Protocol

TITLE

The effect of mental disorders and treatment with psychotropic agents on the course of COVID-19

(COVID19 Psychotropics)

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Brief description:

Beyond the psycho-social consequences of the coronavirus disease 2019 (COVID-19) pandemic, people with severe mental disorders, such as schizophrenia and bipolar disorder have been reported with an up to 2-fold increased 30-days risk of death after a severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) positive test. Recent use of psychotropic agents has also been associated with increased risk of death, varying between 50% in users of antidepressants to a three-fold increase in users of antipsychotics. The importance of maintaining and adjusting pharmacological treatment of people with severe mental disorders during the COVID-19 pandemic has been emphasized. Identifying those drugs with lower risk profiles regarding adverse outcomes to COVID-19 will support guidance of selecting and adjusting acute and maintenance treatment during the COVID-19 pandemic.

The present study aims at providing a population-based description of the association and potential differential impact of frequently used psychotropic drugs on the course and outcomes of COVID-19 in people with hospital diagnosed and without hospital diagnosed psychiatric disorders. We hypothesize that psychotropic treatment patterns differ between community-treated COVID-19 patients and hospitalized or deceased COVID-19 patients with lower risks for unfavourable outcomes in users of a) aripiprazole, haloperidol, risperidone or paliperidone as oral or short-acting injectable antipsychotics vs. other oral or depot long-acting antipsychotics; b) short-acting benzodiazepines vs. long-acting benzodiazepines; c) SSRIs vs. tricyclic antidepressants.

We will use data from the prospectively collected Danish COVID-19 cohort at Statens Serum Institut including all Danish residents tested by the reverse transcriptase polymerase chain reactions (RT-PCR) for SARS-CoV-2.

1. Milestones

Milestone	Date

Start of data collection	February 24, 2020
End of data collection	Not determined
Protocol	Version 1, 03/9/2020 Version 2, 23/9/2020 Version 3, 24/9/2020
Final report of study results/submission of manuscript	January 31, 2021

2. Background

Beyond the psycho-social consequences of the coronavirus disease 2019 (COVID-19) pandemic, people with severe mental disorders are likely to be vulnerable to severe outcomes of COVID-19 such as hospitalization and death. A recent Danish study reported an up to 2-fold increased 30-days risk of death, adjusted for age, sex and other somatic conditions, after a positive SARS-Cov-3 PCR positive test for people with dementia, schizophrenia or bipolar disorder. (Reilek et al 2020)

An additional risk factor for poor outcomes is the use of psychotropic drugs. A previous study has shown that the risk of death was 80% increased in patients with a 6-months prescription history of benzodiazepines before the positive test, three-fold increased in those with a history of antipsychotic use, and 50% increased in patients with a prescription history of antidepressants, adjusted for age, sex and total number of comorbidity. Hospitalization for COVID-19 was only associated with use of benzodiazepines, but not antipsychotic and antidepressant use. (Reilek et al 2020)

However, risk profiles for individual psychotropic drugs differ, potentially affecting complications to COVID-19 differently. For example, pneumonia, bleeding, thrombosis, and metabolic and cardiac effects, which are also complications to COVID-19, are known adverse drug reactions (ADRs) associated with some antipsychotics, e.g. clozapine, and antidepressants, e.g. tricyclic antidepressants, but are not necessarily class effects (Laporte J-

R. 2020). Moreover, selective serotonin reuptake inhibitors (SSRIs) have anti-inflammatory properties and can inhibit serotonin-mediated platelet aggregation, which could have beneficial effects on the course of COVID-19.

Recent publications pointed out the importance of maintaining and adjusting pharmacological treatment of people with severe mental disorders during the COVID-19 pandemic. (Kahl et al 2020, Laporte J-P., et al 2020; Siskind et al 2020). Identifying those drugs with lower risk profiles regarding adverse outcomes to COVID-19 will support guidance of selecting and adjusting acute and maintenance treatment during the COVID-19 pandemic.

3. Objectives

The present study aims at providing a population-based description of the association and potential differential impact of frequently used psychotropic drugs on the course and outcomes of COVID-19 in people with hospital diagnosed and without hospital diagnosed psychiatric disorders.

