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Comparative Effectiveness and Safety of Selective Serotonin Reuptake Inhibitors in Adult Attention-Deficit/Hyperactivity Disorder and comorbid depression : The ASSURE-Extend Study Protocol

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2 List of abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
MPH	Methylphenidate
SSRI	Selective Serotonin Reuptake Inhibitor

3 Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders[1]. Recently, more and more cases of ADHD persisting into adulthood or new-onset ADHD at adulthood suggest that a new approach is needed to manage ADHD. Unlike children, adults can have many deficits in higher-level executive functioning and emotional control and have many comorbid diseases due to diverse environmental exposures.[2, 3] Establishing treatment strategies according to comorbidities in ADHD patients is important, but the related evidence is weak. Most of Adult with ADHD also have many comorbidities such as anxiety disorder, depressive disorder, substance abuse, and autism spectrum disorder.[4-8]

Especially, ADHD is closely related to depressive disorder. There are previous studies on high comorbidity rate, biological linkage or causality and its clinical outcomes.[9-13] When establishing a treatment strategy for ADHD patients with depression, the clinical hurdles for the use of antidepressants are concerns about changes in the patients' condition (i.e., suicidality[14-17], etc.) and an increase in adverse effects.[16]

Although the first-line treatment for ADHD and depressive disorder is recommended in different guidelines,[18, 19] the evidence for effectiveness and safety evaluation of concomitant use of those drugs is sparse. Therefore, in this study, we aimed to evaluate the real-world evidence for comparative effectiveness and safety of the co-use of selective serotonin reuptake inhibitors (SSRIs), the fist recommended drug for depression, in ADHD patients (Adolescent ADHD and SSRI Use in Real-world Data – Extend to Adult: ASSURE Extend study). We also aimed to evaluate the outcome systemically through comparison between user vs non-user, between SSRI ingredient level as head-to-head study.

4 Amendments and Updates

0.1	16 February 2023	C Kim	Initial draft
0.9	25 February 2023	C Kim	Finalize draft
1.0	2 March 2023	C Kim	Release version 1

5 Rationale and Background

The most used drug for the treatment of ADHD is psychostimulant, which includes MPH, dextroamphetamine, and lisdexamfetamine, for about 90% of the total ADHD prescription.[20, 21] MPH effectively ameliorate the symptoms of ADHD and MPH has the best safety/coverage ratio than other ADHD drugs although adverse events including affective symptoms and weight loss.[16, 22]

The prevalence of depression is 16–26% in ADHD,[23] and these patients takes ADHD medications and antidepressants together according to the clinical guidelines.[18, 19] It has been reported that antidepressant resistance occurs a lot in patients with ADHD, therefore a higher intensity treatment should be prescribed.[24, 25] However, there are some concerns for co-medication with antidepressant for ADHD, which are due to adverse events of such as suicidal behaviors.[14-17] In addition, the possibility of increased adverse events due to the drug interactions between ADHD medications and antidepressants have been reported in previous studies. For example, as most of the available antidepressants results in an increase in the synaptic availability of serotonin or norepinephrine, MPH also increases monoamines postsynaptically, as well as increasing additive or synergistic effects and finally increasing adverse reactions like serotonin syndrome.[26-28] Also specific antidepressants induce gene regulation related in MPH, there are concerns about coadministration of them.[29, 30]

In general, guidelines for antidepressants applied to patients with ADHD are applied according to age, but there are few studies in which effectiveness and safety was evaluated according to the presence and type of antidepressants in ADHD patients considering the interaction with MPH. Hence, we aimed to conduct comparative effectiveness research to establish real-world evidence for the safety of MPH and SSRIs in patients with ADHD.

6 Study Objectives

6.1 Objectives

The overall goal of this study is conducting comparative effectiveness research to establish evidence for effectiveness and safety of concomitant antidepressant in adult patients with attention-deficit/hyperactivity disorder.

The primary objective is comparing the risk of safety outcomes which include neuropsychiatric events, cardiovascular events, and other events during concomitant use of methylphenidate and SSRIs among adult patients with ADHD.

The secondary objective is comparing the risk of effectiveness outcomes which include psychiatric hospitalisation during concomitant use of methylphenidate and SSRIs among adult patients with ADHD.

6.2 Primary Hypothesis

There are no differences in the risk of safety outcomes among subjects with or without SSRIs used to treat comorbid depression in adults with ADHD.

There are no differences in the risk of safety outcomes among subjects between SSRI ingredients (Escitalopram, fluoxetine, sertraline, and paroxetine) used to treat comorbid depression in adults with ADHD.

6.3 Secondary Hypothesis

There are no differences in the risk of effectiveness outcomes among subjects with or without SSRIs used to treat comorbid depression in adults with ADHD.

There are no differences in the risk of effectiveness outcomes among subjects between SSRI ingredients (Escitalopram, fluoxetine, sertraline, and paroxetine) used to treat comorbid depression in adults with ADHD.

7 Research methods

7.1 Study Design

7.1.1 Overview

This study will be a retrospective, observational cohort study. By 'retrospective' we mean the study will use data already collected at the start of the study. By 'observational' we mean no intervention will take place in the course of this study. By 'cohort study' we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to specific end date, and assessed for the occurrence of the outcomes of interest.

For primary analysis, the treatment cohort will be users of any SSRIs with MPH. The comparator cohort will be no users of SSRIs (MPH alone user). For both groups we restrict to people with first ADHD and depression diagnoses. For secondary analysis, the treatment cohort will be user of specific ingredient of SSRIs with MPH and the comparator cohort will be another ingredient with MPH (e.g., fluoxetine vs escitalopram, etc.).

The baseline characteristics will be investigated. For minimizing confounding bias between study cohorts, propensity score adjustment will be conducted. The primary outcome of is neuropsychiatric events. The Cox proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts.

