NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Comparison of Antidepressants in the Real-World: Retrospective Cohort Study Using Big Data
Protocol number	B2061147
Protocol version identifier	Amendment 1
Date	10 February 2021
Active substance	DESVENLAFAXINE (N06AX23)
Medicinal product	Pristiq
Research question and objectives	*Research question:* What is the real-world data on antidepressant therapy that can be found in the nationwide claims database in Korea? *Primary objectives:* 1. Explore baseline characteristics and drug utilization patterns of 11 commonly used antidepressant therapy during 90 days of acute treatment phase 2. Explore drug utilization patterns such as therapy changes, medication compliance and recurrence relationship, and risk of adverse outcomes during maintenance phase *Secondary objectives:* 1. Choice of antidepressants and drug utilization patterns in patients with various comorbidities 2. The relationship of non-pharmacologic treatment and discontinuation, medication compliance

	3. Choice of antidepressants by non-psychiatric specialty
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
HIRA	Health Insurance and Review Assessment
MPR	Medication Possession Ratio
ICD-10	International Classification of Diseases 10th revision
KCD-7	Korean Standard Classification of Diseases 7th revision
MDD	Major Depressive Disorder
MCI	Mild cognitive impairment
COPD	Chronic Obstructive Pulmonary Disease
CAD	Coronary Artery Disease
CVA	Cerebrovascular Accident
CBT	Cognitive Behavioral Therapy
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin–norepinephrine reuptake inhibitor
NHI	National Health Insurance
AD	Antidepressants

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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PPD , MA, PhD	Associate Professor	PPD	PPD , Korea

4. ABSTRACT

Title: Comparison of Antidepressants in the Real-World: Retrospective Cohort Study Using Big Data

Rationale and background

While there are many antidepressants from which physicians can select based on efficacy and tolerability profile, evidence on effectiveness and safety outcomes of new antidepressants in real clinical practice among Korean MDD population is limited. Hence, the aim of this study is to investigate medication utilization pattern and risk of adverse outcomes among commonly used antidepressants by using nationwide claims database, in order to assess overall clinical benefit of antidepressant therapy in real-world practice.

Research question and objectives

Research question: What is the real-world data on antidepressant therapy that can be found in the nationwide claims database in Korea?

Primary objectives:

1. Explore baseline characteristics and drug utilization patterns of 11 commonly used antidepressant therapy during 90 days of acute treatment phase
2. Explore drug utilization patterns such as therapy changes, medication compliance and recurrence relationship, and risk of adverse outcomes during maintenance phase

Secondary objectives:

1. Choice of antidepressants and drug utilization patterns in patients with various comorbidities
2. The relationship of non-pharmacologic treatment and discontinuation, medication compliance
3. Choice of antidepressants by non-psychiatric specialty

Study design: Retrospective cohort study

Population:

Subjects who newly initiated antidepressant therapies between Jan 01, 2017 to Jun 30, 2019 in the Health Insurance and Review Assessment (HIRA) database

**Index date is the first prescription date of study drugs, including SSRIs, SNRIs, and other ADs during the intake period (Jan 01, 2017 to Dec 31, 2019)*

Variables – include exposures, outcomes, and key co-variates

Exposure: The exposure to the following will be considered:

1. SSRIs
2. SNRIs
3. Other ADs (including but not limited to mirtazapine, vortioxetine)

Outcome variables: the following will be assessed:

1. Outcomes related to depression
    - AD usage pattern (prescription proportion, dosage and length of treatment, switching, combination, augmentation, discontinuation), compliance, recurrence
2. Adverse outcomes
    - Hyponatremia, GI bleeding, fractures, falls, risk of intracranial hemorrhage, attempted suicide/self-harm, myocardial infarction, epilepsy/seizures, stroke/transient ischemic stroke

Key-Covariates: Variables, including but not limited to, will be age, sex, region, Charlson comorbidity index, psychiatric comorbidities, hospital admission

Data sources

HIRA database from January 01, 2016 to December 31, 2019 will be used for the analysis. It contains the data of universal health insurance system in Korea, wherein patient demographic information, inpatient and outpatient service use, and pharmacy dispensing claims can be obtained.