We hypothesize that psychotropic treatment patterns differ between community-treated COVID-19 patients and hospitalized or deceased COVID-19 patients:

a) Users of aripiprazole, haloperidol, risperidone or paliperidone as oral or short-acting injectable antipsychotics have a lower risk of unfavourable COVID-19 outcomes than users of other oral or depot long-acting antipsychotics.

b) Users of short-acting benzodiazepines have a lower risk of unfavourable COVID-19 outcomes than users of long-acting benzodiazepines.

c) Users of SSRIs have a lower risk for unfavourable outcomes than users of tricyclic antidepressants.

4. Methods

   4.1. Study design and setting

This nationwide register-based cohort study includes all test-positive patients with COVID-19 tested between February 28th, 2020 and the most recent data update of the source population of all Danish inhabitants. The date of the day of testing is the index day of the patients where follow up for the outcomes will start. Among all positively tested patients we will identify all individuals who used the predefined psychotropic drugs within the 6 months prior to the positive test. Among those, we will investigate the association between selected drugs of the drug classes of antipsychotics, antidepressants and benzodiazepines and hospitalization and death.

To investigate the effect of psychiatric or behavioural disorders (Chapter F of the ICD-10 classification system) we will perform stratified analyses for selected disorders of the association between the different drug groups on the COVID-19 outcomes.

4.2. Study period

February 27, 2020 to end of data collection.

4.3. Data sources

We use data from the prospectively collected Danish COVID-19 cohort at Statens Serum Institut (SSI) including all Danish residents tested by the reverse transcriptase polymerase chain reactions (RT-PCR) for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (Pottegård A. (2020)). The details of the cohort are described in Pottegård A. et al 2020. In short, the individuals are identified from the Danish Microbiology Database (MiBa) including results of tests based on the RT-PCR for SARS-CoV-2 from the primary and the secondary health care sector and governmental prevalence studies (Voldstedlund M. (2014)). The five administrative Danish regions directly report information on outcomes related to COVID-19 including hospital admission, intensive care unit admission, mechanical ventilation, and death to SSI.

The cohort is linked on an individual level by the use of a unique personal identifier to

information from the following Danish National Health and administrative registries through the Danish Civil Registration System covering the entire Danish population: (i) MiBa (ii) The Danish National Patient Registry covering all contacts to all Danish Hospitals (Schmidt M (2015)). This registry provides contact history and ICD-10 diagnoses of both somatic and psychiatric conditions and surgical procedures since 1995. (iii) The Danish Register of Causes of Death (vital status) (Helweg-Larsen K (2011)); (iv) Danish National Prescription Registry containing complete data on all prescriptions filled at community pharmacies including prescriptions issued by private practicing specialists and hospital prescribers since 1995 (Pottegård A (2017)); (v) Danish Register of Healthcare Professionals (health care authorization status); (vi) Register of Laboratory Results for Research (selected laboratory values). The study cohort and linked data are updated twice weekly.

4.4. Study population

The study population comprises all Danish patients with at least one positive testing for SARS-CoV-2 by reverse transcriptase polymerase chain reactions (RT-PCR) performed on oro- and nasopharyngal swaps and/or on respiratory tract secretions and aspirates from February 27, 2020 and onwards. (Pottegård A. et al 2020) Among those, we will identify patients with selected psychotropic drug use within 6 months prior to the verified COVID-19. ATC codes for the selected drugs are provided in **Section 9, Methods Table 1.**

4.5. Outcomes:

Primary outcomes: hospitalization within 14 days and death within -2 to 30 days since the verified positive test.

Secondary outcomes: (Among those hospitalized): Length of hospitalization, ICU unit treatment and ventilation (-2 days before the index date). Identification of these outcomes has been described in Reilev et al 2020.

4.6. Exposure definition

4.6.1.

