**Covid-19 pandEmic impacts on mental health Related conditions Via multi-database nEtwork: a LongitutinaL Observational study (CERVELLO)**

**Version:** 2.0

Ian CK Wong, PhD, University of Hong Kong, Hong Kong; UCL School of Pharmacy, United Kingdom

Hao Luo, PhD, University of Hong Kong, Hong Kong

Wallis CY Lau, PhD, UCL School of Pharmacy, United Kingdom

Kenneth KC Man, PhD, UCL School of Pharmacy, United Kingdom

Carmen

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# Table of contents

[1 Table of contents 2](#_Toc89960797)

[2 List of abbreviations 3](#_Toc89960798)

[3 Abstract 3](#_Toc89960799)

[4 Amendment and Updates 3](#_Toc89960800)

[5 Milestones 3](#_Toc89960801)

[6 Rationale and Background 4](#_Toc89960802)

[7 Research Questions and Objectives 4](#_Toc89960803)

[7.1 Research Questions 4](#_Toc89960804)

[7.2 Objectives 5](#_Toc89960805)

[8 Research methods 5](#_Toc89960806)

[8.1 Study Design 5](#_Toc89960807)

[8.2 Data Source(s) 5](#_Toc89960808)

[8.3 Study population 6](#_Toc89960809)

[9 Data Analysis Plan 7](#_Toc89960810)

[9.1 Output 8](#_Toc89960811)

[9.2 Evidence Evaluation 8](#_Toc89960812)

[10 Study Diagnostics 8](#_Toc89960813)

[10.1 Sample Size and Study Power 8](#_Toc89960814)

[10.2 Cohort Comparability 8](#_Toc89960815)

[10.3 Systematic Error Assessment 8](#_Toc89960816)

[11 Strengths and Limitations of the Research Methods 8](#_Toc89960817)

[12 Protection of Human Subjects 9](#_Toc89960818)

[13 Management and Reporting of Adverse Events and Adverse Reactions 9](#_Toc89960819)

[14 Plans for Disseminating and Communicating Study Results 9](#_Toc89960820)

[15 References 9](#_Toc89960821)

[16 Appendix 1: Cohort Definitions 10](#_Toc89960822)

[17 Appendix 2: Concept sets of the ten mental health cohorts 10](#_Toc89960823)

[18 Appendix 3: Concept sets of the eight types of drugs 11](#_Toc89960824)

[18.1.1 Antipsychotics 11](#_Toc89960825)

[18.1.2 Anxiolytics 12](#_Toc89960826)

[18.1.3 Hypnotics/sedatives 13](#_Toc89960827)

[18.1.4 Antidepressants 15](#_Toc89960828)

[18.1.5 Antiepileptics 17](#_Toc89960829)

[18.1.6 Lithium 18](#_Toc89960830)

[18.1.7 ADHD drugs 18](#_Toc89960831)

[18.1.8 Anti-dementia 19](#_Toc89960832)

[19 Appendix 4: Concept sets added after cohort diagnostics 19](#_Toc89960833)

[19.1.1 Anxiety disorders 19](#_Toc89960834)

[19.1.2 Depressive disorders 20](#_Toc89960835)

[19.1.3 Bipolar disorders 20](#_Toc89960836)

[19.1.4 Psychoses 20](#_Toc89960837)

[19.1.5 Personality disorders 20](#_Toc89960838)

[19.1.6 Alcohol misuse and dependence 20](#_Toc89960839)

[19.1.7 Substance misuse and dependence 21](#_Toc89960840)

[19.1.8 Dementia 22](#_Toc89960841)

[19.1.9 ADHD 22](#_Toc89960842)

[19.1.10 Neurodevelopmental disorders 22](#_Toc89960843)

# List of abbreviations

OHDSI Observational Health Data Sciences and Informatics

# Abstract

The mental health effects of COVID-19 may vary across populations. Specific sections of the population are suspected to be more vulnerable than others to the psychological, social, and neuropsychiatric effects. This study will examine the mental health effects of the COVID-19 pandemic across vulnerable groups, including people with established psychiatric disorders including dementia and neurodevelopmental disorders.

# Amendment and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Person | Changes |
| 1.0 | 16 Sep 2020 | Hao Luo | Initial draft |
| 1.1 | 8 Oct 2020 | Hao Luo | Added concept IDs for outcomes of interest |
| 1.2 | 26 Oct 2020 | Hao Luo | Added inclusion criteria for each study cohort |
| 1.3 | Jan 13 2021 | Hao Luo | Added concept sets after cohort diagnostics |
| 1.4 | 4 Feb 2021 | Hao Luo | Added descriptions of data sources and updated drug list |
| 2.0 | 9 Dec 2021 | Hao Luo | Revised study objectives and design |
| 2.1 | 4 Mar 2022 | Hao Luo, Yi Chai | Revised study objectives |

# Milestones

|  |  |
| --- | --- |
| Milestone |  |
| Start cohort definition and cohort diagnosis | 16 Sep 2020 |
| Start of analysis | 1 Mar 2022 |
| End of analysis | 31 Mar 2022 |
| Presentation of results | 31 Mar 2022 |

# Rationale and Background

The COVID-19 pandemic is having a profound effect on the mental health of populations across the globe.[1](#_ENREF_1) For people who have contracted the disease, the coronavirus may infect the brain or trigger an immune response that causes additional adverse effects on brain function and mental health.[2](#_ENREF_2),[3](#_ENREF_3) For the general public, uncertain prognoses, severe shortage of resources, implementation of unprecedented public health measures and financial difficulties will undoubtedly contribute to emotional distress and elevated risk of adverse mental health outcomes.[4](#_ENREF_4) Moreover, some groups may be more vulnerable than others. During school closures, children and adolescents were less likely to interact with peers physically, which might potentially affect their development of social and interpersonal skills, hence leading to subsequent behavioural problems. People with disability, learning difficulties, neurodevelopmental disorders, and existing mental health issues may be affected by social distancing, loneliness, and disruption to daily routine and support.[5](#_ENREF_5" \o "Lee, 2020 #6) Older adults who are frail may be particularly affected by the disruption to end of life care and bereavement process, which may be further exacerbated by the digital divide.[1](#_ENREF_1) Recent surveys of the general population have initially revealed increased anxiety, depression, stress, and other negative emotions during the COVID-19 pandemic.[6](#_ENREF_6) Moving beyond such snapshots of the current situation, high-quality international research is needed for systematically examining the mental health effects of the pandemic on both COVID-19 patients and the general population.[1](#_ENREF_1)

