Study Report

P2-C1-008 DARWIN EU® - Rates of occurrence of treatment-related intercurrent events in patients with major depressive disorder

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Version 5.1

Contents

Study Title	DARWIN EU® - Rates of occurrence of treatment-related *intercurrent events* in patients with major depressive disorder
Study Report Version identifier	V5.1
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EU PAS register number	EUPAS106685
Active substance	See table below
Medicinal product	N/A
Research question and objectives	See below

Drug Class	ATC code
I. Main drugs of interest (antidepressants)	
Non-selective monoamine reuptake inhibitors (NSRIs)	N06AA
Selective serotonin reuptake inhibitors (SSRIs)	N06AB
Other Antidepressants (excluding N06AX25 and N06AX27)	N06AX
II. Concomitant drugs of interest (psycholeptics)	
Antipsychotics	N05A
Anxiolytics	N05B
Hypnotics and sedatives	N05C

Research question

What is the incidence in clinical practice of treatment-related intercurrent events common in clinical trials in patients with major depressive disorder?

Study objectives

1. To examine the proportion of patients with newly diagnosed major depressive disorder who start treatment with antidepressants (NSRIs, SSRIs, or other anti-depressants), and of those the proportion who switch or discontinue treatment by specific timepoints (4, 6, 8, 12, and 24 weeks) after treatment initiation, stratified by age group, sex, and country/database during the study period (2013 - 2022).
2. To estimate the duration of antidepressant use in patients with newly diagnosed major depressive disorder who initiate treatment with antidepressants (NSRIs, SSRIs, or other antidepressants), stratified by age group, sex, and country/database during the study period (2013 - 2022).
3. To assess the proportions of patients with newly diagnosed major depressive disorder who initiate, switch, or discontinue treatment with psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives) by specific timepoints (4, 6, 8, 12, and 24 weeks) after starting antidepressant therapy, stratified by age group, sex, and country/database during the study period (2013 - 2022).

Country(-ies) of study	Germany, Netherlands, Spain, and the United Kingdom
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1 DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
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Data Partner	**Names**	**Organization**
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2 DATA SOURCES

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
UK	CPRD GOLD	Database covers primary care where antidepressants may be prescribed/dispensed.	Primary care	EHR	3 million	20/03/2023
Germany	IQVIA DA Germany	Database covers primary care / outpatient specialist care setting where antidepressants may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Database covers hospital care setting where	Secondary care (in	EHR	0.6 million	31/12/2022

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
		antidepressants may be prescribed/dispensed. For this study, we will only use outpatients from IMASIS	and outpatient)			
The Netherlands	IPCI	Database covers primary care where antidepressants may be prescribed/dispensed.	Primary care	EHR	1.4 million	01/12/2022
Spain	SIDIAP	Database covers primary care where medication antidepressants may be prescribed/dispensed.	Primary care with hospital linkage	EHR	5.8 million	31/12/2022

3 ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY REPORT)

Title:

DARWIN EU® - Rates of occurrence of treatment-related *intercurrent events* in patients with major depressive disorder

Rationale and Background

In clinical trials involving patients with major depressive disorder (MDD), participants who start treatment may experience *intercurrent events* (IEs) during follow-up, such as treatment discontinuation, switch to alternative therapies, or changes in background/concomitant therapies (e.g., sleep aids). The ICH E9(R1) guideline defines IEs as events that occur after treatment initiation and influence the interpretation of the outcome of interest or after which the outcome no longer exists (e.g., death).

While target estimands in these trials may adopt a treatment policy or composite strategy to handle these IEs, it is crucial to recognize that the rate at which these intercurrent events occur significantly impacts the interpretation of estimated treatment effects.

To gain a more comprehensive understanding of the external validity of clinical trials in this indication, it is essential to assess whether the rate of occurrence of these IEs is similar in real-life settings compared to what is observed in the clinical trials. By obtaining such insights, the results of this study aim to provide valuable information regarding the generalisability of clinical trial findings to real-world scenarios.

Research question and Objectives

Research question

What is the incidence in clinical practice of treatment-related intercurrent events common in clinical trials in patients with major depressive disorder?

Study objectives

1. To examine the proportion of patients with newly diagnosed MDD who start treatment with antidepressants (NSRIs, SSRIs, or other anti-depressants), and of those the proportion who switch or discontinue treatment within specific timepoints (4, 6, 8, 12, and 24 weeks) after treatment initiation, stratified by age group, sex, and country/database during the study period (2013 - 2022).
2. To estimate the duration of antidepressant use in patients with newly diagnosed MDD who initiate treatment with antidepressants (NSRIs, SSRIs, or other antidepressants), stratified by age group, sex, and country/database during the study period (2013 - 2022).
3. To assess the proportions of patients with newly diagnosed MDD who initiate, switch, or discontinue treatment with psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives) within specific timepoints (4, 6, 8, 12, and 24 weeks) after starting antidepressant therapy, stratified by age group, sex, and country/database during the study period (2013 - 2022).

Research Methods

Study design

- Patient-level characterisation (Objective 1 and 3, Patient-level characterization of use patterns and sequences, including initiation, discontinuation, and switching, of antidepressants and psycholeptics in patients with newly diagnosed MDD).
- Patient-level drug utilization (Objective 2, Patient-level drug utilization analyses to assess the duration of antidepressant use in patients with newly diagnosed MDD).

Population

Patient-level characterisation: Patient-level characterisation analyses included all patients with newly diagnosed MDD who are aged 12 years and above in the respective databases from 2013 to 2022 (or the latest available date if earlier), with a minimum of 1 year of data visibility before their diagnosis, and no previous record of MDD in the year preceding their diagnosis.

Patient-level utilization: Patient-level drug utilization analyses included all patients aged 12 years and above with newly diagnosed MDD who are users of any of the antidepressant classes of interest in the respective databases from 2013 to 2022 (or the latest available date if earlier), with a minimum of 1 year of data visibility before the MDD diagnosis (index date).

Variables

Drug class of interest:

- Non-selective monoamine reuptake inhibitors
- Selective serotonin reuptake inhibitors
- Other antidepressants (excluding esketamine and Hyperici herba)
- Concomitant medications – Psycholeptics
    - Antipsychotics
    - Anxiolytics
    - Hypnotics and sedatives

Condition of interest:

- Major depressive disorder (MDD)

Data sources

1. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain (for this study, we will only use the outpatients)
4. Integrated Primary Care Information Project (IPCI), The Netherlands
5. The Information System for Research in Primary Care (SIDIAP), Spain

Sample size

No sample size was calculated for this descriptive study, as our primary focus is to summarise the use pattern of antidepressants and psycholeptics in adolescents/adults with newly diagnosed MDD. Based on a preliminary feasibility assessment, the expected number of patients with MDD in the included databases for this study was approximately 380,000.

Data analyses

Objective 1: The number and percentage of patients with newly diagnosed MDD initiating treatment with antidepressants was estimated within 4, 6, 8, 12, and 24 weeks after date of the MDD diagnosis; and the number and percentage of those discontinuing and switching treatment within 4, 6, 8, 12, and 24 weeks following start of antidepressant therapy. These were reported in tabular form as absolute numbers as well as proportions.

Objective 2: The duration of antidepressant use in patients with newly diagnosed MDD during the first treatment era was described (mean, median, quantiles 25% and 75%, minimum and maximum). Statistical analyses were conducted using the "DrugUtilization" R package based on OMOP-CDM mapped data.

Objective 3: The number and percentage of patients with newly diagnosed MDD initiating psycholeptics next to the antidepressant or switching to psycholeptics only was estimated within 4, 6, 8, 12, and 24 weeks after the date of treatment initiation with antidepressants. This was reported in tabular form as absolute numbers as well as proportions.

For all analyses, results are reported with a minimum cell count of 5, and any counts smaller than 5 are reported as <5 to ensure privacy and confidentiality.

Results

In total, 670,371 individuals with newly diagnosed major depression were identified of which the majority was in IQVIA DA Germany (51%), followed by SIDIAP (44%), IPCI (2%) and CPRD GOLD (2%) and IMASIS (1%). The percentages of females in the databases were in the range 58.5-67.5%. In all databases, within the individuals with MDD the proportion of adolescents (age 12-17 years) was lowest with range 0.5-4.3%. For IQVIA DA Germany and SIDIAP the largest proportion of individuals with newly diagnosed MDD was in the age category of 45-64 years. In CPRD GOLD and IPCI, the largest proportion of individuals with newly diagnosed MDD was in the age category 18-44 years (50.8 and 50.6% respectively) whereas for IMASIS more than half of the individuals had an age greater or equal than 65 years at time of diagnosis.

Some of these individuals already had depression-related symptoms or used related treatment in 1 year up to 1 month before the diagnosis of MDD: symptoms of anxiety (8.1% SIDIAP, 11.1% IPCI, 3.1% CPRD GOLD) and depressive disorder (24.6% IPCI, 3.5% IMASIS), depressed mood (11.6% IPCI, 7.0% CPRD GOLD), treatment with oxazepam (19.3% IPCI), temazepam (6.1% IPCI), lorazepam (8.6% IMASIS, 11.7% SIDIAP), diazepam(9.1% SIDIAP), sertraline (7.1% CPRD GOLD), citalopram (5.9% CPRD GOLD).

Within 4 weeks following diagnosis, the proportion of individuals who did not initiate treatment with antidepressants ranged between 18.1% in CPRD and 76.6% in IPCI. The proportion of individuals not receiving any treatment declined within 24 weeks following MDD diagnosis. Mainly SSRI was initiated with proportions ranging between 15.0% for IQVIA DA Germany to 70.8% for CPRD. In contrast, the utilization of NSRI and other antidepressants was much lower.

The proportion of individuals that were lost to follow-up within 24 weeks following diagnosis was low especially for the primary care databases. Overall, females tended to have a slightly higher SSRI usage and use of NSRIs compared to males across all databases whereas use of other antidepressants was higher in males compared to females. When stratified by age, results as described for the overall group remained with highest use of SSRIs and lower use of NSRIs and other antidepressants. In all databases, the proportion of individuals not receiving any treatment was the highest in adolescents aged 12-17 years. (range of individuals not being treated within 24 weeks ranged between 32.1% for IMASIS to 78.2% for IPCI).

For all of the primary care databases, when assessed in the 4 weeks following treatment initiation, individuals still on treatment was more than 80% for SSRI and more than 70% for NSRIs and use of other antidepressants. The proportion of individuals continuing treatment decreased over time with proportions ranging between 14% (CPRD) to 67% (SIDIAP) for SSRI, 5.3% (CPRD) to 39% (SIDIAP) for NSRI and 16% (CPRD) to 57% (SIDIAP) for other antidepressants. In IMASIS, the proportion of individuals continuing treatment was much lower. Regarding the effect of sex on treatment continuation during follow-up, no consistent pattern between databases and between type of antidepressant therapy could be observed. For all antidepressants and for all databases (except for IMASIS) the age category of 18-44 years had the lowest proportion of individuals still on treatment within 24 weeks following treatment initiation.

Switching from one antidepressant class to another antidepressant class was low in CPRD GOLD, IPCI, IQVIA DA Germany and SIDIAP especially for use of SSRI where less than 1% of initial SSRI users switched to NSRI and less than 3% of initials SSRI users switched to other antidepressant agents during follow-up. In IMASIS, the proportion of individuals switching to other antidepressant treatment during follow-up was higher.

When increasing the maximum gap between prescriptions from 7 days to 14 and 21 days, the proportion of individuals still on treatment by the end of follow-up increased in all databases and for all types of antidepressants but the effect was the highest for CPRD and the lowest for SIDIAP and IMASIS.

Within 24 weeks after initiation of treatment, between 13.6% (IQVIA DA Germany) to 32.6% (IPCI) of individuals on SSRIs had received treatment with a psycholeptic. For NSRI this proportion ranged between 10.9% (IQVIA DA Germany) to 40.1% (IMASIS and IPCI) for NSRI and between 16.1% (IQVIA DA Germany) to 39.3% (IMASIS) for use of other antidepressants. Overall, adding psycholeptic treatment on top of antidepressant therapy was the lowest for IQVIA DA Germany. No clear difference in treatment patterns for use of psycholeptics could be observed between sex, except for IMASIS where use of pscholeptics on top of antidepressants was slightly higher for men compared to women. In CPRD, IPCI and IQVIA DA Germany, use of psycholeptics on top of the antidepressant of interest was the lowest for the age category 18-44 except for IMASIS and SIDIAP where use was higher in the 45-64 and >= 65 years age category. The proportion of individuals receiving treatment with psycholeptics increased when applying larger maximum gaps between prescriptions.

The median duration of the first treatment episode of an antidepressant drug was the lowest in IMASIS with a median duration of 12 days for SSRI, 30 days for both NSRIs and other antidepressants. The median duration was higher in the other databases ranging between 56-366 days for the SSRIs, 28-198 days for NSRIs and 56-

366 days for the other antidepressants. When applying different gaps between prescription, the median duration increased.

The initial quantity of the first treatment episode (potentially involving a series of consecutive prescriptions with a gap of no more than 7, 14 or 21 days between prescriptions) was the lowest (for all 3 classes of antidepressant drugs) in IMASIS and CPRD GOLD and the highest for SIDIAP. Large differences in initial quantity were observed between the other databases.

Discussion

This study highlights the multifaceted nature of MDD treatment across diverse healthcare settings.

Antidepressant treatment primarily features SSRIs, aligning with clinical guidelines and tolerability considerations. The proportion of individuals not receiving any treatment was the highest in adolescents aged 12-17 years.

The proportion of individuals still on treatment with any of the antidepressants within 4 weeks was high but decreased with increasing follow-up time. Up to 40% of individuals combined use of an antidepressant with use of a psycholeptic drug.

In conclusion, this study sheds light on the diverse profiles of MDD patients and their corresponding treatment trajectories, including the occurrence of treatment-related intercurrent events common in clinical trials in this indication such as permanent treatment discontinuation, treatment switch and use of concomitant medication.