Study size

The study size will be determined based on the HIRA disease statistics, diagnosis code, inclusion and exclusion criteria, and study period. A previous study was conducted using the HIRA data from January 1, 2011 to December 31, 2015, during which 752,190 patients were identified to have been newly prescribed antidepressants with diagnosis of depressive disorder.

Data analysis

Patients will be matched on demographic and clinical characteristics. All outcome variables will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges and standard deviations of continuous variables of interest and frequency distributions of categorical variables. Safety outcomes of treatments will be estimated from time-to-event models. The 95% confidence intervals for the estimates will be calculated and $p<0.05$ will be considered significant. All analyses will be carried out using SAS version 9.4. Analysis and reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Ammendment 1	10Feb2021	2.	NHIS changed to HIRA.	Correction according to database change
		3.	Name and degree of NISL changed.	Correction according to NISL change
		4.	Population, data sources, study size amended to describe HIRA. Database selection period extended to end in 2019. Outcome variables related to depression added.	Correction according to database change and addition of description of results variable
		6.	Planned dates for start and end of data collection, interim report, and final study report amended.	Correction according to database change.
		9.2	Population amended to describe HIRA. Database selection period extended to end in 2019.	Correction according to database change.
		9.4	Data sources amended to describe HIRA.	Correction according to database change.
		9.5	Study size amended to describe HIRA.	Correction according to database change.
		9.6	Data management amened to describe HIRA.	Correction according to database change.
		9.8	Database name changed to HIRA.	Correction according to database change.
		9.9	Database name changed to HIRA.	Correction according to database change.
		12.	Typo corrected.	Correction of typo
		Figure 1.	Intake and follow-up period extended to end in 2019.	Correction according to database change.
		Table 2.	Drug Main Ingredient Codes source changed to HIRA.	Correction according to database change.
		Table 3.	Data source changed to HIRA.	Correction according to database change.

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	28 Jun 2019
Start of data collection	Mar 2021
End of data collection	Jun 2021
Interim report 1	Dec 2021
Final study report	Dec 2022

7. RATIONALE AND BACKGROUND

Major depressive disorder (MDD) is a prevalent disorder, causing great disability in affected individuals.[1-3] Its lifetime prevalence is estimated at 6.7% in Korea, and has continued to increase gradually since 2006.[4] The approximate economic cost of MDD in 2005 was at $4.5 billion, with indirect cost of $2.96 billion due to loss of work productivity.[5]

Current guidelines recommend antidepressants like selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) as first-line pharmacotherapy for the management of MDD.[6-7] The antidepressant effect not only reduces depressive symptoms but also contributes to patient's overall functional improvement.[8] Despite plenty of available evidences on antidepressant therapy, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that only about 30% of patients achieve remission with first-line treatment.[9] In addition, those patients switching antidepressants compared to those initiating or maintaining first-line antidepressant therapy have different patient characteristics in terms of severity of depressive symptoms, anxiety, worse health-related quality of life, functional impairment.[10] Non-adherence rates are high in MDD, which can lead to suboptimal treatment outcomes.[11]

While there are many antidepressants from which physicians can select based on efficacy and tolerability profile, evidence on effectiveness and safety outcomes of new

antidepressants in real clinical practice among Korean MDD population is limited. Ahn *et al*. (2011) reported that antidepressant adherence among the Korean patients with MDD is less than 50% and recurrence and deterioration of MDD occurs due to the low adherence in Korea.[12] In addition, it is uncertain how patients are being properly managed with index medications and the proportion of switching, combination, and augmentation therapy during both acute and maintenance phases. And medication adherence and persistence rates are clinically important as they can have a major impact on the outcomes such as recurrence and recovery from depressive symptoms.

Therefore, the aim of this study is to investigate medication utilization pattern and risk of adverse outcomes among commonly used antidepressants by using nationwide claims database, in order to assess overall clinical benefit of antidepressant therapy in real-world practice.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: What is the real-world data on antidepressant therapy that can be found in the nationwide claims database in Korea?

