약학석사 학위논문

Safety Signal Detection of Antidepressants:

a Comparison of Korean National Health Insurance Claims Database and Spontaneous Reporting System Database

항우울제 부작용 실마리정보 탐색: 건강보험청구자료와 자발적부작용보고자료 비교연구

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약학과 사회약학전공

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장신잉의 약학석사 학위논문을 인준함

2021 년 6 월

위 원 장 이 장 익

부위원장 홍 송 희

위 원 강 현 진

Abstract

Background: The spontaneous reporting system (SRS), such as the Korea Adverse Event Reporting System (KAERS), has a limitation in detecting all safety signals because the reports do not come from all drug uses. On the other hand, the claims data of the Korean National Health Insurance Review & Assessment (HIRA) has information on drug-induced conditions for all insurance-covered patients along with their prior prescription records, which helps investigate the temporal association between drugs and adverse drug reactions (ADRs). Therefore, complementing the HIRA to KAERS for drug safety signal detection would generate a more substantial list of safety signals than KAERS alone. This study has the following objectives: 1) compare the profiles of the signals (signal classes, common ADR coverage (CAC), and labeling information coverage (LIC)) detected in HIRA and KAERS databases; 2) verify the validity of the signals detected but not covered by the labeling information with protopathic bias evaluation and relative risk (RR) assessment; 3) determine whether the signal profile depends on demographics (age and gender) and different time windows (4, 8, 12 weeks) used to define the prior drug exposure.

Methods: ADR signal detection on the KAERS and HIRA databases (1st January 2017 to 31st December 2017) was conducted with Bayesian and non-Bayesian methods. The signal classes were constructed based on System Organ Class (SOC) as well as types of antidepressants. CAC was computed as the proportion of common ADRs among all the signals detected. LIC was represented by the mean average precision (mAP). Protopathic bias was controlled using Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD). RR for each drug-ADR combination was based on prescription drug events and follow-up of ADR conditions.

Results: The numbers of signals detected in the KAERS and HIRA databases were 51 and 62, respectively. Most of the signals detected in KAERS consisted of autonomic nervous system disorders of SOC (N=17, 33.3%) and TCA (N=21, 41.2%) antidepressants while those in HIRA consisted of central & peripheral nervous system disorders of SOC (N=31, 50%) and SSRI (N=22, 35.5%) antidepressants. HIRA had 5 of the signals detected that are not found in the drug labeling information while KAERS had 0. The signals detected from KAERS had a higher CAC (68.63% [K] VS. 29.03% [H]) as well as a higher LIC (mAP for EB05: 1.00 [K] VS. 0.983 [H]) than those from HIRA. The unlabeled signal of myelopathy on duloxetine was a protopathic bias (P-value = 0.01026). Three of the four unlabeled signals did not show a statistically significant association between drug events and ADRs (lower bound of RR < 1). As for demographic subgroups, HIRA always showed lower CACs and LICs than KAERS. As for different time windows of drug-ADR pairing in HIRA, CACs decreased (29.03%, 27.87%, 27.27%) with a narrower window while LICs increasing (0.983, 1.0, 1.0).

Conclusion: The safety signals detected for antidepressants in HIRA (healthcare claims database) and KAERS (SRS) databases exhibited different signal profiles. The signals detected but not covered by drug labeling information, which were only detected in HIRA, need to be verified with further research. Safety signal detection in both healthcare claims and SRS databases would provide additional regulatory insight for pharmacovigilance.

