsychotic alone</i>	14,751		19,204		23,393		24,775		15,953	
<i>Treatment combinations</i>										
<i>Ketamine and benzodiazepine</i>	907		1,112		1,127		1,293		861	
<i>Ketamine and antipsychotics</i>	84		109		146		200		145	
<i>Benzodiazepine and antipsychotics</i>	13,857		17,659		20,434		22,225		17,201	
<i>Ketamine and benzodiazepine and antipsychotics</i>	282		482		495		578		445	

HCO = Health Care Organization

ED = Emergency Department

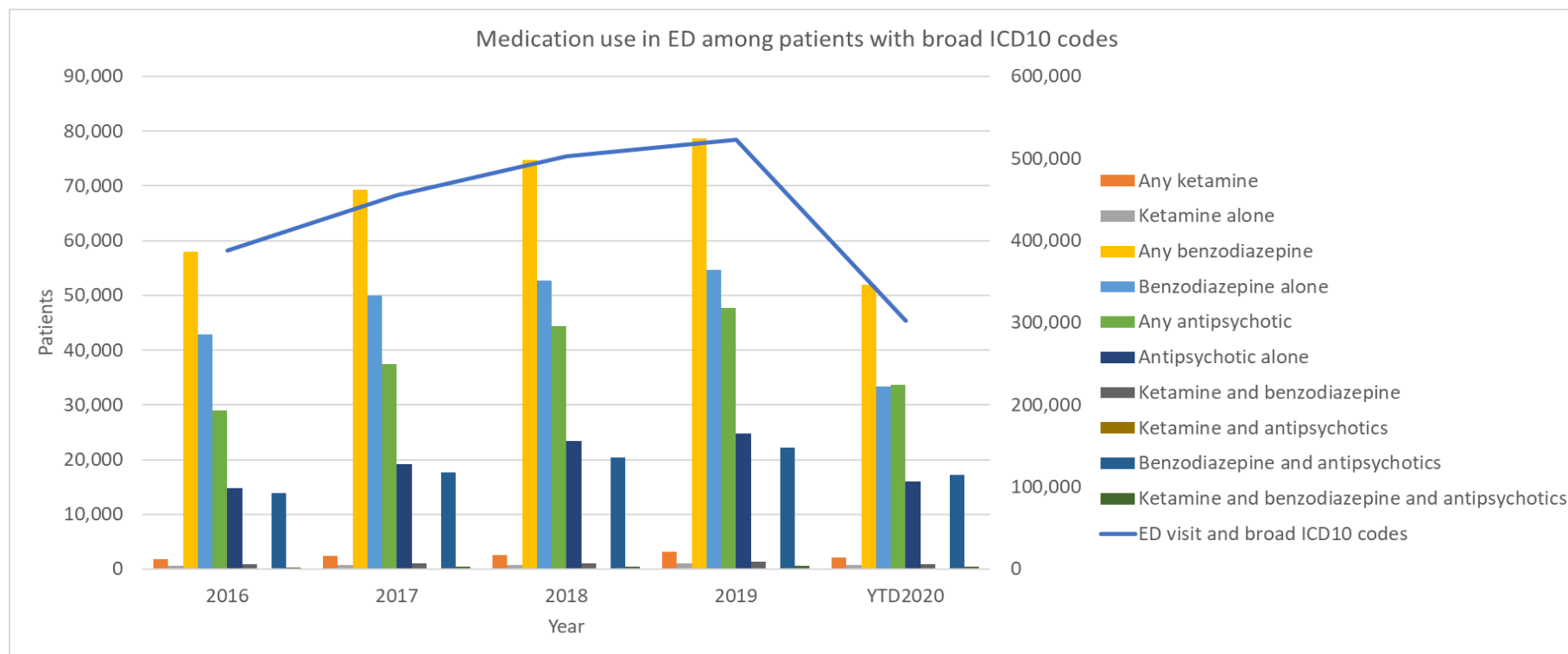
Table 1b. Counts of Patients with Psychiatric Indications (Specific Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020

	2016		2017		2018		2019		YTD2020	
	Patients	HCOs	Patients	HCOs	Patients	HCOs	Patients	HCOs	Patients	HCOs
<i>ED visit and specific ICD-10 codes</i>	276,190		318,060		350,490		363,530		214,450	54
<i>Any ketamine</i>	1,579	0	2,088	0	2,216	0	2,689	0	1,889	
<i>Ketamine alone</i>	443		569		660		865		611	
<i>Any benzodiazepine</i>	48,441	0	57,400	0	62,574	0	65,727	0	43,679	
<i>Benzodiazepine alone</i>	35,608		41,416		44,150		45,569		28,275	
<i>Any antipsychotic</i>	23,184	0	29,208	0	34,989	0	37,508	0	26,706	
<i>Antipsychotic alone</i>	11,097		14,111		17,416		18,346		11,929	
<i>Treatment combinations</i>										
<i>Ketamine and benzodiazepine</i>	816		979		980		1,155		752	
<i>Ketamine and antipsychotics</i>	70		92		129		159		125	
<i>Benzodiazepine and antipsychotics</i>	11,767		14,557		16,997		18,493		14,251	
<i>Ketamine and benzodiazepine and antipsychotics</i>	250		448		447		510		401	