7.2 Study population

7.2.1 Primary study population

The primary study population is designed for a comparative analysis of users of concomitant SSRI and MPH, and users of MPH alone. This population will include all subjects in the database who meet the following criteria: (Note: the index date refers to the day of the first prescription of the SSRI for the SSRI group, or the day of the first MPH prescription for the MPH alone group).

- Adolescents who prescribed MPH for ADHD and have depressive disorder
  - ≥18 years old adults
  - ADHD diagnosis for the first time in the patient's history on or before the index date
  - Depressive disorder diagnosis for the first time in the patient's history on or before the index date
  - At least 365 days of observation time prior to the index date
  - No other ADHD medications such as atomoxetine, clonidine, or bupropion.

7.2.2 Secondary study population

The secondary study population is intended for a comparative analysis of SSRI ingredients. This population will include all subjects in the database who meet the following criteria (Note: the index date refers to the days of the first prescription of the SSRIs)

- Adults who prescribed MPH for ADHD and prescribed any SSRI for depressive disorder.
  - ≥18 years old adults
  - ADHD diagnosis for the first time in the patient's history on or before the index date
  - Depressive disorder diagnosis for the first time in the patient's history on or before the index date
  - At least 365 days of observation time prior to the index date
  - No other ADHD medications such as atomoxetine, clonidine, and bupropion
  - No other antidepressant drugs except the target ingredient before the index date

7.2.3 Study population for sensitivity analyses

In South Korea, there are other treatment options for ADHD treatment such as atomoxetine, clonidine, besides MPH. A sensitivity analysis including the corresponding options will be conducted. The study population for the sensitivity analysis will be included who meet the following criteria: (note: the index date is the day of the first prescription of SSRI)

- Adults who prescribed ADHD medications and have depressive disorder
  - ≥18 years old adults
  - ADHD diagnosis for the first time in the patient's history on or before the index date

- Depressive disorder diagnosis for the first time in the patient's history on or before the index date
- At least 365 days of observation time prior to the index date

7.3 Exposures

7.3.1 Comparison summary

Type	Treatment (target)	Comparator (reference)
Main analysis	SSRI + MPH	MPH alone
	Fluoxetine + MPH	Escitalopram + MPH
	Sertraline + MPH	Escitalopram + MPH
	Paroxetine + MPH	Escitalopram + MPH
	Sertraline + MPH	Fluoxetine + MPH
	Paroxetine + MPH	Fluoxetine + MPH
	Sertraline + MPH	Paroxetine + MPH
Sensitivity analysis 1. Expand MPH to any of ADHD medications	SSRI + ADHD medication	ADHD medication alone
	Fluoxetine + ADHD medication	Escitalopram + ADHD medication
	Sertraline + ADHD medication	Escitalopram + ADHD medication
	Paroxetine + ADHD medication	Escitalopram + ADHD medication
	Sertraline + ADHD medication	Fluoxetine + ADHD medication
	Paroxetine + ADHD medication	Fluoxetine + ADHD medication
	Sertraline + ADHD medication	Paroxetine + ADHD medication
Sensitivity analysis 2. Allow 30 days gap between the two drugs	SSRI + MPH (within gap)	MPH alone
	Fluoxetine + MPH (within gap)	Escitalopram + MPH (within gap)
	Sertraline + MPH (within gap)	Escitalopram + MPH (within gap)
	Paroxetine + MPH (within gap)	Escitalopram + MPH (within gap))
	Sertraline + MPH (within gap)	Fluoxetine + MPH (within gap)
	Paroxetine + MPH (within gap)	Fluoxetine + MPH (within gap)
	Sertraline + MPH (within gap)	Paroxetine + MPH (within gap)
	SSRI + ADHD med (within gap)	ADHD medication alone
	Fluoxetine + ADHD med (within gap)	Escitalopram + ADHD med (within gap)
	Sertraline + ADHD med (within gap)	Escitalopram + ADHD med (within gap)
	Paroxetine + ADHD med (within gap)	Escitalopram + ADHD med (within gap)
	Sertraline + ADHD med (within gap)	Fluoxetine + ADHD med (within gap)
	Paroxetine + ADHD med (within gap)	Fluoxetine + ADHD med (within gap)
	Sertraline + ADHD med (within gap)	Paroxetine + ADHD med (within gap)
Sensitivity analysis 3. Expand SSRI to antidepressants	Antidepressant + MPH	MPH alone
	Antidepressant + ADHD med	ADHD medication alone
	Antidepressant + MPH (within gap)	MPH alone
	Antidepressant + ADHD med (within gap)	ADHD medication alone

7.3.2 Treatment 1: new SSRI user with MPH

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any SSRI prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the 1 day before the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to SSRI and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration.

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except SSRIs

7.3.3 Treatment 2: new fluoxetine user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort.

when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to 1 day before the index date.

4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration.

The patient exits the cohort when encountering any of the following events:

- Other antidepressant without fluoxetine

7.3.4 Treatment 3: new sertraline user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any sertraline prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to 1 day before the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to sertraline and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressant without sertraline

7.3.5 Treatment 4: new paroxetine user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort.

when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**
  1. Patients with ADHD
     - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date.
  2. Patients with depression
     - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
  3. Patients without antidepressants prior to the index date
     - Entry events having no prescription of the antidepressant, starting any time prior to 1 day before the index date.
  4. Patients without other ADHD medications
     - Entry events having no prescription of other ADHD medications.

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to paroxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration.

  The patient exits the cohort when encountering any of the following events:
  - Other antidepressant without paroxetine

7.3.6 Sensitivity treatment 1: new SSRI user with ADHD medication

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort when observing any of the following:
  - Any SSRI prescription for the first time in the person's history (index date)
  - with age greater or equal to 18
  - having at least 1 prescription of ADHD medication at the date of index date

  Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**
  1. Patients with ADHD
     - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
  2. Patients with depression
     - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
  3. Patients without antidepressants prior to the index date
     - Entry events having no prescription of the antidepressant, starting any time prior to 1 day before the index date.