4 LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IEs	Intercurrent Events
IP	Inpatient
IPCI	Integrated Primary Care Information Project
MDD	Major Depressive Disorder
NSRIs	Non-Selective monoamine Reuptake Inhibitors
OHDSI	Observational Health Data Sciences and Informatics
OP	Outpatient

OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SSRIs	Selective Serotonin Reuptake Inhibitors
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	15th February 2024	9.6.1 - exposure	No wash-out was applied for use of antidepressant drugs	As in some individuals with MDD, antidepressants were already prescribed prior to the diagnosis of MDD, we did not exclude prescriptions when there was a previous prescription in the year before. So no washout period was used.
2	29th March 2024	9.9.4 – sensitivity analysis	Amendment where additional time windows as maximum gaps between prescriptions were allowed. In particular, in addition to the maximum gap of 7 days between prescriptions to define a treatment era, this gap was extended to 14 and	To study the effect of different windows between prescriptions on the proportion of individuals discontinuing treatment

			21 days.	
3	29th March 2024	9.6.2 - outcomes	The proportion of individuals initiating treatment and the proportion of individuals continuing, switching or discontinuing treatment with the antidepressants of interest was assessed **within** specific time windows after treatment intiation. In contrast to the first 3 versions of the study report where use of antidepressants was assessed **at** the respective time windows.	This has been amended to align with the study protocol
4	29th March 2024	9.6.2 - outcomes	The proportion of individuals also on treatment with psycholeptics was assessed **within** specific time windows. In contrast to the first 3 versions of the study report where use of psycholeptics was assessed **at** the respective timewindows.	This has been amended to align with the study protocol

6 MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	11th August 2023	15th August 2023
Final Study Protocol	26th October 2023	26th October 2023
Creation of Analytical code	October 2023	October 2023
Execution of Analytical Code on the data	November 2023	January 2024
Interim Study Report (if applicable)	Not Applicable	Not Applicable
Draft Study Report	30th November 2023	16th February 2024
Final Study Report	7th February 2024	2nd April 2024
Final study report for archiving purposes	Not Applicable	23rd May 2024

7 RATIONALE AND BACKGROUND

Major depressive disorder (MDD) is a significant and escalating global health burden, ranked as the third leading cause of disease burden worldwide in 2008 and projected to be the first by 2030.(Malhi and Mann 2018) The prevalence of MDD in Europe is 2.1%,(Fischer, Zocholl et al. 2023) with higher rates in women and a global lifetime prevalence ranging from 5% to 17%.(Pedersen, Mors et al. 2014) Recent trends show an alarming increase in MDD cases among younger populations due to substance abuse. Comorbidity is common in MDD, often involving concurrent substance use disorders, anxiety disorders, or other psychiatric conditions, increasing the risk of suicide.(Bains and Abdijadid 2023)

MDD is characterized by persistent low or depressed mood, anhedonia, guilt or worthlessness feelings, lack of energy, impaired concentration, appetite changes, psychomotor disturbances, sleep disturbances, and, in severe cases, suicidal thoughts.(Bains and Abdijadid 2023) Its etiology is multifactorial, involving complex interactions between biological, genetic, environmental, and psychosocial factors. Early theories focused on neurotransmitter abnormalities, particularly involving serotonin, norepinephrine, and dopamine, leading to the development of antidepressants targeting these systems. Thyroid and growth hormone abnormalities, as well as childhood adversity and trauma, are also linked to increased susceptibility to major depression later in life.(Sullivan, Neale et al. 2000, Bradley, Binder et al. 2008, Bains and Abdijadid 2023)

The management of MDD requires a comprehensive and multimodal approach, including pharmacological, psychotherapeutic, interventional, and lifestyle modifications.(Bains and Abdijadid 2023) Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are common first-line pharmacological agents, with cognitive-behavioural therapy and interpersonal therapy proving highly effective as psychotherapeutic interventions. When these therapies fail, interventions such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS) offer alternative options.(Pagnin, de Queiroz et al. 2004, Cuijpers, Dekker et al. 2009, Gartlehner, Wagner et al. 2017)

Despite the available treatments, a considerable proportion of MDD patients, estimated at 10% to 30%, exhibit limited or no response to medications, highlighting the need for novel therapeutic approaches.(Al-Harbi 2012) Clinical trials (CTs) play a crucial role in evaluating treatment efficacy and safety but understanding *intercurrent events* (IEs) occurring after starting therapy is essential for translating CT findings to real-life clinical practice.(Mitroiu, Teerenstra et al. 2022) IEs, events that arise after treatment initiation and impact the interpretation of outcomes, can include treatment discontinuation, switches to alternative therapies, and initiation or modifications in concomitant treatments, introducing complexity in the definition and the estimation of a treatment effect.(Mitroiu, Teerenstra et al. 2022, Stensrud and Dukes 2022, Polverejan, O'Kelly et al. 2023) Addressing IEs in CTs requires the definition of a target estimand. Where such estimands include strategies defined as treatment policy (considering the outcomes regardless of the occurrence of IEs) or composite (as a signal of treatment failure), their incidence in the trial is a determinant of the treatment effect estimated, raising a question around the external validity of such estimate.

This study aims to provide valuable insights into the incidence in clinical practice of such IEs, and in particular of treatment discontinuation, initiation of (other) treatments, and switching among newly diagnosed MDD patients prescribed antidepressants and psycholeptics in various European clinical settings. Understanding the impact of IEs in real-life clinical practice will facilitate extrapolation of CT findings to improve everyday patient care and outcomes in MDD management.

8 RESEARCH QUESTION AND OBJECTIVES

Research question

What is the incidence in clinical practice of treatment-related intercurrent events common in clinical trials in patients with major depressive disorder?

Study objectives

1. To examine the proportion of patients with newly diagnosed major depressive disorder who start treatment with antidepressants (NSRIs, SSRIs, or other anti-depressants), as well as those who switch or discontinue treatment by specific timepoints (4, 6, 8, 12, and 24 weeks after treatment initiation), stratified by age, sex, and country/database during the study period (2013 - 2022).

2. To estimate the duration of antidepressant use in patients with newly diagnosed major depressive disorder who initiate treatment with antidepressants (NSRIs, SSRIs, or other antidepressants), stratified by age, sex, and country/database during the study period (2013 - 2022).

3. To assess the proportions of patients with newly diagnosed major depressive disorder who initiate, switch, or discontinue treatment with psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives) by specific timepoints (4, 6, 8, 12, and 24 weeks) after starting antidepressant therapy, stratified by age, sex, and country/database during the study period (2013 - 2022).

9 RESEARCH METHODS

9.1 Study Type and Study Design

A retrospective drug utilisation study in individual with major depression disorder was conducted using routinely collected health data from 5 databases. The study comprised two consecutive parts:

- A patient-level characterisation study was conducted to address objective 1 and 3, assessing the proportions of treatment initiation, switching, and discontinuation of antidepressants and psycholeptics as classes of interest in patients newly diagnosed with MDD who are aged 12 years and above.
- A patient-level drug utilisation study was used to address objective 2; estimating the duration (in days) of antidepressant use among new users of the specified drug class, in patients with newly diagnosed MDD who are aged 12 years and above.

The Study Types with related Study Designs were selected from the DARWIN EU® Complete Catalogue of Data Analytics.

9.2 Study Setting and Data Sources

This study was conducted using routinely collected data from 5 databases in 4 European countries (Germany, Spain, The Netherlands and the United Kingdom). All databases were previously mapped to the OMOP Common Data Model (CDM). The specific databases were:

1. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain (for this study, we will only use the outpatients)
4. Integrated Primary Care Information Project (IPCI), The Netherlands
5. The Information System for Research in Primary Care (SIDIAP), Spain

The data sources were selected out of the 10 databases available in the DARWIN EU® network of Data Partners. The selection was based on the reliability of the data and their relevance for the research question of interest (see below).

These selected databases fulfilled the requirements (having information on prescribing of antidepressant agents and psycholeptics) for conducting both a patient-level characterisation study and a patient-level drug utilization study. This enabled us to estimate the ocurrence of treatment initiation, switching, and discontinuation for antidepressants in the context of incident MDD. Moreover, it facilitates the assessment of utilization proportions concomitant therapies (specifically psycholeptics) within this MDD patient cohort. Importantly, this selection encompasses databases from diverse clinical settings, thus allowing us to capture both inpatient and outpatient prescriptions or dispensing of drugs.

Additionally, these selected databases possess comprehensive data on MDD, along with representation of at least five substances from each of the three main antidepressant classes of interest. The rationale and justification for selecting these specific data sources, underpinned by their capacity to capture pertinent information, are detailed below and summarised in **Table 1**.

Table 1: Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
UK	CPRD GOLD	Database covers primary care where antidepressants may be prescribed/dispensed.	Primary care	EHR	3 million	20/03/2023
Germany	IQVIA DA Germany	Database covers primary care / outpatient specialist care setting where antidepressants may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Database covers hospital care setting where antidepressants may be prescribed/dispensed. For this study, we will only use outpatients from IMASIS	Secondary care (in and outpatient)	EHR	0.6 million	31/12/2022
The Netherlands	IPCI	Database covers primary care where antidepressants may be prescribed/dispensed.	Primary care	EHR	1.4 million	01/12/2022
Spain	SIDIAP	Database covers primary care where medication antidepressants may be prescribed/dispensed.	Primary care with hospital linkage	EHR	5.8 million	31/12/2022

In general, drug utilization studies have been extensively conducted across the selected databases(Hedenmalm, Quinten et al. 2023, Tan, Robinson et al. 2023, Voss, Shoaibi et al. 2023). Consequently, these databases serve as highly suitable resources for examining intercurrent events linked to the pharmacological management of MDD. Furthermore, prior research on MDD has been undertaken in a minimum of three of the participating databases, namely CPRD GOLD, IQVIA DA Germany, and SIDIAP (Lane, Weaver et al. 2020, Denee, Kerr et al. 2021, Roca, Bonelli et al. 2023). This observation holds significant relevance in validating the accuracy of MDD cases within the scope of this study.

When it comes to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the onboarding procedure. In addition, they are asked to share the results from three data quality assurance R packages: CdmOnboarding, Data Quality Dashboard (DQD) and DashboardExport (OHDSI 2019, Moinat 2023, Moinat 2023) The latter exports a subset of analyses from the Achilles tool (https://github.com/OHDSI/Achilles), which systematically characterizes the data and presents it in a dashboard format to ease the detection of potential quality issues. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution can be compared against the national healthcare data. CdmOnboarding creates a report with select characterisation of the clinical data within the DP and details on mapping coverage statistics that are closely inspected upon onboarding. DQD provides more objective checks on conformance and plausibility, applied consistently across the data sources.

Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, a more study-specific diagnostic tool, CohortDiagnostics, was developed. This package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain on a monthly basis. This allows to get insights when data collection started, when new sources of data were added and until when data was collected. Finally, in a previous feasibility assessment, the number of individuals with MDD and the counts of antidepressant class of interest across databases, as well as the geographical spread were considered adequate to address the research question of interest.

A brief description of the individual databases has been added as an appendix to this report.

9.3 Study Period

The study period was from 1st of January 2013 to 31st December 2022 or the end of available data in each of the data sources if earlier (see **Table 1** for more details).

9.4 Follow-up

Study participants were followed from the date of MDD diagnosis (index date) until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022).

Additional follow-up criteria were applied in line with the objective of interest:

To assess the proportions of patients with newly diagnosed MDD initiating antidepressant therapy, incident MDD cases were followed from the date of MDD diagnosis (index date) up to for 4, 6, 8, 12 and 24 weeks following MDD diagnosis, loss to follow up or end of study period, whatever came first.

To assess the proportions of patients with newly diagnosed MDD switching or discontinuing specific antidepressant therapy, incident MDD cases on antidepressant therapy were followed from the date of the first prescription of the specific antidepressant class of interest up to 4, 6, 8, 12 and 24 weeks after starting antidepressant therapy, loss to follow up or end of study period, whatever came first.

To assess the proportions of patients with newly diagnosed MDD starting, switching, and discontinuing concomitant therapy with psycholeptics, incident MDD cases on antidepressant therapy were followed from the date of the first prescription of the specific antidepressant class of interest up to 4, 6, 8, 12 and 24 weeks after starting antidepressant therapy, loss to follow up or end of study period, whatever came first.

To explore characteristics of individuals initiating treatment with antidepressants, study participants were followed up from the date of incident prescription and/or dispensation of antidepressant class of interest until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022).

9.5 Study Population with inclusion and exclusion criteria

This section describes how the study population was selected based on specific inclusion and exclusion criteria.

9.5.1 Patient-level characterization of MDD treatment

The study cohort comprised all patients, aged 12 years or older, with newly diagnosed MDD present in the respective databases during the study period (2013-2022) and with at least 365 days of data availability before this diagnosis.

9.5.2 Patient-level utilization of antidepressants

All individuals aged 12 and above who are new users of antidepressants with incident MDD diagnosis in the period between 1st of January 2013 and 31st of December 2022 (or latest date available), with at least 1 year of data visibility prior to the date of their first prescription of the antidepressant class of interest. Because in this selection of new users, the criterion of 365 days data available before the MDD diagnosis was not applied, individuals can be included who were not included in the cohort of newly diagnosed MDD patients.

More details on the inclusion criteria are provided in Table 2 below.

Table 2. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Incident MDD	Patients with newly diagnosed MDD during the study period, that is individuals without a diagnosis of MDD 1 year prior.	After	1 year	IP, OP, OT	SNOMED	First	All study participants aged 12 years and above	N/A	N/A
Prior database history	Study participants are required to have a year of prior history observed before diagnosis	After	1 year	IP and OP	n/a	n/a	All patients, aged ≥ 12 years, with newly diagnosed MDD in the selected databases	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6 Variables

9.6.1 Exposure(s)

For this study, the exposure of interest was used (during study period) of antidepressants and concomitant medications (psycholeptics). Exposure was assessed at drug class level.

The list of drug classes of interest is described in **Table 3.**

Table 3: Exposures of interest

Drug Class of interest	ATC code
I. Main drugs of interest (antidepressants)	
Non-selective monoamine reuptake inhibitors (NSRIs)	N06AA
Selective serotonin reuptake inhibitors (SSRIs)	N06AB
Other Antidepressants (excluding N06AX25 and N06AX27)	N06AX
II. Concomitant drugs of interest (psycholeptics)	
Antipsychotics	N05A
Anxiolytics	N05B
Hypnotics and sedatives	N05C

Drug exposure calculations

Drug eras were defined as follows: Exposure started at date of the first prescription after the MDD diagnosis. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions for the same drug were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the time gap in days between end of the first era and start of the second era was ≤ 7 days. Sensitivity analyses were done using a maximum distance of ≤ 14 and ≤ 21 between drug eras. The time between the two joined eras was considered as exposed to the first era as show in in **Figure 1**.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 1. Gap era joint mode

If two eras overlapped, the overlap time was considered exposed to the first era (**Figure 2**). No time was added at the end of the combined drug era to account for the overlap.

If two eras started at the same date, the overlapping period was considered exposed to both. We did not consider repetitive exposure.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

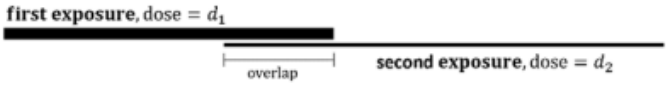

Figure 2. Gap era overlap mode

Patient-level characterisation: Duration of antidepressant use

The calculation of individual prescription/dispensing durations (in days) was derived from the DRUG_EXPOSURE table within the CDM. This table contains variables with self-explanatory names "drug_exposure_start_date" and the "drug_exposure_end_date", which are populated during the Extraction Transform and Load (ETL) process based on available source data. The advantage of this approach is that the drug exposure duration is directly obtained, eliminating the need to infer it from other information during analysis. This ensures a consistent analytical pipeline across all databases. Users were selected based on their first prescription of the respective antidepressant class of interest after a diagnosis of MDD. For each patient, at least 1 year of data visibility was required prior to that prescription.

More details on the operational description of exposure are described in **Table 4**.

Table 4. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Antidepressants (classes)	Code list provided in Table 3	No washout	Calendar year	Primary and secondary care	RxNorm	n/a	All patients with newly diagnosed MDD present in the database during the study period.	n/a	n/a	n/a
Psycholeptics (classes)	Code list provided in Table 3	No washout	Calendar year	Primary and secondary care	RxNorm	n/a	All patients with newly diagnosed MDD present in the database during the study period and being treated with an antidepressant.	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable; 2 Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6.2 Outcome(s)

The outcomes in this study were:

- Treatment with SSRI, NSRI or other antidepressants started by individuals with newly diagnosed MDD.
- In patients who started treatments with SSRI, NSRI or other antidepressants: occurrence of treatment-related IEs, namely treatment discontinuation, switching to other anti-depressant treatments , and add-on of other treatments.

For the analysis of antidepressants use in all individuals with newly diagnosed MDD, it was determined which antidepressant treatment was started within the window of 4, 6, 8, 12 and 24 weeks following diagnosis. Use of psycholeptics was not considered in this analysis. The following categories were reported:

- SSRI
- NSRI
- Other antidepressants
- No AD treatment

Table 5 and **Figures 3-**and **5** describe the operational definitions of the outcomes.