HCO = Health Care Organization

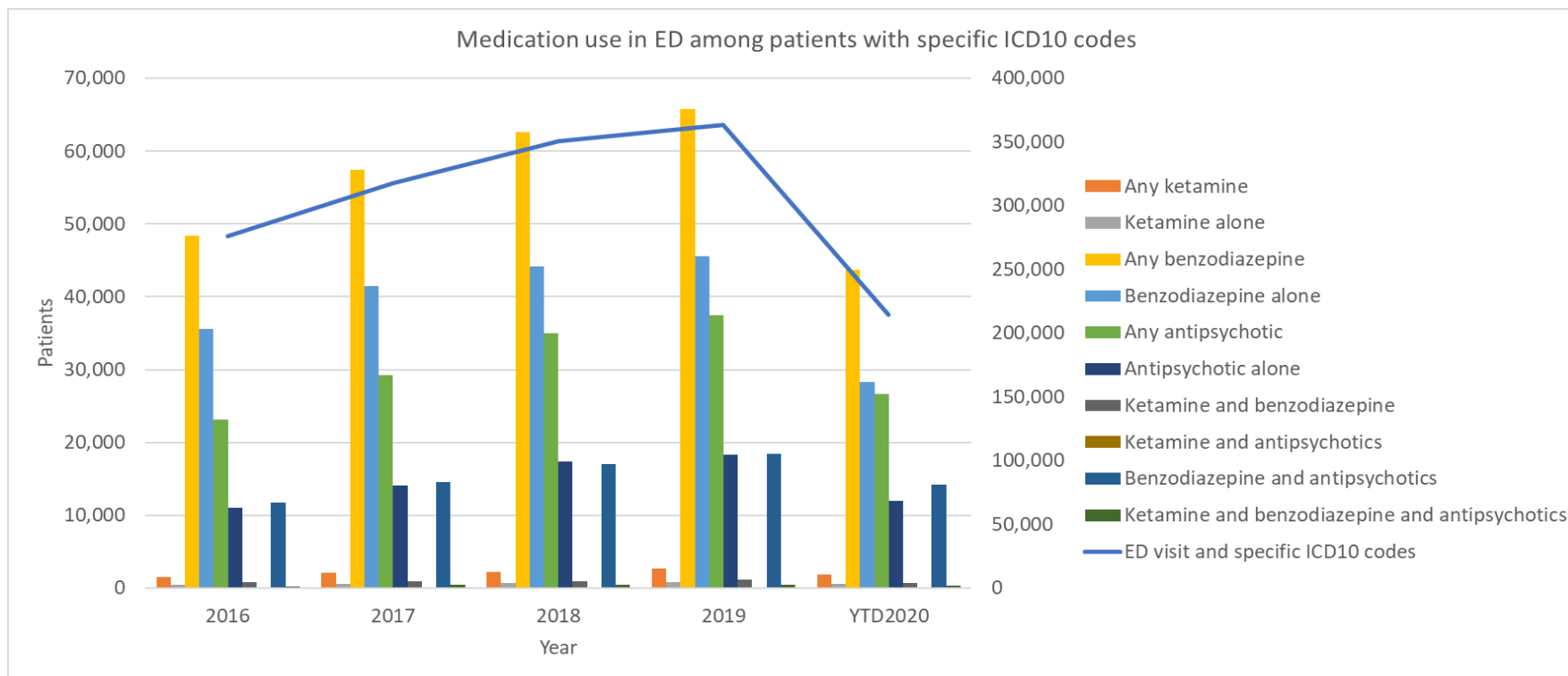
ED = Emergency Department

Figure 1a. Counts of Patients with Psychiatric Indications (Broad Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020



ED = Emergency Department

Figure 1b. Counts of Patients with Psychiatric Indications (Specific Definition) by Treatment within One Day of an Emergency Department Visit from January 1, 2016 through August 31, 2020