Prescription information including dates of prescription redemptions, number of pills and strength of pills will be assessed from the Danish National Prescription Registry. We will categorize the psychotropic drug classes of antidepressants, antipsychotics and benzodiazepines into high risk and low risk drug categories according to half-lives or suspected/known adverse cardiac, metabolic or respiratory events or anti-inflammatory or antiplatelet aggregation activity **(Section 9, Methods Table 1)**. Combination therapy or polypharmacy is common in people with psychiatric disorders and with increasing age. Thus, we will categorize patients exposed to several drugs within and across drug classes, into users of polypharmacy including high risk drugs versus polypharmacy including no high risk drugs. We apply the following approaches to identify current and combined drug use: Please note that prescription duration of prescriptions filled before the 6 months window, but lasting into the 6 months window will be carried over with the respective number of days of exposure falling into the 6 months window:

- *Current drug use* is defined as filling of at least one prescription for the drugs of interest during the 6 months prior to the index date of the positive COVID-19 test.
- For determining polypharmacy and supplementary analyses looking at dose-response like patterns we will apply the following approach: For each prescription of the selected psychotropics, we will estimate the *prescription duration* by calculating the total amount of drug supplied (number of packages * number of pills * strength) divided by Defined Daily Dose (WHO) for the specific drugs (=VOLUME) and adding a grace period of 15 days.
- *Treatment periods* are defined as subsequent prescriptions without gaps between the end date of the previous prescription duration and the starting

date of the following prescription. Days of overlapping treatment periods will be only counted once.

- *Prescription days coverage* (PDC) during the 6 months prior to the index date is defined as the number of days with estimated exposure based on summed treatment periods divided by 180 days.
- The *cumulative dose* is estimated by summing up the (number packages * the number of pills * the strength of pills) of all prescriptions (ATC level 7) during the 6-months period. (Mainly for supplementary analyses)

4.7. Potential confounders/covariates **see section 9, Methods Table 2**

4.7.1 Age, Sex: assessed from the Danish Civil Registration System, comorbidity (other than ICD-10 F diagnoses) will be assessed from the National Patient Register, number of different co-medication drugs (by ATC code) (any other than selected psychotropic drugs) from the National Prescription register (as an indicator for somatic comorbidity load), comedication drugs or drug classes (other than psychotropic drugs); pandemic phase (calendar time periods, defined as Phase 1-4), geography of residence (region, not place of testing), categorized into the five Danish regions: Capital region, Zealand, Southern Denmark, Central Denmark, Northern Denmark.

4.8. Bias

4.8.1. Confounding: We will adjust or stratify for the variables described under 4.7. in the statistical analysis. The number of variables to account for confounding may exceed the power of the study population, in particular when focusing on strata of the patient population. Therefore, we will apply propensity score methodology. Propensity scores will also be applied to account for confounding by indication, because indications and characteristics of patients using different psychotropics can differ according to the severity

of the disorder.

4.8.2. Selection bias

Danish testing strategy changes have led to a selection bias regarding testing and hospitalizations, which will be considered by adjustment or stratification. (www.DKMA.dk/DACCOVID). People with severe mental disorders may be not capable of the situation under the COVID-19 pandemic and may not be in contact with the health care system or remain not tested in spite of symptoms.

4.8.3. Information bias

Data on in-hospital medication use is not available to investigate their immediate impact, but our focus is on pre-COVID-19 prescription drug exposure and effect of outcome.. Information on health care professional status is limited to a registered authorization from the Danish register of Healthcare Professionals, which does not inform about the current working activity in the primary or secondary health care sector. Information on the indication for treatment may be incomplete based on the variable (INDO) and will not be assessed. Information on prescribed doses is considered incomplete and is therefore not used from the register (DOSO).

4.9. Statistical analyses

4.9.1. We will describe the prevalence of specific drug use within 6 months before testing for community treated, hospitalized and deceased patients, stratified by age, sex and psychiatric comorbidity. In the primary analyses, we will investigate the association between cumulative and current psychotropic drug use prior to testing and risk of hospitalization and death using logistic regression analysis among all positively tested individuals. The analyses will be stratified, following clinical and power considerations, by psychiatric diagnoses (any diagnosis) and by individual psychiatric disorders (see 4.9.3). PS methodology will be applied by either matching of adjustment for each drug-outcome

association of the respective drug pairs. We will apply formal testing for interactions between psychiatric diagnoses/hospital contacts and psychotropic drug use. Adjustment **(coding see section 9; Table 2)**: age, sex, number of comorbidities (ever since 1995), calendar year of first recorded psychiatric disorder, number of different drugs (somatic) (within 6 months prior to the index date), adjustment or weighting for PS scores for specific drugs; sub-periods of the pandemic (containment phase, mitigation phase, reopening phase, 4th phase), and geography (region).

We will report odds ratios (ORs) and 95% confidence intervals (95% CI).