In **Figure 3**, observation period and exposure periods of five MDD patients are given, with indication how treatment initiated within 4-, 6-, 8- and 12-weeks post-diagnosis was reported (week 24 is left out for practical reasons). Patient 1 starts SSRI before week 4, this is reported as having initiated SSRI treatment within 4 weeks of diagnosis and all subsequent timepoints as well (as indicated by the horizontal arrow to the right). For these same patients, treatment with NSRI starts before week 6, and this is reported as having initiated NSRI treatment within 6 weeks and all the following timepoints. For patient 2, it is reported that no antidepressants are yet initiated by week 4 post-diagnosis. From week 6 onwards, SSRI initiation is reported. Patient 3 starts treatment with other antidepressants before week 4 and SSRI treatment before week 6. Although the observation period of this patients ends at 10 weeks after the MDD diagnosis, the previous initiated treatments are reported throughout the remainder of the follow-up windows. For patient 4, both SSRI and NSRI are reported for all timepoints. Patient 5 is not initiating any treatment until the end of his/her observation time at 7 weeks after diagnosis of MDD. Therefore, from week 8 on this patient is reported as 'Lost to follow up'.

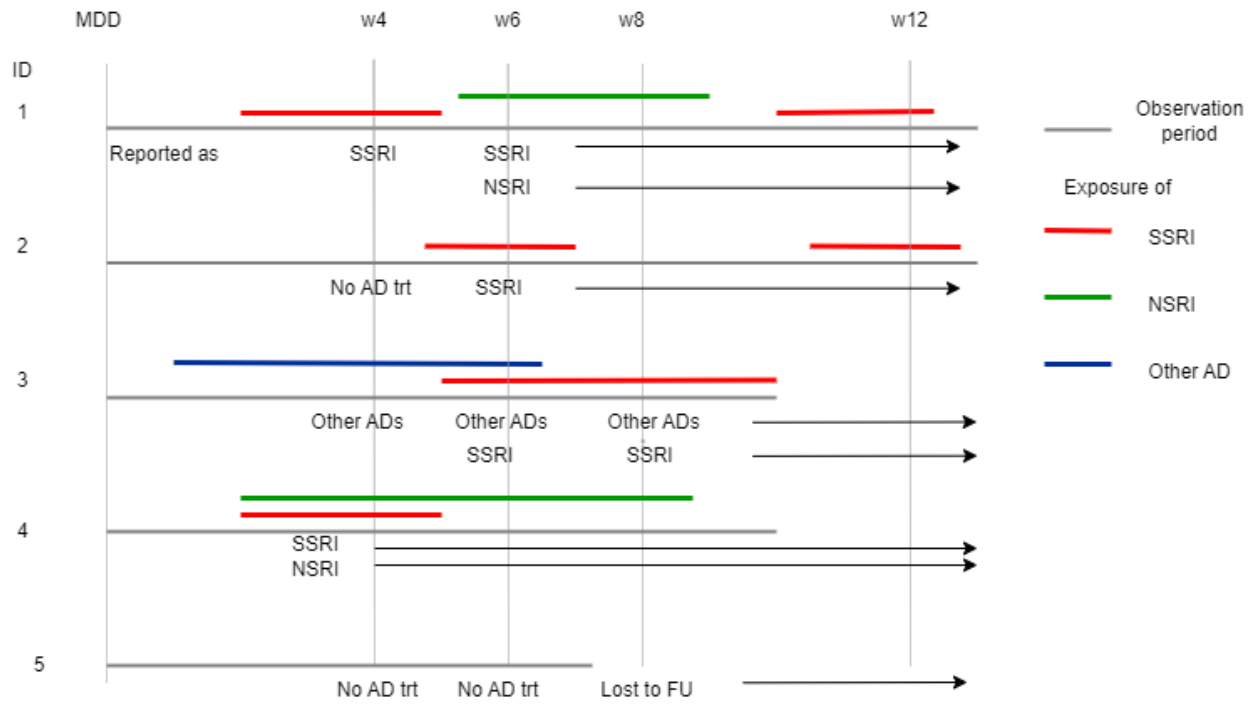

Figure 3 Examples of reporting drug initiation after MDD diagnosis.

For individuals who started therapy with SSRI, NSRI or another antidepressant following diagnosis, it was then determined if and which intercurrent event occurred within 4, 6, 8, 12 and 24 weeks after the start of the initial treatment. For the main analysis, a time gap of 7 days was used, while sensitivity analyses using 14 and 21 days were also carried out. For overlapping periods of two different treatments, a minimum period of 7 days is used always. If an overlap is less than 7 days, the change is reported as a switch to the new treatment. If the overlap is 7 days or more, it is reported as a switch to combination treatment.

First, we focussed on antidepressant use:

- use of the initial treatment
- switch to another antidepressant
- Overlap with a second antidepressant class, reported as a combination of antidepressants
- discontinuation of antidepressant. This category includes permanent discontinuation from the initial therapy as well as temporary discontinuations if the interruption lasted 7 days or more (14 and 21 days in the sensitivity analyses).

Examples of patients who initially started treatment with SSRI are presented in **Figure 4**. Patient 1 is still on SSRI treatment by week 4 and has switched to NSRI treatment by week 5. So, from week 6 on, switch to NSRI is reported. Resuming SSRI therapy before week 8 is ignored (NB: in the sensitivity analysis where drug eras are joined if the time gap is less or equal than 21 days, patient 1 would be reported as switching to combination therapy within 6, 8, 12 and 24 weeks from first therapy start). Patient 2 has already stopped SSRI treatment before week 4. This discontinuation is reported for this patient by all the following timepoints. The start of NSRI at week 7 is ignored. Patient 3 is starting with another antidepressant while SSRI treatment is ongoing. If the overlap of both treatment periods is 7 days or more, this is reported as switch to

combination therapy. If the overlap is less than 7 days, this is reported as switch to another antidepressant. This change is reported for all timepoints. Lost to follow-up is not reported for this patient, despite the end of the observation period at week 10, because this is the intercurrent event for the second SSRI exposure, and only intercurrent events for the first exposure period are reported. Patient 4 continues with SSRI until the end of his/her observation period at week 10. This is reported as 'Lost to follow-up' by week 12 and by week 24. Patient 5 is reported as discontinuing SSRI by week 4 already, if the gap between the first and second SSRI exposure is larger than the pre-specified threshold (of 7, 14 or 21 days), otherwise the two exposure periods would have been joined into one long continuing period and the patient would be reported as continuing with SSRI treatment. In the SSRI exposure period of patient 6 there is first an intercurrent event of addition of NSRI. The NSRI exposure started in week 5 and continued until week 7. The switch to combination therapy is reported for week 6. The end of observation period of this patient is before week 8, while the initial SSRI exposure was stil ongoing. This second intercurrent event is reported for week 8 and for subsequent timepoints.

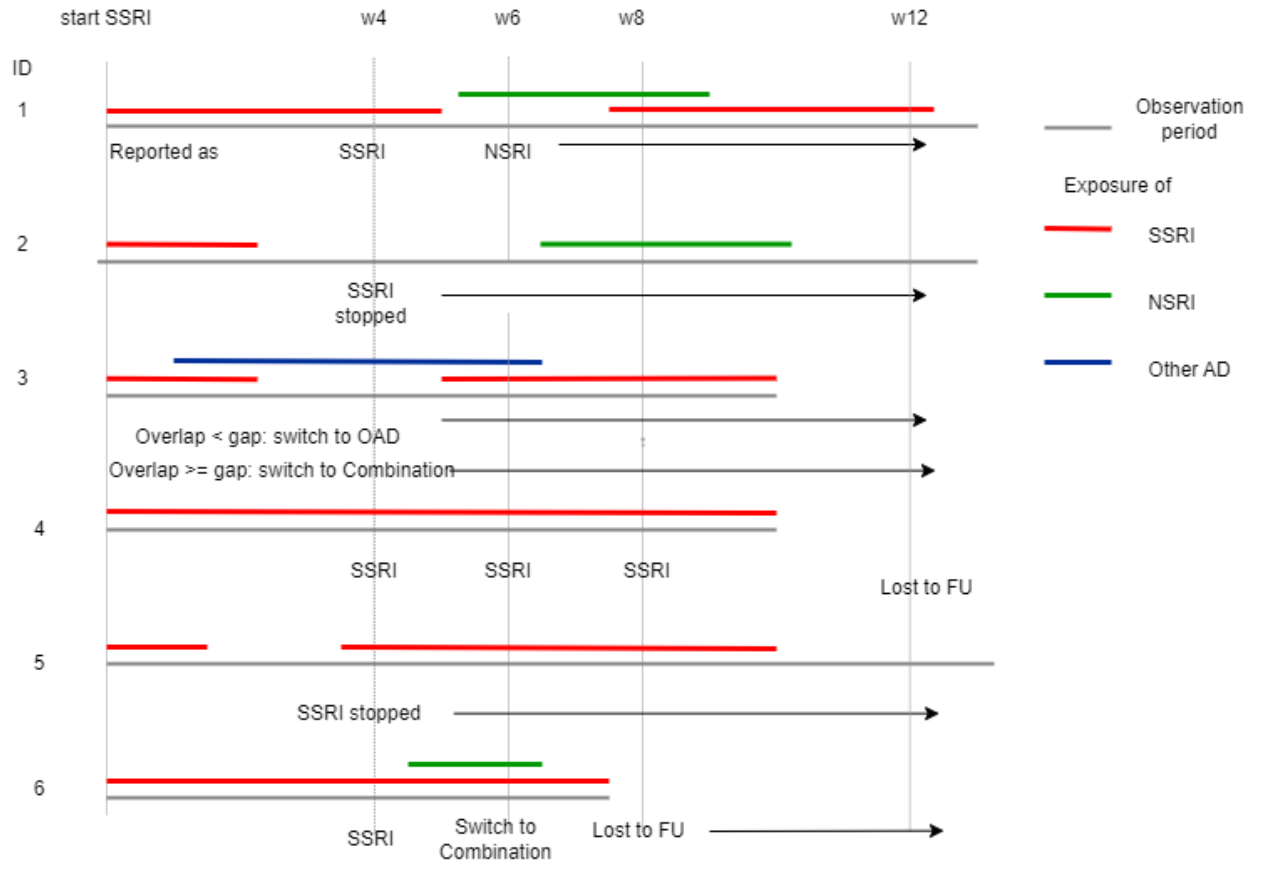

Figure 4 Examples of reporting drug use after start of SSRI with focus on antidepressants

For individuals who started therapy with SSRI, NSRI or another antidepressant, a second reporting on concomitant treatment use was done, now focussed on additional use of psycholeptics:

- continuation of the initial antidepressant without add-on of psycholeptics
- add-on of psycholeptics next to the initial antidepressant

- switch from initial antidepressant to psycholeptics
- discontinuation of the initial antidepressant and no use of psycholeptics

Figure 5 shows patients who started with SSRI therapy. For patient 1, continuing SSRI is reported at week 4. Because of the start of psycholeptic treatment at week 5, from week 6 onwards combination of SSRI and psycholeptics is reported. Patient 2 has already stopped SSRI and switched to psycholeptics before week 4. This switch is also reported for all following timepoints. Patient 3 has already stopped SSRI before week 4 and the gap between this stop and the start of psycholeptics at week 7 is larger than 7 days, resulting in reporting discontinuation of SSRI treatment. For patient 4, SSRI treatment is ongoing until the end of observation period at week 10. At week 4,6 and 8, continuing SSRI is reported, and for the subsequent timepoints the patient is reported as lost to follow-up.

Figure 5 Examples of reporting drug use after start of SSRI with focus on psycholeptic use

Table 5. Operational Definitions of Outcome

Outcome name	Details	Primary outcome	Type of outcome: summary measure	Washout window	Care Setting	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Antidepressant treatment	Initiated within 4, 6, 8, 12 and 24 weeks after MDD diagnosis. Code list provided in Table 3	Yes	Binary: Counts and percentages	No washout.	IP and OP care	RxNorm	N/A	All patients with incident MDD	N/A	N/A
Subsequent antidepressant treatment	Change from initial treatment within 4, 6, 8, 12 and 24 weeks after initial start with antidepressant. Code list provided in Table 3	Yes	Binary: Counts and percentages	No washout	IP and OP care	RxNorm	N/A	All patients with incident MDD and started with antidepressant	N/A	N/A
Subsequent antidepressant and/or psycholeptic treatment	Change from initial treatment within 4, 6, 8, 12 and 24 weeks after initial start with antidepressant. Code lists provided in Table 3	Yes	Binary: Counts and percentages	No washout	IP and OP care	RxNorm	N/A	All patients with incident MDD and started with antidepressant	N/A	N/A

[1]IP = inpatient, OP = outpatient, n/a = not applicable

9.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

Age at MDD diagnosis was described. The following age groups were used: 12 – 17, 18 – 44, 45 – 64, and 65 years and above. The sex (male/ female) of study participants was also identified.

All co-morbidities and concomitant-medications recorded prior to the ID (any time prior to the ID, 365 to 31 days prior to the ID and 30 to 1 day prior to the ID) were used for large-scale patient characterisation, identified as concept/code and descendants.

In addition, the distribution of the initial quantity of the antidepressant of interest at time of first prescribing was provided. This was presented by minimum, first quartile, median, third quartile and maximum.

The operational definition of the covariates of interest is described in **Table 6**.

Table 6. Operational Definitions of Covariates

Characteristic	Details	Type of variable: summary measures	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Large-scale summary characteristics of newly diagnosed MDD	Large-scale patient-level characterization with regard to baseline covariates	Binary: counts and percentages	Any time prior to date of diagnosis as well as 365 to 31 days prior to this date and 30 to 1 day prior to this date	Primary and secondary care	RxNorm	n/a	Persons with new MDD diagnosis	n/a	n/a
Initial quantity (i.e. number of tablets of first drug era) of antidepressant of interest	Characterisation	Continuous: Min, P25, median, P75, max	At date of first prescribing of the antidepressant of interest	Primary and secondary care	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

[1] ID = index date, IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.7 Study size

A formal sample size calculation was not undertaken for this descriptive study, given that our main objective was to summarise the characteristics and utilization patterns of antidepressants and psycholeptics in newly diagnosed MDD patients. Based on a preliminary feasibility assessment, the expected number of patients with MDD records in the included databases for this study will be approximately 380,000.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. After all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the results.

The study results of all data sources were checked after they were made available to the DARWIN EU® Coordination Centre. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

9.9.1 Main Summary Measures

For all continuous variables, summary descriptive statistics were reported: median and interquartile interval. For all categorical analyses, counts and percentages were reported. A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as “<5”. All analyses were reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached).

9.9.2 Main Statistical Methods

For reporting of patient-level characterizations of drug use, the R package "DrugUtilization" (https://cran.r-project.org/web/packages/DrugUtilisation/)(Catala 2023) was used. (see also 9.6.2) For other patient characteristics, the R package "PatientProfiles" (Catala 2024) was used.

For all variables, summary descriptive statistics were reported. For continuous variables, minimum, mean, median, maximum and interquartile interval were reported. For all categorical variables, counts and percentages were reported.

A minimum cell counts of 5 was used when reporting results, with any smaller counts reported as “<5”. All analyses were reported by country/database, overall and stratified by age and sex when possible (minimum cell count reached).

9.9.3 Missing Data

For the drug utilisation studies we assumed that the absence of a prescription record meant that the person did not receive the respective drug. For conditions, we assumed that the absence of a record of the respective condition meant that that condition was not present for the individual. This type of assumptions could not be verified within the report as we just do not know whether this occurs or not.

When during the follow-up window period after MDD diagnosis the observation period of an individual ended or the end of the study period was reached before any initiation of antidepressant was seen, this individual

was reported as 'Lost to follow-up'. Similarly, after start of initial treatment, if no intercurrent event was observed and the end of observation or the end of the study period was reached before the end of the follow-up window, this was reported as 'Lost to follow-up'.