The mental health effects of COVID-19 may vary across populations. Specific sections of the population are suspected to be more vulnerable than others to the psychological, social, and neuropsychiatric effects. These include the direct effect of COVID-19 on mental health outcomes in those who contracted the disease; the indirect effect of the pandemic and lockdown on mental health outcomes in the whole population; and the impact of the pandemic on people with existing mental health issues and neurodevelopmental disorders.[1](#_ENREF_1) To ensure limited mental health resources are efficiently targeted to crucial areas of mental health problems, high-quality data on the short-, medium- and long-term mental health effects of the COVID-19 pandemic across the whole-population and vulnerable groups are needed. In this project, vulnerable groups of interest include patients with COVID-19 diagnosis, people with established psychiatric disorders (including dementia) and neurodevelopmental disorders.

# Research Questions and Objectives

## Research Questions

Before and during the pandemic, are there any changes in

* incidence rates of mental health conditions and of neurodevelopmental disorders
* proportions of people with visits/contacts for mental health conditions and neurodevelopmental disorders
* proportions of people who have been prescribed a psychotropic drug
* proportions of people who have been prescribed a psychotropic drug in people with mental health conditions and with neurodevelopmental disorders

## Objectives

To examine temporal trends of the incidence and prevalence of mental health and neurodevelopmental disorder diagnosis; the prevalence of eight types of psychotropic drug prescribing before and during the pandemic; and the prevalence of psychotropic drug prescribing in people with mental health issues and with neurodevelopmental disorders by condition. The incidence and prevalence will be stratified by year, month, sex, and age groups.

# Research methods

## Study Design

This study includes both database-level characterization and cohort characterization. All analysis will be conducted by month/year between 01/01/2016 and 31/12/2019 and between 11/03/2020 and 31/12/2021, stratified by sex and age groups. The end of study period is subject to change based on data availability in each database. We will include all individuals with observed time of at least 1 day during the study period (01/01/2016 to 31/12/2021).

At the database-level, we will assess 1) the incidence rates of selected mental health conditions, 2) the percentages of persons with visits/contacts for selected mental health conditions, 3) proportions of persons who have been prescribed selected types of psychotropic drugs.

At the cohort-level, we will examine the proportions of persons with a prescription of each type of psychotropic drugs in each selected mental health cohort.

## Data Source(s)

The study will aim to be conducted using multiple databases in the OHDSI network (subject to change).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Data source** | **Country** | **Patient Count** | **History** | **Patient Type** | **Data collection** |
| IQVIA  LPD France EMR | France | 30.9 M | 2009 - | Outpatient / General population/ Patients seen in the primary care setting | Electronic health records in ambulatory setting |
| IQVIA  Disease Analyser Germany EMR | Germany | 39.2 M | 1992 - | Outpatient only / General population/Public and private insurance | Electronic health records in ambulatory setting |
| IQVIA  UK IMRD | United Kingdom | 12.7 M | 1994 - | General population / Primary care records with hospitalisation / referral information | Pseudonymised Electronic Medical Records collected from Patient Management software used within UK Primary Care |
| IQVIA  LPD Italy | Italy | 2.2 M | 2011 - | Outpatient / General population/ Patients seen in the primary care setting | Electronic health records in ambulatory setting |
| IQVIA  US Ambulatory EMR | United States | 75.7 M | 2006 – | Outpatient | Electronic health records in ambulatory setting |

## Study population

The study population include all persons in the databases from OHDSI as listed in **Section 8.2** with the following existing conditions and all persons with a record of psychotropic drug prescription. We include patients with at least 1 year of previous database observation before the first recorded mental health diagnosis and before the first exposure of drugs of interest. Mental health cohorts include

1. anxiety disorders,
2. depression,
3. bipolar disorders,
4. psychoses,
5. personality disorders,
6. alcohol misuse or dependence,
7. substance misuse or dependence,
8. dementia,
9. attention-deficit/hyperactivity disorder (ADHD),
10. autism and other neurodevelopmental disorders

The eight drug class cohorts are

1. antipsychotics,
2. anxiolytics,
3. hypnotics/sedatives,
4. antidepressants,
5. antiepileptics,
6. lithium,
7. ADHD drugs
8. anti-dementia drugs.

The cohort definitions are summarized in Appendix 1. The concept sets are defined in Appendix 2 for conditions and in Appendix 3 for drug exposures.

# Data Analysis Plan

Age will be assessed at July 1st each year, and grouped as <18, 18-24, 25-44, 45-64, 65-74, 75-84, 85+ years.

For the database-level characterization, we use the person count of each database as the denominator to calculate the prevalence rates. We define the database prevalence of concept C as

where is the number of unique persons observed with concept C in a given period, and is the number of unique persons observed in the database in the same period. If a person was observed for at least one day in an age group, that person will be counted in the denominator for that category. Over the study period, and within a calendar year/month, a person can contribute to more than one age category and more than one cohort.

For the cohort characterization, we will estimate user prevalence by counting the number of persons who have been prescribed a specific drug in each cohort, stratified by calendar year, month, sex, and age group.

The full list of all drugs of interest are listed in Appendix 3. This classification is based on pharmacological class using ATC codes. For each drug class, we will assess the sex, age, and database specific user prevalence rates. Trends over time (by calendar year/month) will also be examined. Drugs of interest for each mental health cohort are summarised below.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cohorts** | antipsychotics | anxiolytics | hypnotics/  sedatives | antidepressants | antiepileptics | lithium | ADHD drugs | anti-dementia drugs |
| 1 | Anxiety disorders | X | X | X | X | X | X |  |  |
| 2 | Depressive disorders | X | X | X | X | X | X |  |  |
| 3 | Bipolar disorders | X | X | X | X | X | X |  |  |
| 4 | Psychoses | X | X | X | X | X | X |  |  |
| 5 | Personality disorders | X | X | X | X | X | X |  |  |
| 6 | Alcohol misuse or dependence | X | X | X | X | X | X |  |  |
| 7 | Substance misuse or dependence | X | X | X | X | X | X |  |  |
| 8 | Dementia | X | X | X | X | X | X |  | X |
| 9 | ADHD | X | X | X | X | X | X | X |  |
| 10 | Neruodevelopmental disorder | X | X | X | X | X | X | X |  |

## Output

Summary statistics on baseline characteristics, incidences, and prevalence.