Secondary outcomes are length of hospitalization, treatment in intensive care units, need of ventilation.

4.9.2. Propensity scores

To account for potential differences in characteristics and confounding by indication between treatment groups we will calculate pair-wise propensity scores for each subgroup of the three drug classes. (i) Short-acting antipsychotics (reference group) versus long-acting antipsychotics and short acting versus intermediate acting antipsychotics; (ii) SSRIs (reference group) versus TCAs and SSRIs versus other antidepressants (N06A – SSRI – TCA); (Lee YC et al 2013; Wong J. et al 2016; Musliner KL. Et al 2019) (iii) Short acting benzodiazepines (reference group) versus long-acting (Patorno E. et al 2017; Bushnell GA. 2017). PS will be estimated separately for those with and without psychiatric disease. The variables included in the PS selected by the investigators are either variables unrelated to exposure but related to the outcome, or related to both exposures and outcomes. Variables are defined in Methods Table 2.

4.9.3. Interaction

We address effect modification and interaction by performing stratified analysis by psychiatric disorders (any) yes/no among users of specific drugs, and by subgroup analyses of specific psychiatric disorders, i.e. (i) dementia (as defined under covariates),

(ii) alcohol abuse (as defined under covariates), (iii) substance abuse (as defined under covariates), (iv) schizophrenia and schizotypal and delusional disorders (F20-F29), (v) Depression (as defined in covariates), (vi) Bipolar disorder (as defined in covariates), (vii) Mood (affective) disorder (F32-33), (viii) Neurotic, stress-related and somatoform disorders (F40-49); and Any other psychiatric disorder ((F34-F39; F50-F99). Moreover, we will add interaction terms in the multivariable analyses and perform formal statistical tests for interactions (Wald test).

4.9.4 Sensitivity analyses/supplementary analysis:

Depending on the results of the primary analysis and sufficient power, we will investigate the cumulative dose effect and combination therapy determined as described in 4.6.1.

5. Sample size considerations

Based on a feasibility count and preliminary data, of 15,000 positively tested patients, we expect approximately 1500 users of psychotropic drugs, and a third of those with a diagnosis within chapter V of ICD-10. The selected drugs will not be used mutually exclusively (combinations and polypharmacy are common in clinical practice), which will reduce the number of users in each class, and category when considering the use of specific drugs alone. Thus we will not exclude patients using several drugs at a time, also because this reflects clinical practice and should be described and investigated.

6. Ethical/data protection issues

We will not report numbers below 5, or provide any information, that in combination can enable identification of individuals. The cohort is governed by a steering committee with representatives from the Danish Medicines Agency, Statens Serum Institut, the Danish Health Authority, the Danish Health Data Authority, Danish Patients, The Faculties of Health Sciences at the Danish Universities, and Danish Regions. The

Danish COVID-19 cohort data are kept at the Danish Health Data Authority (record no 00004874) and approved by the Data Protection office at University of Southern Denmark (record no 10.960). Data are pseudonymized centrally at the Danish Health Data Authority. According to Danish law, ethical permission is not required for registry-based research. Individual-level data will not be made publicly available in accordance with Danish law. Dedicated website hosted by the Danish Medicines Agency, which can be found at www.DKMA.dk/DACCOVID. (Pottegård A. 2020)

7. Plans for communication of results

Publication in national and international peer-reviewed journal and conferences.

8. Amendments and deviations

9. Figures, tables and codes

Methods: Table 1. ATC codes for the definition of exposure drugs 6 months before positive test result (index date)