Keywords: signal detection, pharmacovigilance, HIRA, KAERS, antidepressants

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Abbreviations

HIRA: Korean National Health Insurance Review & Assessment

HIRA-NPS: National patient sample of HIRA

KAERS: Korea Adverse Event Reporting System

KIDS: Korea Institute of Drug Safety and Risk Management

RR: Relative risk

SRS: Spontaneous reporting system

PV: Pharmacovigilance

ADR: Adverse drug reaction

AE: Adverse event

WHO: World Health Organization

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System

MedDRA: Medical Dictionary for Regulatory Activities

ICH: International Conference on Harmonisation

PEM: Prescription–Event Monitoring

DSRU: Drug Safety Research Unit

OHDSI: Observational Health Data Sciences and Informatics

CDM: Common data model

EMR: Electronic medical record

ICSR: Individual Case Safety Report

MFDS: Ministry of Food and Drug Safety

NHIS: National Health Insurance System

MDD: Major depressive disorder

MAOI: Monoamine oxidase inhibitor

TCA: Tricyclic antidepressants

SSRI: Selective serotonin reuptake inhibitor

SNRI: Serotonin-norepinephrine reuptake inhibitor

SMS: Serotonin modulator and stimulator

SARI: Serotonin antagonist and reuptake inhibitor

NaSSA: Noradrenergic and Specific Serotonergic Antidepressant

SRA: Serotonin receptor agonists

ATC: Anatomical Therapeutic Chemical

WHO-ART: World Health Organization-Adverse Reaction Terminology

SDA: Signal Detection Algorithm

PRR: Proportional reporting ratio

ROR: Reporting odds ratio

PRRCI: Confidence interval of proportional reporting ratio

RORCI: Confidence interval of reporting odds ratio

IC: Information component

EBGM: Empirical Bayes geometric mean

EB05: The lower 5% point of empirical Bayes geometric mean

KCD: Korean Standard Classification of Diseases

FDA: Food and Drug Administration

SOC: System Organ Class

CAC: Common ADR coverage

LIC: Labeling information coverage

LEOPARD: Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs

1. Introduction

1.1 Pharmacovigilance (PV) and safety signal detection around the world

An adverse drug reaction (ADR) is defined by the World Health Organization as a harmful and unintended response to a drug, which occurs at doses commonly used in man for the prophylaxis, diagnosis or therapy of disease, or the modification of physiological function [1].

In PV, a signal is defined as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to prompt verificatory action." in CIOMS VIII [2]. At the same time, signal detection in PV is an act of looking for and/or identifying signals using event data from any source according to CIOMS VIII.

ADR or adverse event (AE) monitoring is such an important part of pharmacovigilance (PV) that several kinds of PV systems are maintained worldwide.

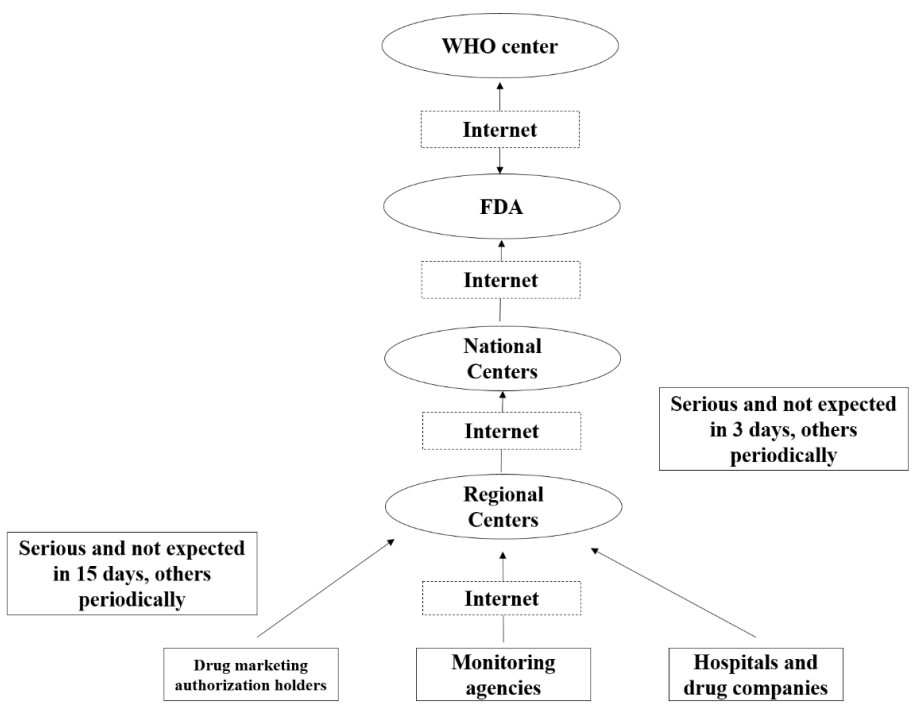
1.1.1 Spontaneous reporting system (SRS)

For drug safety signal detection, spontaneous reporting system (SRS) databases, such as the World Health Organization (WHO) spontaneous reporting database, Adverse Event Reporting System (AERS) database in the USA, "Yellow Card" database in the UK and The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) database in Canada, are applied to detect ADR signals [2-5]. SRS collects spontaneous AE reports from drug companies, monitoring agencies, and hospitals. Relevant policies have been implemented to ensure the obligations to report AEs so that public health or hygiene risks can be detected and mitigated [6]. As a result, the number of corresponding reports would increase.