# Protection of Human Subjects

This study will only use de-identified patient data which will not involve any direct contact or primary collection of individual human subject data. The study results will be aggregated and presented in tabular form that omits subject identification. Any publications will not include subject identifiers. Cells with patient counts <5 will be masked to prevent unintentional disclosure of patient identity.

# Management and Reporting of Adverse Events and Adverse Reactions

There is no potential to collect adverse events or adverse reactions during the conduct of this research, as the minimum criteria needed to report adverse events (e.g. an identifiable patient) are not available in any databases.

# Plans for Disseminating and Communicating Study Results

The study results will be made available in the OHDSI website after completion of the study. We intend to publish our findings in a peer reviewed journal as well as to present them at relevant scientific conferences.

# References

1. Holmes EA, O'Connor RC, Perry VH, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry* 2020; **7**(6): 547-60.

2. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci* 2020; **11**(7): 995-8.

3. Talan J. Neurologists in Italy to Colleagues in US: Look for Poorly-Defined Neurologic Conditions in Patients with COVID-19. *Neurology Today* 2020; **20**(8): 1-20.

4. Pfefferbaum B, North CS. Mental Health and the Covid-19 Pandemic. *N Engl J Med* 2020: published online April 13. DOI: 0.1056/NEJMp2008017.

5. Lee J. Mental health effects of school closures during COVID-19. *Lancet Child Adolesc Health* 2020; **4**(6): 421.

6. Wang C, Pan R, Wan X, et al. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. *Int J Environ Res Public Health* 2020; **17**(5).

# Appendix 1: Cohort Definitions

|  |  |
| --- | --- |
| Name | Atlas link |
| Anxiety disorders | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777957) |
| Depressive disorders | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1778278) |
| Bipolar disorders | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777958) |
| Psychoses | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777959) |
| Personality disorders | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777975) |
| Alcohol misuse or dependence | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777976) |
| Substance misuse or dependence | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777977) |
| Dementia | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777978) |
| ADHD | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777979) |
| Neruodevelopmental disorder | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1777967) |
|  |  |
| Antipsychotics | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775299) |
| Anxiolytics | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775358) |
| Hypnotics/sedatives | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775359) |
| Antidepressants | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775360) |
| Antiepilepitcs | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775361) |
| Lithium | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775362) |
| ADHD drugs | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775363) |
| Anti-dementia | [ATLAS: Cohort Definitions (ohdsi.org)](https://atlas-demo.ohdsi.org/#/cohortdefinition/1775364) |

# Appendix 2: Concept sets of the ten mental health cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Existing Conditions** | **Concept Id** | **Concept Name** | **Excluded** |
| 1 | Anxiety disorders | 442077 | Anxiety disorder | FALSE |
| 2 | Depressive disorders | 440383 | Depressive disorder | FALSE |
| 3 | Bipolar disorders | 436665 | Bipolar disorder | FALSE |
| 4 | Psychoses | 436073 | Psychotic disorder | FALSE |
| 5 | Personality disorders | 441838 | Personality disorder | FALSE |
| 6 | Alcohol misuse or dependence | 433753 | Alcohol abuse | FALSE |
|  |  | 435243 | Alcohol dependence | FALSE |
| 7 | Substance misuse or dependence | 4279309 | Substance abuse | FALSE |
|  |  | 440069 | Drug dependence | FALSE |
| 8 | Dementia | 4182210 | Dementia | FALSE |
| 9 | ADHD | 438409 | Attention deficit hyperactivity disorder | FALSE |
| 10 | Neruodevelopmental disorder | 45771096 | Neurodevelopmental disorder | FALSE |