9.9.4 Sensitivity Analysis

The original protocol stated that if the percentage of people who dropped from the analysis at week 24 would be high (where high is defined as more than 50% of individuals observable at week 4), the plan was to conduct a sensitivity analysis where i) we assumed that the people who were lost for follow-up continued treatment and ii) we assumed that people who were lost to follow-up discontinued treatment. As the number of individuals who were lost to follow-up was less than 50%, there was no need to conduct this sensitivity analysis.

To study the effect of different time gaps between drug eras on the proportion of individuals discontinuing treatment, we conducted a sensitivity analysis. For that sensitivity analysis, drug eras were created where the maximum gap between prescriptions was extended from 7 days to 14 and 21 days respectively. The same maximum gap was used for the time between prescriptions of two different substances. If this period was less than the maximum gap, the change was considered as switch to the new treatment. If the period was longer, discontinuation of treatment was reported.

The following deviations from the original protocol (protocol version 3.1) were applied. (Arinze 2023).

First, patients with a history of use of antidepressants prior to the first diagnosis of MDD were not excluded. Second, amongst patients initiating treatment with antidepressant drugs after MDD diagnosis, the inclusion criterion of 365 days observation time before the MDD diagnosis was not applied. And finally, additional sensitivity analyses were conducted where the maximum gap between prescriptions was extended from 7 days to 14 and 21 days respectively.

10 DATA MANAGEMENT

10.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and returned the results set which only contained aggregated data. The results from each of the contributing data sites was then combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from patients which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal

medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

11 QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners would have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion was identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). A pharmacist reviewed the codes. This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, DrugExposureDiagnostics (al 2023) was run if needed to assess the use of different codes across the databases contributing to the study.

The study code was based on two R packages developed to (1) extract patient characteristics and (2) characterize drug utilization (duration of use) using the OMOP common data model. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R packages were made publicly available via GitHub.

For testing the study cohort, data of test patients as presented in the figures in 9.6.2 Outcomes were generated and their result output was checked.

12 RESULTS

12.1 Individuals

The number of individuals with newly diagnosed depression during the study period is described in **Table 7**. In total, 670,371 individuals with newly diagnosed major depression were identified of which the majority was in IQVIA DA Germany (51%), followed by SIDIAP (44%), IPCI (2%) and CPRD GOLD (2%) and IMASIS (1%).

Table 7: Number of individuals with newly diagnosed major depression in the study period

	CPRD GOLD Primary Care UK	IMASIS Secondary Care Spain	IPCI Primary Care The Netherlands	IQVIA DA Germany Primary and Secondary Care Germany	SIDIAP Primary Care Spain
N	12,705	6,173	13,019	345,035	293,439

12.2 Descriptive Data

The characteristics of the patients with newly diagnosed major depression in terms of sex and age is described in **Table 8.**

Table 8. Characteristics of patients with newly diagnosed MDD in terms of sex and age

	CPRD GOLD		IMASIS		IPCI		IQVIA DA Germany		SIDIAP	
	N	%	N	%	N	%	N	%	N	%
Total	12,705	100.0	6,173	100.0	13,019	100.0	345,035	100.0	293,439	100.0
Females	7,431	58.5	4,165	67.5	8,194	62.9	218,703	63.4	195,646	66.7
Males	5,274	41.5	2,008	32.5	4,825	37.1	126,021	36.5	97,793	33.3
Unknown							311	0.1		
12-17	240	1.9	32	0.5	554	4.3	6,350	1.8	6,498	2.2
18-44	6,456	50.8	968	15.7	6,589	50.6	107,386	31.1	84,265	28.7
45-64	4,066	32.0	1,903	30.8	4,423	34.0	143,672	41.6	102,742	35.0
>=65	1,943	15.3	3,270	53.0	1,453	11.2	87,627	25.4	99,934	34.1

In all databases, the proportion of females with MDD was higher (range 58.5-67.5%) than the proportion of males (range 32.7-41.5%). In all databases, within the individuals with MDD, the proportion of adolescents (age 12-17 years) was lowest with range 0.5-4.3%. In CPRD GOLD and IPCI, the largest proportion of individuals with newly diagnosed MDD was in the age category 18-44 years (50.8 and 50.6% respectively) whereas for IMASIS (which is a hospital database) more than half of the individuals had an age greater or equal than 65 years at time of diagnosis. For IQVIA DA Germany and SIDIAP the largest proportion of individuals with newly diagnosed MDD was in the age category of 45-64 years.

Tables 9 and **10** describe the top 10 of disease codes (by database) in patients with newly diagnosed MDD assessed in the 1 year to 1 month prior to the index date (i.e. the date of first diagnosis of MDD) and in the 1 month prior to the index date.

As these tables report disease codes (and not aggregated codes for a specific comorbidity of interest), large variations in conditions were observed however when looking in the one year prior to diagnosis, hypertension (7.8% IMASIS and 15.3% IQVIA DA Germany) or blood pressure findings (46.6% CPRD GOLD) was the disease code most frequently reported.

Table 9 shows that prior to index date individuals already had symptoms of anxiety (8.1% SIDIAP, 11.1% IPCI, 3.1% CPRD GOLD) and symptoms of depression like depressive disorder (24.6% IPCI, 3.5% IMASIS), depressed mood (11.6% IPCI, 7.0% CPRD GOLD). Also, symptoms like fatigue, feeling tense and nervous, emotional exhaustion were reported, especially in IPCI.

The large share of the top 10 conditions related to anxiety, feeling depressed, etc. became even more prominent in the last month before the diagnosis (**Table 10**) especially for IPCI (only 1 of the top 10 diseases is not related to a psychological condition and/or psychological complaints).

Tables 11 and **12** describe the 10 most frequent medicines (by database) in patients with newly diagnosed MDD assessed in the 1 year to 1 month prior to the index date (i.e., the date of first diagnosis of MDD) and in the 1 month prior to the index date. For IQVIA DA Germany, no drug use in the 1 month prior to the index date is reported, because for none of the drug concepts a percentage of 0.5% of users was reached.

Table 11 shows that many individuals, especially in IPCI, IMASIS and CPRD GOLD, already received treatment with anxiolytics in the 1 year to 1 month prior to MDD diagnosis. In IPCI for instance, 19.3% of individuals received treatment with oxazepam and 6.1% with temazepam. In Spain, mainly lorazepam was prescribed, namely 8.6% for IMASIS and 11.7% for SIDIAP. In SIDIAP 9.1 % of individuals had received diazepam in the 1 year to 1 month prior to diagnosis. Use of anxiolytics did not belong to the top 10 of drugs for CPRD GOLD, however 7.1% of individuals had prescriptions for sertraline and 5.9% prescriptions for citalopram in the 1 year to 1 month prior to diagnosis.

Use of psycholeptics or antidepressants did not belong to the top 10 medicines for IQVIA DA Germany but use of dipyrone (a strong pain killer) belonged to the top 10 of most prescribed drugs (prevalence of around 2%).

Table 12 describes the 10 most prescribed medicines in the 1 month prior to diagnosis of MDD and it shows that the psychological symptoms are becoming more prominent as – especially in IPCI – prescribing of antidepressants and/or psycholeptics take a large share of the top 10 medicines. For CPRD GOLD, three of the top 10 medicines are related to antidepressants, for IMASIS one of the 10 is related to a psycholeptic drug, for IPCI nine of the 10 medicines are related to antidepressants or psycholeptics and for SIDIAP this was six of the top 10. This illustrates that prior to the diagnoses of MDD, many patients were already on treatment of psycholeptics or antidepressants for reason of depressive disorder (but not yet MDD).

Table 9: Top 10 most frequent diseases in the period from 1 year to 1 month prior to the date of diagnosis of MDD

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
Blood pressure finding	5923 (46.62)	Essential hypertension	482 (7.81)	Depressive disorder	3,214 (24.63)	Essential hypertension	52,901 (15.32)	Anxiety disorder	23,701 (8.05)
Finding of pulse rate	1196 (9.41)	Hyperlipidemia	331 (5.36)	Depressed mood	1,519 (11.64)	Depressive disorder	38,167 (11.05)	Common cold	22,064 (7.50)
Depressed mood	892 (7.02)	Type 2 diabetes mellitus without complication	250 (4.05)	Anxiety	1,454 (11.14)	Acute upper respiratory infection	34,156 (9.89)	Urinary tract infectious disease	17,251 (5.86)
Cervical smear - negative	888 (6.99)	Urinary tract infectious disease	232 (3.76)	Fatigue	1,071 (8.21)	Nerve root disorder	29,585 (8.57)	Traumatic or non-traumatic injury	16,591 (5.64)
Cough	867 (6.82)	Depressive disorder	217 (3.52)	Feeling tense	837 (6.42)	Illness	29,431 (8.52)	Low back pain	15,480 (5.26)
Exercise grading	557 (4.38)	COVID-19	203 (3.29)	Feeling nervous	837 (6.42)	Inflammatory disorder of digestive tract	19,766 (5.72)	Dizziness and giddiness	11,400 (3.87)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
Abdominal pain	537 (4.23)	Acute renal failure syndrome	198 (3.21)	Physical AND emotional exhaustion state	810 (6.21)	Acute bronchitis	18,219 (5.27)	Abdominal pain	10,974 (3.73)
Asthma not disturbing sleep	483 (3.8)	Atrial fibrillation	164 (2.66)	Localized abdominal pain	651 (4.99)	Type 2 diabetes mellitus without complication	13,969 (4.04)	Gastrointestinal infection	10,970 (3.73)
Asthma not limiting activities	452 (3.56)	Heart failure	156 (2.53)	Finding of region of thorax	626 (4.8)	Acute stress disorder	13,773 (3.99)	Acute lower respiratory tract infection	9,511 (3.23)
Anxiety	398 (3.13)	Low back pain	148 (2.4)	Cough	618 (4.74)	Gastritis	13,452 (3.89)	Acute pharyngitis	9,045 (3.07)

Table 10: Top 10 most frequent diseases in 1 month prior to the date of diagnosis of MDD

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
Blood pressure finding	1061 (8.35)	COVID-19	300 (4.86)	Depressive disorder	846 (6.48)	Essential hypertension	15,399 (4.46)	Anxiety disorder	10,184 (3.46)
Depressed mood	475 (3.74)	Essential hypertension	218 (3.53)	Depressed mood	297 (2.28)	Illness	9,314 (2.7)	Common cold	2,561 (0.87)
Patient self-report	198 (1.56)	Hyperlipidemia	153 (2.48)	Anxiety	279 (2.14)	Depressive disorder	8,917 (2.58)	Urinary tract infectious disease	2,534 (0.86)
Finding of pulse rate	175 (1.38)	Type 2 diabetes mellitus without complication	125 (2.03)	Feeling tense	130 (1)	Nerve root disorder	4,418 (1.28)	Dizziness and giddiness	2,129 (0.72)
Anxiety	134 (1.06)	Heart failure	105 (1.7)	Feeling nervous	130 (1)	Acute upper respiratory infection	4,288 (1.24)	Traumatic or non-traumatic injury	2,020 (0.69)
Depressive disorder	120 (0.94)	Acute renal failure syndrome	89 (1.44)	Physical AND emotional exhaustion state	122 (0.94)	Acute stress disorder	3,865 (1.12)	Nonorganic insomnia	1,873 (0.64)
Exercise grading	86 (0.68)	Atrial fibrillation	86 (1.39)	Type 2 diabetes mellitus	113 (0.87)	Type 2 diabetes mellitus without complication	3,539 (1.02)	Low back pain	1,867 (0.63)
Overdose	79 (0.62)	Osteoporosis	77 (1.25)	Fatigue	112 (0.86)	Malaise and fatigue	2,969 (0.86)	Gastrointestinal infection	1,657 (0.56)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
Cervical smear - negative	78 (0.61)	Delirium	73 (1.18)	Acute panic state due to acute stress reaction	97 (0.74)	Sleep disorder	2,867 (0.83)	Abdominal pain	1,491 (0.51)
Anxiety disorder	74 (0.58)	Osteoarthritis of knee	72 (1.17)	Psychological sign or symptom	97 (0.74)	Inflammatory disorder of digestive tract	2,805 (0.81)	NAP	NAP

NAP= not applicable

Table 11: Top 10 most frequent medicines in the period from 1 year to 1 month prior to the date of diagnosis of MDD

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
Influenza, seasonal, injectable	2436 (19.17)	omeprazole 20 MG Delayed Release Oral Capsule	898 (14.55)	oxazepam 10 MG Oral Tablet	2521 (19.32)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	9,152 (2.65)	acetaminophen 1000 MG Oral Tablet	67,987 (23.1)
omeprazole 20 MG Delayed Release Oral Capsule	1761 (13.86)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	896 (14.52)	omeprazole 20 MG Delayed Release Oral Capsule	1038 (7.96)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A	6,587 (1.91)	omeprazole 20 MG Delayed Release Oral Capsule	63,953 (21.73)
amoxicillin 500 MG Oral Capsule	1728 (13.6)	sodium chloride	680 (11.02)	diclofenac sodium 50 MG Delayed Release Oral Tablet	975 (7.47)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi	6,411 (1.86)	ibuprofen 600 MG Oral Tablet	44,571 (15.15)
acetaminophen 500 MG Oral Tablet	1228 (9.67)	acetaminophen	569 (9.22)	polyethylene glycol 3350 13100 MG / potassium chloride 46.6 MG / sodium bicarbonate 179 MG / sodium	871 (6.68)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe	6,146 (1.78)	dipyrone	41,797 (14.2)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
				chloride 351 MG Powder for Oral Solution					
Albuterol 0.095 MG/ACTUAT Metered Dose Inhaler	1035 (8.15)	lorazepam 1 MG Oral Tablet	530 (8.59)	ethinyl estradiol 0.03 MG / levonorgestrel 0.15 MG Oral Tablet	857 (6.57)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A	5,393 (1.56)	lorazepam 1 MG Oral Tablet	34,558 (11.74)
acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet	959 (7.55)	omeprazole	466 (7.55)	temazepam 10 MG Oral Capsule	790 (6.06)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A	4,607 (1.33)	diazepam 5 MG Oral Tablet	26,698 (9.07)
sertraline 50 MG Oral Tablet	899 (7.08)	glucose	462 (7.48)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	725 (5.56)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A	4,383 (1.27)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet	18,559 (6.31)
trimethoprim 200 MG Oral Tablet	823 (6.48)	dexketoprofen	462 (7.48)	omeprazole 40 MG Delayed Release Oral Capsule	657 (5.04)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi	4,284 (1.24)	acetaminophen 650 MG Oral Tablet	17,993 (6.11)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
citalopram 20 MG Oral Tablet	747 (5.88)	dipyrone 400 MG/ML Injectable Solution	415 (6.7)	tramadol hydrochloride 50 MG Oral Capsule	592 (4.54)	Ibuprofen 600 MG Extended Release Oral Tablet [Ibu 1a Pharma] Box of 20 by 1 A	3,979 (1.15)	dexketoprofen 25 MG Oral Tablet	17,065 (5.8)
floxacillin 500 MG Oral Capsule	738 (5.81)	amoxicillin / clavulanate	387 (6.3)	pantoprazole 40 MG Delayed Release Oral Tablet	591 (4.53)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A	3,855 (1.12)	naproxen sodium 550 MG Oral Tablet	15,680 (5.33)

Table 12: Top 10 most frequent medicines in 1 month prior to the date of diagnosis of MDD