Drug group or class	Drug name	ICD-10/ATC	Additional information
Antipsychotics			
Antipsychotics with lower complication profile	Aripiprazole	N05AX12	
	Haloperidol* (Oral or short acting injection)	N05AD01	if not long-acting see codes below
	Risperidone* (oral)	N05AX08	if not long-acting, see codes below
	Paliperidone* (oral)	N05AX13	if not long-acting, see codes below
Antipsychotics higher complication	Sertindol	N05AE03	
	Ziprasidone	N05AE04	
	Clozapin	N05AH02	
	Olanzapine	N05AH03	
	Quetiapin	N05AH04	
	Amisulpiride	N05AL05	
	Paliperidone (depot)	N05AX13	Varenr: 058609 – 078591 – 159849 – 379384 – 409745 – 412581 – 536460
	Risperidone (depot)	N05AX08	Varenr=012704 – 012715 – 012726 – 018991 – 018993 – 019015 – 025555 – 025698 – 025709 – 028105 – 028114 – 028123 – 028205 – 028214 – 038631 – 070020 – 070031 – 070042 – 071070 – 071081 – 071093 – 087974 – 103856 – 104330 – 105547 – 125155 – 132812 – 148328 – 397922 – 451699 – 486626 – 555271 – 593006 – 598909
	Haloperidol (depot)	N05AD01	Varenr: 000283 – 001511 – 547398
Other antipsychotics	Levomepromazin	N05AA02	
	Perphenazin	N05AB03	Longacting: varenr: 055673 – 079269
	Prochlorperazin	N05AB04	
	Periciazin	N05AC01	
	Melperon	N05AD03	
	Pipamperon	N05AD05	
	Flupentixol	N05AF01	Longacting: Varenr: 032219 – 060616 – 062257 – 121400 – 121426 – 151175 – 151183 –

Drug group or class	Drug name	ICD-10/ATC	Additional information
			151191 – 151209 – 465468 – 465518 – 499327 – 590745 – 590752
	Chlorprothixen	N05AF03	
	Zuclopenthixol	N05AF05	Longacting: varenr: 002105 – 011353 – 036457 – 106047 – 140418 – 140442 – 140459 – 140525 – 375766 – 377911 – 509034 – 509042 – 525878 – 559641 – 576430 – 580648
	Pimozid	N05AG02	
	Sulpirid	N05AL01	
	Lurasidon	*N05AE05*	
	Cariprazin	*N05AX15*	
	Brexpiprazol	*N05AX16*	
	Asenapin	*N05AH05*	
Antidepressants			
SSRI		N06AB	
TCA		N06AA	
Other antidepressants		N06AX16	
		N06AX21	
		N06AX03	
		N06AX11	
		N06AX18	
		N06AX22	
		NO6AX26	
		N06AX12	
Benzodiazepines: Anxiolytics or hypnotics			
Short-acting benzodiazepines			
	Lorazepam	N05BA06	A
	Midazolam	N05CD08	H
	Oxazepam	N05BA04	A
	Triazolam	N05CD05	H
	Alprazolam	N05BA12	A
	Bromazepam	N05BA08	A
Long-acting and/or long-acting metabolites benzodiazepines (half-life >= 24 hours)			
	Chlordiazepoxide	N05BA02	A
	Clobazam	N05BA09	A
	Clonazepam	N03AE01	A
	Diazepam	N05BA01	
	Nitrazepam	N05CD02	H

References (Table 1):

1. http://pro.medicin.dk/Laegemiddelgrupper/Grupper/239010#forsigtighedsregle

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2. Kahl KG, Correll CU. Management of Patients With Severe Mental Illness During the Coronavirus Disease 2019 Pandemic [published online ahead of print, 2020 Jun 24]. *JAMA Psychiatry*. 2020;10.1001/jamapsychiatry.2020.1701. doi:10.1001/jamapsychiatry.2020.1701

3. Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. *J Psychiatry Neurosci*. 2020;45(3):222-223. Doi:10.1503/jpn.200061

http://jpn.ca/wp-content/uploads/2020/04/45-3-222.pdf

4. Varenr: see medicinpriser.dk

Methods: Table 2. Medical history based on hospital diagnoses (primary or secondary at in or out patient contacts) since 1995 or prescription drug use during the 6 months prior to the index date.

Covariate	Coding system	Codes
Mental and behavioural disorders	**ICD-10**	**Chapter V**
Dementia	ICD-10	F00 F01 F02 F03 F1073 F1173 F1273 F1373 F1473 F1573 F1673 F1873 F1973
AND/OR	ATC	N06D
Alcohol abuse	ICD-10	F10 E244 G312 G621 G721 I426 K292 K70 K852 K860 Q860 Z502 Z714 Z721
AND/OR	ATC	N07BB
Substance abuse	ICD-10	F11-F19
AND/OR	ATC	N07BC
Schizophrenia , schizotypal and delusional disorders	ICD-10	F20-F29
Manic episodes, Bipolar disorder	ICD-10	F30-31
AND/OR	ATC	N05AN (Lithium)
Depressive episode or recurrent depressive disorder	ICD-10	F32-F33
AND/OR	ATC	N06A AND INDO=0000168
Other affective disorders	ICD-10	F34, F38, F39
Neurotic, stress-related and somatoform disorders	ICD-10	F40-F48
Behavioural syndromes associated with physiological disturbances and physical factors	ICD-10	F50-F59
Disorders of adult personality and behaviour	ICD-10	F60-F69
Mental retardation	ICD-10	F70-F79
Disorders of psychological development	ICD-10	F80-F89
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	ICD-10	F90-F98