# Appendix 3: Concept sets of the eight types of drugs

### Antipsychotics

|  |  |  |  |
| --- | --- | --- | --- |
| Phenothiazines with aliphatic side-chain | 794852 | chlorpromazine | RxNorm |
|  | 21604493 | levomepromazine | ATC |
|  | 19052903 | promazine | RxNorm |
|  | 19018226 | acepromazine | RxNorm |
|  | 19005104 | triflupromazine | RxNorm |
|  | 19051234 | cyamemazine | RxNorm |
|  | 19122262 | chlorproethazine | RxNorm |
| Phenothiazines with piperazine structure | 40798772 | dixyrazine | RxNorm Extension |
|  | 756018 | fluphenazine | RxNorm |
|  | 733008 | perphenazine | RxNorm |
|  | 752061 | prochlorperazine | RxNorm |
|  | 19041817 | thiopropazate | RxNorm |
|  | 704984 | trifluoperazine | RxNorm |
|  | 19029555 | acetophenazine | RxNorm |
|  | 19000305 | thioproperazine | RxNorm |
|  | 40798666 | butaperazine | RxNorm Extension |
|  | 19131663 | perazine | RxNorm |
| Phenothiazines with piperidine structure | 19053565 | periciazine | RxNorm |
|  | 700299 | thioridazine | RxNorm |
|  | 703083 | mesoridazine | RxNorm |
|  | 19133992 | pipotiazine | RxNorm |
| Butyrophenone derivatives | 766529 | haloperidol | RxNorm |
|  | 19005101 | trifluperidol | RxNorm |
|  | 40684643 | melperone | RxNorm Extension |
|  | 40798964 | moperone | RxNorm Extension |
|  | 19093225 | pipamperone | RxNorm |
|  | 19039227 | bromperidol | RxNorm |
|  | 19016440 | benperidol | RxNorm |
|  | 739323 | droperidol | RxNorm |
|  | 40798823 | fluanisone | RxNorm Extension |
| [Indole derivatives](https://www.whocc.no/atc_ddd_index/?code=N05AE&showdescription=no) | 19025922 | Oxypertine | RxNorm |
|  | 709699 | Molindone | RxNorm |
| [Thioxanthene derivatives](https://www.whocc.no/atc_ddd_index/?code=N05AF&showdescription=yes) | 19055982 | Flupentixol | RxNorm |
|  | 970011 | Clopenthixol | RxNorm |
|  | 19095002 | Chlorprothixene | RxNorm |
|  | 700465 | Tiotixene | RxNorm |
|  | 19010886 | Zuclopenthixol | RxNorm |
| [Diphenylbutylpiperidine derivatives](https://www.whocc.no/atc_ddd_index/?code=N05AG&showdescription=yes) | 19056465 | Fluspirilene | RxNorm |
|  | 745790 | Pimozide | RxNorm |
|  | 19028044 | Penfluridol | RxNorm |
| [Diazepines, oxazepines, thiazepines and oxepines](https://www.whocc.no/atc_ddd_index/?code=N05AH&showdescription=yes) | 792263 | Loxapine | RxNorm |
|  | 19100363 | Clotiapine | RxNorm |
| [Benzamides](https://www.whocc.no/atc_ddd_index/?code=N05AL&showdescription=yes) | 19008012 | Tiapride | RxNorm |
|  | 19043327 | Veralipride | RxNorm |
| [Other antipsychotics](https://www.whocc.no/atc_ddd_index/?code=N05AX&showdescription=yes) | 19115044 | Prothipendyl | RxNorm |
| Atypical antipsychotics | 19050633 | Sertindole | RxNorm |
|  | 712615 | Ziprasidone | RxNorm |
|  | 40230761 | Lurasidone | RxNorm |
|  | 800878 | Clozapine | RxNorm |
|  | 785788 | Olanzapine | RxNorm |
|  | 766814 | Quetiapine | RxNorm |
|  | 40164052 | Asenapine | RxNorm |
|  | 19136626 | Sulpiride | RxNorm |
|  | 19100431 | Sultopride | RxNorm |
|  | 19035226 | Remoxipride | RxNorm |
|  | 19057607 | Amisulpride | RxNorm |
|  | 43009023 | Levosulpiride | RxNorm Extension |
|  | 735979 | Risperidone | RxNorm |
|  | 35198101 | Mosapramine | RxNorm Extension |
|  | 19102109 | Zotepine | RxNorm |
|  | 757688 | Aripiprazole | RxNorm |
|  | 703244 | Paliperidone | RxNorm |
|  | 19017241 | Iloperidone | RxNorm |
|  | 35603277 | Cariprazine | RxNorm |
|  | 46275300 | Brexpiprazole | RxNorm |
|  | 42628962 | Pimavanserin | RxNorm |

### Anxiolytics

|  |  |  |  |
| --- | --- | --- | --- |
| Benzodiazepine derivatives | 723013 | diazepam | RxNorm |
|  | 990678 | chlordiazepoxide | RxNorm |
|  | 19125106 | medazepam | RxNorm |
|  | 724816 | oxazepam | RxNorm |
|  | 21604570 | potassium clorazepate | ATC |
|  | 791967 | lorazepam | RxNorm |
|  | 21604572 | adinazolam | ATC |
|  | 19030353 | bromazepam | RxNorm |
|  | 19050832 | clobazam | RxNorm |
|  | 19003946 | ketazolam | RxNorm |
|  | 19050461 | prazepam | RxNorm |
|  | 781039 | alprazolam | RxNorm |
|  | 801396 | halazepam | RxNorm |
|  | 2100521 | pinazepam | RxNorm Extension |
|  | 40798714 | camazepam | RxNorm Extension |
|  | 19080959 | nordazepam | RxNorm |
|  | 35198139 | fludiazepam | RxNorm Extension |
|  | 19095467 | ethyl loflazepate | RxNorm |
|  | 43009000 | etizolam | RxNorm Extension |
|  | 19068821 | clotiazepam | RxNorm |
|  | 19051096 | cloxazolam | RxNorm |
|  | 19100773 | tofisopam | RxNorm |
|  | 1123816 | bentazepam | ATC |
|  | 21604588 | lorazepam, combinations | ATC |
| Diphenylmethane derivatives | 777221 | hydroxyzine | RxNorm |
|  | 19135828 | captodiame | RxNorm |
|  | 21604592 | hydroxyzine, combinations | ATC |
| Carbamates | 702865 | meprobamate | RxNorm |
|  | 21604595 | emylcamate | ATC |
|  | 21604596 | mebutamate | ATC |
|  | 21604597 | meprobamate, combinations | ATC |
| Dibenzo-bicyclo-octadiene derivatives | 40798650 | benzoctamine | RxNorm Extension |
| Azaspirodecanedione derivatives | 733301 | buspirone | RxNorm |
| Other anxiolytics | 37493797 | mephenoxalone | RxNorm Extension |
|  | 21604604 | gedocarnil | ATC |
|  | 19059441 | etifoxine | RxNorm |
|  | 45893272 | fabomotizole | ATC |
|  | 1502097 | Lavandulae aetheroleum | ATC |

