Non-Interventional Study Protocol
B2061147

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

Statistical Analysis Plan
(SAP)

Version: 1.1

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

- The status of the study when the amendment is made: During data analysis
- Details and rationale of the changes to the SAP:

Change	Before	After	Rationale
The period of data acquisition	01 Jan 2016 ~ 31 Dec 2019	01 Jan 2017 ~ 31 Dec 2020	To acquire and analyze the latest data available du to the delay of the data acquisition
Inclusion criteria	Patients aged ≥18 years on the index date	Patients aged ≥18 years and ≤ 70 years on the index date.	Due to a considerable incidence of depression resulting from concomitant diseases in the elderly and limitation of data capacity
MPR	Calculated by (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)	Calculated by (Days of medication possession from the prescriptions filled in the 180 days) / (180 days + extra days of drug supply from the last prescription fill during the 180 days)	To lead to more reasonable results that reflects the real-world situation
Operational definition of 'persistence'	For each of 11 study drugs, the average length of treatment on the index drug (allowing a 14-day permissible gap) will be calculated	For each of 11 study drugs, the average length of treatment on the index drug during the first 180-day period (allowing a 14-day permissible gap) will be calculated	Same as above
Operational definition of 'adherence'	For each of 11 study drugs chosen as index drug, adherence will be measured by MPR during the first 90-day period from the index date (acute treatment phase)	For each of 11 study drugs chosen as index drug, adherence will be measured by MPR and persistence during the first 90-day and 180-day period from the index date, respectively (acute treatment phase) - MPR ≥ 0.75 and persistence ≥ 90 will be considered as adherence	Same as above
Operational definition of 'recurrence'	Recurrence was operationally defined as either one of the following being satisfied: 1) Inpatient episode with a diagnosis code in Table 1 2) Emergency room visit with a diagnosis code in Table 1 Suicide attempt identified by the following KCD-7 codes (the rest omitted)	Recurrence during the acute treatment phase was operationally defined as either one of the following being satisfied: 1) Inpatient episode with a diagnosis code in Table 1 2) Inpatient episode via the department of psychiatry or emergency medicine 3) Inpatient episode via nursing hospital	Same as above

		4) Emergency room visit with a diagnosis code in Table 1 5) Suicide attempt identified by the following KCD-7 codes (the rest omitted) 6) Augmentation of the following non-AD drugs - Antipsychotic: amisulpride, ariprazole, olanzapine, quetiapine, risperidone, perphenazine - Anticonvulsant: carbamazepine, valproic acid, lamotrigine - Mood stabilizer: lithium - Anxiolytic: buspirone - Thyroid hormone: levothyroxine, liothyronine Recurrence after the acute treatment phase was operationally defined as either on of the following being satisfied: 1) ~6) the same as above 7) AD prescription after 30 days of drug holiday	

2 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

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.

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

<u>Primary objectives:</u>

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:

