

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

Version: 2.1

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2 List of abbreviations

OHDSI Observational Health Data Sciences and Informatics

3 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.

4 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

5 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

6 Rationale and Background

The COVID-19 pandemic is having a profound effect on the mental health of populations across the globe.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.^{2,3} 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 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 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 Recent surveys of the general population have initially revealed increased anxiety, depression, stress, and other negative emotions during the COVID-19 pandemic.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

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 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.

7 Research Questions and Objectives

7.1 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

7.2 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.

8 Research methods

8.1 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.

8.2 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	Electronic health records in ambulatory setting

				the primary care setting	
IQVIA US Ambulatory EMR	United States	75.7 M	2006 –	Outpatient	Electronic health records in ambulatory setting

8.3 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.

9 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

$$P_{Database}^C = \frac{N_C}{N_p}$$

where N_C is the number of unique persons observed with concept C in a given period, and N_p 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	Neurodevelopmental disorder	X	X	X	X	X	X	X	

9.1 Output

Summary statistics on baseline characteristics, incidences, and prevalence.

10 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.

11 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.

12 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.

13 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).

14 Appendix 1: Cohort Definitions

Name	Atlas link
Anxiety disorders	ATLAS: Cohort Definitions (ohdsi.org)
Depressive disorders	ATLAS: Cohort Definitions (ohdsi.org)
Bipolar disorders	ATLAS: Cohort Definitions (ohdsi.org)
Psychoses	ATLAS: Cohort Definitions (ohdsi.org)
Personality disorders	ATLAS: Cohort Definitions (ohdsi.org)
Alcohol misuse or dependence	ATLAS: Cohort Definitions (ohdsi.org)
Substance misuse or dependence	ATLAS: Cohort Definitions (ohdsi.org)
Dementia	ATLAS: Cohort Definitions (ohdsi.org)
ADHD	ATLAS: Cohort Definitions (ohdsi.org)
Neurodevelopmental disorder	ATLAS: Cohort Definitions (ohdsi.org)
Antipsychotics	ATLAS: Cohort Definitions (ohdsi.org)
Anxiolytics	ATLAS: Cohort Definitions (ohdsi.org)
Hypnotics/sedatives	ATLAS: Cohort Definitions (ohdsi.org)
Antidepressants	ATLAS: Cohort Definitions (ohdsi.org)

Antiepileptics	ATLAS: Cohort Definitions (ohdsi.org)
Lithium	ATLAS: Cohort Definitions (ohdsi.org)
ADHD drugs	ATLAS: Cohort Definitions (ohdsi.org)
Anti-dementia	ATLAS: Cohort Definitions (ohdsi.org)

15 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	Neurodevelopmental disorder	45771096	Neurodevelopmental disorder	FALSE

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

16.1.1 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	thiopropazine	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	trifluoperidol	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	19025922	Oxypertine	RxNorm
	709699	Molindone	RxNorm
Thioxanthene derivatives	19055982	Flupentixol	RxNorm
	970011	Clopenthixol	RxNorm
	19095002	Chlorprothixene	RxNorm
	700465	Tiotixene	RxNorm
	19010886	Zuclopenthixol	RxNorm
Diphenylbutylpiperidine derivatives	19056465	Fluspirilene	RxNorm
	745790	Pimozide	RxNorm
	19028044	Penfluridol	RxNorm
Diazepines, oxazepines, thiazepines and oxepines	792263	Loxapine	RxNorm
	19100363	Clotiapine	RxNorm
Benzamides	19008012	Tiapride	RxNorm
	19043327	Veralipride	RxNorm
Other antipsychotics	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	lloperidone	RxNorm
	35603277	Cariprazine	RxNorm
	46275300	Brexipiprazole	RxNorm
	42628962	Pimavanserin	RxNorm

16.1.2 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	captodiamine	RxNorm
	21604592	hydroxyzine, combinations	ATC
Carbamates	702865	meprobamate	RxNorm
	21604595	emylcamate	ATC
	21604596	mebutamate	ATC
	21604597	meprobamate, combinations	ATC
Dibenzo-bicyclo-octadiene derivatives	40798650	benzocetamine	RxNorm Extension
Azaspirodecanedione derivatives	733301	buspirone	RxNorm
Other anxiolytics	37493797	mephenoqualone	RxNorm Extension

	21604604	gedocarnil	ATC
	19059441	etifoxine	RxNorm
	45893272	fabomotizole	ATC
	1502097	Lavandulae aetheroleum	ATC

16.1.3 [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	methypylon	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

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

16.1.5 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	sultiamine	RxNorm
	19023286	phenacetamide	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

16.1.6 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

16.1.7 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

16.1.8 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

17 Appendix 4: Concept sets added after cohort diagnostics

17.1.1 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

17.1.2 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

17.1.3 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
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17.1.4 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

17.1.5 Personality disorders

nil

17.1.6 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

17.1.7 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

17.1.8 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

17.1.9 ADHD

See the following link:

[ATLAS: Concept Sets \(ohdsi.org\)](https://atlas.ohdsi.org)

17.1.10 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