### Hypnotics/sedatives

|  |  |  |  |
| --- | --- | --- | --- |
| Barbiturates, plain | 730729 | pentobarbital | RxNorm |
|  | 712757 | amobarbital | RxNorm |
|  | 19039767 | butobarbital | RxNorm |
|  | 19015346 | barbital | RxNorm |
|  | 19030299 | aprobarbital | RxNorm |
|  | 766067 | secobarbital | RxNorm |
|  | 19059149 | talbutal | RxNorm |
|  | 21604615 | vinylbital | ATC |
|  | 19135827 | vinbarbital | RxNorm |
|  | 19072082 | cyclobarbital | RxNorm |
|  | 21604618 | heptabarbital | ATC |
|  | 21604619 | reposal | ATC |
|  | 19005015 | methohexital | RxNorm |
|  | 19068964 | hexobarbital | RxNorm |
|  | 700253 | thiopental | RxNorm |
|  | 21604623 | etallobarbital | ATC |
|  | 19113034 | allobarbital | RxNorm |
|  | 19134133 | proxibarbal | RxNorm |
| Barbiturates, combinations | 21604627 | combinations of barbiturates | ATC |
|  | 21604628 | barbiturates in combination with other drugs | ATC |
| Aldehydes and derivatives | 21604630 | chloral hydrate | ATC |
|  | 21604631 | chloralodol | ATC |
|  | 21604632 | acetylglycinamide chloral hydrate | ATC |
|  | 1189490 | dichloralphenazone | RxNorm |
|  | 19027181 | paraldehyde | RxNorm |
| Benzodiazepine derivatives | 756349 | flurazepam | RxNorm |
|  | 19020021 | nitrazepam | RxNorm |
|  | 19055224 | flunitrazepam | RxNorm |
|  | 748010 | estazolam | RxNorm |
|  | 704599 | triazolam | RxNorm |
|  | 19007977 | lormetazepam | RxNorm |
|  | 836715 | temazepam | RxNorm |
|  | 708298 | midazolam | RxNorm |
|  | 19039262 | brotizolam | RxNorm |
|  | 731188 | quazepam | RxNorm |
|  | 21604646 | loprazolam | ATC |
|  | 21604647 | doxefazepam | ATC |
|  | 21604648 | cinolazepam | ATC |
|  | 35197946 | nimetazepam | RxNorm Extension |
| Piperidinedione derivatives | 19061124 | glutethimide | RxNorm |
|  | 19006742 | methyprylon | RxNorm |
|  | 40799066 | pyrithyldione | RxNorm Extension |
| Benzodiazepine related drugs | 19044883 | zopiclone | RxNorm |
|  | 744740 | zolpidem | RxNorm |
|  | 720727 | zaleplon | RxNorm |
|  | 757352 | eszopiclone | RxNorm |
| Melatonin receptor agonists | 1301152 | melatonin | RxNorm |
|  | 781182 | ramelteon | RxNorm |
|  | 44814600 | tasimelteon | RxNorm |
| Other hypnotics and sedatives | 19004160 | methaqualone | RxNorm |
|  | 19092283 | clomethiazole | RxNorm |
|  | 40798676 | bromisoval | RxNorm Extension |
|  | 19033243 | carbromal | RxNorm |
|  | 965748 | scopolamine | RxNorm |
|  | 19053610 | propiomazine | RxNorm |
|  | 19042692 | triclofos | RxNorm |
|  | 749727 | ethchlorvynol | RxNorm |
|  | 21604670 | Valerianae radix | ATC |
|  | 21604671 | hexapropymate | ATC |
|  | 21604672 | bromides | ATC |
|  | 21604673 | apronal | ATC |
|  | 21604674 | valnoctamide | ATC |
|  | 40798942 | methylpentynol | RxNorm Extension |
|  | 19082402 | niaprazine | RxNorm |
|  | 19061088 | dexmedetomidine | RxNorm |
|  | 45775760 | suvorexant | RxNorm |
| Hypnotics and sedatives in combination, excl. barbiturates | 21604679 | meprobamate, combinations | ATC |
|  | 21604680 | methaqualone, combinations | ATC |
|  | 21604681 | methylpentynol, combinations | ATC |
|  | 21604682 | clomethiazole, combinations | ATC |
|  | 21604683 | emepronium, combinations | ATC |
|  | 21604684 | dipiperonylaminoethanol, combinations | ATC |

### Antidepressants

|  |  |  |  |
| --- | --- | --- | --- |
| Non-selective monoamine reuptake inhibitors | 716968 | desipramine | RxNorm |
|  | 778268 | imipramine | RxNorm |
|  | 21604690 | imipramine oxide | ATC |
|  | 798834 | clomipramine | RxNorm |
|  | 19129635 | opipramol | RxNorm |
|  | 705755 | trimipramine | RxNorm |
|  | 19091830 | lofepramine | RxNorm |
|  | 19023846 | dibenzepin | RxNorm |
|  | 710062 | amitriptyline | RxNorm |
|  | 721724 | nortriptyline | RxNorm |
|  | 754270 | protriptyline | RxNorm |
|  | 738156 | doxepin | RxNorm |
|  | 19122204 | iprindole | RxNorm |
|  | 19110751 | melitracen | RxNorm |
|  | 19039883 | butriptyline | RxNorm |
|  | 21604703 | dosulepin | ATC |
|  | 713109 | amoxapine | RxNorm |
|  | 40798767 | dimetacrine | RxNorm Extension |
|  | 21604706 | amineptine | ATC |
|  | 794147 | maprotiline | RxNorm |
|  | 19098514 | quinupramine | RxNorm |
| Selective serotonin reuptake inhibitors | 40799195 | zimeldine | RxNorm Extension |
|  | 755695 | fluoxetine | RxNorm |
|  | 797617 | citalopram | RxNorm |
|  | 722031 | paroxetine | RxNorm |
|  | 739138 | sertraline | RxNorm |
|  | 21604715 | alaproclate | ATC |
|  | 751412 | fluvoxamine | RxNorm |
|  | 21604717 | etoperidone | ATC |
|  | 715939 | escitalopram | RxNorm |
| Monoamine oxidase inhibitors, non-selective | 781705 | isocarboxazid | RxNorm |
|  | 19127550 | nialamide | RxNorm |
|  | 733896 | phenelzine | RxNorm |
|  | 703470 | tranylcypromine | RxNorm |
|  | 21604724 | iproniazide | ATC |
|  | 21604725 | iproclozide | ATC |
| Monoamine oxidase A inhibitors | 19010652 | moclobemide | RxNorm |
|  | 19100775 | toloxatone | RxNorm |
| Other antidepressants | 21604730 | oxitriptan | ATC |
|  | 19006186 | tryptophan | RxNorm |
|  | 19007737 | mianserin | RxNorm |
|  | 19128066 | nomifensine | RxNorm |
|  | 703547 | trazodone | RxNorm |
|  | 714684 | nefazodone | RxNorm |
|  | 19072123 | minaprine | RxNorm |
|  | 19058055 | bifemelane | RxNorm |
|  | 19008261 | viloxazine | RxNorm |
|  | 21604739 | oxaflozane | ATC |
|  | 725131 | mirtazapine | RxNorm |
|  | 750982 | bupropion | RxNorm |
|  | 19072021 | medifoxamine | RxNorm |
|  | 19041910 | tianeptine | RxNorm |
|  | 21604744 | pivagabine | ATC |
|  | 743670 | venlafaxine | RxNorm |
|  | 19080226 | milnacipran | RxNorm |
|  | 19084693 | reboxetine | RxNorm |
|  | 21604748 | gepirone | ATC |
|  | 715259 | duloxetine | RxNorm |
|  | 36878783 | agomelatine | RxNorm Extension |
|  | 717607 | desvenlafaxine | RxNorm |
|  | 40234834 | vilazodone | RxNorm |
|  | 40252223 | Hyperici herba | ATC |
|  | 44507700 | vortioxetine | RxNorm |
|  | 1366610 | esketamine | RxNorm |