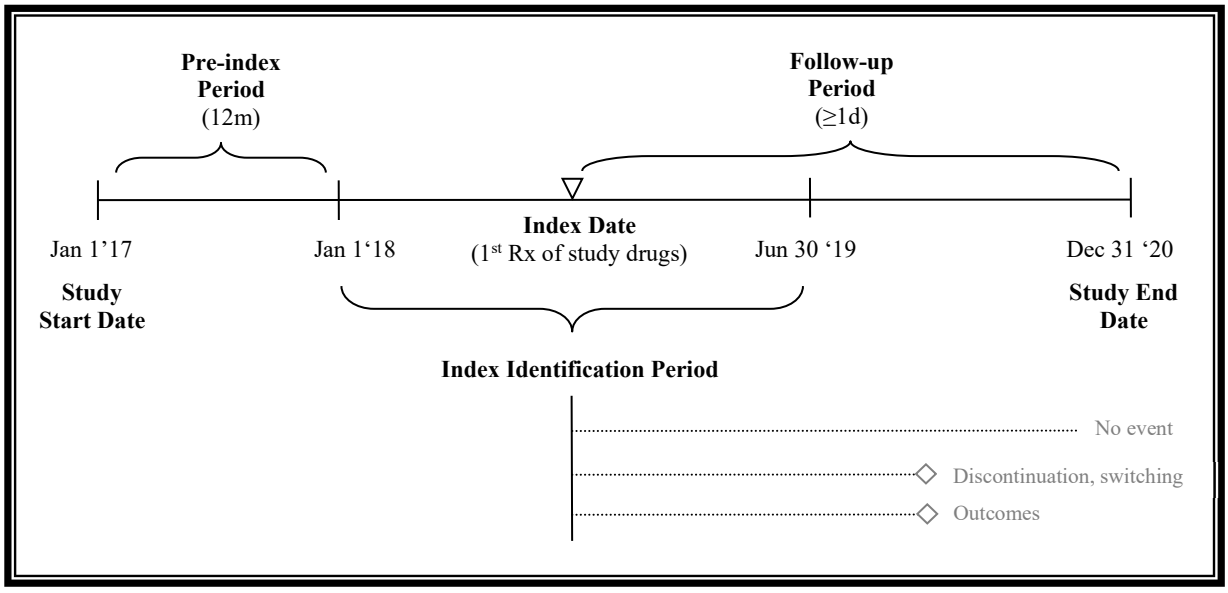
1. *Choice of antidepressants and drug utilization patterns in patients with various comorbidities*
2. *The relationship of non-pharmacologic treatment and discontinuation, medication compliance*
3. *Choice of antidepressants by non-psychiatric specialty*

2.1 STUDY DESIGN

Retrospective cohort study design is used on Subjects who newly initiated antidepressant therapies between Jan 01, 2018 to Jun 30, 2019 in the Health Insurance Review and Service (HIRA) database
**Index date is the first prescription date of study drugs, including SSRIs, SNRIs, and other ADs during the intake period (Jan 01, 2018 to Jun 30, 2019)*

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



Study population

Subjects who newly initiated antidepressant therapies between Jan 01, 2018 to Jun 30, 2019 in the Health Insurance Review and Service (HIRA) database

** Index date is the first prescription date of study drugs, including SSRIs, SNRIs, and other ADs during the intake period (Jan 01, 2018 to Jun 30, 2019).*

Data source

The Korean HIRA claims data covers 97% of Korean population (about 50 million people) in the Korean National Health Insurance and 3% of Korean population in Medical Aid program.
HIRA claims database from January 01, 2017 to December 31, 2020 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, pharmacy dispensing claims, and death 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.

2.2 STUDY OBJECTIVES

Primary objectives:

1. *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*
2. *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.*

3 HYPOTHESES AND DECISION RULES

N/A

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Subjects who newly initiated antidepressant therapies between Jan 01, 2018 to Jun 30, 2019 in the Health Insurance Review and Service (HIRA) database
** Index date is the first prescription date of study drugs, including SSRIs, SNRIs, and other ADs during the intake period (Jan 01, 2018 to Jun 30, 2019).*

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 and 70 years or younger 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 Code[1)]	*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, 2018 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*	*196201ATB*
	15mg	*196201ATD*
	30mg	*196202ATB*
	30mg	*196202ATD*
	7.5mg	*196204ATB*
	7.5mg	*196204ATD*
Duloxetine	*30mg*	*495501ACE*
	30mg	*495501ATE*
	60mg	*495502ACE*
	60mg	*495502ATE*
Sertraline	*50mg*	*227001ATB*
	0.1g	*227002ATB*
Venlafaxine	*75mg*	*247502ACR*
	37.5mg	*247504ACR*
Tianeptine	*12.5mg*	*229601ATB*
Vortioxetine	*5mg*	*628501ATB*
	10mg	*628502ATB*
	15mg	*628503ATB*