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
omeprazole 20 MG Delayed Release Oral Capsule	743 (5.85)	omeprazole 20 MG Delayed Release Oral Capsule	522 (8.46)	oxazepam 10 MG Oral Tablet	864 (6.62)	NA	NA	acetaminophen 1000 MG Oral Tablet	10,434 (3.55)
acetaminophen 500 MG Oral Tablet	405 (3.19)	100 ML Acetaminophen 10 MG/ML Injection [PARACETAMOL B BRAUN] Box of 10 by B.Braun	513 (8.31)	quetiapine 25 MG Delayed Release Oral Tablet	298 (2.28)	NA	NA	lorazepam 1 MG Oral Tablet	9,818 (3.34)
fluoxetine 20 MG Oral Capsule	392 (3.09)	sodium chloride	407 (6.59)	lorazepam 1 MG Oral Tablet	280 (2.15)	NA	NA	omeprazole 20 MG Delayed Release Oral Capsule	9,805 (3.33)
sertraline 50 MG Oral Tablet	371 (2.92)	glucose	329 (5.33)	omeprazole 20 MG Delayed Release Oral Capsule	264 (2.02)	NA	NA	diazepam 5 MG Oral Tablet	7,183 (2.44)
simvastatin 40 MG Oral Tablet	331 (2.61)	omeprazole	315 (5.1)	sertraline 50 MG Oral Tablet	250 (1.92)	NA	NA	dipyrone	6,876 (2.34)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
citalopram 20 MG Oral Tablet	314 (2.47)	acetaminophen	313 (5.07)	temazepam 10 MG Oral Capsule	230 (1.76)	NA	NA	ibuprofen 600 MG Oral Tablet	5,383 (1.83)
aspirin 75 MG Disintegrating Oral Tablet	313 (2.46)	lorazepam 1 MG Oral Tablet	263 (4.26)	citalopram 20 MG Oral Tablet	216 (1.66)	NA	NA	alprazolam 0.25 MG Oral Tablet	4,282 (1.46)
acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet	289 (2.28)	dipyrone 400 MG/ML Injectable Solution	249 (4.03)	mirtazapine 15 MG Oral Tablet	203 (1.56)	NA	NA	citalopram 20 MG Oral Tablet	3,697 (1.26)
Albuterol 0.095 MG/ACTUAT Metered Dose Inhaler	282 (2.22)	ipratropium	215 (3.48)	polyethylene glycol 3350 13100 MG / potassium chloride 46.6 MG / sodium bicarbonate 179 MG / sodium chloride 351 MG Powder for Oral Solution	180 (1.38)	NA	NA	sertraline 50 MG Oral Tablet	3,549 (1.21)

CPRD GOLD	N (%)	IMASIS	N (%)	IPCI	N (%)	IQVIA DA Germany	N (%)	SIDIAP	N (%)
lansoprazole 30 MG Delayed Release Oral Capsule	274 (2.16)	furosemide	203 (3.29)	zopiclone 7.5 MG Oral Tablet	169 (1.3)	NA	NA	paroxetine hydrochloride 20 MG Oral Tablet	2,684 (0.91)

NA= not available

12.3 Main Results

12.3.1 Treatment with antidepressants in patients newly diagnosed with MDD

Next, we explored use of antidepressant drugs in patients newly diagnosed with MDD focusing on antidepressant initiation, switching or discontinuation. Drug initiation was assessed within different time windows namely 4, 6-, 8-, 12- and 24-weeks following diagnoses.

Results are described in **Table 13**. Large differences between databases can be observed with regard to the proportion of patients with newly diagnosed MDD initiating treatment with an antidepressant.

Within 4 weeks following diagnosis, the proportion of individuals who did not initiate treatment with antidepressants ranged between 18.1% in CPRD and 76.6% in IPCI. Within 24 weeks following MDD diagnosis, the proportion of individuals who had not yet initiated treatment with any of the antidepressants of interest declined and ranged between 10.1% for CPRD and 56.7% for IQVIA DA Germany.

Mainly use of SSRIs was initiated with usage ranging from 11.2% in IQVIA DA Germany to 64.9% in CPRD. When assessed at 24 weeks follow-up, the proportion of individuals who had initiated treatment with SSRIs increased and ranged from 15.0% for IQVIA DA Germany to 70.8% for CPRD.

In contrast, the utilization of NSRI and other antidepressants was much lower except for IMASIS where use of other antidepressants was as high as use of SSRIs. For NSRIs the use within 4 weeks following MDD diagnosis ranged from 1.7% for SIDIAP to 7.2% for IQVIA DA Germany. This proportion increased over time where 3.1% of individuals for SIDIAP to 9.9% for IQVIA DA Germany had initiated treatment with NSRIs within 24 weeks following diagnosis. Regarding use of other antidepressants, within 4 weeks following MDD diagnosis, the proportion ranged between 7.2% for IPCI up to 32.8% for IMASIS. Here as well the proportion of initiators of other antidepressants had increased at the end of follow-up. (13.4% for IPCI to 38.1% for IMASIS).

The proportion of individuals that were lost to follow-up within 24 weeks following diagnosis was low especially for the primary care databases (0.5% for SIDIAP up to 4.4% for IPCI) and somewhat lower for IMASIS (hospital database) (9.2%) and IQVIA DA Germany (containing both primary and secondary care data) (9.8%).

Stratification of treatment of newly diagnosed MDD by sex and age is presented in **Appendix III – Tables 1 and 2.** Overall, females tend to have a slightly higher SSRI usage and use of NSRIs compared to males across all databases whereas use of other antidepressants was higher in males compared to females.

When stratified by age, results as described for the overall group remained with highest use of SSRIs and lower use of NSRIs and other antidepressants. In all databases, the proportion of individuals not receiving any treatment was the highest in adolescents aged 12-17 years. (range of individuals not being treated within 24 weeks 32.1% for IMASIS to 78.2% for IPCI).

Table 13: Treatment initiation among individuals with newly diagnosed major depression within 4/6/8/12/24 weeks after date of diagnosis.

		4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database		number	%	number	%	number	%	number	%	number	%
CPRD GOLD	SSRI	8,246	64.9	8,476	66.7	8,622	67.9	8,772	69.0	8,999	70.8
	NSRI	470	3.7	539	4.2	593	4.7	669	5.3	803	6.3
	Other AD	2,307	18.2	2,506	19.7	2,653	20.9	2,836	22.3	3,141	24.7
	No AD trt	2,302	18.1	1,968	15.5	1,755	13.8	1,562	12.3	1,289	10.1
	Lost to FU	32	0.3	45	0.4	62	0.5	77	0.6	139	1.1
IMASIS	SSRI	2,179	35.3	2,241	36.3	2,270	36.8	2,320	37.6	2,397	38.8
	NSRI	182	2.9	193	3.1	204	3.3	216	3.5	240	3.9
	Other AD	2,025	32.8	2,121	34.4	2,171	35.2	2,231	36.1	2,354	38.1
	No AD trt	2,104	34.1	1,958	31.7	1,886	30.6	1,779	28.8	1,577	25.5
	Lost to FU	392	6.4	427	6.9	456	7.4	495	8.0	571	9.2
IPCI	SSRI	1,742	13.4	2,109	16.2	2,349	18.0	2,679	20.5	3,131	24.0
	NSRI	483	3.7	595	4.6	682	5.2	786	6.0	931	7.1
	Other AD	942	7.2	1,150	8.8	1,283	9.8	1,488	11.4	1,745	13.4
	No AD trt	9,995	76.6	9,325	71.5	8,869	68.0	8,242	63.2	7,340	56.3
	Lost to FU	106	0.8	169	1.3	233	1.8	318	2.4	580	4.4

		4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database		number	%	number	%	number	%	number	%	number	%
IQVIA DA Germany	SSRI	38,799	11.2	41,024	11.9	43,050	12.5	46,253	13.4	51,684	15.0
	NSRI	24,710	7.2	26,318	7.6	27,789	8.0	30,005	8.7	34,144	9.9
	Other AD	35,252	10.2	37,415	10.8	39,286	11.4	42,256	12.2	47,376	13.7
	No AD trt	238,383	69.0	231,541	67.0	225,713	65.3	216,583	62.7	195,836	56.7
	Lost to FU	15,936	4.6	18,231	5.3	20,061	5.8	23,016	6.7	33,904	9.8
SIDIAP	SSRI	155,173	52.7	160,072	54.4	163,573	55.6	168,853	57.4	178,459	60.6
	NSRI	4,949	1.7	5,568	1.9	6,126	2.1	7,072	2.4	9,226	3.1
	Other AD	46,250	15.7	50,246	17.1	53,526	18.2	58,611	19.9	68,931	23.4
	No AD trt	98,912	33.6	92,342	31.4	87,658	29.8	80,802	27.5	68,755	23.4
	Lost to FU	413	0.1	556	0.2	685	0.2	929	0.3	1,506	0.5

12.3.2 Treatment pattern of antidepressant use amongst individuals being treated with antidepressant drugs

Next, amongst patients initiating treatment with antidepressant drugs after MDD diagnosis, the proportion of patients continuing, switching or discontinuation treatment was assessed for different intervals following treatment initiation. Importantly, in this cohort of users of antidepressants, the inclusion criterion of 365 days observation time before the MDD diagnosis was not applied. This means that this cohort is not a subset of the cohort reported in Table 13 and consequently the total numbers in Table 14 and 15 can be higher than those in Table 13.

The results focusing on treatment with antidepressants are described in **Table 14**. The percentages of individuals continuing treatment with SSRI, NSRI or other antidepressants over time are shown in **Figure 6**. For SSRI users, in IMASIS (hospital data) the percentage still on treatment in the period of 4 weeks following treatment initiation was only 31.3%. In the other databases this percentage ranged between 89.2 to 95.0%. The percentages of individuals continuing treatment dropped to 66.7% by 24 weeks following treatment initiation in SIDIAP whereas it was between 6.9% and 24.1% in the other databases.

The proportion of individuals continuing NSRI was lower than that of SSRIs. Of NSRI users, in SIDIAP 86.7% was still on treatment in the 4 weeks following treatment initiation decreasing to 39.2% by week 24. In CPRD GOLD, IPCI and IQVIA DA Germany around 76% was still using NSRI therapy within 4 weeks of therapy start, decreasing to percentages below 22% 24 weeks after therapy start.

For the class of 'other antidepressants', highest percentages (90%) of continuing use were found in SIDIAP and IQVIA DA Germany, decreasing to 57.0% and 21.2% respectively at week 24.

As can be observed in **Figure 6,** an important proportion of individuals already discontinued treatment within the 4 and 6 follow-up windows for IMASIS and CPRD Gold whereas a steadier decline was observed for the other databases.

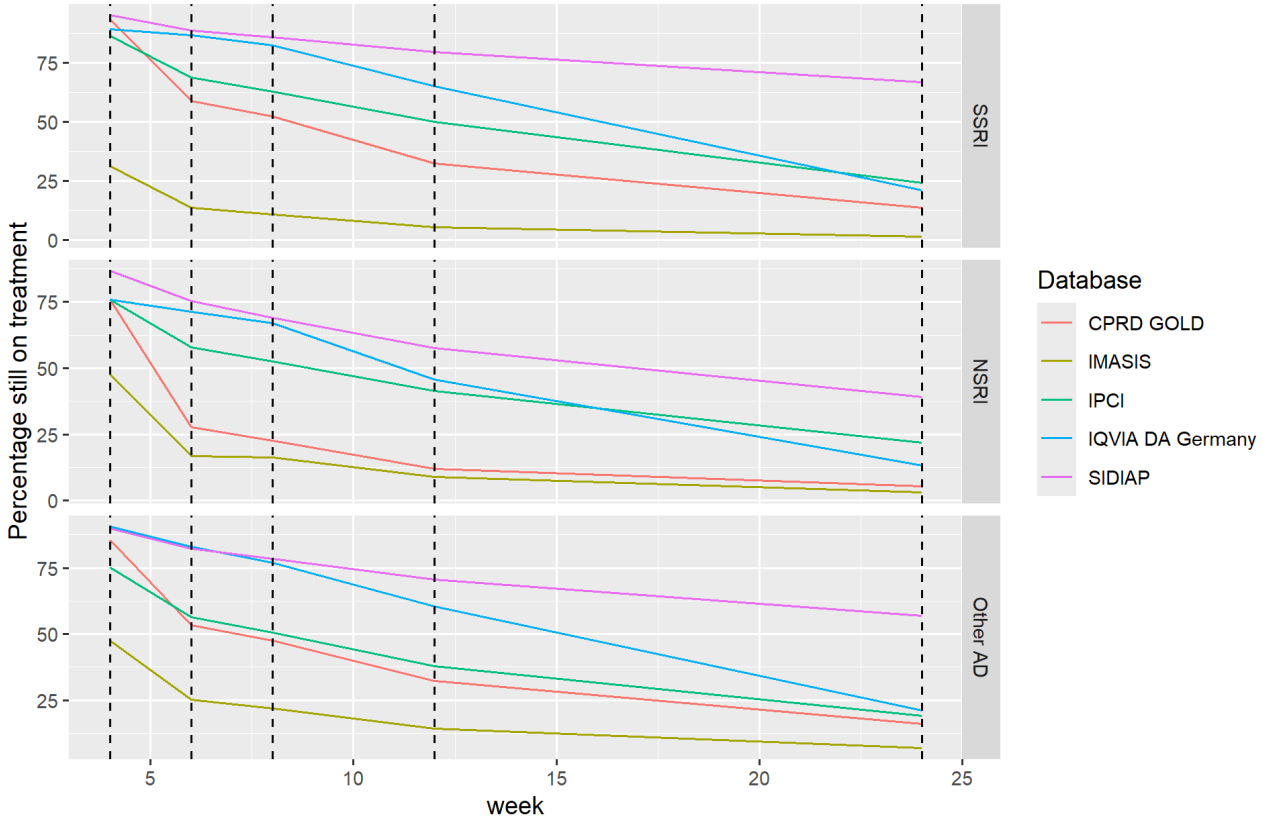

Figure 6 Percentages continuing treatment of SSRI, NSRI or other antidepressants

Table 14: Treatment changes regarding antidepressant treatments amongst individuals with MDD being treated within 4/6/8/12/24 weeks after starting initial antidepressant treatment (gap of 7 days used)

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
CPRD GOLD	SSRI	SSRI continued	28,519	93.5	17,914	58.7	15,925	52.2	9,867	32.3	4,137	13.6
		Switch to NSRI	46	0.2	87	0.3	93	0.3	103	0.3	112	0.4
		Switch to OAD	127	0.4	211	0.7	256	0.8	299	1.0	334	1.1
		Combination of ADs	1,463	4.8	1,850	6.1	2,030	6.7	2,197	7.2	2,351	7.7
		SSRI stopped, no ADs	152	0.5	10,158	33.3	11,823	38.8	17,545	57.5	22,894	75.1
		Lost to FU	195	0.6	282	0.9	375	1.2	491	1.6	674	2.2
	NSRI	NSRI continued	8,870	76.0	3,241	27.8	2,637	22.6	1,402	12.0	623	5.3
		Switch to SSRI	229	2.0	377	3.2	399	3.4	415	3.6	418	3.6
		Switch to OAD	108	0.9	166	1.4	176	1.5	184	1.6	187	1.6
		Combination of ADs	2,254	19.3	2,597	22.2	2,713	23.2	2,791	23.9	2,809	24.1
		NSRI stopped, no ADs	110	0.9	5,154	44.1	5,582	47.8	6,689	57.3	7,391	63.3
		Lost to FU	106	0.9	142	1.2	170	1.5	196	1.7	249	2.1
	Other AD	OAD continued	13,207	85.5	8,249	53.4	7,312	47.4	5,005	32.4	2,487	16.1
		Switch to SSRI	179	1.2	286	1.9	320	2.1	355	2.3	384	2.5
		Switch to NSRI	49	0.3	74	0.5	80	0.5	88	0.6	98	0.6