Primary objectives:

- Explore baseline characteristics and drug utilization patterns of 11 commonly used antidepressant therapy during 90 days of acute treatment phase
    - Top 11 commonly used antidepressants according to local market data are as follows:
        - Escitalopram, paroxetine, fluoxetine, mirtazapine, duloxetine, sertraline, venlafaxine, tianeptine, vortioxetine, desvenlafaxine, bupropion
    - Proportion of antidepressants prescribed by sex, age (≤20, 21-64, ≥ 65), sex and age combined
    - Initial doses used, average daily doses of each antidepressants
    - Average length of treatment with index medication before therapy change occurs (switching, combination, augmentation, discontinuation)

- Adherence and persistence measured by medication possession ratio during first 90 days of treatment period

- Explore drug utilization patterns such as therapy changes, medication compliance and recurrence relationship, and risk of adverse outcomes during maintenance phase
  - The choice of antidepressant, average length of new treatment maintenance, average number of co-administered medications (e.g., atypical antipsychotics, mood stabilizer, thyroid hormone, psychostimulant) when following changes occur from initial monotherapy:
    - Switching
    - Combination
    - Augmentation
  - Medication compliance and recurrence
    - Compliance measured as adherence and persistence
    - Recurrence
    - Relationship between recurrence and compliance
  - Risk of adverse outcomes measurement between individual ADs that are well known to be treatment-related (e.g., hyponatremia, GI bleeding, fractures, falls, risk of intracranial hemorrhage, attempted suicide/self-harm, myocardial infarction, epilepsy/seizures, stroke/transient ischemic stroke)

Secondary objectives:

1. Choice of antidepressants and drug utilization patterns in patients with various comorbidities
   - Psychiatric comorbidities
   - Mild cognitive impairment (MCI)
2. The relationship of non-pharmacologic treatment and discontinuation, medication compliance
   - Non-pharmacologic treatments may include: cognitive behavioral therapy (CBT),

frequency of physician visit during acute and maintenance phase of treatment

- Frequency of visit during the first 3 months of acute phase and its relationship to treatment maintenance at 4, 5, 6, 7, 8, 9 month time points and discontinuation rate

3. Choice of antidepressants by non-psychiatric specialty
   - Rheumatology, cardiology, pulmonology, infectious diseases, nephrology, endocrinology and metabolism, gastroenterology, rehabilitative medicine, neurology, neurosurgery, urology, otorhinolaryngology, gynecology & obstetrics, etc.

9. RESEARCH METHODS

9.1. Study design

Using a retrospective cohort design, this study will evaluate treatment utilization pattern, medication compliance, incidence of recurrence, risk of adverse outcomes of antidepressant therapy, choice of therapy in various comorbidities, and choice of therapy in other specialty that are recorded in national health insurance database.

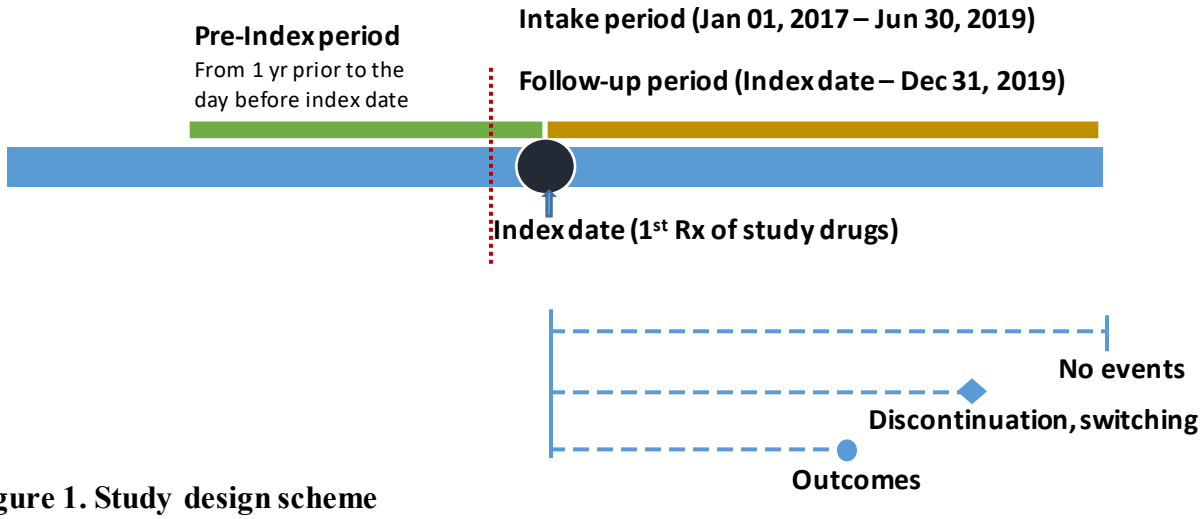

Figure 1. Study design scheme

9.2. Setting

Population

Subjects who newly initiated antidepressant therapies between Jan 01, 2017 to Jun 30, 2019 in the HIRA database