	20mg	*628504ATB*
Desvenlafaxine	*50mg* *100mg*	*626401ATR* *626402ATR*
Bupropion	*0.1g* *0.15g* *0.3g*	*428101ATB* *428102ATR* *428103ATR*

Exclusion criteria

1. *Patients meeting any of the following criteria will not be included in the study:*
2. *Patients with a claim of diagnosis codes in Table 1 during the 12 month pre-index period*
3. *Patients with a claim of prescription in Table 2 during the 12 month pre-index period*
4. *Patient who had a claim as a beneficiary of Medical Aid program (Korean Medicaid program with free or minimum copay)*
5. *Patients who are hospitalized at the index date*
6. *Patients who are under hospice care (procdure codes WG*-WO*)*

4.2 SAFETY ANALYSIS SET

The safety analysis set is the same as the full analysis set.

4.3 OTHER ANALYSIS SET

N/A

4.4 SUBGROUPS

Subgroup analysis may be considered, including but not limited to subgroup analyses by age (<20, 21-64, >65), gender, comorbidities, and prescribing physician's specialty.

5 ENDPOINTS AND COVARIATES

Endpoints are categorized by primary objectives and secondary objectives.

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Medication compliance (persistence, discontinuation, adherence) along with recurrence are main primary efficacy endpoints and they are defined as follows:

1. MPR (medication possision ratio)
   For each of 11 study drugs, the MPR will be calculated by (Days of medication possession from the prescriptions filled in the 180 days) / (180 days + extra days of drug supply from the last prescription fill during the 180 days)
2. Persistence
   For each of 11 study drugs, the average length of treatment on the index drug during the first 180 day period (allowing 14 day permissible gap) will be

calculated. Switching, combination, augmentation, discontinuation will terminate the persistent period.

3. Discontinuation
   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)
4. Adherence
   For each of 11 study drugs chosen as index drug, adherence will be measured by MPR and persistence during the first 90 day and 180 day from the index date, respectively (acute treatment phase). MPR ≥ 0.75 and persistence ≥ 90 will be considered as adherence.
   * For those period with any identified adverse outcome such as GI bleeding will be considered as a non-adherent period.
5. Recurrence
   Recurrence during the acute treatment phase was operationally defined as either one of the following being satisfied:
   1) Inpatient episode with a diagnosis code in Table 1
   2) Inpatient episodes via the department of psychiatry or emergency medicine
   3) Inpatient episode via nursing hospital
   4) Emergency room visit with a diagnosis code in Table 1
   5) 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
   6) Augmentation of the following non-AD drugs
      - Antipsychotic: amisulpride, ariprazole, olanzapine, quetiapine, risperidone, perphenazine
      - Anticonvulsant: carbamazepine, valproic acid, lamotrigine
      - Mood stabilizer: lithium
      - Anxiolytic: buspirone
      - Thyroid hormone: levothyroxine, liothyronine

   Recurrence after the acute treatment phase was operationally defined as either on of the following being satisfied:
   1) ~6) the same as above
   7) AD prescription after 30 days of drug holiday

5.2 SAFETY ENDPOINTS

Adverse outcomes are primary endpoints in this study and they include the following categories defined by KCD-7 diagnosis codes and/or NHI procedure codes appearing in medical claims data after the index date.

- 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)