Covariate	Coding system	Codes
Unspecific mental disorders	ICD-10	F99
Year of first diagnosis (for the categories as defined above)		
Other disorders		
Organ transplantation	ICD-10	Z94
Rheumatoid arthritis		
Chronic lung disease	ICD 10	J41-J47
AND/OR	ATC	R03AK, R03AL, R03BA, R03AC12, R03AC13, R03AC18, R03AC19, R03CC12, R03BB04, R03BB05, R03BB06, R03BB07
Hypertension	ICD	I10 I11 I12 I13 I15
AND/OR	ATC	C03A C07 C08 C09
Ischemic heart disease	ICD	I20 I21 I22 I23 I24 I25
AND/OR	ATC	N02BA C01DA B01AC24
Heart failure	ICD	I099A I110 I130 I132 I50
AND/OR		
Diabetes	ICD	E10 E11 E13 E14
AND/OR	ATC	A10
Atrial fibrillation	ICD-10	I48
Stroke	ICD-10	I60 I61 I62 I63 I64 I69
Any cancer	ICD-10	C00-C97, excluding C44
Chronic liver disease	ICD-10	K700-K704 K709 K71-K74 K760 K766 B150 B160 B162 B18 B190 I85
Kidney disease	ICD-10	I12 I13 N00-N05 N07 N08 N11 N14 N18 N19 E102 E112 E142
Overweight and obesity	ICD-10	E66
AND/OR	ATC	A08, N05AN
Migraine	ICD-10	G43, G44
	ATC	N02C
Thyroid disease	ICD-10	E00-E07, H58.8, I43.8; H06.2; E21.4, E21.5
	ATC	H03
Peptic ulcer disease	ICD-10	K22.1; K25-K28
	ATC	
GI bleeding	ICD-10	K29.0
Neuropathy	ICD-10	
	ATC	
Seizure (Epilepsy)	ICD-10	G40
Urinary incontinence	ICD-10	R32, N39.3, N39.4, F98.0
Gout	ICD-10	M10

Covariate	Coding system	Codes
Indicators of healthcare utilization		
Number of any somatic hospital contacts (in- or out patients, ER) within the 6 months prior to the index date	ANY, count unique contacts, categories	
Number of any psychiatric hospital contacts (In- and outpatients, and ER) within the 6 months prior to the index date	ANY, count unique categories	
Number of different ATC prescription drugs (excluding psychotropic drugs)	ANY Count unique Categories (ATC level 7)	
Drug classes or groups	**Coding system**	**Codes**
Antihypertensive drugs	ATC	C03A C07 C08 C09
ACE/ARBs	ATC	C09
Calcium channel blockers	ATC	C08
Beta-blockers	ATC	C07
Thiazides	ATC	C03A
Loop-diuretics	ATC	C03C
Glucose-lowering drugs	ATC	A10A A10B
Non-insulin glucose lowering drugs	ATC	A10B
Insulin	ATC	A10A
Insulin monotherapy	ATC	A10A, not A10B
Antiplatelets	ATC	B01AC
Anticoagulant therapy	ATC	B01AA, B01AE07, B01AF
Opioids	ATC	N02A
Systemic glucocorticoids	ATC	H02AB
Inhaled corticosteroids	ATC	R03AK R03AL R03BA
Lipid modifying agents	ATC	C10
NSAIDs	ATC	M01A (excluding M01AX)
Methotrexate	ATC	L04AX03
Biologics	SKS	BOHJ16A BOHJ18A1-5 BOHJ18B1-8 BOHJ18C1 BOHJ19H4 BOHJ19H6 BOHJ26 BWHB84
	ATC	L04AA21 L04AA23-6 L04AA28 L04AA33 L04AA34 L04AA36 L04AB01 L04AB02 L04AB04 L04AB05 L04AC02 L04AC03 L04AC05 L04AC07 L04AC08 L04AC10-4 L04AC16 L04AC17 D11AH05 L01XC02