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to SSRI and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:

  - Other antidepressants except SSRIs

7.3.7 Sensitivity treatment 2: new fluoxetine user with ADHD medication

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

  - Any fluoxetine prescription for the first time in the person's history (index date)
  - with age greater or equal to 18
  - having at least 1 prescription of ADHD medication at the date of index date

  Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to fluoxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:

  - Other antidepressant except fluoxetine

7.3.8 Sensitivity treatment 2: new sertraline user with ADHD medication

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

  - Any sertraline prescription for the first time in the person's history (index date)
  - with age greater or equal to 18
  - having at least 1 prescription of ADHD medication at the date of index date

  Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**
  1. Patients with ADHD
     - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
  2. Patients with depression
     - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
  3. Patients without antidepressants prior to the index date
     - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to sertraline and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:
  - Other antidepressants except sertraline

7.3.9 Sensitivity treatment 3: new paroxetine user with ADHD medication

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort

  when observing any of the following:
  - Any paroxetine prescription for the first time in the person's history (index date)
  - with age greater or equal to 18
  - having at least 1 prescription of ADHD medication at the date of index date

  Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**
  1. Patients with ADHD
     - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
  2. Patients with depression
     - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
  3. Patients without antidepressants prior to the index date
     - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to paroxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.3.10 Sensitivity treatment 5: new SSRI user with MPH (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any SSRI prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to SSRI and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except SSRIs

7.3.11 Sensitivity treatment 6: new fluoxetine user with MPH (allowing 30 days gap between two treatment)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.12 Sensitivity treatment 7: new sertraline user with MPH (allowing 30 days gap between two treatment)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any sertraline prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to sertraline and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:

  - Other antidepressants except sertraline

7.3.13 Sensitivity treatment 8: new paroxetine user with MPH (allowing 30 days gap between

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort

  when observing any of the following:

  - Any paroxetine prescription for the first time in the person's history (index date)
  - with age greater or equal to 18
  - having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

  Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

  The cohort end date will be based on a continuous exposure to paroxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

  The patient exits the cohort when encountering any of the following events:

  - Other antidepressants except paroxetine

7.3.14 Sensitivity treatment 9: new SSRI user with ADHD medication (allowing 30 days gap between treatments)

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any SSRI prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to SSRI and ADHD medications allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except SSRIs

7.3.15 Sensitivity treatment 10: new fluoxetine user with ADHD medication (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date

- Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.16 Sensitivity treatment 11: new sertraline user with ADHD medication (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any sertraline prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to sertraline and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except sertraline

7.3.17 Sensitivity treatment 12: new paroxetine user with ADHD medication (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to paroxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.3.18 Sensitivity treatment 13: new antidepressant user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any antidepressant prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

4. Patients without other ADHD medications
    - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to antidepressant and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- No censoring in this cohort

7.3.19 Sensitivity treatment 14: new antidepressant user with ADHD medication

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any antidepressant prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
    - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
    - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
    - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to antidepressant and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- No censoring in this cohort

7.3.20 Sensitivity treatment 15: new antidepressant user with MPH (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any antidepressant prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to antidepressant and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- No censoring in this cohort

7.3.21 Sensitivity treatment 16: new antidepressant user with ADHD medication (allowing 30 days gap between treatments)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any antidepressant prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.

3. Patients without antidepressants prior to the index date
    - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to antidepressant and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- No censoring in this cohort

7.3.22 Comparator 1: new MPH alone user

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any MPH prescription for the first time in the person's history (index date)
- with age greater or equal to 18

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
    - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
    - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
    - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
    - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration.

The patient exits the cohort when encountering any of the following events:

- Any antidepressant exposure

7.3.23 Comparator 2: new escitalopram user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any escitalopram prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to escitalopram and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except escitalopram

7.3.24 Comparator 2: new fluoxetine user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

4. Patients without other ADHD medications
    - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.25 Comparator 3: new paroxetine user with MPH

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
    - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
    - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
    - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
    - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to paroxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.3.26 Sensitivity comparator 1: new ADHD medication alone user

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any ADHD medication prescription for the first time in the person's history (index date)
- with age greater or equal to 18

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- No censoring in this cohort

7.3.27 Sensitivity comparator 2: new escitalopram user with ADHD medication

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any escitalopram prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to escitalopram and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except escitalopram

7.3.28 Sensitivity comparator 3: new fluoxetine user with ADHD medication

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.29 Sensitivity comparator 4: new paroxetine user with ADHD medication

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication at the date of index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to paroxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.3.30 Sensitivity comparator 5: new escitalopram user with MPH (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any escitalopram prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to escitalopram and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except escitalopram

7.3.31 Sensitivity comparator 6: new fluoxetine user with MPH (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.32 Sensitivity comparator 7: new paroxetine user with MPH (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)

- with age greater or equal to 18
- having at least 1 prescription of MPH starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.
4. Patients without other ADHD medications
   - Entry events having no prescription of other ADHD medications

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to paroxetine and MPH allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.3.33 Sensitivity comparator 8: new escitalopram user with ADHD medication (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort
when observing any of the following:

- Any escitalopram prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date

- Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to escitalopram and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except escitalopram

7.3.34 Sensitivity comparator 9: new fluoxetine user with ADHD medication (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any fluoxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to fluoxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except fluoxetine

7.3.35 Sensitivity comparator 10: new paroxetine user with ADHD medication (allowing 30 days gap between two medications)

- **Cohort Entry Events**

People with continuous observation of 365 days before event may enter the cohort

when observing any of the following:

- Any paroxetine prescription for the first time in the person's history (index date)
- with age greater or equal to 18
- having at least 1 prescription of ADHD medication starting between 30 days before and 0 days after the index date

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patients with ADHD
   - Entry events having at least 1 diagnosis of ADHD for the first time in the person's history, starting anytime on or before the index date
2. Patients with depression
   - Entry events having at least 1 diagnosis of depression for the first time in the person's history, starting anytime on or before the index date.
3. Patients without antidepressants prior to the index date
   - Entry events having no prescription of the antidepressant, starting any time prior to the index date.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to paroxetine and ADHD medication allowing 30 days between prescriptions, adding 30 days after exposure ends using the days supply and exposure end date for exposure duration

The patient exits the cohort when encountering any of the following events:

- Other antidepressants except paroxetine

7.4 Outcomes

7.4.1 Primary Outcomes

- **Neuropsychiatric events**

Primary outcomes are neuropsychiatric events that include as below. All conditions could be detected by diagnostic codes.