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5.4 COVARIATES

Table 3. List of Variable Categories

Variable	*Role*	*Data source(s)*	*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)* *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:* *Initial dosage at the index date* *The average dosage during the first 90 day period from the index date (acute treatment phase)*
MPR (medication possession ratio)	*Primary outcome*	*HIRA Database*	*For each of 11 study drugs, the MPR will be calculated by (Days of medication possession from the prescriptions filled in the 180 days) / (180 days + extra days of drug supply from the last prescription fill during the 180 days)*
Persistence	*Primary outcome*	*HIRA Database*	*For each of 11 study drugs, the average length of treatment on the index drug during the first 180 day period (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 and persistence during the first 90 day and 180 day period from the index date, respectively (acute treatment phase). MPR ≥ 0.75 and persistence ≥ 90 will be considered as adherence.* ** 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 during the acute treatment phase was operationally defined as either one of the following being satisfied:* *1) inpatient episode with a diagnosis code in Table 1* *2) inpatient episodes via the department of psychiatry or emergency medicine* *3) inpatient episode via nursing hospital* *4) emergency room visit with a diagnosis code in Table 1* *5) 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* *6) augmentation of the following non-AD drugs* *- Antipsychotic* *amisulpride, ariprazole, olanzapine, quetiapine, risperidone, perphenazine* *- Anticonvulsant* *carbamazepine, valproic acid, lamotrigine* *- Mood stabilizer* *lithium* *- Anxiolytic* *buspirone* *- Thyroid hormone* *levothyroxine, liothyronine* *Recurrence after the acute treatment phase was operationally defined as either on of the following being satisfied:* *1) ~6) the same as above* *7) AD prescription after 30 days of drug holiday*
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 pesticidesX60-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*	*The number of provider visits will be calculated from medical claims* - *Inpatients visits* - *Outpatient visits* - *Emergency room visits*

6 HANDLING OF MISSING VALUES

Since this study analyses actual medical claims data which was reviewed by HIRA, no imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (e.g., t-test, chi-square test) will be used based on the distribution of the measure. The cumulative incidence rate for clinical outcomes (major bleeding event, and stroke) will be calculated. The incidence rate will be calculated as the number of patients who experience the event divided by the observed time at risk. An unadjusted Kaplan Meier curve will be drawn to illustrate time-to-event.

The propensity score matching (PSM) technique and the propensity score weighting technique will be used to control for confounders when comparing the antidepressants. After PSM, no significant differences are expected among all pre-index measures between the antidepressant cohorts except for clinical indication diffrences. Also covariates in Table 3 will be included in multivariate logistic regression framework for each antidepressant choice (binary variable of 1 for choice and 0 for no choice). Covariates will include variables such as age, geographic region, CCI score, and comorbidities. Non-pharmacologic treatments will be used as a covariate if depedent variable is adherence, persistence, or discontinuation since a previous study reported accompanying number of non-pharmacologic treatments significantly increase adherence of antidepressants (Ahn J et al., 2011). The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing the pre-matched descriptive tables and post-matched pre-index measures. All data analysis will be executed using statistical software SAS version 9.4 or later.

7.2 STATISTICAL ANALYSES

7.2.1 Study Drug Analysis in Acute Phase

- To understand the top 11 antidepressants usage among the Korean patients with depression in acute treatment phase
- Primary analysis
- Endpoints:
  - Proportion of 11 antidepressants, by age (<20, 21-64, > 65), by gender, by age and gender
  - Choice of index drug
  - Initial doses used, average daily doses of each antidepressant
  - The average length of treatment with index medication before therapy change occurs (switching, combination, augmentation, discontinuation)
  - Adherence measured by medication possession ratio and persistence during first 90 days and 180 days of treatment period, respectively
- Population: patients who meet inclusion criteria and exclusion criteria in section 4.1 and classified by the index antidepressant out of 11 top antidepressants in the Korean market (Table 2)
- Significance on continuous variables will be tested by ANOVA (if equal variance condition satisfied) or the Kruskal-Wallis H test (otherwise). Provider specialty and other patient characteristics will be used to fit antidepressant choice by multivariate logistic regression analysis of each study drug choice.
- Covariates: antidepressant class covariates such as SSRIs, SNRIs, otand her ADs will be used as grouping variables.
- Missing values will be dropped from the analysis
- The role of this analysis is to provide information on study antidepressants in the acute phase of drug therapy for Korean patients with depression.