Covariate	Coding system	Codes
COPD/Asthma therapy	ATC	R03
Anticonvulsants	ATC	N03 (without N03AE01)
Biphosphonates	ATC	M05BB
Anti-parkinson therapy	ATC	N04
Dementia therapy	ATC	N06D
Barbiturates	ATC	N05CA, N05CB
Anticholinergics	ATC	R03BB
Sedating antihistamines	ATC	R06A
Uric acid lowering drugs (Antigout preparations)	ATC	M04A
Estrogenes	ATC	G03C (In combinations: G03AA, G03AB, G03E, G03F)
Thyroid therapy	ATC	H03

Output Tables:

Table of characteristics of SARS-COV-2 PCR-positive cases by treatment status with psychotropic drugs used within 6 months prior to a positive PCR.

Characteristics	All n (%)	With AP and/or, BENZO and/or AND n=			Without AP, AND or BENZO n=
		AND n=	Benzo n=	AP n=	
Sex					
Female					
Male					
Age (mean, SD)					
Age groups					
<60 years					
60-74 years					
>74 years					
Geography					
Capital region					
Zealand					
Central Denmark Region					
Southern Denmark					
Northern Denmark					
F diagnoses (ever since 1995)					
F0-9					
F10-19					

Characteristics	All n (%)	With AP and/or, BENZO and/or AND n=			Without AP, AND or BENZO
		AND n=	Benzo n=	AP n=	n=
F20-29					
F30-31					
F32-F33					
F35-39					
F40-41					
F50-59					
F60-69					
F70-79					
F80-89					
F90-99					
Number of comorbidity (ever since 1995)					
0					
1					
2					
3					
4+					
Psychotropic drug use (within last 6 months)					
Antipsychotics					
Low risk					
High risk					

Characteristics	All n (%)	With AP and/or, BENZO and/or AND n=			Without AP, AND or BENZO
		AND n=	Benzo n=	AP n=	n=
Intermediate					
Antidepressants					
SSRI					
TCA					
Other AND					
Benzodiazepines					
Short-acting					
Long-acting					
Number of prescriptions (within last 6 months) any different ATC (without psychotropics)					
Hospital contacts with the last year (Median [IQR]					
0					
1					
2					
3					
4+					
Phases					
Before 13th March					
March 13-April 15th					

Characteristics	All n (%)	With AP and/or, BENZO and/or AND n=			Without AP, AND or BENZO
		AND n=	Benzo n=	AP n=	n=
After April 15th					
After August 10th					
Authorized health care worker					
Nurse					
Physician					
Other					
Comorbidity/Comedication					
… Codes and categories see Method tables					
Current drug use (at least one prescription during the 6 months prior to the test)					

Results: Table 1. Crude (age, sex adjusted) and PS adjusted odds ratios (ORs) and 95% confidence intervals for the association between psychiatric diagnoses and psychotropic drug groups and 14-days hospitalization due to COVID-19.

Characteristics	Age, sex adjusted	PS adjusted	Age, sex adjusted	PS adjusted	Age, adjusted	PS adjusted
	AND n=		Benzo n=		AP n=	
Low risk	1.0	1.0	1.0	1.0	1.0	1.0
High risk						
Other risk						
No F diagnosis	1.0	1.0	1.0	1.0	1.0	1.0
F diagnoses (ever since 1995)						
F0-9						
F10-19						
F20-29						
F30-31						
F32-F33						
F35-39						
F40-41						
F50-59						
F60-69						
F70-79						
F80-89						
F90-99						

Results Table 2. Crude (age, sex adjusted) and PS adjusted odds ratios (ORs) and 95% confidence intervals for the association between psychiatric diagnoses and psychotropic drug groups and 30-days mortality due to COVID-19.