ED = Emergency Department

Appendix A. List of International Classification of Diseases, Tenth Edition (ICD-10) Diagnosis Codes and Curated Visit Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type
Psychiatric Disorders			
F01-F03, F05-F06, parent and child codes	Mental disorders	Broad	ICD-10
F10-F11, F14-F16, parent and child codes	Alcohol substance use, dependence, and abuse	Broad	ICD-10
F20-29, parent and child codes	Schizophrenia	Broad	ICD-10
F30, parent and child codes	Manic episode	Broad	ICD-10
F31, parent and child codes	Bipolar disorder	Broad	ICD-10
F53.1	Puerperal psychosis	Broad	ICD-10
F84.0	Autistic disorder	Broad	ICD-10
G30, parent and child codes	Alzheimer's disease	Broad	ICD-10
G31, parent and child codes	Dementia	Broad	ICD-10
G31.83	Dementia with Lewy bodies	Broad	ICD-10
G92	Toxic encephalopathy	Broad	ICD-10
R41, parent and child codes	Other symptoms and signs involving cognitive functions and awareness	Broad	ICD-10
R44-R46, parent and child codes	Other symptoms and signs	Broad	ICD-10
F01.51	Vascular dementia with behavioral disturbance	Specific	ICD-10
F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance	Specific	ICD-10
F03.91	Unspecified dementia with behavioral disturbance	Specific	ICD-10
F05	Delirium due to known physiological condition	Specific	ICD-10
F06.0	Psychotic disorder with hallucinations due to known physiological condition	Specific	ICD-10
F06.2	Psychotic disorder with delusions due to known physiological condition	Specific	ICD-10
F06.33-F06.34	Mood disorder due to known physiological condition with manic features	Specific	ICD-10
F10-F11, F14-F16, parent and child codes	Substance use, dependence, and abuse	Specific	ICD-10
F20-29, parent and child codes	Schizophrenia	Specific	ICD-10
F30, parent and child codes	Manic episode	Specific	ICD-10
F31.2	Bipolar disorder, current episode manic severe with psychotic features	Specific	ICD-10
F31.64	Bipolar disorder, current episode mixed, severe, with psychotic features	Specific	ICD-10
F31.73-F31.34	Bipolar disorder, most recent episode manic	Specific	ICD-10
F31.77-F31.78	Bipolar disorder, most recent episode mixed	Specific	ICD-10
F53.1	Puerperal psychosis	Specific	ICD-10
F84.0	Autistic disorder	Specific	ICD-10
G30, parent and child codes	Alzheimer's disease	Specific	ICD-10
G31.0 and child codes	Frontotemporal dementia	Specific	ICD-10
G31.1-G31.2	Degeneration of brain	Specific	ICD-10
G31.83	Dementia with Lewy bodies	Specific	ICD-10

Appendix A. List of International Classification of Diseases, Tenth Edition (ICD-10) Diagnosis Codes and Curated Visit Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type
G92	Toxic encephalopathy	Specific	ICD-10
R41.82	Altered mental status, unspecified	Specific	ICD-10
R44.0	Hallucinations, auditory	Specific	ICD-10
R44.2-R44.3	Hallucinations, other or unspecified	Specific	ICD-10
R45.1	Restlessness and agitation	Specific	ICD-10
R45.4	Irritability and anger	Specific	ICD-10
R45.6	Violent behavior	Specific	ICD-10
Emergency Department Visit			
N/A	Emergency Department	Custom TriNetX Cod	TNX Curated

N/A: Not Applicable

Appendix B. List of Healthcare Common Procedure Coding System (HCPCS) Procedure Codes and RxNorm Codes Used to Define Characteristics in this Request

Code	Description	Code Category	Code Type
Antipsychotics			
J0400	INJECTION, ARIPIPRAZOLE, INTRAMUSCULAR, 0.25 MG	Procedure	HCPCS
J1630	INJECTION, HALOPERIDOL, UP TO 5 MG	Procedure	HCPCS
J2950	INJECTION, PROMAZINE HCL, UP TO 25 MG	Procedure	HCPCS
J3310	INJECTION, PERPHENAZINE, UP TO 5 MG	Procedure	HCPCS
J3400	INJECTION, TRIFLUPROMAZINE HCL, UP TO 20 MG	Procedure	HCPCS
J3486	INJECTION, ZIPRASIDONE MESYLATE, 10 MG	Procedure	HCPCS
S0166	INJECTION, OLANZAPINE, 2.5 MG	Procedure	HCPCS
10502	thioridazine	Medication	RxNorm
10510	thiothixene	Medication	RxNorm
10800	trifluoperazine	Medication	RxNorm
10805	triflupromazine	Medication	RxNorm
16735	acetophenazine	Medication	RxNorm
2403	chlorpromazine	Medication	RxNorm
4496	fluphenazine	Medication	RxNorm
8076	perphenazine	Medication	RxNorm
1040028	lurasidone	Medication	RxNorm
115698	ziprasidone	Medication	RxNorm
1658314	brexpiprazole	Medication	RxNorm
1667655	cariprazine	Medication	RxNorm
1673265	aripiprazole lauroxil	Medication	RxNorm
1791685	pimavanserin	Medication	RxNorm
2274602	Lumateperone	Medication	RxNorm
2626	clozapine	Medication	RxNorm
35636	risperidone	Medication	RxNorm
5093	haloperidol	Medication	RxNorm
51272	quetiapine	Medication	RxNorm
61381	olanzapine	Medication	RxNorm
6475	loxapine	Medication	RxNorm
679314	paliperidone	Medication	RxNorm
7019	molindone	Medication	RxNorm
73178	iloperidone	Medication	RxNorm
784649	asenapine	Medication	RxNorm
89013	aripiprazole	Medication	RxNorm
Benzodiazepines			
J1990	INJECTION, CHLORDIAZEPOXIDE HCL, UP TO 100 MG	Procedure	HCPCS
J2060	INJECTION, LORAZEPAM, 2 MG	Procedure	HCPCS
J2250	INJECTION, MIDAZOLAM HYDROCHLORIDE, PER 1 MG	Procedure	HCPCS
J3360	INJECTION, DIAZEPAM, UP TO 5 MG	Procedure	HCPCS
10355	temazepam	Medication	RxNorm
10767	triazolam	Medication	RxNorm
2353	clorazepate	Medication	RxNorm
2356	chlordiazepoxide	Medication	RxNorm
2598	clonazepam	Medication	RxNorm