Abnormal gait	ADHD hospitalisation	Agitation	Anorexia
Anxiety	Appetite loss	Delirium	Dizziness
Dystonia	Eating disorder	Epilepsy	Extrapyramidal symptoms
Gambling	Insomnia	Mania	Parkinsonism (drug-induced)
Schizophrenia related hospitalisation	Seizure	Sleep disorder	Substance abuse
Suicidal event	Tremor	Psychosis	

7.4.2 Secondary Outcomes

- **Secondary outcomes**

  Secondary outcomes are other safety events. Those are including each individual event as below. All conditions could be detected by diagnostic codes.

Abdominal pain	Accident	Acute respiratory failure	Anemia
Arrhythmia	Asthma outcome	Atrial fibrillation	Bleeding
Cardiomyopathy	Cerebrovascular disease	Chronic kidney disease	Diarrhea
Essential hypertension	Fatigue	Fever	Gynecomastia
Headache	Heart failure	Hyperlipidemia	Hyperprolactinemia
Hypo/hyperthyroidism	Hyponatremia	Hypotension	Ischemic heart disease
Liver disease	Myocardial infarction	Myocarditis	Nasopharyngitis
Nausea vomiting	Obesity	Osteoporosis	Thrombocytopenia
Traumatic injury	Type 2 diabetes mellitus	Upper respiratory tract infection or pneumonia	

7.5 Covariates

7.5.1 Propensity score covariates

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the treatment and comparator cohorts in baseline covariates[31]. The propensity score is the probability of a patient being classified in the treatment cohort vs. the comparator cohort, given a set of observed covariates. All covariates that occur in fewer than 0.1% of the persons between the treatment and comparator cohorts combined will be excluded prior to model fitting for computational efficiency. Large-scale propensity score matching methods will be applied[32].

The types of baseline covariates used to fit the propensity score model will be:

- Demographics
  - Sex
  - Age group (5-year bands)
  - Index year
- Aggregated conditions by SNOMED
  - In prior 365d
- Aggregated drugs codes by ATC/Ingredient levels
  - In prior 365d
  - Overlapping index date
- Charlson comorbidity index

Specific covariates which composed of exposures are excluded from the propensity score model.

7.5.2 Other variables

None

8 Data Sources

The analyses will be performed using the national ADHD dataset from the Health Insurance Review and Assessment Service of South Korea. This claim database includes data on Korean patients with a diagnosis of ADHD or a prescription for an ADHD drug from 2016 to February 2021. Since Korea's health insurance system is a single national insurance system, this database includes all citizens and includes information on diagnosis, prescription, examination, surgery, and treatment listed in the national reimbursement list.

The database has been transformed into the OMOP Common Data Model, version 5.3.1. The complete specification for OMOP Common Data Model, version 5.3.1 is available at: https://github.com/OHDSI/CommonDataModel.

9 Data Analysis Plan

9.1 Epidemiological consideration

9.1.1 Calculation of time-at-risk

- Primary analyses: As-treated risk window
  To avoid time-dependent bias, as-treated risk window is considered as the primary analysis outcome windows, of which time-at-risk starts on initiation of concomitant medications (antidepressant or ADHD medications) and ends when the treatment ends.
- Secondary analyses: As-treated risk window
  As-treated risk window is considered as the primary analysis outcome windows, of which time-at-risk starts on initiation of antidepressant treatment and ends when the treatment ends.
- Sensitivity analyses: Intention-to-treat risk window
  Risk window starts from 1 day to last observation after the index date.

9.1.2 Reducing bias

- Preventing bias from left censoring of data
  In order to prevent bias in the first visit and first prescription due to left censoring, the patients diagnosed and prescribed for the first year of the data period will not be used.
- Preventing bias from time-related settings
  In order to reduce time-related bias, sensitivity analysis will be additionally performed in addition to the main analysis. Sensitivity analyses according to time-at-risk setting (As-treated or

Intention-to-treat) and different gap durations between the concomitant drugs will be performed (e.g., between MPH and SSRI: 30 days, 0 days).

- Preventing bias from reverse causality
  In order to avoid reverse causality due to outcome variables, especially related to symptoms, additional sensitivity analysis will be conducted in which symptomatic patients are removed and compared.

9.2 Model specification

In this study, we compare the treatment cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model. A pre-specified $P<0.05$ was considered statistically significant for all two-sided tests.

The time-to-event of outcome among patients in the treatment and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window (the cohort start date), until the earliest event among 1) the first occurrence of the outcome, 2) the end of the time-at-risk window, and 3) the end of the observation period that spans the time-at-risk start.

9.2.1 Statistical model for analyses

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation using 10 replications per fold, a starting variance of 0.01 and a tolerance of 2e-7. Covariates to be used in the propensity score model are listed in section 7.5.1.

- Primary analysis: After estimating the PS, stratification (PS stratification) will be performed. The number of strata will be 5. The outcome model will be fitted using an unconditional Cox regression, with only the treatment variable as predictor.

- Sensitivity analysis: After estimating the PS, matching (1:1 and 1: maximum [1: n] matching) will be performed. A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used. The outcome model will be fitted using an unconditioned Cox regression, with only the treatment variable as predictor.

9.3 Analyses to perform

The following analyses will be performed:

- 7 main comparisons
- 25 sensitivity comparisons
- 60 outcomes

- 2 types of outcomes (prevalent case and incident case)
- 2 time-at-risk definitions: As-treated risk window, Intention-to-treat risk window.
- 3 adjustments: PS stratification, 1:1 PS matching, 1: n PS matching

The total number of analyses is 23,040 (32 comparisons x 120 outcomes x 2 TAR x 3 PS methods).

9.4 Output

Covariate balance will be summarized in tabular form by showing the mean value (percentage for categorical) for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported. A plot showing the preference score distributions for both cohorts after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score matching against the standardized mean difference for each covariate after propensity score matching.

An attrition diagram (study flowchart) will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

9.5 Quality control

We will evaluate the PS by

- Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
- Inspection of the PS distribution.
- Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching. Standardized differences greater than 0.1 will be reported and investigated.

We will investigate the outcome model by

- Inspection of the fitted outcome model for large coefficients and predictors that we cannot explain (post-hoc).

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

9.6 Strengths and Limitations of the Research Methods

Strength

- Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
- PS matching and full outcome models allow balancing on a large number of baseline potential confounders.

Limitations

- Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or mis-specified confounders.

10 Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

11 Plans for Disseminating and Communicating Study Results

The study protocol will be submitted for publication to an online repository before initiation of the study. Analytic codes will be posted on the online repository after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

12 References

1. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. The Lancet Psychiatry. 2018;5(2):175-86.
2. Adler LA, Faraone SV, Spencer TJ, Berglund P, Alperin S, Kessler RC. The structure of adult ADHD. International Journal of Methods in Psychiatric Research. 2017;26(1):e1555.
3. Fredriksen M, Dahl AA, Martinsen EW, Klungsoyr O, Faraone SV, Peleikis DE. Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD. ADHD Attention Deficit and Hyperactivity Disorders. 2014;6(2):87-99.
4. Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatry. 2017;17(1):302.
5. Tsang TW, Kohn MR, Efron D, Clarke SD, Clark CR, Lamb C, et al. Anxiety in Young People With ADHD: Clinical and Self-Report Outcomes. Journal of Attention Disorders. 2012;19(1):18-26.

6. Eyre O, Riglin L, Leibenluft E, Stringaris A, Collishaw S, Thapar A. Irritability in ADHD: association with later depression symptoms. European Child & Adolescent Psychiatry. 2019;28(10):1375-84.
7. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, Smit F, Crunelle CL, Swets M, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. Drug Alcohol Depend. 2012;122(1-2):11-9.
8. Antshel KM, Zhang-James Y, Faraone SV. The comorbidity of ADHD and autism spectrum disorder. Expert Review of Neurotherapeutics. 2013;13(10):1117-28.
9. Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, et al. New Insights Into the Comorbidity Between ADHD and Major Depression in Adolescent and Young Adult Females. Journal of the American Academy of Child & Adolescent Psychiatry. 2008;47(4):426-34.
10. Posner J, Siciliano F, Wang Z, Liu J, Sonuga-Barke E, Greenhill L. A multimodal MRI study of the hippocampus in medication-naive children with ADHD: What connects ADHD and depression? Psychiatry Research: Neuroimaging. 2014;224(2):112-8.
11. Riglin L, Leppert B, Dardani C, Thapar AK, Rice F, O'Donovan MC, et al. ADHD and depression: investigating a causal explanation. Psychological Medicine. 2021;51(11):1890-7.
12. Fenesy MC, Lee SS. Childhood ADHD and Executive Functioning: Unique Predictions of Early Adolescent Depression. Research on Child and Adolescent Psychopathology. 2021.
13. Blackman GL, Ostrander R, Herman KC. Children with ADHD and Depression: A Multisource, Multimethod Assessment of Clinical, Social, and Academic Functioning. Journal of Attention Disorders. 2005;8(4):195-207.
14. Jick H, Kaye JA, Jick SS. Antidepressants and the Risk of Suicidal Behaviors. JAMA. 2004;292(3):338-43.
15. Levy T, Kronenberg S, Crosbie J, Schachar RJ. Attention-deficit/hyperactivity disorder (ADHD) symptoms and suicidality in children: The mediating role of depression, irritability and anxiety symptoms. Journal of Affective Disorders. 2020;265:200-6.
16. Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020;19(2):214-32.
17. Sun S, Kuja-Halkola R, Faraone SV, D'Onofrio BM, Dalsgaard S, Chang Z, et al. Association of Psychiatric Comorbidity With the Risk of Premature Death Among Children and Adults With Attention-Deficit/Hyperactivity Disorder. JAMA Psychiatry. 2019;76(11):1141-9.
18. Wolraich ML, Hagan JF, Jr, Allan C, Chan E, Davison D, Earls M, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4).
19. Cheung AH, Zuckerbrot RA, Jensen PS, Laraque D, Stein REK, GROUP G-PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and Ongoing Management. Pediatrics. 2018;141(3).
20. Raman SR, Man KKC, Bahmanyar S, Berard A, Bilder S, Boukhris T, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. The Lancet Psychiatry. 2018;5(10):824-35.
21. Bachmann CJ, Wijlaars LP, Kalverdijk LJ, Burcu M, Glaeske G, Schuiling-Veninga CCM, et al. Trends in ADHD medication use in children and adolescents in five western countries, 2005–2012. European Neuropsychopharmacology. 2017;27(5):484-93.
22. Schachar RJ, Tannock R, Cunningham C, Corkum PV. Behavioral, Situational, and Temporal Effects of Treatment of ADHD With Methylphenidate. Journal of the American Academy of Child & Adolescent Psychiatry. 1997;36(6):754-63.

23. Sonnby K, Åslund C, Leppert J, Nilsson KW. Symptoms of ADHD and depression in a large adolescent population: Co-occurring symptoms and associations to experiences of sexual abuse. Nordic Journal of Psychiatry. 2011;65(5):315-22.
24. Sakai C, Tsuji T, Nakai T, Namba Y, Mishima H, Fujiwara M, et al. Change in Antidepressant Use After Initiation of ADHD Medication in Japanese Adults with Comorbid Depression: A Real-World Database Analysis. Neuropsychiatr Dis Treat. 2021;17:3097-108.
25. Chen M-H, Pan T-L, Hsu J-W, Huang K-L, Su T-P, Li C-T, et al. Attention-deficit hyperactivity disorder comorbidity and antidepressant resistance among patients with major depression: A nationwide longitudinal study. European Neuropsychopharmacology. 2016;26(11):1760-7.
26. Nevels RM, Weiss NH, Killebrew AE, Gontkovsky ST, editors. Methylphenidate and Its Underrecognized , Under-explained , and Serious Drug Interactions : A Review of the Literature with Heightened Concerns2013.
27. Ishii M, Tatsuzawa Y, Yoshino A, Nomura S. Serotonin syndrome induced by augmentation of SSRI with methylphenidate. Psychiatry and Clinical Neurosciences. 2008;62(2):246-.
28. Methylphenidate/sertraline interaction. Reactions Weekly. 2008;1200(1):24-.
29. Steiner H, Van Waes V, Marinelli M. Fluoxetine Potentiates Methylphenidate-Induced Gene Regulation in Addiction-Related Brain Regions: Concerns for Use of Cognitive Enhancers? Biological Psychiatry. 2010;67(6):592-4.
30. Van Waes V, Ehrlich S, Beverley JA, Steiner H. Fluoxetine potentiation of methylphenidate-induced gene regulation in striatal output pathways: Potential role for 5-HT1B receptor. Neuropharmacology. 2015;89:77-86.
31. ROSENBAUM PR, RUBIN DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
32. Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. International journal of epidemiology. 2018;47(6):2005-14.

13 Appendix: Code Set for Definitions

All codes are available in ATHENA (athena.ohdsi.org)

1. Attention-Deficit/Hyperactivity Disorder

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
438409	Attention deficit hyperactivity disorder	Condition	SNOMED	NO	YES	NO
4047120	Disorders of attention and motor control	Condition	SNOMED	NO	YES	NO

2. Methylphenidate

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
705944	methylphenidate	Drug	RxNorm	NO	YES	NO

3. Anti-ADHD drugs

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
705944	methylphenidate	Drug	RxNorm	NO	YES	NO
21604757	methylphenidate, oral	Drug	ATC	NO	YES	NO
742185	Atomoxetine	Drug	RxNorm	NO	YES	NO
21604762	Atomoxetine; oral	Drug	ATC	NO	YES	NO
21600398	Clonidine; systemic	Drug	ATC	NO	YES	NO

4. Other Anti-ADHD drugs for methylphenidate

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
742185	Atomoxetine	Drug	RxNorm	NO	YES	NO
21604762	Atomoxetine; oral	Drug	ATC	NO	YES	NO
21600398	Clonidine; systemic	Drug	ATC	NO	YES	NO

5. Depression

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
440383	Depressive disorder	Condition	SNOMED	NO	YES	NO
442306	Adjustment disorder with depressed mood	Condition	SNOMED	NO	YES	NO
4175329	Organic mood disorder of depressed type	Condition	SNOMED	NO	YES	NO
436665	Bipolar disorder	Condition	SNOMED	YES	YES	NO

6. Antidepressant

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO

21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO
738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO
21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

7. Selective serotonin reuptake inhibitor

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO

8. Escitalopram

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO

9. Fluoxetine

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO

10. Sertraline

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO

11. Paroxetine

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO

12. Other Antidepressant except SSRIs

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO
21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO
738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO
21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

13. Other Antidepressant except escitalopram

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO
21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO

738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO
21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

14. Other Antidepressant except fluoxetine

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO
21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO
738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO
21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

15. Other Antidepressant except sertraline

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO
21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO
738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO
21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
722031	paroxetine	Drug	RxNorm	NO	YES	NO
21604713	paroxetine; oral	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

16. Other Antidepressant except paroxetine

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
710062	amitriptyline	Drug	RxNorm	NO	YES	NO
21604696	amitriptyline; systemic	Drug	ATC	NO	YES	NO
750982	bupropion	Drug	RxNorm	NO	YES	NO
21604741	bupropion; oral	Drug	ATC	NO	YES	NO
797617	citalopram	Drug	RxNorm	NO	YES	NO
21604712	citalopram; systemic	Drug	ATC	NO	YES	NO
717607	desvenlafaxine	Drug	RxNorm	NO	YES	NO
21604751	desvenlafaxine; oral	Drug	ATC	NO	YES	NO
738156	doxepin	Drug	RxNorm	NO	YES	NO
21604699	doxepin; systemic	Drug	ATC	NO	YES	NO
715259	duloxetine	Drug	RxNorm	NO	YES	NO
21604749	duloxetine; oral	Drug	ATC	NO	YES	NO
715939	escitalopram	Drug	RxNorm	NO	YES	NO
21604718	escitalopram; oral	Drug	ATC	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO
21604711	fluoxetine; oral	Drug	ATC	NO	YES	NO
778268	imipramine	Drug	RxNorm	NO	YES	NO

21604689	imipramine; systemic	Drug	ATC	NO	YES	NO
725131	mirtazapine	Drug	RxNorm	NO	YES	NO
21604740	mirtazapine; oral	Drug	ATC	NO	YES	NO
721724	nortriptyline	Drug	RxNorm	NO	YES	NO
21604697	nortriptyline; systemic	Drug	ATC	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
21604714	sertraline; oral	Drug	ATC	NO	YES	NO
21604693	trimipramine; systemic	Drug	ATC	NO	YES	NO
743670	venlafaxine	Drug	RxNorm	NO	YES	NO
21604745	venlafaxine; oral	Drug	ATC	NO	YES	NO

17. Abdominal pain

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
200219	Abdominal pain	Condition	SNOMED	NO	YES	NO

18. Abnormal gait

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
437643	Abnormal gait	Observation	SNOMED	NO	YES	NO

19. Accident

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
432532	Accidental event	Observation	SNOMED	NO	YES	NO

20. Acute respiratory failure

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
319049	Acute respiratory failure	Condition	SNOMED	NO	YES	NO

21. ADHD hospitalisation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4047120	Disorder of attention and motor control	Condition	SNOMED	NO	YES	NO
438409	Attention deficit hyperactivity disorder	Condition	SNOMED	NO	YES	NO

22. Agitation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4168212	Restlessness and agitation	Condition	SNOMED	NO	YES	NO

23. Anemia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439777	Anemia	Condition	SNOMED	NO	YES	NO

24. Anorexia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
436675	Anorexia nervosa	Condition	SNOMED	NO	YES	NO

25. Anxiety

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
442077	Anxiety disorder	Condition	SNOMED	NO	YES	NO
37109206	Anxiety disorder caused by drug	Condition	SNOMED	NO	YES	NO
4199892	Anxiety disorder due to a general medical condition	Condition	SNOMED	NO	YES	NO
434613	Generalized anxiety disorder	Condition	SNOMED	NO	YES	NO
4338031	Mixed anxiety and depressive disorder	Condition	SNOMED	NO	YES	NO
381537	Organic anxiety disorder	Condition	SNOMED	NO	YES	NO
436074	Panic disorder	Condition	SNOMED	NO	YES	NO
4304010	Phobic disorder	Condition	SNOMED	NO	YES	NO

26. Appetite loss

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
442165	Loss of appetite	Observation	SNOMED	NO	YES	NO

27. Arrhythmia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4068155	Atrial arrhythmia	Condition	SNOMED	NO	YES	NO
44784217	Cardiac arrhythmia	Condition	SNOMED	NO	YES	NO
4111552	Re-entry ventricular arrhythmia	Condition	SNOMED	NO	YES	NO
4248028	Supraventricular arrhythmia	Condition	SNOMED	NO	YES	NO
315643	Tachyarrhythmia	Condition	SNOMED	NO	YES	NO
444070	Tachycardia	Condition	SNOMED	NO	YES	NO
4185572	Ventricular arrhythmia	Condition	SNOMED	NO	YES	NO

28. Asthma

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped

317009	Asthma	Condition	SNOMED	NO	YES	NO

29. Atrial fibrillation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4141360	Chronic atrial fibrillation	Condition	SNOMED	NO	NO	NO
4154290	Paroxysmal atrial fibrillation	Condition	SNOMED	NO	NO	NO
4232697	Persistent atrial fibrillation	Condition	SNOMED	NO	NO	NO
36714994	Typical atrial flutter	Condition	SNOMED	NO	NO	NO

30. Bleeding

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
437312	Bleeding	Condition	SNOMED	NO	YES	NO

31. Cardiomyopathy

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
321319	Cardiomyopathy	Condition	SNOMED	NO	NO	NO
320746	Cardiomyopathy associated with another disorder	Condition	SNOMED	NO	NO	NO
4163710	Dilated cardiomyopathy	Condition	SNOMED	NO	NO	NO
318773	Dilated cardiomyopathy secondary to alcohol	Condition	SNOMED	NO	NO	NO
4124693	Hypertrophic cardiomyopathy	Condition	SNOMED	NO	NO	NO
316428	Hypertrophic obstructive cardiomyopathy	Condition	SNOMED	NO	NO	NO
321320	Myocardial degeneration	Condition	SNOMED	NO	NO	NO
4190773	Restrictive cardiomyopathy	Condition	SNOMED	NO	NO	NO

32. Cerebrovascular disease

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
381591	Cerebrovascular disease	Condition	SNOMED	NO	YES	NO

33. Chronic kidney disease

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
46271022	Chronic kidney disease	Condition	SNOMED	NO	YES	NO

34. Constipation

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
75860	Constipation	Condition	SNOMED	NO	YES	NO

35. Coronary heart disease

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
435081	Abnormal findings diagnostic imaging heart+coronary circulat	Condition	SNOMED	NO	NO	NO
43020480	Acquired coronary artery fistula	Condition	SNOMED	NO	NO	NO
321109	Congenital anomaly of coronary artery	Condition	SNOMED	NO	NO	NO
317576	Coronary arteriosclerosis	Condition	SNOMED	NO	NO	NO
42872402	Coronary arteriosclerosis in native artery	Condition	SNOMED	NO	NO	NO
42537730	Coronary artery graft present	Condition	SNOMED	NO	NO	NO
4127089	Coronary artery spasm	Condition	SNOMED	NO	NO	NO
4108215	Coronary thrombosis not resulting in myocardial infarction	Condition	SNOMED	NO	NO	NO

36. Delirium

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
373995	Delirium	Condition	SNOMED	NO	YES	NO

37. Diarrhea

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
196523	Diarrhea	Condition	SNOMED	NO	YES	NO

38. Dizziness

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4223938	Dizziness	Condition	SNOMED	NO	YES	NO

39. Dystonia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
375800	Dystonia	Condition	SNOMED	NO	YES	NO

40. Eating disorder

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439002	Eating disorder	Condition	SNOMED	NO	YES	NO

41. Epilepsy

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
380378	Epilepsy	Condition	SNOMED	NO	YES	NO

42. Extrapyramidal symptoms

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
443782	Tremor	Condition	SNOMED	NO	YES	NO
4171569	Parkinsonism due to drug	Condition	SNOMED	NO	YES	NO
374013	Secondary parkinsonism	Condition	SNOMED	NO	YES	NO
375800	Dystonia	Condition	SNOMED	NO	YES	NO