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Combination of ADs	1,564	10.1	1,880	12.2	2,009	13.0	2,120	13.7	2,234	14.5
		OAD stopped, no ADs	299	1.9	4,745	30.7	5,464	35.4	7,543	48.9	9,779	63.3
		Lost to FU	140	0.9	204	1.3	253	1.6	327	2.1	456	3.0
IMASIS	SSRI	SSRI continued	1,030	31.3	450	13.7	355	10.8	179	5.4	49	1.5
		Switch to NSRI	28	0.9	38	1.2	38	1.2	38	1.2	38	1.2
		Switch to OAD	243	7.4	287	8.7	287	8.7	290	8.8	294	8.9
		Combination of ADs	407	12.4	500	15.2	497	15.1	505	15.4	507	15.4
		SSRI stopped, no ADs	1,372	41.7	1,782	54.2	1,860	56.6	2,008	61.1	2,115	64.3
		Lost to FU	209	6.4	232	7.1	252	7.7	269	8.2	286	8.7
	NSRI	NSRI continued	277	47.8	97	16.8	95	16.4	52	9.0	18	3.1
		Switch to SSRI	33	5.7	37	6.4	37	6.4	40	6.9	41	7.1
		Switch to OAD	34	5.9	59	10.2	59	10.2	61	10.5	63	10.9
		Combination of ADs	118	20.4	175	30.2	174	30.1	181	31.3	187	32.3
		NSRI stopped, no ADs	96	16.6	188	32.5	189	32.6	216	37.3	241	41.6
		Lost to FU	21	3.6	23	4.0	25	4.3	29	5.0	29	5.0
	Other AD	OAD continued	1,781	47.5	948	25.3	821	21.9	536	14.3	257	6.9

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Switch to SSRI	246	6.6	289	7.7	291	7.8	298	8.0	301	8.0
		Switch to NSRI	17	0.5	27	0.7	28	0.7	28	0.7	28	0.7
		Combination of ADs	457	12.2	556	14.8	549	14.7	560	14.9	565	15.1
		OAD stopped, no ADs	1,016	27.1	1,666	44.5	1,774	47.3	2,012	53.7	2,259	60.3
		Lost to FU	230	6.1	261	7.0	284	7.6	313	8.4	337	9.0
IPCI	SSRI	SSRI continued	5,092	86.2	4,061	68.7	3,711	62.8	2,951	49.9	1,426	24.1
		Switch to NSRI	6	0.1	9	0.2	10	0.2	12	0.2	15	0.3
		Switch to OAD	12	0.2	24	0.4	29	0.5	34	0.6	41	0.7
		Combination of ADs	305	5.2	404	6.8	444	7.5	505	8.5	550	9.3
		SSRI stopped, no ADs	435	7.4	1,330	22.5	1,613	27.3	2,281	38.6	3,684	62.3
		Lost to FU	59	1.0	81	1.4	102	1.7	126	2.1	193	3.3
	NSRI	NSRI continued	1,760	75.9	1,346	58.0	1,217	52.5	963	41.5	505	21.8
		Switch to SSRI	14	0.6	23	1.0	23	1.0	23	1.0	27	1.2
		Switch to OAD	7	0.3	11	0.5	12	0.5	13	0.6	15	0.6
		Combination of ADs	177	7.6	212	9.1	233	10.0	263	11.3	276	11.9
		NSRI stopped, no ADs	342	14.7	697	30.1	794	34.2	1,003	43.3	1,414	61.0

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Lost to FU	19	0.8	30	1.3	40	1.7	54	2.3	82	3.5
	Other AD	OAD continued	2,860	75.2	2,140	56.3	1,920	50.5	1,441	37.9	726	19.1
		Switch to SSRI	35	0.9	59	1.6	60	1.6	64	1.7	72	1.9
		Switch to NSRI	9	0.2	13	0.3	15	0.4	18	0.5	20	0.5
		Combination of ADs	398	10.5	488	12.8	522	13.7	573	15.1	608	16.0
		OAD stopped, no ADs	466	12.3	1,058	27.8	1,225	32.2	1,622	42.6	2,249	59.1
		Lost to FU	36	0.9	46	1.2	62	1.6	86	2.3	129	3.4
IQVIA DA Germany	SSRI	SSRI continued	146,668	89.2	142,309	86.5	135,358	82.3	106,678	64.9	34,927	21.2
		Switch to NSRI	98	0.1	116	0.1	276	0.2	292	0.2	570	0.3
		Switch to OAD	180	0.1	196	0.1	449	0.3	492	0.3	967	0.6
		Combination of ADs	5,653	3.4	9,025	5.5	12,016	7.3	16,805	10.2	21,754	13.2
		SSRI stopped, no ADs	11,034	6.7	11,853	7.2	12,825	7.8	36,326	22.1	92,650	56.3
		Lost to FU	846	0.5	980	0.6	3,555	2.2	3,886	2.4	13,611	8.3
	NSRI	NSRI continued	92,016	75.9	86,408	71.3	81,035	66.9	55,301	45.6	15,947	13.2
		Switch to SSRI	225	0.2	248	0.2	482	0.4	513	0.4	857	0.7
		Switch to OAD	197	0.2	226	0.2	481	0.4	508	0.4	858	0.7

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Combination of ADs	4,185	3.5	6,885	5.7	9,244	7.6	12,978	10.7	16,407	13.5
		NSRI stopped, no ADs	23,508	19.4	26,230	21.6	27,196	22.4	48,924	40.4	79,905	65.9
		Lost to FU	1,050	0.9	1,184	1.0	2,743	2.3	2,957	2.4	7,207	5.9
	Other AD	OAD continued	149,363	90.5	136,750	82.9	126,814	76.9	99,820	60.5	34,897	21.2
		Switch to SSRI	235	0.1	317	0.2	615	0.4	661	0.4	1,179	0.7
		Switch to NSRI	179	0.1	236	0.1	411	0.2	430	0.3	654	0.4
		Combination of ADs	5,664	3.4	8,813	5.3	11,637	7.1	16,114	9.8	20,672	12.5
		OAD stopped, no ADs	8,575	5.2	17,479	10.6	21,953	13.3	44,127	26.7	95,409	57.8
		Lost to FU	979	0.6	1,400	0.8	3,565	2.2	3,843	2.3	12,184	7.4
SIDIAP	SSRI	SSRI continued	328,508	95.0	306,245	88.5	296,696	85.8	275,444	79.6	230,692	66.7
		Switch to NSRI	165	0.0	310	0.1	423	0.1	616	0.2	958	0.3
		Switch to OAD	1,626	0.5	3,032	0.9	4,176	1.2	5,976	1.7	9,471	2.7
		Combination of ADs	11,028	3.2	14,171	4.1	17,109	4.9	21,656	6.3	30,676	8.9
		SSRI stopped, no ADs	3,879	1.1	21,007	6.1	25,939	7.5	39,865	11.5	69,814	20.2
		Lost to FU	717	0.2	1,158	0.3	1,580	0.5	2,366	0.7	4,312	1.2
	NSRI	NSRI continued	51,345	86.7	44,635	75.4	40,858	69.0	34,087	57.6	23,238	39.2

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Switch to SSRI	309	0.5	600	1.0	778	1.3	1,057	1.8	1,508	2.5
		Switch to OAD	276	0.5	561	0.9	741	1.3	1,014	1.7	1,469	2.5
		Combination of ADs	6,112	10.3	7,385	12.5	8,439	14.2	10,112	17.1	13,256	22.4
		NSRI stopped, no ADs	1,110	1.9	5,924	10.0	8,256	13.9	12,729	21.5	19,395	32.7
		Lost to FU	71	0.1	118	0.2	151	0.3	224	0.4	357	0.6
	Other AD	OAD continued	185,632	89.9	169,826	82.2	161,702	78.3	145,822	70.6	117,662	57.0
		Switch to SSRI	1,627	0.8	3,059	1.5	4,019	1.9	5,370	2.6	7,643	3.7
		Switch to NSRI	154	0.1	287	0.1	379	0.2	525	0.3	779	0.4
		Combination of ADs	15,924	7.7	19,099	9.2	21,729	10.5	25,839	12.5	33,634	16.3
		OAD stopped, no ADs	2,519	1.2	13,089	6.3	17,111	8.3	26,631	12.9	42,791	20.7
		Lost to FU	713	0.3	1,209	0.6	1,629	0.8	2,382	1.2	4,060	2.0

SSRI= Selective Serotonin Reuptake Inhibitors, NSRI = Non-Selective monoamine Reuptake Inhibitors, AD= antidepressants, FU= follow-up

Switching from one antidepressant class to another antidepressant class was low in CPRD GOLD, IPCI, IQVIA DA Germany and SIDIAP especially for use of SSRI as first therapy where less than 1% of initial SSRI users switched to NSRI and less than 3% of initials SSRI users switched to other antidepressant agents during follow-up. In IMASIS, the proportion of individuals switching to other treatment during follow-up was higher namely switching to OAD in 8.9% of SSRI users and 11% of NSRI users. Switching to SSRIs occurred in 7.1% of NSRI users and 8% of OAD users and finally switching to NSRI was much lower namely 1.2% of SSRI users and 0.7% of OAD users. The numbers initially on SSRI and changing to combination of ADs decreased between week 6 and week 8. This means that some of the patients who first changed to combination of ADs later had a second intercurrent event for the initial SSRI exposure, namely lost to follow-up. For these patients then this lost to follow-up is reported. The same is the case for patients initially on NSRI and changing to combination of ADs.

The proportion of patients considered as “lost to follow-up” was less than 10% by week 24 in all databases and was the highest for IMASIS and IQVIA DA Germany.

Tables 3 and 4 in Appendix III describe the results of the sensitivity analysis where the maximum gap between prescriptions to define a drug era is extended from 7 days to 14 and 21 days respectively. As could be anticipated, by increasing the maximum gap, the proportion of individuals continuing treatment increased especially for CPRD where the proportion of individuals continuing treatment increased (using the proportion of the main analysis, i.e. 7 days between gaps as reference) with more than 60% when allowing 14-day gaps and with more than doubled when allowing 21-day gaps between prescriptions. Also, for IPCI and IQVIA DA Germany the proportion of individuals continuing treatment increased but less prominently compared to CPRD. In contrast, increasing the maximum gap had a minimal effect on the proportion of individuals continuing treatment for SIDIAP. For IMASIS, the effect was negligible when applying the 14-day gap but increased the proportion of individuals continuing treatment with 30% at minimum when allowing gaps of 21 days between prescriptions.

Results stratified by sex (and using the different gaps between the prescriptions) are presented in **Tables 5 to 7 from appendix III**. Regarding the effect of sex on treatment continuation during follow-up, no consistent pattern between databases and between type of antidepressant therapy could be observed except for IMASIS where the proportion of individuals continuing treatment was higher for males compared to females especially for SSRIs (1.3% of females still on treatment with SSRI at end of follow-up vs. 1.8% for males). It should be noted however that the proportion of individuals still on treatment at the end of 24 weeks was low. The other treatment patterns as described for the overall population (and by database) also applied to females and males separately.

Results stratified by age (and using the different gaps between the prescriptions) are presented in **Tables 8 to 10 in Appendix III**. For all antidepressants and for all databases (except for IMASIS) the age category of 18-44 years had the lowest proportion of individuals still on treatment at the end of follow-up with ranges between 3.4% (IMASIS) to 62.7% (SIDIAP) for SSRI, <1% (IMASIS) to 34.7% for NSRI and 8.8% (IMASIS) to 52.7% for SIDIAP. (**table 8 Appendix III).** Similar findings were observed when repeating the analysis using different gaps between the prescriptions.

12.3.3 Use of psycholeptics amongst individuals being treated with antidepressant drugs

Next, amongst patients initiating treatment with antidepressant drugs after MDD diagnosis, use of psycholeptics within different intervals following treatment initiation with an antidepressant drug was investigated.

The results of this analysis are described in **Table 15**. At the end of follow-up (i.e. 24 weeks following initiation), use of psycholeptics on top of SSRI treatment ranged between 13.6% (IQVIA DA Germany) to 32.6% (IPCI), 10.9% (IQVIA DA Germany) to 40.1% (IMASIS and IPCI) for NSRI and 16.1% (IQVIA DA Germany) to 39.3% (IMASIS) for other antidepressants. Overall, adding psycholeptic treatment on top of antidepressant therapy was the lowest for IQVIA DA Germany.

Tables 11 and 12 in Appendix III describe the results of the sensitivity analysis where the maximum gap between prescriptions to define a drug era is extended from 7 days to 14 and 21 days respectively. As could be expected the proportion of individuals receiving treatment with psycholeptics increased when the maximum gap between prescriptions was increased but this increase was modest.

Results stratified by sex (and using the different gaps between the prescriptions) are presented in **tables 13-15 from appendix III**. No clear difference in treatment patterns for use of psycholeptics could be observed between sex except for IMASIS where use of psycholeptics on top of antidepressants was slightly higher for men compared to women for all 3 classes of antidepressant use.

Results stratified by age (and using the different gaps between the prescriptions) are presented in **Tables 16 – 18 from Appendix III**. In CPRD, IPCI and IQVIA DA Germany, use of psycholeptics on top of the antidepressant of interest was the lowest for the age category 18-44 except for IMASIS and SIDIAP where use was higher in the 45-64 and >= 65 years age category. The proportion of individuals receiving treatment with psycholeptics increased when applying larger maximum gaps between prescriptions.