### Antiepileptics

|  |  |  |  |
| --- | --- | --- | --- |
| Barbiturates and derivatives | 21604392 | methylphenobarbital | ATC |
|  | 734275 | phenobarbital | RxNorm |
|  | 751347 | primidone | RxNorm |
|  | 19112534 | barbexaclone | RxNorm |
|  | 19004254 | metharbital | RxNorm |
| Hydantoin derivatives | 750146 | ethotoin | RxNorm |
|  | 740910 | phenytoin | RxNorm |
|  | 21604400 | amino(diphenylhydantoin) valeric acid | ATC |
|  | 702661 | mephenytoin | RxNorm |
|  | 713192 | fosphenytoin | RxNorm |
|  | 21604403 | phenytoin, combinations | ATC |
|  | 21604404 | mephenytoin, combinations | ATC |
| Oxazolidine derivatives | 19021932 | paramethadione | RxNorm |
|  | 19005629 | trimethadione | RxNorm |
|  | 21604408 | ethadione | ATC |
| Succinimide derivatives | 750119 | ethosuximide | RxNorm |
|  | 19023842 | phensuximide | RxNorm |
|  | 759401 | mesuximide | RxNorm |
|  | 21604413 | ethosuximide, combinations | ATC |
| Benzodiazepine derivatives | 798874 | clonazepam | RxNorm |
| Carboxamide derivatives | 740275 | carbamazepine | RxNorm |
|  | 718122 | oxcarbazepine | RxNorm |
|  | 19006586 | rufinamide | RxNorm |
|  | 44507780 | eslicarbazepine | RxNorm |
| Fatty acid derivatives | 19010963 | valproic acid | RxNorm |
|  | 36878958 | valpromide | RxNorm Extension |
|  | 19126447 | aminobutyric acid | RxNorm |
|  | 19020002 | vigabatrin | RxNorm |
|  | 19095776 | progabide | RxNorm |
|  | 715458 | tiagabine | RxNorm |
| Other antiepileptics | 19000921 | sultiame | RxNorm |
|  | 19023286 | phenacemide | RxNorm |
|  | 705103 | lamotrigine | RxNorm |
|  | 795661 | felbamate | RxNorm |
|  | 742267 | topiramate | RxNorm |
|  | 797399 | gabapentin | RxNorm |
|  | 21604435 | pheneturide | ATC |
|  | 711584 | levetiracetam | RxNorm |
|  | 744798 | zonisamide | RxNorm |
|  | 734354 | pregabalin | RxNorm |
|  | 35200286 | stiripentol | RxNorm |
|  | 19087394 | lacosamide | RxNorm |
|  | 21604441 | carisbamate | ATC |
|  | 40255957 | retigabine | ATC |
|  | 42904177 | perampanel | RxNorm |
|  | 35604901 | brivaracetam | RxNorm |
|  | 1510417 | cannabidiol | RxNorm |
|  | 19018520 | beclamide | RxNorm |
|  | 753860 | fenfluramine | RxNorm |

### Lithium

|  |  |  |  |
| --- | --- | --- | --- |
| lithium | 19124477 | lithium | RxNorm |
|  | 751246 | lithium carbonate | RxNorm |
|  | 19127934 | lithium aspartate 20 MG Oral Capsule | RxNorm |
|  | 43136335 | Lithium acetate 10.8 MEQ Oral Tablet [TERALITHE] Box of 60 by Sanofi | RxNorm Extension |
|  | 43136332 | Lithium acetate 6.8 MEQ Oral Tablet [TERALITHE] Box of 100 by Sanofi | RxNorm Extension |
|  | 43186485 | 30000 MG Lithium acetate 0.00275 MG/MG Topical Gel [LITHIODERM] Box of 1 by Labcatal | RxNorm Extension |
|  | 4147954 | On lithium | SNOMED |
|  | 40732886 | lithium citrate 104 MG/ML Oral Solution [Priadel] by Sanofi | RxNorm Extension |
|  | 19128968 | lithium citrate 60 MG/ML Oral Solution | RxNorm |
|  | 19063847 | lithium citrate 104 MG/ML Oral Solution | RxNorm |
|  | 19071905 | lithium sulfate | RxNorm |
|  | 19064064 | lithium citrate 102 MG/ML Oral Solution | RxNorm |

### ADHD drugs

|  |  |  |  |
| --- | --- | --- | --- |
| 714785 | amfetamine | RxNorm | N06BA01 |
| 742185 | atomoxetine | RxNorm | N06BA09 |
| 719311 | dexamfetamine | RxNorm | N06BA02 |
| 731533 | dexmethylphenidate | RxNorm | N06BA11 |
| 709567 | lisdexamfetamine | RxNorm | N06BA12 |
| 704053 | metamfetamine | RxNorm | N06BA03 |
| 705944 | methylphenidate | RxNorm | N06BA04 |

See Appendix 4 for ADHD drugs added after cohort diagnosis

### Anti-dementia

|  |  |  |  |
| --- | --- | --- | --- |
| 836654 | Tacrine | RxNorm | N06DA01 |
| 715997 | Donepezil | RxNorm | N06DA02 |
| 733523 | Rivastigmine | RxNorm | N06DA03 |
| 757627 | Galantamine | RxNorm | N06DA04 |
| 43534831 | Ipidacrine | ATC | N06DA05 |
| 40252271 | Donepezil and memantine | ATC | N06DA52 |
| 45893515 | Donepezil, memantine and Gingo folium | ATC | N06DA53 |
| 701322 | memantine | RxNorm | N06DX01 |