* Index date is the first prescription date of study drugs, including SSRIs, SNRIs, and other ADs during the intake period (Jan 01, 2017 to Dec 31, 2019).

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients aged 18 years or older on the index date

2. Patients who had at least one inpatient claim or two outpatient claims in the intake period with any of the following diagnosis codes

Table 1. Diagnosis codes for inclusion

KCD-7 Code1)	Description
F06.3	Organic mood[affective] disorders
F32*	Depressive episode
F33*	Recurrent depressive disorder
F34.1	Neurotic depression
F38.1	Other recurrent mood[affective] disorders
F41.2	Mixed anxiety and depressive disorder

1) KCD-7 = Korean version of ICD-10

3. Patients prescribed any of the following antidepressant during intake period (from January 1, 2017 to June 30, 2019)

Table 2. Study Drug List

Active Ingredient	Dosage	HIRA Drug Main Ingredient Codes
Escitalopram	5mg	474801ATB
	10mg	474802ATB
	20mg	474803ATB
	15mg	474804ATB
	10mg	521101ATD
	20mg	521102ATD
Paroxetine	10mg	209301ATB
	20mg	209302ATB
	12.5mg	209304ATR
	25mg	209305ATR
Fluoxetine	10mg	161501ACH
	10mg	161501ATB
	20mg	161502ACH
	20mg	161502ATB
	20mg	161502ATD

Mirtazapine	15mg 15mg 30mg 30mg 7.5mg 7.5mg	196201ATB 196201ATD 196202ATB 196202ATD 196204ATB 196204ATD
Duloxetine	30mg 30mg 60mg 60mg	495501ACE 495501ATE 495502ACE 495502ATE
Sertraline	50mg 0.1g	227001ATB 227002ATB
Venlafaxine	75mg 37.5mg	247502ACR 247504ACR
Tianeptine	12.5mg	229601ATB
Vortioxetine	5mg 10mg 15mg 20mg	628501ATB 628502ATB 628503ATB 628504ATB
Desvenlafaxine	50mg 100mg	626401ATR 626402ATR
Bupropion	0.1g 0.15g 0.3g	428101ATB 428102ATR 428103ATR

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with a claim of diagnosis codes in Table 1 during the 12 month pre-index period
2. Patients with a claim of prescription in Table 2 during the 12 month pre-index period
3. Patient who had a claim as a beneficiary of Medical Aid program (Korean Medicaid program with free or minimum copay)
4. Patients who are hospitalized at the index date
5. Patients who are under hospice care (procedure codes WG*-WO*)

9.3. Variables

Table 3. List of Variable Categories

Variable	Role	Data Source	Operational Definition
SSRIs	Exposure	HIRA Database	Prescription claims with a HIRA Drug Main Ingredient code for the following drugs defined in Table 2 will be used individually for each drug: Escitalopram, paroxetine, fluoxetine, sertraline
SNRIs	Exposure	HIRA Database	Prescription claims with a HIRA Drug Main Ingredient code for the following drugs defined in Table 2 will be used individually for each drug: Duloxetine, venlafaxine, desvenlafaxine
Other ADs	Exposure	HIRA Database	Prescription claims with a HIRA Drug Main Ingredient code for the following drugs defined in Table 2 will be used individually for each drug: Mirtazapine, tianeptine, vortioxetine, bupropion
Proportion of Antidepressants	Primary outcome	HIRA Database	For each of 11 study drugs, the following proportions will be calculated 1) Proportion out of total prescriptions in the first 90 days from the index date (acute treatment phase) 2) Proportion out of each gender in the first 90 days from the index date (acute treatment phase) 3) Proportion out of three age groups (≤20, 21-64, ≥65) in the first 90 days from the index date (acute