Characteristics	Age, sex adjusted	PS adjusted	Age, sex adjusted	PS adjusted	Age, adjusted	PS adjusted
	AND n=		Benzo n=		AP n=	
Low risk	1.0	1.0	1.0	1.0	1.0	1.0
High risk						
Other risk						
No F diagnosis	1.0	1.0	1.0	1.0	1.0	1.0
F diagnoses (ever since 1995)						
F0-9						
F10-19						
F20-29						
F30-31						
F32-F33						
F35-39						
F40-41						
F50-59						
F60-69						
F70-79						
F80-89						
F90-99						

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ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)](#) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the [ENCePP Guide on Methodological Standards in Pharmacoepidemiology](#), which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the [Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies](#)). The Checklist is a supporting document and does not replace the format of the

protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: The effect of mental disorders and treatment with psychotropic agents on the course of COVID-19 (COVID19 Psychotropic)

EU PAS Register® number: Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				1.
1.1.1 Start of data collection[1]	X	☐	☐	
1.1.2 End of data collection[2]	☐	X	☐	
1.1.3 Progress report(s)	☐	X	☐	
1.1.4 Interim report(s)	☐	X	☐	
1.1.5 Registration in the EU PAS Register®	☐	X	☐	
1.1.6 Final report of study results.	X	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	X	☐	☐	3.
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	
2.1.2 The objective(s) of the study?	X	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	4.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	X	☐	☐	3.
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	X	☐	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X	☐	☐	4.1.
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	4.1.
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X	☐	☐	4.10.1.

Section 3: Study design	Yes	No	N/A	Section Number
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	x	☐	☐	4.10.1.
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	x	

Comments:

3.5. Observational register-based study

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	X	☐	☐	4.3.
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	X	☐	☐	4.2
4.2.2 Age and sex	X	☐	☐	4.4.
4.2.3 Country of origin	X	☐	☐	4.4
4.2.4 Disease/indication	X	☐	☐	4.4.
4.2.5 Duration of follow-up	X	☐	☐	4.5.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	4.4.

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	X	☐	☐	4.6.
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	X	☐	☐	4.9.3.
5.3 Is exposure categorised according to time windows?	X	☐	☐	4.6.1.
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	X	☐	☐	4.6.1.
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	X	☐	☐	4.6.1.
5.6 Is (are) (an) appropriate comparator(s) identified?	X	☐	☐	4.6.1.

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X	☐	☐	4.5.
6.2 Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	4.5.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	X	☐	☐	4.3.
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	X	☐	☐	4.5

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	X	☐	☐	4.7. 4.9.2.
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	X	☐	☐	4.8.2.
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	☐	☐	4.8.3.

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X	☐	☐	4.9.3.

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X	☐	☐	4.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	4.3
9.1.3 Covariates and other characteristics?	X	☐	☐	4.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	4.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	4.5

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	4.7
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X	☐	☐	4.6.
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	4.5.
9.3.3 Covariates and other characteristics?	X	☐	☐	4.7.
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	X	☐	☐	4.3

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	X	☐	☐	4.9
10.2 Is study size and/or statistical precision estimated?	X	☐	☐	5
10.3 Are descriptive analyses included?	X	☐	☐	4.9.1
10.4 Are stratified analyses included?	X	☐	☐	4.9.1.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☐	4.9.1.
10.6 Does the plan describe methods for analytic control of outcome misclassification?	X	☐	☐	4.5.
10.7 Does the plan describe methods for handling missing data?	☐	☐	X	
10.8 Are relevant sensitivity analyses described?	X	☐		4.9.4

Comments:

4.5. Extension of the assessement window to 2 days prior to the test date.

10.7. Complete data or minimal occurrence of missings.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X ☐	☐	☐	6
11.2 Are methods of quality assurance described?	☐	X ☐	☐	
11.3 Is there a system in place for independent review of study results?	X ☐	☐	☐	

Comments:

11.3.Peer-review

11.2. Steering committee and a scientific board oversee the study.

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	X	☐	☐	4.8.2
12.1.2 Information bias?	X	☐	☐	4.8.3.
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	X	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	X	☐	☐	5.

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	X	☐	☐	6.
13.2 Has any outcome of an ethical review procedure been addressed?	X	☐	☐	6.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.3 Have data protection requirements been described?	X	☐	☐	6.

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	X	☐	☐	8.

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	7
15.2 Are plans described for disseminating study results externally, including publication?X	X	☐	☐	7

Comments:

Name of the main author of the protocol: Christiane Gasse

Date: 24/09/2020

Signature:

12.