# Appendix 4: Concept sets added after cohort diagnostics

### Anxiety disorders

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_id |
| 4058397 | Claustrophobia | Condition | SNOMED | Clinical Finding | S | 4058397 |
| 4322025 | Mild anxiety | Condition | SNOMED | Clinical Finding | S | 4322025 |
| 4214746 | Severe anxiety | Condition | SNOMED | Clinical Finding | S | 4214746 |
| 440985 | Phobia | Condition | SNOMED | Clinical Finding | S | 440985 |
| 4087190 | Performance anxiety | Condition | SNOMED | Clinical Finding | S | 4087190 |
| 4008683 | Anxiety neurosis | Condition | SNOMED | Clinical Finding | S | 4008683 |
| 4263429 | Moderate anxiety | Condition | SNOMED | Clinical Finding | S | 4263429 |
| 4338032 | Anxiety hysteria | Condition | SNOMED | Clinical Finding | S | 4338032 |
| 4332995 | Needle phobia | Condition | SNOMED | Clinical Finding | S | 4332995 |
| 4261239 | Anticipatory anxiety | Condition | SNOMED | Clinical Finding | S | 4261239 |
| 4209114 | Phonophobia | Condition | SNOMED | Clinical Finding | S | 4209114 |
| 4155074 | School phobia | Condition | SNOMED | Clinical Finding | S | 4155074 |
| 4103273 | Recurrent anxiety | Condition | SNOMED | Clinical Finding | S | 4103273 |
| 42538968 | Anxiety in pregnancy | Condition | SNOMED | Clinical Finding | S | 42538968 |
| 4114006 | Parental anxiety | Observation | SNOMED | Clinical Finding | S | 4114006 |
| 4102977 | Disturbance of anxiety and fearfulness in childhood and adolescence | Condition | SNOMED | Clinical Finding | S | 4102977 |
| 4012101 | Nosophobia | Condition | SNOMED | Clinical Finding | S | 4012101 |
| 4112929 | Parasitophobia | Condition | SNOMED | Clinical Finding | S | 4112929 |
| 4084699 | Anxiety about body function or health | Condition | SNOMED | Clinical Finding | S | 4084699 |
| 4021501 | Anxiety about treatment | Condition | SNOMED | Clinical Finding | S | 4021501 |

### Depressive disorders

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 35625752 | Depression care management | Procedure | SNOMED | Procedure | S | 768835002 |
| 44788304 | Depression - enhanced service completed | Observation | SNOMED | Clinical Finding | S | 1.66E+14 |
| 4114513 | Depression - motion | Observation | SNOMED | Qualifier Value | S | 255339005 |
| 4295031 | Depression management program | Observation | SNOMED | Procedure | S | 401174001 |
| 44788282 | Depression - enhanced services administration | Observation | SNOMED | Procedure | S | 1.66E+14 |
| 2106305 | Major depressive disorder, moderate (MDD) | Observation | CPT4 | CPT4 | S | 3089F |
| 2106304 | Major depressive disorder, mild (MDD) | Observation | CPT4 | CPT4 | S | 3088F |
| 40756912 | Plan for follow-up care for major depressive disorder, documented (MDD ADOL) | Observation | CPT4 | CPT4 | S | 0545F |

### Bipolar disorders

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 4128935 | Bipolar | Observation | SNOMED | Qualifier Value | S | 260994008 |
| 19127934 | lithium aspartate 20 MG Oral Capsule | Drug | RxNorm | Clinical Drug | S | 749153 |
| 43136335 | Lithium acetate 10.8 MEQ Oral Tablet [TERALITHE] Box of 60 by Sanofi | Drug | RxNorm Extension | Marketed Product | S | OMOP460318 |
| 43136332 | Lithium acetate 6.8 MEQ Oral Tablet [TERALITHE] Box of 100 by Sanofi | Drug | RxNorm Extension | Marketed Product | S | OMOP460305 |
| 43186485 | 30000 MG Lithium acetate 0.00275 MG/MG Topical Gel [LITHIODERM] Box of 1 by Labcatal | Drug | RxNorm Extension | Marketed Product | S | OMOP519209 |
| 4147954 | On lithium | Observation | SNOMED | Clinical Finding | S | 268514004 |
| 40732886 | lithium citrate 104 MG/ML Oral Solution [Priadel] by Sanofi | Drug | RxNorm Extension | Marketed Product | S | OMOP4724021 |
| 19128968 | lithium citrate 60 MG/ML Oral Solution | Drug | RxNorm | Clinical Drug | S | 756059 |
| 19063847 | lithium citrate 104 MG/ML Oral Solution | Drug | RxNorm | Clinical Drug | S | 250860 |
| 19071905 | lithium sulfate | Drug | RxNorm | Ingredient | S | 28818 |
| 19064064 | lithium citrate 102 MG/ML Oral Solution | Drug | RxNorm | Clinical Drug | S | 250973 |

### Psychoses

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 4168389 | Borderline schizophrenia | Condition | SNOMED | Clinical Finding | S | 2.75E+08 |
| 432590 | Delusional disorder | Condition | SNOMED | Clinical Finding | S | 48500005 |
| 44805667 | [X]Paranoid state in remission | Condition | SNOMED | Clinical Finding | S | 7.55E+14 |
| 375229 | Organic delusional disorder | Condition | SNOMED | Clinical Finding | S | 5510009 |
| 439706 | Psychosis with origin in childhood | Condition | SNOMED | Clinical Finding | S | 1.92E+08 |

### Personality disorders

nil

### Alcohol misuse and dependence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 44788279 | Alcohol misuse - enhanced services administration | Observation | SNOMED | Procedure | S | 1.66E+14 |
| 44788303 | Alcohol misuse - enhanced service completed | Observation | SNOMED | Clinical Finding | S | 1.66E+14 |
| 4218106 | Alcoholism | Condition | SNOMED | Clinical Finding | S | 7200002 |
| 439005 | Chronic alcoholism in remission | Condition | SNOMED | Clinical Finding | S | 191813001 |
| 436953 | Continuous chronic alcoholism | Condition | SNOMED | Clinical Finding | S | 191811004 |
| 4275257 | Detoxication psychiatric therapy for alcoholism | Procedure | SNOMED | Procedure | S | 64297001 |
| 435532 | Episodic chronic alcoholism | Condition | SNOMED | Clinical Finding | S | 191812006 |
| 378726 | Dementia associated with alcoholism | Condition | SNOMED | Clinical Finding | S | 281004 |
| 433735 | Acute alcoholic intoxication in alcoholism | Condition | SNOMED | Clinical Finding | S | 191802004 |
| 432609 | Acute alcoholic intoxication in remission, in alcoholism | Condition | SNOMED | Clinical Finding | S | 191806001 |