			treatment phase) 4) Proportion out of 6 subgroups generated by 2 genders and 3 age groups in the first 90 days from the index date (acute treatment phase)
Dosage	Primary outcome	HIRA Database	For each of 11 study drugs, the following dosages will be calculated 1) Initial dosage at the index date 2) The average dosage during the first 90 day period from the index date (acute treatment phase)
Persistence	Primary outcome	HIRA Database	For each of 11 study drugs, the average length of treatment on the index drug (allowing 14 day permissible gap) will be calculated - Switching, combination, augmentation, discontinuation will terminate the persistent period
Discontinuation	Primary outcome	HIRA Database	For each of 11 study drugs chosen as index drug, the percentage of discontinuation in the first 90 days from the index date (acute treatment phase) will be measured (allowing 14 day permissible gap)
Adherence	Primary outcome	HIRA Database	For each of 11 study drugs chosen as index drug, adherence will be measured by MPR during the first 90 days from the index date (acute treatment phase) * MPR = (Days of medication possession from the prescriptions filled in the 90 days) / (90 days + extra days of drug supply from the last prescription fill during the 90 days) ** For those period with any identified adverse outcome such as GI bleeding will be considered as

			non-adherent period
Drug utilization pattern in acute phase	Secondary outcome	HIRA Database	During the first 90 day period starting from the index date, the following types of drug utilization pattern is recorded - monotherapy (kept on the index medication) - switching (switched to other antidepressant) - combination (adding other antidepressant) - augmentation (adding other non-AD drug such as antipsychotic)
Drug utilization pattern in maintenance phase	Secondary outcome	HIRA Database	During the second 90 day period (91 ~ 180 days) starting from the index date, the following types of drug utilization pattern is recorded - choice of antidepressant - monotherapy (kept on the same medication) - switching (switched to other antidepressant) - combination (adding other antidepressant) - augmentation (adding other non-AD drug such as antipsychotic)
Recurrence	Primary outcome	HIRA Database	Recurrence was operationally defined as either one of the following was satisfied: 1) inpatient episode with a diagnosis code in Table 1 2) emergency room visit with a diagnosis code in Table 1 3) suicide attempt identified by the following KCD-7 codes: T40 Poisoning by narcotics and psychodysleptics [hallucinogens] T41 Poisoning by anaesthetics and

			therapeutic gases T42 Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs T43 Poisoning by psychotropic drugs, not elsewhere classified T54 Toxic effect of corrosive substances T60 Toxic effect of pesticides X60-X84 intentional self harm
Adverse outcomes	Primary outcome	HIRA Database	The following known treatmwent related outcomes will be operationally defined by KCD-7 diagnosis codes and/or NHI procedure codes in medical claims - GI bleeding I850, I983, K2211, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K3181, K5521, K625, K920, K921, K922 - Fractures S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2 - Falls W00-W19 - Intracranial hemorrhage I60, I61, I62, I690, I691, I692, S064, S065, S066, S068 - Suicide attempt, self-harm T40 Poisoning by narcotics and psychodysleptics [hallucinogens] T41 Poisoning by anaesthetics and therapeutic gases T42 Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs T43 Poisoning by psychotropic drugs, not elsewhere classified T54 Toxic effect of corrosive substances T60 Toxic effect of pesticides X60-X84 intentional self-harm - Myocardial infarction I21.9, I21.4, I21.0, I21.1, I21.2, I21.3, I22.0A, I22.0B, I22.0C, I22.8A,