Table 15: Treatment changes regarding psycholeptics amongst individuals with MDD being treated within 4/6/8/12/24 weeks after start initial antidepressant treatment (gap of 7 days used)

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
CPRD GOLD	SSRI	SSRI, no psych	26,299	86.2	15,626	51.2	13,729	45.0	8,170	26.8	3,190	10.5
		SSRI+Psych	3,685	12.1	4,408	14.5	4,661	15.3	4,863	15.9	5,055	16.6
		Only psycholeptics	176	0.6	283	0.9	312	1.0	338	1.1	359	1.2
		SSRI stopped, no psych	147	0.5	9,903	32.5	11,425	37.5	16,640	54.6	21,224	69.6
		Lost to FU	195	0.6	282	0.9	375	1.2	491	1.6	674	2.2
	NSRI	NSRI, no psych	9,869	84.5	3,766	32.3	3,154	27.0	1,724	14.8	722	6.2
		NSRI+Psych	1,433	12.3	1,617	13.8	1,679	14.4	1,731	14.8	1,783	15.3
		Only psycholeptics	155	1.3	232	2.0	250	2.1	268	2.3	278	2.4
		NSRI stopped, no psych	114	1.0	5,920	50.7	6,424	55.0	7,758	66.4	8,645	74.0
		Lost to FU	106	0.9	142	1.2	170	1.5	196	1.7	249	2.1
	Other AD	Other ADs, no psych	11,589	75.1	6,231	40.4	5,328	34.5	3,309	21.4	1,328	8.6
		Other ADs+Psych	3,264	21.1	3,868	25.1	4,071	26.4	4,215	27.3	4,341	28.1
		Only psycholeptics	164	1.1	237	1.5	257	1.7	283	1.8	303	2.0
		Other ADs stopped, no psych	281	1.8	4,898	31.7	5,529	35.8	7,304	47.3	9,010	58.4
		Lost to FU	140	0.9	204	1.3	253	1.6	327	2.1	456	3.0

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
IMASIS	SSRI	SSRI, no psych	761	23.1	229	7.0	201	6.1	85	2.6	23	0.7
		SSRI+Psych	901	27.4	1,041	31.7	1,028	31.3	1,039	31.6	1,030	31.3
		Only psycholeptics	605	18.4	669	20.3	670	20.4	677	20.6	678	20.6
		SSRI stopped, no psych	813	24.7	1,118	34.0	1,138	34.6	1,219	37.1	1,272	38.7
		Lost to FU	209	6.4	232	7.1	252	7.7	269	8.2	286	8.7
	NSRI	NSRI, no psych	269	46.5	68	11.7	65	11.2	27	4.7	9	1.6
		NSRI+Psych	138	23.8	222	38.3	221	38.2	231	39.9	232	40.1
		Only psycholeptics	73	12.6	98	16.9	99	17.1	101	17.4	101	17.4
		NSRI stopped, no psych	78	13.5	168	29.0	169	29.2	191	33.0	208	35.9
		Lost to FU	21	3.6	23	4.0	25	4.3	29	5.0	29	5.0
	Other AD	Other ADs, no psych	1,323	35.3	441	11.8	414	11.0	214	5.7	66	1.8
		Other ADs+Psych	1,144	30.5	1,428	38.1	1,418	37.8	1,460	39.0	1,471	39.3
		Only psycholeptics	491	13.1	581	15.5	582	15.5	590	15.7	593	15.8
		Other ADs stopped, no psych	559	14.9	1,036	27.6	1,049	28.0	1,170	31.2	1,280	34.2
		Lost to FU	230	6.1	261	7.0	284	7.6	313	8.4	337	9.0
IPCI	SSRI	SSRI, no psych	4,164	70.5	3,033	51.3	2,692	45.6	2,009	34.0	881	14.9

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		SSRI+Psych	1,249	21.1	1,555	26.3	1,660	28.1	1,810	30.6	1,927	32.6
		Only psycholeptics	54	0.9	75	1.3	81	1.4	93	1.6	102	1.7
		SSRI stopped, no psych	383	6.5	1,165	19.7	1,374	23.3	1,871	31.7	2,806	47.5
		Lost to FU	59	1.0	81	1.4	102	1.7	126	2.1	193	3.3
	NSRI	NSRI, no psych	1,280	55.2	833	35.9	705	30.4	492	21.2	199	8.6
		NSRI+Psych	668	28.8	796	34.3	841	36.3	903	38.9	929	40.1
		Only psycholeptics	49	2.1	66	2.8	70	3.0	71	3.1	76	3.3
		NSRI stopped, no psych	303	13.1	594	25.6	663	28.6	799	34.5	1,033	44.5
		Lost to FU	19	0.8	30	1.3	40	1.7	54	2.3	82	3.5
	Other AD	Other ADs, no psych	2,333	61.3	1,555	40.9	1,349	35.5	957	25.2	414	10.9
		Other ADs+Psych	937	24.6	1,148	30.2	1,212	31.9	1,281	33.7	1,333	35.0
		Only psycholeptics	61	1.6	87	2.3	89	2.3	94	2.5	103	2.7
		Other ADs stopped, no psych	437	11.5	968	25.4	1,092	28.7	1,386	36.4	1,825	48.0
		Lost to FU	36	0.9	46	1.2	62	1.6	86	2.3	129	3.4
IQVIA DA Germany	SSRI	SSRI, no psych	144,244	87.7	139,410	84.8	132,547	80.6	104,436	63.5	34,737	21.1
		SSRI+Psych	8,087	4.9	11,959	7.3	14,987	9.1	19,131	11.6	22,445	13.6

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		Only psycholeptics	269	0.2	300	0.2	608	0.4	638	0.4	1,172	0.7
		SSRI stopped, no psych	11,033	6.7	11,830	7.2	12,782	7.8	36,388	22.1	92,514	56.2
		Lost to FU	846	0.5	980	0.6	3,555	2.2	3,886	2.4	13,611	8.3
	NSRI	NSRI, no psych	90,953	75.1	85,796	70.8	81,353	67.1	56,853	46.9	17,683	14.6
		NSRI+Psych	5,249	4.3	7,553	6.2	9,179	7.6	11,371	9.4	13,200	10.9
		Only psycholeptics	395	0.3	438	0.4	723	0.6	763	0.6	1,124	0.9
		NSRI stopped, no psych	23,534	19.4	26,210	21.6	27,183	22.4	49,237	40.6	81,967	67.6
		Lost to FU	1,050	0.9	1,184	1.0	2,743	2.3	2,957	2.4	7,207	5.9
	Other AD	Other ADs, no psych	145,207	88.0	131,302	79.6	120,860	73.3	93,885	56.9	31,186	18.9
		Other ADs+Psych	9,918	6.0	14,348	8.7	17,822	10.8	22,504	13.6	26,596	16.1
		Only psycholeptics	359	0.2	462	0.3	853	0.5	892	0.5	1,403	0.9
		Other ADs stopped, no psych	8,532	5.2	17,483	10.6	21,895	13.3	43,871	26.6	93,626	56.7
		Lost to FU	979	0.6	1,400	0.8	3,565	2.2	3,843	2.3	12,184	7.4
SIDIAP	SSRI	SSRI, no psych	286,671	82.9	257,427	74.4	243,417	70.4	216,285	62.5	164,305	47.5
		SSRI+Psych	53,036	15.3	64,755	18.7	73,249	21.2	86,316	25.0	110,256	31.9
		Only psycholeptics	1,735	0.5	2,893	0.8	3,661	1.1	4,795	1.4	6,985	2.0

			4 weeks		6 weeks		8 weeks		12 weeks		24 weeks	
Database	Original		number	%	number	%	number	%	number	%	number	%
		SSRI stopped, no psych	3,764	1.1	19,690	5.7	24,016	6.9	36,161	10.5	60,065	17.4
		Lost to FU	717	0.2	1,158	0.3	1,580	0.5	2,366	0.7	4,312	1.2
	NSRI	NSRI, no psych	48,837	82.5	41,989	70.9	38,112	64.4	31,336	52.9	20,419	34.5
		NSRI+Psych	8,641	14.6	10,325	17.4	11,654	19.7	13,660	23.1	17,426	29.4
		Only psycholeptics	526	0.9	953	1.6	1,234	2.1	1,665	2.8	2,331	3.9
		NSRI stopped, no psych	1,148	1.9	5,838	9.9	8,072	13.6	12,338	20.8	18,690	31.6
		Lost to FU	71	0.1	118	0.2	151	0.3	224	0.4	357	0.6
	Other AD	Other ADs, no psych	164,389	79.6	145,199	70.3	134,310	65.0	114,908	55.6	81,450	39.4
		Other ADs+Psych	37,149	18.0	44,927	21.7	51,038	24.7	60,204	29.1	76,876	37.2
		Only psycholeptics	1,857	0.9	3,315	1.6	4,216	2.0	5,410	2.6	7,227	3.5
		Other ADs stopped, no psych	2,461	1.2	11,919	5.8	15,376	7.4	23,665	11.5	36,956	17.9
		Lost to FU	713	0.3	1,209	0.6	1,629	0.8	2,382	1.2	4,060	2.0

Psych= psycholeptics, AD= antidepressant, AD+Psych = antidepressant different from the initial treatment plus psycholeptics, ADs no psych = antidepressant different from the initial treatment without psycholeptics

12.3.4 Characteristics of use of antidepressant drugs with regard to duration and initial quantity

Next, amongst patients with newly diagnosed MDD we explored the duration of use of antidepressant drugs and the initial quantity of antidepressant treatment following diagnosis. **Table 16** describes the duration and **Table 17** the initial quantity of the first treatment episode (i.e. drug era) of the antidepressant of interest.

The median duration of the first treatment episode of an antidepressant drug (Table 16) was the lowest in IMASIS – which is a hospital database with a median duration of 12 days for SSRI, 30 days for both NSRIs and other antidepressants. The median duration was higher in the other databases ranging between 56-366 days for the SSRIs, 28-198 days for NSRIs and 56-366 days for the other antidepressants. When applying different gaps between prescription, the median duration increased. The maximum duration of drug eras in some data sources showed extreme values exceeding 10 years, which is unlikely and probably due to errors in the data.

Regarding the initial quantity of the first treatment episodes (Table 17), these were the lowest (for the 3 classes of antidepressant drugs) within IMASIS. IMASIS is a hospital database where registration of drug use is registered daily within the electronical medical file explaining the small median quantity. Large differences in initial quantity were observed between the other databases where the initial quantity was the lowest for CPRD GOLD (70 tablets for SSRI, 56 tablets for NSRI and 86 for the other antidepressants) and the highest for SIDIAP (initial quantity of 373 for SSRI, 194 tablets for NSRI and 422 tablets for OAD). As before, maximum values are too extreme and likely to be data errors.

Table 16: Duration (days) of exposure of antidepressant agents

				Duration						
Database	AD class	N drug eras	Gap (days)	Min	Q05	Q25	Median	Q75	Q95	Max
CPRD GOLD	SSRI	30,502	7	1	28	28	56	110	351	3,621
			14	1	28	30	69	177	720	3,629
			21	1	28	30	87	244	1,015	3,629
	NSRI	11,677	7	1	28	28	28	62	299	3,606
			14	1	28	28	28	90	591	3,633
			21	1	28	28	32	116	853	3,633
	Other AD	15,438	7	1	28	28	56	131	477	3,621
			14	1	28	28	78	228	1,046	3,628
			21	1	28	30	101	329	1,465	3,633
IMASIS	SSRI	3,289	7	1	1	4	12	30	122	1,612
			14	1	1	4	13	34	123	1,612
			21	1	1	4	14	37	140	1,612
	NSRI	579	7	1	1	8	30	61	224	1,806
			14	1	1	9	30	61	242	1,806
			21	1	1	10	30	65	243	1,806

				Duration						
Database	AD class	N drug eras	Gap (days)	Min	Q05	Q25	Median	Q75	Q95	Max
	Other AD	3,747	7	1	1	7	30	60	245	2,585
			14	1	1	7	30	61	272	2,585
			21	1	1	8	30	62	273	2,585
IPCI	SSRI	5,909	7	1	15	34	90	176	491	2,953
			14	1	15	51	118	278	833	3,480
			21	1	15	60	153	360	1,170	3,811
	NSRI	2,319	7	1	14	30	72	169	602	2,618
			14	1	14	30	90	254	828	3,827
			21	1	14	30	111	329	1,110	3,827
	Other AD	3,804	7	1	14	30	66	157	537	3,264
			14	1	14	30	90	237	840	3,679
			21	1	14	32	102	316	1,109	3,679
IQVIA DA Germany	SSRI	164,479	7	1	20	67	100	180	409	3,736
			14	1	20	78	100	198	525	3,736
			21	1	20	96	100	211	641	3,741
	NSRI	121,181	7	1	1	50	100	106	403	3,741
			14	1	1	50	100	134	505	3,741
			21	1	1	50	100	151	606	3,741
	Other AD	164,995	7	1	20	50	100	176	448	3,741
			14	1	20	50	100	196	571	3,741
			21	1	20	50	100	208	707	3,742
SIDIAP	SSRI	345,923	7	1	31	148	366	971	3,209	3,833
			14	1	31	153	369	1,004	3,270	3,833
			21	1	31	157	380	1,038	3,319	3,833
	NSRI	59,223	7	1	31	64	198	623	2,556	3,833
			14	1	31	66	205	641	2,620	3,833
			21	1	31	67	212	663	2,678	3,833
	Other AD	206,569	7	1	31	112	366	1,037	3,225	3,833
			14	1	31	118	379	1,087	3,287	3,833

				Duration						
Database	AD class	N drug eras	Gap (days)	Min	Q05	Q25	Median	Q75	Q95	Max
			21	1	31	121	394	1,127	3,346	3,833

Table 17: Initial quantity of exposure of antidepressant agents

				Quantity						
Database	AD class	N drug eras	Gap (days)	Min	Q05	Q25	Median	Q75	Q95	Max
CPRD GOLD	SSRI	30,502	7	0	28	30	70	142	504	8,176
			14	0	28	56	90	224	980	22,800
			21	0	28	56	112	308	1,440	22,800
	NSRI	11,677	7	0	28	28	56	112	616	20,384
			14	0	28	28	56	168	1,215	30,763
			21	0	28	28	56	224	1,792	30,763
	Other AD	15,438	7	0	28	30	84	189	806	13,666
			14	0	28	56	112	336	1,721	19,714
			21	0	28	56	140	448	2,394	19,714
IMASIS	SSRI	3,289	7	0.5	1	2	5	15	66	4,880
			14	0.5	1	2	6	16	67	4,880
			21	0.5	1	2	6	16	71	4,880
	NSRI	579	7	0.4	1	2	6	18	93	3,808
			14	0.4	1	2	6	19	94	3,808
			21	1.0	1	2	6	19	104	3,808
	Other AD	3,747	7	0.5	1	2	6	21	98	8,900
			14	0.5	1	2	7	22	101	8,900
			21	0.5	1	2	7	23	105	8,900
IPCI	SSRI	5,909	7	1	15	45	100	240	775	7,650
			14	1	15	60	150	375	1,260	12,050
			21	1	15	60	180	485	1,664	15,330
	NSRI	2,319	7	1	15	42	150	420	1,810	22,003
			14	1	15	60	180	632	2,520	22,003

				Quantity						
Database	AD class	N drug eras	Gap (days)	Min	Q05	Q25	Median	Q75	Q95	Max
			21	1	15	60	240	828	3,509	22,006
	Other AD	3,804	7	1	10	30	90	220	900	6,662
			14	1	10	30	110	352	1,346	7,380
			21	1	12	30	120	435	1,742	8,700
IQVIA DA Germany	SSRI	164,479	7	1	20	100	100	200	500	16,000
			14	1	20	100	100	200	600	16,000
			21	1	20	100	100	250	800	16,000
	NSRI	121,181	7	1	1	50	100	120	550	20,500
			14	1	1	50	100	170	700	20,500
			21	1	1	50	100	200	800	20,500
	Other AD	164,995	7	1	20	50	100	200	688	21,446
			14	1	20	50	100	224	850	21,446
			21	1	20	50	100	294	1,000	21,446
SIDIAP	SSRI	345,923	7	0	21	142	373	1,086	3,469	60,419
			14	0	22	149	388	1,123	3,523	60,419
			21	0	23	154	402	1,166	3,576	60,419
	NSRI	59,223	7	0	7	60	194	773	3,424	70,663
			14	0	7	60	204	806	3,538	70,663
			21	0	7	60	212	830	3,619	70,663
	Other AD	206,569	7	0	12	104	422	1,379	4,656	1,352,878
			14	0	13	112	445	1,443	4,789	1,352,878
			21	0	13	118	467	1,500	4,904	1,352,878

12.4 Other Analysis

None

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices

(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14 DISCUSSION

14.1 Key Results

Characteristics of patients with Major Depressive Disorder (MDD)

The clinicodemographic profile of the 670,371 patients with MDD in this study demonstrated high prevalence of mental health and pain conditions, preponderance of adults aged 19 to 64 years, and female predominance. Across all databases, females constituted the majority of patients with newly diagnosed MDD, ranging from 59% in CPRD GOLD to 68% in IMASIS.

Treatment initiation with antidepressants

Substantial variations exist in antidepressant treatment patterns across databases, highlighting potential differences in practice and data capture. Within 4 weeks following diagnosis, the proportion of individuals who did not initiate treatment with antidepressants ranged between 18.1% in CPRD and 76.6% in IPCI. The proportion of individuals not receiving any treatment declined within 24 weeks following MDD diagnosis. Mainly SSRI was initiated with proportions of individuals being treated with SSRI ranging between 15.0% for IQVIA DA Germany to 70.8% for CPRD when assessed at the end of follow-up (i.e. 24 weeks following MDD diagnosis). In contrast, the utilization of NSRI and other antidepressants was much lower. The proportion of individuals that were lost to follow-up within 24 weeks following diagnosis was low especially for the primary care databases. Overall, females tended to have a slightly higher SSRI usage and use of NSRIs compared to males across all databases whereas use of other antidepressants was higher in males compared to females. When stratified by age, results as described for the overall group remained with highest use of SSRIs and lower use of NSRIs and other antidepressants. In all databases, the proportion of individuals not receiving any treatment was the highest in children aged 12-17 years. (range of individuals not being treated within 24 weeks 32.1% for IMASIS to 78.2% for IPCI).