### Substance misuse and dependence

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 44788279 | Alcohol misuse - enhanced services administration | Observation | SNOMED | Procedure | S | 1.66E+14 |
| 44788303 | Alcohol misuse - enhanced service completed | Observation | SNOMED | Clinical Finding | S | 1.66E+14 |
| 4004672 | Psychoactive substance use disorder | Condition | SNOMED | Clinical Finding | S | 11061003 |
| 4275257 | Detoxication psychiatric therapy for alcoholism | Procedure | SNOMED | Procedure | S | 64297001 |
| 44786481 | Documentation that patient is a current tobacco user | Observation | HCPCS | HCPCS | S | G9276 |
| 4296409 | Substance use treatment: alcohol withdrawal | Procedure | SNOMED | Procedure | S | 386449006 |
| 4302387 | Substance use treatment: drug withdrawal | Procedure | SNOMED | Procedure | S | 386450006 |
| 2796056 | Substance Abuse Treatment, Pharmacotherapy | Procedure | ICD10PCS | ICD10PCS Hierarchy | S | HZ9 |
| 440787 | Drug dependence in mother complicating pregnancy, childbirth AND/OR puerperium | Condition | SNOMED | Clinical Finding | S | 34150001 |
| 434697 | Maternal tobacco abuse | Observation | SNOMED | Clinical Finding | S | 169940006 |
| 378726 | Dementia associated with alcoholism | Condition | SNOMED | Clinical Finding | S | 281004 |
| 443274 | Psychostimulant dependence | Condition | SNOMED | Clinical Finding | S | 275471001 |
| 44790195 | Delivery of rehabilitation for drug addiction | Procedure | SNOMED | Procedure | S | 2.31E+14 |
| 37116661 | Cocaine user | Condition | SNOMED | Clinical Finding | S | 733461000 |
| 4269905 | Referral to drug abuse counselor | Observation | SNOMED | Procedure | S | 401266006 |
| 432884 | Amphetamine or psychostimulant dependence in remission | Condition | SNOMED | Clinical Finding | S | 191845006 |
| 441262 | Amphetamine or psychostimulant dependence, episodic | Condition | SNOMED | Clinical Finding | S | 191844005 |
| 4217840 | Substance misuse behavior | Condition | SNOMED | Clinical Finding | S | 415658005 |
| 44790195 | Delivery of rehabilitation for drug addiction | Procedure | SNOMED | Procedure | S | 2.31E+14 |
| 434916 | Amphetamine or psychostimulant dependence, continuous | Condition | SNOMED | Clinical Finding | S | 191843004 |
| 4151569 | Drug addiction notification | Observation | SNOMED | Procedure | S | 270393005 |
| 433735 | Acute alcoholic intoxication in alcoholism | Condition | SNOMED | Clinical Finding | S | 191802004 |
| 4219382 | Persistent substance misuse | Condition | SNOMED | Clinical Finding | S | 417471002 |
| 44787894 | Referral to community drug dependency team | Observation | SNOMED | Procedure | S | 1.13E+14 |
| 432609 | Acute alcoholic intoxication in remission, in alcoholism | Condition | SNOMED | Clinical Finding | S | 191806001 |
| 4149607 | Drug addiction therapy - methadone | Procedure | SNOMED | Procedure | S | 310653000 |

### Dementia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 35610623 | Dementia advance care plan agreed | Observation | SNOMED | Clinical Finding | S | 1.10E+15 |
| 44791022 | Dementia annual review | Observation | SNOMED | Procedure | S | 2.49E+14 |
| 46284876 | Dementia care plan agreed | Observation | SNOMED | Clinical Finding | S | 9.57E+14 |
| 46284877 | Dementia care plan reviewed | Observation | SNOMED | Context-dependent | S | 9.57E+14 |
| 44790944 | Dementia monitoring | Observation | SNOMED | Procedure | S | 2.49E+14 |
| 44803643 | Dementia monitoring first letter | Observation | SNOMED | Procedure | S | 7.16E+14 |
| 44803915 | Dementia monitoring second letter | Observation | SNOMED | Procedure | S | 7.17E+14 |
| 44803843 | Dementia monitoring telephone invitation | Observation | SNOMED | Procedure | S | 7.17E+14 |
| 44803781 | Dementia monitoring third letter | Observation | SNOMED | Procedure | S | 7.17E+14 |
| 44803706 | Dementia monitoring verbal invitation | Observation | SNOMED | Procedure | S | 7.16E+14 |
| 4043378 | Frontotemporal dementia | Condition | SNOMED | Clinical Finding | S | 230270009 |
| 42742407 | Functional status for dementia assessed and results reviewed (DEM) | Observation | CPT4 | CPT4 | S | 1175F |
| 4059191 | H/O: dementia | Observation | SNOMED | Context-dependent | S | 161465002 |
| 44782763 | Lewy body dementia with behavioral disturbance | Condition | SNOMED | Clinical Finding | S | 1.36E+14 |

### ADHD

See the following link:

[ATLAS: Concept Sets (ohdsi.org)](https://atlas-demo.ohdsi.org/#/conceptset/1867988/expression)

### Neurodevelopmental disorders

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| concept\_id | concept\_name | domain\_id | vocabulary\_id | concept\_class\_id | standard\_concept | concept\_code |
| 40480225 | Adult attention deficit hyperactivity disorder | Condition | SNOMED | Clinical Finding | S | 444613000 |
| 4165912 | On learning disability register | Observation | SNOMED | Clinical Finding | S | 416075005 |
| 442335 | Dyslexia | Condition | SNOMED | Clinical Finding | S | 59770006 |
| 40483181 | History of neurodevelopmental disorder | Observation | SNOMED | Context-dependent | S | 442414004 |
| 4136053 | Learning disabilities health action plan reviewed | Observation | SNOMED | Procedure | S | 413163007 |
| 45765570 | Drug therapy for attention deficit hyperactivity disorder | Procedure | SNOMED | Procedure | S | 702538008 |
| 4024717 | Dyslexia AND/OR speech dysfunction | Condition | SNOMED | Clinical Finding | S | 106170009 |