			I22.8B, I22.8C, I22.8D, I22.8E, I22.8F, I22.8G, I22.8H, I22.8I, I22.8, I22.9, I22.1A, I22.1B, I22.1C - Epilepsy/seizures G40.XX - Stroke - Transient ischemic attack G459, I63, I693 - Hemorrhagic stroke I60, I61, I62, I690, I691, I692 - Ischemic stroke I63 *[NOTE] Hospitalization and CT or MRI codes such as brain CT or MRI procedure code for ischemic stroke and hemorrhagic stroke, or any CT or MRI for systemic embolism are also required for identification.* * Brain CT HA441, HA451, HA461, HA471, HA851 * Brain MRI HE101, HE102, HE135, HE201, HE202, HE235, HE301, HE302, HE401, HE402, HE501, HE502, HE535 * Any CT or MRI or CT HA401-HA416, HA424, HA425, HA434, HA435, HA443-HA449, HA453, HA456-HA459, HA463-HA469, HA473-HA479, HA496, HA497, HA801, HA805, HA809, HA813, HA834, HA835, HA853, HA856, HA857-HA859, S852 * MRI HE103-HE142, HE203-HE234, HE236-HE241, HE303-HE334, HE403-HE434, HE430-HE434, HE503-HE534, HE536-HE541, HF101, HF102, HF104-HF107, HF201, HF202, HF305, HF306 - Hyponatremia - will be identified by

			prescription codes for vasopressin receptor antagonists such as tolvaptan (drug code=616501ATB)
Comorbidities	Covariates	HIRA Database	The following comorbidities which may affect the drug utilization patterns of antidepressants will be operationally defined using KCD-7 diagnosis codes in medical claims - Psychiatric comorbidities: panic disorder (F41.0), bipolar disorder (F31), PTSD (F43.1), acute stress (F43.0), personality disorder (F60-69), GAD (generalized anxiety disorder) (F41.1), adjustment disorder (F43.2), sleep disorder ((F51), g470, f108), dementia (F00-F03, G30), OCD (obsessive compulsive disorder) ((F42), F429, F605, F428)), substance related disorders (F10-19), schizophrenia (F20-29), eating disorder (F50), sexual dysfuntion (F52), mental retardation (F70-F79), developmental disorder (F80-F89), somatoform disorder F45, eating disorder F50 - Mild cognitive impairment (MCI): diagnosis code F06.7 along with a procedure code for neurocognitive function test FB001-FB060* - Charlson Comorbidity Index (CCI)
Non-pharmacologic treatments	Covariates	HIRA Database	The following non-pharmacologic treatments which may affect antidepressant adherence and persistence/discontinuation will be

			defined using NHI procedure codes* in medical claims - Individual psychotherapy** NN012 intensive analytic NN013 intensive - Group psychotherapy NN021 general NN022 analytic NN023 psychodrama - Family psychotherapy NN031 individual NN032 group NN040 occupational or recreation therapy NN050 narcosynthesis - Electroconvulsive therapy NN071 simple ETC NN072 modified ETC - Continuous sleep treatment NN081 electro sleep treatment NN082 drug induced sleep treatment NN083 sleep treatment with anesthesia NN090 psychiatric rehabilitation NN100 psychiatric emergency treatment - Psychiatric social work NN111 individual history taking NN112 social work guidance NN113 social investigation NN114 home visiting * Since January 2018, new code system was employed for psychotherapy and expert advisor consensus will be used to align the new codes to the codes above NN001-NN005 individual psychotherapy NN061 Cognitive Behavioral Therapy-Individual NN062 Cognitive Behavioral Therapy-Group ** NN011 supportive was excluded since it is more of a routine code used for majority of patients according to Ahn et al.

			(2012)[13]
Patient demographics and provider characteristics	Covariates	HIRA Database	The following patient demographics and provider characteristics will be defined using medical claims - Age - Gender - Region of provider - Specialty of provider - Class of clinic/hospital
Number of visits	Covariates	HIRA Database	Number of provider visits will be calculated from medical claims - Inpatients visits - Outpatient visits - Emergenccy room visits

9.4. Data sources

The Korean HIRA claims data covers 97% of Korean population (about 50 million people) in NHI and 3% of Korean population in Medical Aid program. Patients in Medical Aid program are excluded from analysis because the estimated drug compliance may be different from those patients covered by NHI due to the fact that patients in Medical Aid program make no self-payment or very little payment for medical services (Ahn et al, 2011).

HIRA database from January 01, 2016 to December 31, 2019 will be used for the analysis. It contains the data of universal health insurance system in Korea, wherein patient demographic information, inpatient and outpatient service use, and pharmacy dispensing claims can be obtained.

The main limitation of HIRA data is lack of clinical lab data and other clinical marekrs since it is a data collected for claims for reimbursement purpose.