Treatment patterns and occurrence of intercurrent events in patients with newly diagnosed MDD initiating treatment with antidepressants

For all of the primary care databases, when assessed in the 4 weeks following treatment initiation, individuals still on treatment was more than 80% for SSRI and more than 70% for NSRIs and use of other antidepressants. The proportion of individuals continuing treatment decreased over time with proportions ranging between 14% (CPRD) to 67% (SIDIAP) for SSRI, 5.3% (CPRD) to 39% (SIDIAP) for NSRI and 16% (CPRD) to 57% (SIDIAP). In IMASIS, the proportion of individuals continuing treatment was much lower. Within 4 weeks following initiation, only 31% of SSRI users and 48% of NSRI and other antidepressants were still on treatment. This proportion further decreased at the end of follow-up (24 weeks) with only 1.5% still on treatment with SSRI, 3.1% on NSRI and 6.9% on other antidepressants. Regarding the effect of sex on treatment continuation during follow-up, no consistent pattern between databases and between type of antidepressant therapy could be observed. For all antidepressants and for all databases (except for IMASIS) the age category of 18-44 years had the lowest proportion of individuals still on treatment at the end of follow-up.

Switching from one antidepressant class to another antidepressant class was low in CPRD GOLD, IPCI, IQVIA DA Germany and SIDIAP especially for use of SSRI where less than 1% of initial SSRI users switched to NSRI and less than 3% of initials SSRI users switched to other antidepressant agents during follow-up. In IMASIS, the proportion of individuals switching to other treatment during follow-up was higher.

When increasing the maximum gap between prescriptions from 7 days to 14 and 21 days, the proportion of individuals still on treatment by the end of follow-up increased in all databases and for all types of antidepressants but the effect was the highest for CPRD and the lowest for SIDIAP and IMASIS.

Use of psycholeptics among individuals being treated with antidepressant drugs

At the end of follow-up, between 13.6% (IQVIA DA Germany) to 32.6% (IPCI) of individuals on SSRIs had received treatment with a psycholeptic. For NSRI this proportion ranged between 10.9% (IQVIA DA Germany) to 40.1% (IMASIS and IPCI) for NSRI and between 16.1% (IQVIA DA Germany) to 39.3% (IMASIS) for use of other antidepressants. Overall, adding psycholeptic treatment on top of antidepressant therapy was the lowest for IQVIA DA Germany. No clear difference in treatment patterns for use of psycholeptics could be observed between sex except for IMASIS where use of pscholeptics on top of antidepressants was slightly higher for men compared to women for all 3 classes of antidepressant use. In CPRD, IPCI and IQVIA DA Germany, use of psycholeptics on top of the antidepressant of interest was the lowest for the age category 18-44 except for IMASIS and SIDIAP where use was higher in the 45-64 and >= 65 years age category. The proportion of individuals receiving treatment with psycholeptics increased when applying larger maximum gaps between prescriptions.

Duration and initial quantity of antidepressant use

The median duration of the first treatment episode of an antidepressant drug was the lowest in IMASIS – which is a hospital database with a median duration of 12 days for SSRI, 30 days for both NSRIs and other antidepressants. The median duration was higher in the other databases ranging between 56-366 days for the SSRIs, 28-198 days for NSRIs and 56-366 days for the other antidepressants. When applying different gaps between prescription, the median duration increased.

With regard to the initial quantity of the first treatment episodes, these were the lowest (for the 3 classes of antidepressant drugs) within IMASIS. IMASIS is a hospital database where registration of drug use is registered daily within the electronical medical file explaining the small median quantity. Large differences in initial quantity were observed between the other databases where the initial quantity was the lowest for CPRD GOLD (70 tablets for SSRI, 56 tablets for NSRI and 86 for the other antidepressants) and the highest for SIDIAP (initial quantity of 373 for SSRI, 194 tablets for NSRI and 422 tablets for OAD).

14.2 Limitations of the research methods

The study was informed by routinely collected health care data and so data quality issues must be considered, despite the data quality checks at time of onboarding and while checking the study code. One crucial aspect pertains to the identification of patients with MDD. It is worth noting that the accuracy of these records may vary across different databases. In this study, the MDD phenotype was defined solely based on physician-diagnosed cases identified using relevant SNOMED codes, rather than relying on standardized depression rating scales or individual clinical interviews, of critical value for MDD diagnosis.

Furthermore, the documentation of medication use and co-morbidities, necessary for patient-level characterization, may vary across databases. Additionally, it is essential to highlight that the mere recording of a prescription or dispensing does not necessarily imply that the patient used the prescribed medication.

Furthermore, assumptions around the duration of drug use such as using the medication throughout the prescribed duration may not accurately reflect the actual duration of drug exposure.

The proportion of individuals newly diagnosed with MDD and initiating treatment with the different classes of antidepressants differed between databases (i.e. lowest proportion of individuals being treated in IQVIA DA Germany). In line with the protocol, we checked for use of antidepressants following the new diagnosis of MDD. However, from the patient characteristics, we observed that an important proportion of individuals already had symptoms of depression prior to diagnosis and some of these patients were already treated with antidepressants in the month prior to diagnosis. These patients would not be classified as initiating treatment with an antidepressant when this exposure started prior to diagnosis of MDD and there was no new prescription of the antidepressant following the MDD diagnoses.

Large differences – between databases - in duration and quantity of the first treatment episode were reported between IMASIS (hospital database) and the other databases. In IMASIS, the duration and initial quantity was the lowest which can be explained by the fact that in hospital databases, for each day of drug use, a new prescription is issued. In contrast, the duration and initial quantity was the highest for SIDIAP. As the median duration of SIDIAP was already high, (373 days for SSRIs, 194 days for NSRIs and 422 days for other antidepressants) the sensitivity analysis where the maximum gap between prescriptions from 7 days to 14 and 21 days, had limited effect on the proportion of individuals continuing treatment.

In addition, some extreme and implausible values with regard to treatment duration and number of tablets prescribed were observed. The information on duration and number of tablets is based on what is available within the databases and is not an analytical coding issue. Information on these extreme values was shared with DPs for eventual correction in the next release.

For the treatment pattern analysis, we looked within specific time intervals following MDD diagnosis and following treatment initiation namely at week 4, 6, 8, 12 and 24. As part of the results, we provided the number of individuals lost to follow-up at different time intervals. Lost to follow-up was less than 10% for all databases within the different strata of antidepressant use and thus no sensitivity analysis (see 9.9.4) was needed.

14.3 Interpretation

With regard to the characteristics of individuals with major depression, we reported that the proportion of females with MDD was higher than the proportion of males. This is in line with literature describing a gender difference in depression where up to twice as many females experience major depression as males. (Salk, Hyde et al. 2017) With regard to age, we reported that the largest proportion of individuals with newly diagnosed MDD was in the age category of 18-44 years for CPRD GOLD and IPCI and in the age category of 45-64 years for IQVIA Germany and SIDIAP. This is in line with literature describing mean age at onset of about 40 years (with increasing incidence in younger population in more recent years). (Bains and Abdijadid 2024) Also, in line with literature we report that many of the patients with newly diagnosed MDD already had symptoms of anxiety and symptoms of depression like depressive disorder prior to diagnosis. (Kern, Cepeda et al. 2021, Bains and Abdijadid 2024).

Within 24 weeks following MDD diagnosis, large differences in individuals with MDD initiating treatment with any of the antidepressants of interest were observed but at least 1 in 5 individuals has initiated treatment. The retrospective cohort study from Waitzfelder et al using data from Kaiser Permanente reported that around 1 patient in 3 initiated treatment with an antidepressant drug following diagnosis. (Waitzfelder, Stewart et al. 2018). In a systematic review and meta-analysis, it was reported that approximately one third of people with depression receive treatment. (Mekonen, Chan et al. 2021).

Antidepressant treatment primarily features SSRIs, aligning with clinical guidelines and tolerability considerations. This is also in line with literature reporting high use of SSRI (mainly as monotherapy) in patients with MDD especially in primary care. (Jain, Higa et al. 2022). In IMASIS which is a secondary care database, use of other antidepressants was as high as use of SSRIs which is in line with guidelines on treatment of major depression in secondary care. (NICE 2022)

The proportion of individuals continuing treatment decreased over time with proportions by the end of longest follow-up (24 weeks) ranging between 14% (CPRD) to 67% (SIDIAP) for SSRI, 5.3% (CPRD) to 39% (SIDIAP) for NSRI and 16% (CPRD) to 57% (SIDIAP). In IMASIS, the proportion of individuals continuing treatment was much lower.. A US claims study in patients with major depression also explored treatment patterns and reported a high proportion of treatment discontinuation (49%) with a median time to discontinuation of 23 weeks. (Gauthier, Guerin et al. 2017) A large primary care database cohort study of all patients with a newly initiated course of eligible antidepressant treatment during 1 year, from a database of 237 Scottish practices reported that 75% of patients continued treatment beyond 30 days, 56% beyond 90 days, and 40% beyond 180 days which is higher than what we observed for CPRD (Burton, Anderson et al. 2012). A high proportion of patients discontinuing treatment (75%) was also reported in the study by Jain et al, describing treatment patterns in individuals with newly diagnosed major depression using data from the IBM® MarketScan® Commercial database. (Jain, Higa et al. 2022)

Switching from one antidepressant class to another antidepressant class was low especially in the primary care databases where less than 1% of initial SSRI users switched to NSRI and less than 3% of initials SSRI users switched to other antidepressant agents during follow-up. In IMASIS (which is a hospital database), the proportion of individuals switching to other treatment during follow-up was higher with proportions around 10% for switching from SSRIs to OAD and from NSRI to OAD. The PERFORM study, which was an observational cohort study in outpatients with MDD in five European countries reported switching in up to 1 patient in 5 but this was a prospective cohort study including patients with MDD from both primary and secondary care. (Haro, Lamy et al. 2018)

By the end of longest follow-up window (i.e. 24 weeks following treatment initiation), use of psycholeptics on top of SSRI treatment ranged between 13.6% (IQVIA DA Germany) to 32.6% (IPCI), 10.9% (IQVIA DA Germany) to 40.1% (IMASIS and IPCI) for NSRI and 16.1% (IQVIA DA Germany) to 39.3% (IMASIS) for other antidepressants. Overall, the lowest proportion of subjects with added psycholeptic treatment on top of antidepressant therapy was found in IQVIA DA Germany. These results are in line with a European cross-sectional multicenter study reporting that up to 32% of individuals with MDD added treatment with benzodiazepines on top of treatment with antidepressants. (Dold, Bartova et al. 2020)

In conclusion, this study sheds light on the diverse profiles of MDD patients and their corresponding treatment trajectories. The identified patterns and demographic influences underscore the importance of context-specific approaches to enhance the effectiveness of depression management strategies.

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16 ANNEXES

16.1 Appendix I – List with concept definitions for exposure

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

CONCEPT ID	Name	ATC code
21604687	Non-selective monoamine reuptake inhibitors (NSRIs)	N06AA
21604709	Selective serotonin reuptake inhibitors (SSRIs)	N06AB
21604729	Other antidepressants (excluding N06AX25 and N06AX27)	N06AX
21604489	Psycholeptics	N05
21604490	Antipsychotics	N05A
21604564	Anxiolytics	N05B
21604606	Hypnotics and sedatives	N05C

16.2 Appendix II – List with concept definitions for major depressive disorder

Major Depressive Disorder

concept_id	concept_name
4031328	Chronic major depressive disorder, single episode
4094358	Chronic recurrent major depressive disorder
4148630	Major depression in partial remission
4176002	Major depression in remission
4323418	Major depression single episode, in partial remission
37111697	Major depression with psychotic features
4154391	Major depression, melancholic type
4282096	Major depression, single episode
4181807	Major depressive disorder, single episode with atypical features
4287238	Major depressive disorder, single episode with catatonic features
4270907	Major depressive disorder, single episode with melancholic features
4093584	Major depressive disorder, single episode with postpartum onset
4336957	Mild major depression
4195572	Mild major depression, single episode
37109052	Mild major depressive disorder co-occurrent with anxiety single episode
4228802	Mild recurrent major depression
36715000	Minimal major depression
36714999	Minimal major depression single episode
36714997	Minimal recurrent major depression
4307111	Moderate major depression
4049623	Moderate major depression, single episode
37109053	Moderate major depressive disorder co-occurrent with anxiety single episode
4077577	Moderate recurrent major depression
36714389	Moderately severe major depression
36717389	Moderately severe major depression single episode
36714998	Moderately severe recurrent major depression
42534817	Postpartum major depression in remission
4282316	Recurrent major depression
4141454	Recurrent major depression in partial remission
433991	Recurrent major depression in remission
35615155	Recurrent major depressive disorder in partial remission co-occurrent with anxiety
4304140	Recurrent major depressive disorder with atypical features
4220023	Recurrent major depressive disorder with catatonic features
4205471	Recurrent major depressive disorder with melancholic features
4324959	Recurrent major depressive disorder with postpartum onset
432285	Recurrent major depressive episodes
44805549	Recurrent major depressive episodes, in partial remission
44813499	Recurrent major depressive episodes, in remission

concept_id	concept_name
438998	Recurrent major depressive episodes, mild
432883	Recurrent major depressive episodes, moderate
44805542	Recurrent major depressive episodes, severe
434911	Recurrent major depressive episodes, severe, with psychosis
44805669	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
35615151	Recurrent mild major depressive disorder co-occurrent with anxiety
35615153	Recurrent moderate major depressive disorder co-occurrent with anxiety
35615152	Recurrent severe major depressive disorder co-occurrent with anxiety
42872722	Severe major depression
4250023	Severe major depression with psychotic features
4144233	Severe major depression with psychotic features, mood-congruent
4243822	Severe major depression with psychotic features, mood-incongruent
4327337	Severe major depression without psychotic features
42872411	Severe major depression, single episode
438406	Severe major depression, single episode, with psychotic features
4299785	Severe major depression, single episode, with psychotic features, mood-congruent
4067409	Severe major depression, single episode, with psychotic features, mood-incongruent
441534	Severe major depression, single episode, without psychotic features
37109054	Severe major depressive disorder co-occurrent with anxiety single episode
43531624	Severe recurrent major depression
4154309	Severe recurrent major depression with psychotic features
4141292	Severe recurrent major depression with psychotic features, mood-congruent
4034842	Severe recurrent major depression with psychotic features, mood-incongruent
435220	Severe recurrent major depression without psychotic features
44805550	Single major depressive episode, in remission
439259	Single major depressive episode, severe, with psychosis
44805668	Single major depressive episode, severe, with psychosis, psychosis in remission

16.3 Appendix III – Supplementary tables

Appendix III is in a separate document.

16.4 Appendix IV – Description of databases

Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD(Herrett, Gallagher et al. 2015) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.(Planas Domingo, Gallen Castillo et al. 1988) Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation.(Martín-Baranera, Planas et al. 1995) Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.(Vlug, van der Lei et al. 1999) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.(Vlug, van der Lei et al. 1999) The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.(Vlug, van der Lei et al. 1999)

Information System for Research in Primary Care (SIDIAP), Spain

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams, consisting of GPs, nurses and non-clinical staff.(Recalde, Manzano-Salgado et al. 2019) The Catalan Health Institute manages 328 out of 370 such Primary Care Teams with a coverage of 5.8M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.