7.2.2 Study Drug Analysis in Maintenance Phase

- To understand the top 11 antidepressants usage among the Korean patients with depression in maintenance treatment phase
- Primary analysis
- Endpoints:
  - Choice of study drug
  - Average length of new treatment maintenance
  - Average number of co-medications (e.g., atypical antipsychotics, mood stabilizer, thyroid hormone, psychostimulant) when following changes occur from initial monotherapy: switching, combination, augmentation
  - Medication compliance (adherence, discontinuation, and persistence)
  - Recurrence by each antidepressant, by compliance
  - Risk of adverse events
- Population: patients from the acute treatment phase who started maintenance treatment (after 90 days from the index date)
- Significance on continuous variables will be tested by ANOVA (if equal variance condition satisfied) or Kruskal-Wallis H test (otherwise). Provider specialty and other patient characteristics will be used to fit antidepressant choice by multivariate logistic regression analysis of each study drug choice.
- Covariates: antidepressant class covariates such as SSRIs, SNRIs, and other ADs will be used as grouping variables.
- Missing values will be dropped from the analysis
- The role of this analysis is to provide information on study antidepressants in the maintenance phase of drug therapy for Korean patients with depression.

7.2.3 Patients with Depression and Comorbidity Analysis

- To understand the antidepressant choice among Korean patients with depression and other comorbidities (psychiatric comorbidities or mild cognitive impairment (MCI))
- Secondary analysis
- Endpoints:
  - Proportion of 11 antidepressants
  - Choice of study drug
- Population: patients who satisfy the acute treatment phase population and with a prespecified comorbidity
- Significance on continuous variables will be tested by ANOVA (if equal variance condition satisfied) or Kruskal-Wallis H test (otherwise). Provider specialty and other patient characteristics will be used to fit antidepressant choice by multivariate logistic regression analysis of each study drug choice.
- Covariates: antidepressant class covariates such as SSRIs, SNRIs, other ADs will be used as grouping variables.
- Missing values will be dropped from the analysis.

- The role of this analysis is to provide information on antidepressant selection in the acute phase of drug therapy for Korean patients with depression and comorbidity by each comorbidity group.

7.2.4 Relationship between Non-pharmacological Treatments and Antidepressant Compliance Analysis

- To understand the relationship between non-pharmacological treatments and antidepressant compliance among Korean patients with depression
- Secondary analysis
- Endpoints:
  - Medication compliance (adherence, discontinuation, and persistence) by the number of non-pharmacological treatments
- Population: patients who satisfy the acute treatment phase population
- Significance on continuous variables will be tested by ANOVA (if equal variance condition satisfied) or the Kruskal-Wallis H test (otherwise).
- Covariates: antidepressant class covariates such as SSRIs, SNRIs, and other ADs will be used as grouping variables.
- Missing values will be dropped from the analysis.
- The role of this analysis is to provide information on the relationship between non-pharmacological treatments and antidepressant compliance among Korean patients with depression.

7.2.5 Selection of Antidepressant by Specialty Analysis

- To understand the antidepressant choice among the Korean providers by specialty
- Secondary analysis
- Endpoints:
  - Proportion of 11 antidepressants by provider specialty
- Population: patients who satisfies the acute treatment phase population and with a prespecified comorbidity
- Significance on continuous variables will be tested by ANOVA (if equal variance condition satisfied) or Kruskal-Wallis H test (otherwise). Provider specialty and other patient characteristics will be used to fit antidepressant choice by multivariate logistic regression analysis of each study drug choice.
- Covariates: antidepressant class covariates such as SSRIs, SNRIs, other ADs will be used as grouping variables. Provider specialty and other patient characteristics will be used to fit antidepressant choice by multivariate logistic regression analysis of each study drug choice.
- Missing values will be dropped from the analysis.
- The role of this analysis is to provide information on antidepressant selection in the acute phase of drug therapy for Korean patients with depression and comorbidity by each comorbidity group.

8 REFERENCES

1. Ahn J et al., 2011. Economic evaluation and analysis of factors influencing antidepressant adherence. NECA research report.
2. Ahn J et al., 2012. Korean research status on mental disorders and sucides from depression. NECA research report.