The Medical Dictionary for Regulatory Activities (MedDRA®), developed by the International Conference on Harmonisation (ICH), is internationally used in coding all the reported events and indications [7]. The MedDRA® version 22.1 has been available since September 2019 and used for recording adverse events and medical history in clinical trials, in the analysis and tabulations of data from these trials and the expedited submission of safety data to government regulatory authorities, as well as in constructing standard product information and documentation for applications for marketing authorisation [7, 8].

Usually, reports submitted to the regional centers will be analyzed and transmitted to the national center, and then the national center will share the reports with the WHO center. All the members of the WHO center can use the AEs reporting data. The structure of an SRS is shown in Figure 1 [9].

Figure 1. The structure and procedures for the ADR monitoring and reporting network in an SRS



1.1.2 Prescription–Event Monitoring (PEM) system

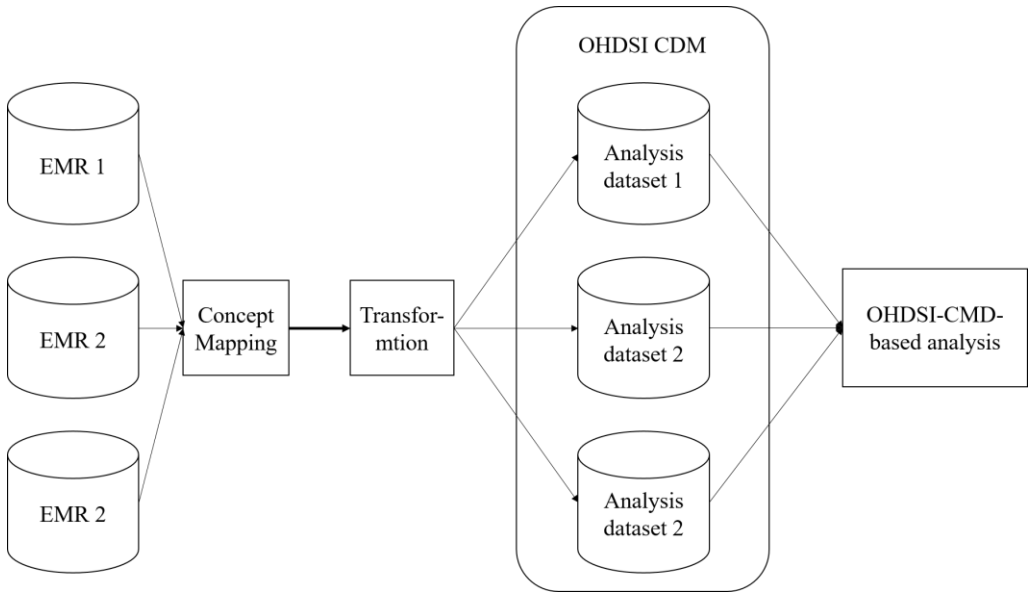
As SRS has some limitations to identify all hazards, prescription-based monitoring systems are used to compensate. These systems are intended to provide information on populations of known size so that the incidence of ADRs could be estimated with reasonable accuracy [10]. Prescription-Event Monitoring (PEM) is one of the prescription-based monitoring systems to monitor events regardless of the relatedness to drug exposure maintained by the Drug Safety Research Unit (DSRU), which is a non-profit medical organization in the UK [11].

The purpose of PEM is to examine the safety of new drugs in large cohorts of exposed patients in the immediate post-marketing period [12]. PEM studies are usually observational to evaluate the use of a new drug in the naturalistic setting. Data are collected through a two-phased approach, where the first phase is the collection of prescription data to capture patient and prescriber details, then the next is the collection of exposure and outcome data [13].

1.1.3 Observational Health Data Sciences and Informatics (OHDSI)

The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. As an international program, OHDSI has three principal objectives: 1) develop statistical tools, 2) conduct research, 3) establish resources. The data used in OHDSI are observational data that are generally based on a defined population where various research methods could be applied [14]. The observational data are transformed with a common data model (CDM) into a common format, which allows all the program partners from all over the world to utilize the data (Figure 2).

Figure 2. The OHDSI-CDM-based analysis framework



1.1.4 Healthcare databases

Medication safety requires that each drug be monitored throughout its market life as early detection of ADRs can lead to alerts that prevent patient harm. Electronic medical records (EMRs) have recently emerged as a valuable resource for pharmacovigilance [15]. An EMR is the systematized collection of patient and population electronically stored health information in a digital format [16].