9.5. Study size

Determined based on the HIRA disease statistics, diagnosis code, inclusion and exclusion criteria, and study period. A previous study was conducted using the HIRA data from January 1, 2011 to December 31, 2015, during which 752,190 patients were identified to have been newly prescribed antidepressants with diagnosis of depressive disorder.

9.6. Data management

Ewha Womans University (EWU) team will submit the data request to the HIRA big data division. After HIRA prior consultation procedure and data release committee review and approval, the requested data will be uploaded only to the HIRA internal server which can be accessed from HIRA analysis room available in Wonju or remotely. Even if the data can be remotely accessed, copying and moving of data to personal computer is blocked and data provision will be suspended in the situation of screen capture, handwriting, or photography, all of which are subject to sactions. EWU team hopes to analyze the data in remote access, however HIRA has a policy that does not allow remote access to industry-related users, and so the data provision method for this study cannot be predicted. Among the analyzed data, only summary data such as tables and graphs can be requested to send out to the research team. HIRA big data division checks the export requests for patient privacy protection and will email the summary file to EWU team.

Data protection is guaranteed by the HIRA data providing server which is disconnected from any outside access and only final anonymized form of tables and figures are allowed to be delivered to researcher computers. Before releasing these final output, HIRA Big Data Division checks for privacy protection again and makes approval of data export. Hence, there will be no violation of privacy of research subjects.

9.7. Data analysis

The proportions and drug utilization patterns comparisons of 11 study drugs will use all the patients satisfying inclusion and exclusion criteria (raw data). Adherence, persistence, discontinuation, recurrence, and adverse outcomes comparison of 11 study drugs will use both raw data and matched data where patients will be matched on demographic and clinical characteristics. All outcome variables will be summarized *descriptively* through the tabular and graphical display of mean values, medians, ranges and standard deviations of continuous variables of interest and frequency distributions of categorical variables. Safety outcomes of treatments will be estimated from time-to-event models. The 95% confidence intervals for the estimates will be calculated and $p<0.05$ will be considered significant. All analyses will be carried out using SAS version 9.4 which is installed on HIRA server. Analysis and reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

9.8. Quality control

HIRA claims data files are large and complex. The study analysis will be thoroughly evaluated and assessed for quality in twofolds: 1) EWU professors with 30+ years of claims data analysis will guide analysts to perform data analyses accurately and efficiently; and 2)

clinical expert advisors who are leading clinicains in mental health in Korea will evaluate the summary statistics of all levels of data and results and will guide correct interpretation.

SAS programs used in the data analysis will be checked and stored to ensure integrity and quality of analysis.

9.9. Limitations of the research methods

Even though HIRA claims data is from the whole population of Korea, the data is not collected for research purpose. Its original purpose was to claim reimbursement. There might be intentional or unintentional miscoding of services performed and diagnosis. These errors are generally undetectable but the dominant majority of data is valid according to the previous studies on the feasibility of Korean NHI claims data.

To reduce chances of including antidepressants use for a disease other than major deressive disorders, operational definitions of at least two outpatient claims or one inpatient claims with diagnosis codes in Table 1 is used. However, it is not 100% accurate since proviers are afraid of denial of reimbursement from the HIRA which is empowered with reimbursement review and denial of payment. Hence, in some cases, diagnosis code is put strategically to minimize a chance of denial. For this reason, this study focuses on antidepressants prescribed by a specialist in mental health and only analyze antidepressant prescritions from other specialists as secondary analysis to identify antidepressant practice patterns from other specialties.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required. An exemption of informed consent will be sought from the EWU IRB and the approval will be forwarded to Pfizer.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

An exemption of IRB review will be sought from the EWU IRB and the approval will be forwarded to Pfizer..

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) Good Practices for Outcomes Research issued by the International Society forPharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness:Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council forInternational Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data and FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this research will be submitted for publication in scientific peer-reviewed journals and for presentation at appropriate research conferences in either poster or podium presentation,

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data (2) drafting the article or revising it critically for important intellectual contgent; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.

All publications based on this study must be submitted to Pfizer for corporate review. The vender agreement will detail the procedures for, and timing of, Pfizers review of publications.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable