Safety outcomes of Selective Serotonin Reuptake Inhibitors in Adolescent Attention-Deficit/Hyperactivity Disorder: The ASSURE Study Protocol

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2 List of abbreviations

AAP	American Academy of Pediatrics
ADHD	Attention-Deficit/Hyperactivity Disorder
ESC	Escitalopram
FLX	Fluoxetine
MPH	Methylphenidate
SSRI	Selective Serotonin Reuptake Inhibitor
SRT	Sertraline

3 Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of adolescents[1]. In addition to ADHD, patients with ADHD also have many comorbidities such as anxiety disorder, depressive disorder, substance abuse, and autism spectrum disorder[2-5]. Therefore, the American Academy of Pediatrics recommends that comorbidity evaluation be performed at least once when diagnosing ADHD as one of the key action statements in their 2019 clinical practice guideline[6].

Especially, ADHD is closely related to depressive disorder. There are previous studies on high comorbidity rate, biological linkage or causality and its clinical outcomes[7-11]. 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[12-15], etc.) and an increase in adverse effects[14].

Although the first-line treatment for adolescent ADHD and depressive disorder is recommended in different guidelines[6, 16], the evidence for safety evaluation of concomitant use of those drugs is sparse. Therefore, in this study, we aimed to evaluate the safety of the co-use of selective serotonin reuptake inhibitors (SSRIs), the first recommended drug for adolescent depression, in ADHD patients (Adolescent ADHD and SSRI Use in Real-world data: ASSURE study). We also aimed to evaluate the safety outcome within the SSRI class as head-to-head study.

4 Amendments and Updates

0.1	03 December 2021	C Kim	Initial draft
0.9	24 December 2021	C Kim	Finalize initial draft
1.0	3 January, 2022	C Kim	First release

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 anti-ADHD prescription[17, 18]. MPH effectively ameliorate the symptoms of ADHD and MPH has the best safety/coverage ratio than other anti-ADHD drugs although adverse events including affective symptoms and weight loss [14, 19].

The prevalence of depression is 16–26% in ADHD[20], and these patients takes anti-ADHD drugs and antidepressants together according to the clinical guidelines[6, 16]. It has been reported that antidepressant resistance occurs a lot in ADHD patients, therefore a higher intensity treatment should be prescribed[21, 22]. However, there are some concerns for co-medication with antidepressant for ADHD, which are due to adverse events of such as suicidal behaviors[12-15]. In addition, the possibility of increased side effects due to the drug interactions between anti-ADHD drugs 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 [23, 24 25]. Also specific antidepressants induce gene regulation related in MPH, there are concerns about coadministration of them [26 27].

In general, guidelines for antidepressants applied to ADHD patients are applied according to age, but there are few studies in which 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 safety of MPH and antidepressants 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 safety of concomitant antidepressant in 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 SSRI among adolescent ADHD patients.

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 adolescent ADHD.

6.3 Secondary Hypothesis

- There are no differences in the risk of safety outcomes within SSRIs used to treat comorbid depression in adolescent 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 SSRI with MPH. The comparator cohort will be no users of SSRI (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 SSRI drugs with MPH and the comparator cohort will be another SSRI drug with MPH (e.g., escitalopram vs fluoxetine, etc.). 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. Adjustment for baseline confounders will be done using propensity scores.

7.2 Study population

7.2.1 Primary Study population

The primary study population is for a comparative study between concomitant SSRI and MPH users and MPH alone users. All subjects in the database will be included who meet the following criteria: (note: the index date is the day of the first prescription of SSRI or MPH)

- Adolescents who prescribed MPH for ADHD and have depressive disorder
    - Between 10 - 19 years old
    - 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 anti-ADHD drugs such as atomoxetine, clonidine, and bupropion
    - No other antidepressant drugs except SSRI before the index date

7.2.2 Secondary Study population

The secondary study population is for a comparative study within the SSRI class co-using MPH. All subjects in the database will be included who meet the following criteria: (note: the index date is the day of first prescription of SSRI)

- Adolescents who prescribed MPH for ADHD and prescribed SSRI for depressive disorder
    - Between 10 - 19 years old
    - 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 anti-ADHD drugs such as atomoxetine, clonidine, and bupropion
    - No other antidepressant drugs except target drugs (escitalopram, fluoxetine, sertraline, respectively) before the index date

7.2.3 Study population for additional analyses

In South Korea, there are other treatment options for ADHD treatment such as atomoxetine, clonidine, and bupropion besides MPH. A sensitivity analysis including the corresponding drugs 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 or Anti-ADHD drugs)

- Adolescents who prescribed anti-ADHD drugs for ADHD and have depressive disorder
    - Between 10 - 19 years old
    - 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 antidepressant drugs except SSRI before the index date

Since ADHD and depression are with differences between boys and girls, subgroup analyses will be performed on boy and girl patients. Cohort criteria are the same except sex limited to male or female.

7.3 Exposures

7.3.1 Treatment: new SSRI user with MPH for the ADHD and depressive disorder

- **Cohort Entry Events**

  People with continuous observation of 365 days before event may enter the cohort when observing any of the following:
    - SSRI prescription for the first time in the person's history
    - between 10 and 19 years old
    - having at least 1 prescription of MPH for the first time in the person's history
    - starting between 30 days before and 0 days after SSRI start 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 cohort entry start 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 cohort entry start 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 anti-ADHD
   - Entry events having no prescription of other anti-ADHD drugs

- **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 days supply and exposure end date for exposure duration

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

- prescription of other antidepressants except SSRIs

7.3.2 Comparator: new MPH user for the ADHD and depressive disorder

- **Cohort Entry Events**

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

- MPH prescription for the first time in the person's history
- between 10 and 19 years old

Limit cohort entry events to the earliest event per person.

- **Inclusion Criteria**

1. Patient 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 cohort entry start date
2. Patient 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. Patient without antidepressants
   - Entry events having no prescription of the antidepressant, starting anytime on or before cohort entry start date.
4. Patient without other anti-ADHD drugs
   - Entry events having no prescription of other anti-ADHD.

- **Cohort Exit**

The cohort end date will be based on a continuous exposure to MPH allowing 30 days between exposures, adding 30 days after exposure ends, and using days supply and exposure end date for exposure duration. The person exits the cohort when encountering any of the following events:

- prescription of antidepressants

7.4 Outcomes

7.4.1 Primary Outcomes

- **Neuropsychiatric events**
  Primary outcome is a neuropsychiatric event that includes agitation, first-time psychosis, first-time tic disorder, mania, sleep disorder, suicidality, and tremor. All conditions could be detected by diagnostic codes.

7.4.2 Secondary Outcomes

Secondary outcomes are cardiovascular and other events. Those are including each individual event as below.

- **Cardiovascular events**
  Cardiovascular events are including arrhythmia and hypertension. All conditions could be detected by diagnostic codes.
- **Other events**
  Other events are including abdominal pain, constipation, headache, nausea/vomiting, seizure, and traumatic injury. All conditions could be detected by diagnostic codes.

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[28]. 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[29].

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 drug use of SSRI is 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 treatment (SSRI or MPH) 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 treatment (SSRI) 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 (PS Matching): After estimating the PS, one-to-one 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:

- 8 comparisons: One primary comparison (SSRI with MPH vs MPH alone) and seven secondary comparisons (ESC with MPH vs MPH alone, FLX with MPH vs MPH alone, SRT with MPH vs MPH alone, FLX with MPH vs ESC with MPH, SRT with MPH vs ESC with MPH, SRT with MPH vs FLX with MPH)

- 15 outcomes: agitation, first-time psychosis, first-time tic disorder, mania, suicidality, tremor, arrhythmia, hypertension, abdominal pain, constipation, headache, nausea/vomiting, seizure, and traumatic injury.
- 2 time-at-risk definitions: As-treated risk window, Intention-to-treat risk window
- 1 model: Cox regression after 1:1 PS matching
- 5 Additional analyses (3 sensitivity analyses: expansion exposure from MPH to all anti-ADHD drugs, remove prior outcomes, narrow definition of concomitant prescription of SSRI and MPH; 2 subgroup analyses: male, female)

The total number of analyses is 1,440 (8 comparisons x 15 outcomes x 2 TAR x 1 statistical models x (1+3+2) (main and sensitivity analyses)).

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 0.2 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.

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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
742185	Atomoxetine	Drug	RxNorm	NO	YES	NO
750982	Bupropion	Drug	RxNorm	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
750982	Bupropion	Drug	RxNorm	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	Excluded	Descendants	Mapped
21604686	ANTIDEPRESSANTS	Drug	ATC	NO	YES	NO
750982	Bupropion	Drug	RxNorm	YES	YES	NO

7. Selective serotonin reuptake inhibitor

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped

715939	Escitalopram	Drug	RxNorm	NO	YES	NO
739138	sertraline	Drug	RxNorm	NO	YES	NO
755695	fluoxetine	Drug	RxNorm	NO	YES	NO

8. Escitalopram

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
715939	Escitalopram	Drug	RxNorm	NO	YES	NO

9. Fluoxetine

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
755695	fluoxetine	Drug	RxNorm	NO	YES	NO

10. Sertraline

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
739138	sertraline	Drug	RxNorm	NO	YES	NO

11. Other Antidepressant for escitalopram

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
21604686	ANTIDEPRESSANTS	Drug	ATC	NO	YES	NO
750982	Bupropion	Drug	RxNorm	YES	YES	NO
715939	Escitalopram	Drug	RxNorm	YES	YES	NO

12. Other Antidepressant for fluoxetine

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
21604686	ANTIDEPRESSANTS	Drug	ATC	NO	YES	NO
750982	Bupropion	Drug	RxNorm	YES	YES	NO
755695	fluoxetine	Drug	RxNorm	YES	YES	NO

13. Other Antidepressant for sertraline

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
21604686	ANTIDEPRESSANTS	Drug	ATC	NO	YES	NO
750982	Bupropion	Drug	RxNorm	YES	YES	NO
739138	sertraline	Drug	RxNorm	YES	YES	NO

14. Mania

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4333677	Mania	Condition	SNOMED	NO	YES	NO

15. Psychosis

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

16. Sleep disorder

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

17. Suicidality

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
4219484	Suicide attempt	Observation	SNOMED	NO	YES	NO
4303690	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
4025215	Emotional state finding	Condition	SNOMED	NO	NO	NO
4075235	Drowning self	Condition	SNOMED	NO	YES	NO

18. Tic disorder

Concept Id	Concept Name	Domain	Vocabulary	Excluded	Descendants	Mapped
381839	Tic disorder	Condition	SNOMED	NO	YES	NO

19. Tremor

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

20. Arrhythmia

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

4068155	Atrial arrhythmia	Condition	SNOMED	NO	YES	NO

21. Hypertension

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

22. Abdominal pain

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

23. Constipation

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

24. Headache

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

25. Nausea/vomiting

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

26. Seizure

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

27. Traumatic injury

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