43. Essential hypertension

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
320128	Essential hypertension	Condition	SNOMED	NO	YES	NO

44. Fatigue

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
439926	Malaise and fatigue	Condition	SNOMED	NO	YES	NO

45. Fever

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
437663	Fever	Condition	SNOMED	NO	YES	NO

46. Gambling

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4023166	Gambling	Observation	SNOMED	NO	YES	NO
436959	Compulsive gambling	Condition	SNOMED	NO	YES	NO

47. Gynecomastia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4168447	Gynecomastia	Condition	SNOMED	NO	YES	NO
79884	Galactorrhea not associated with childbirth	Condition	SNOMED	NO	YES	NO

48. Headache

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
378253	Headache	Condition	SNOMED	NO	YES	NO

49. Heart failure

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
316139	Heart failure	Condition	SNOMED	NO	YES	NO

50. Hyperlipidemia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
437312	Bleeding	Condition	SNOMED	NO	YES	NO

51. Hyperprolactinemia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4030186	Hyperprolactinemia	Condition	SNOMED	NO	YES	NO

52. hypo and hyperthyroidism

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
140673	Hypothyroidism	Condition	SNOMED	NO	YES	NO
4142479	Hyperthyroidism	Condition	SNOMED	NO	YES	NO

53. Hyponatremia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
435515	Hypo-osmolality and or hyponatremia	Condition	SNOMED	NO	YES	NO

54. Hypotension

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
319041	Orthostatic hypotension	Condition	SNOMED	NO	YES	NO
4112334	Idiopathic hypotension	Condition	SNOMED	NO	YES	NO
4120275	Drug-induced hypotension	Condition	SNOMED	NO	YES	NO

55. Insomnia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4102985	Nonorganic insomnia	Condition	SNOMED	NO	YES	NO

56. Ischemic heart disease

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4185932	Ischemic heart disease	Condition	SNOMED	NO	YES	NO

57. Liver disease

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4212540	Chronic liver disease	Condition	SNOMED	NO	YES	NO
4243475	Acute hepatitis	Condition	SNOMED	NO	YES	NO

58. Mania

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
35610112	Mania with psychotic features	Condition	SNOMED	NO	YES	NO
4333677	Mania	Condition	SNOMED	NO	YES	NO

59. Myocardial infarction

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	Condition	SNOMED	NO	YES	NO

60. Myocarditis

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
314383	Myocarditis	Condition	SNOMED	NO	YES	NO

61. Nasopharyngitis

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4197268	Nasopharyngitis	Condition	SNOMED	NO	YES	NO

62. Nausea and vomiting

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
31967	Nausea	Condition	SNOMED	NO	YES	NO
441408	Vomiting	Condition	SNOMED	NO	YES	NO

63. Obesity

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
433736	Obesity	Condition	SNOMED	NO	YES	NO

64. Osteoporosis

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
80502	Osteoporosis	Condition	SNOMED	NO	YES	NO

65. Parkinsonism (Drug induced)

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
374013	Secondary parkinsonism	Condition	SNOMED	NO	YES	NO
4171569	Parkinsonism due to drug	Condition	SNOMED	NO	YES	NO

66. Psychosis

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
436073	Psychotic disorder	Condition	SNOMED	NO	YES	NO

67. Schizophrenia related hospitalisation

Commented [김청1]: Schizophrenia 자체는 outcome 에 없음

Concept ID	Concept Name	Domain	Vocabulary	Exclude	Descendants	Mapped
4335169	Acute transient psychotic disorder	Condition	SNOMED	NO	YES	NO
432590	Delusional disorder	Condition	SNOMED	NO	YES	NO
4286201	Schizoaffective disorder	Condition	SNOMED	NO	YES	NO
435783	Schizophrenia	Condition	SNOMED	NO	YES	NO
434010	Schizotypal personality disorder	Condition	SNOMED	NO	YES	NO
35207135	Shared psychotic disorder	Condition	ICD10CM	NO	YES	NO
37117049	Substance induced psychotic disorder	Condition	SNOMED	NO	YES	NO

68. Seizure

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
377091	Seizure	Condition	SNOMED	NO	YES	NO

69. Sleep disorder

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
435524	Sleep disorder	Condition	SNOMED	NO	YES	NO

70. Substance abuse

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4279309	Substance abuse	Condition	SNOMED	NO	YES	NO

71. Suicidal event

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4219484	Suicide attempt	Observation	SNOMED	NO	YES	NO
4092411	Self-injurious behavior	Condition	SNOMED	NO	YES	NO
4304690	Intentionally harming self	Observation	SNOMED	NO	YES	NO
439235	Self inflicted injury	Condition	SNOMED	NO	YES	NO
435446	Late effect of self inflicted injury	Condition	SNOMED	NO	YES	NO
4152376	Intentional self poisoning	Condition	SNOMED	NO	YES	NO
4152408	H/O: deliberate self harm	Condition	SNOMED	NO	YES	NO
4075235	Drowning self	Condition	SNOMED	NO	YES	NO

72. Thrombocytopenia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
40321716	Secondary thrombocytopenia	Condition	SNOMED	NO	YES	NO
441264	Primary thrombocytopenia	Condition	SNOMED	NO	YES	NO

73. Traumatic injury

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
440921	Traumatic injury	Condition	SNOMED	NO	YES	NO

74. Tremor

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
443782	Tremor	Condition	SNOMED	NO	YES	NO

75. Type 2 diabetes mellitus

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
201826	Type 2 diabetes mellitus	Condition	SNOMED	NO	YES	NO

76. Upper respiratory tract infection and pneumonia

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4181583	Upper respiratory infection	Condition	SNOMED	NO	YES	NO
255848	Pneumonia	Condition	SNOMED	NO	YES	NO