Appendix B. List of Healthcare Common Procedure Coding System (HCPCS) Procedure Codes and RxNorm Codes Used to Define Characteristics in this Request

Code	Description	Code Category	Code Type
3322	diazepam	Medication	RxNorm
35185	quazepam	Medication	RxNorm
4077	estazolam	Medication	RxNorm
4501	flurazepam	Medication	RxNorm
596	alprazolam	Medication	RxNorm
6470	lorazepam	Medication	RxNorm
6960	midazolam	Medication	RxNorm
7781	oxazepam	Medication	RxNorm
8627	prazepam	Medication	RxNorm
Ketamine			
6130	ketamine	Medication	RxNorm

Appendix C. Specifications Defining Parameters in this Request

Study Cohorts	
2016	
Cohort 1: ED Visit with Broad ICD - 2016	
<u>Event 1 - ED Visit w Psychiatric Indication</u>	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2016 - 12/31/2016
1B. Broad definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Time frame: Same day as ED visit	
1) Any ketamine or benzo use (will return mutually exclusive breakdown of ketamine, benzo, and ketamine AND benzo use)	
2) Any ketamine or antipsychotic use (will return mutually exclusive breakdown of ketamine, antipsychotic, and ketamine AND antipsychotic use)	
Cohort 2: ED Visit with Narrow ICD - 2016	
<u>Event 1 - ED Visit w Psychiatric Indication</u>	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2016 - 12/31/2016
1B. Narrow definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Time frame: Same day as ED visit	
1) Any ketamine or benzo use (will return mutually exclusive breakdown of ketamine, benzo, and ketamine AND benzo use)	
2) Any ketamine or antipsychotic use (will return mutually exclusive breakdown of ketamine, antipsychotic, and ketamine AND antipsychotic use)	

Appendix C. Specifications Defining Parameters in this Request

Study Cohorts	
2017	
Cohort 3: ED Visit w Broad ICD - 2017	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2017 - 12/31/2017
1B. Broad definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Cohort 4: ED Visit with Narrow ICD - 2017	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2017 - 12/31/2017
1B. Narrow definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	

Appendix C. Specifications Defining Parameters in this Request

Study Cohorts	
2018	
Cohort 5: ED Visit with Broad ICD - 2018	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2018 - 12/31/2018
1B. Broad definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Cohort 6: ED Visit with Narrow ICD - 2018	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2018 - 12/31/2018
1B. Narrow definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	

Appendix C. Specifications Defining Parameters in this Request

Study Cohorts	
2019	
Cohort 7: ED Visit with Broad ICD - 2019	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2019 - 12/31/2019
1B. Broad definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Cohort 8: ED Visit with Narrow ICD - 2019	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2019 - 12/31/2019
1B. Narrow definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	

Appendix C. Specifications Defining Parameters in this Request

Study Cohorts	
2020	
Cohort 9: ED Visit with Broad ICD - 2020	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2020 - 08/31/2020
1B. Broad definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	
Cohort 10: ED Visit with Narrow ICD - 2020	
Event 1 - ED Visit w Psychiatric Indication	Time Restrictions:
<i>Must Have:</i>	
1A. Emergency visit	01/01/2020 - 08/31/2020
1B. Narrow definition ICD code	Same day or day after 1A
<i>Cannot Have:</i>	
None	
Demographic Restrictions: N/A	
Analytic Module (Treatment Pathways) Outcomes:	

N/A: Not Applicable











Appendix D. Study Design Diagram for Cohort Entry Requirements