Compared to SRS databases, healthcare databases provide more comprehensive patient information, including demographics, medical history, medication and allergies, immunization status, personal characteristics like age and weight, and billing information. Nevertheless, patient records are typically spread across multiple databases. The task of accessing information in a variety of databases can be very complicated, sometimes because of distinct technology used in different databases [17]. Also, there may exist some problems concerning patients' privacy [18].

There are some applications of healthcare databases in safety signal detection. In September 2007, the FDA of the United States was mandated to establish a post-market risk identification and analysis surveillance system to monitor drug safety. Afterwards, the Sentinel System, which is a national electronic healthcare data derived from healthcare databases, was created [19]. In Europe, the EU-ADR Project is an attempt to combine electronic healthcare databases in Europe to allow for large-scale drug safety monitoring [20]. Nevertheless, healthcare databases have not been widely applied in safety signal detection yet.

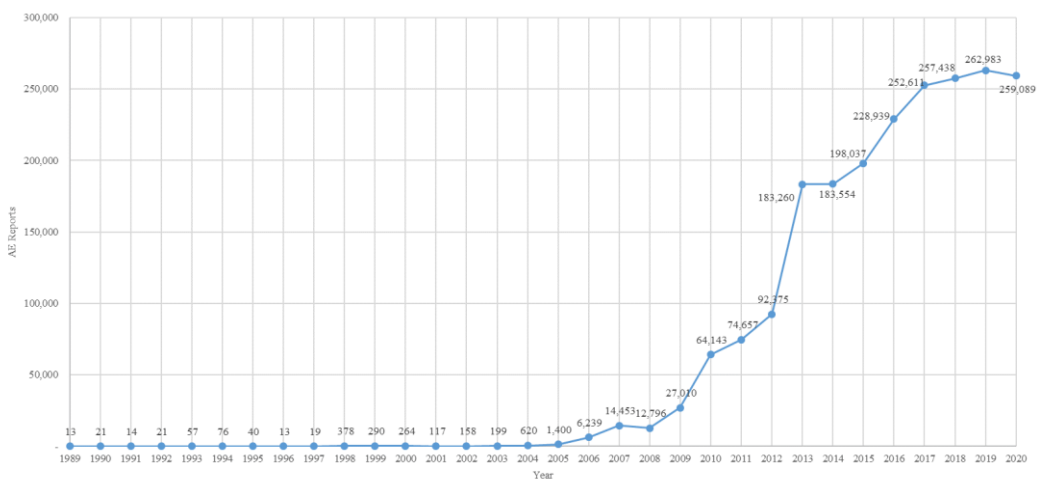
1.2 Pharmacovigilance (PV) in South Korea

1.2.1 Korea Adverse Event Reporting System (KAERS)

The Korea Adverse Event Reporting System (KAERS) is a computerized system developed by the Korea Institute of Drug Safety and Risk Management (KIDS) in 2012 to facilitate reporting and management of AE reports. KAERS receives reports from anyone experiencing AEs, including consumers, healthcare professionals, regional pharmacovigilance centers and marketing authorization holders who are mostly pharmaceutical companies. Suspected drug and AE information are reported to KIDS by Individual Case Safety Reports (ICSRs). In addition, reports from the ADR call center and other routes such as fax and e-mail are received and transformed into ICSRs. With the AE information, KIDS periodically reports statistical results and safety information to the Ministry of Food and Drug Safety (MFDS) [21].

In Korea, spontaneous AE reports have been collected since 1989 when a spontaneous AE reporting system was first initiated. However, the number of reporting in the first 20 years was relatively small. After KAERS was developed in 2012, started to increase sharply and exceeded 250,000 in 2017 (Figure 3) [22].

Figure 3. Number of annual AE reports in KAERS from 1989 to 2020



1.2.2 Re-examination System & Re-evaluation System

Considering problems for pre-market trials such as limited observation period and the limited number of target products, Korea MFDS implemented a re-examination system in 1995. Four to six years after marketing authorization is issued, the product must be subject to re-examination by the MFDS. The purpose of the system is to monitor drug use after approval and investigate and verify AEs that did not appear in clinical trials. The re-examination is conducted based on post-marketing information collected from surveys, post-market clinical trials, spontaneous AE reports and literature [23].

The re-evaluation system was developed in 1975, aiming to re-evaluate the safety and effectiveness of certain drugs when a review is considered necessary.

1.2.3 Claims data of Korean National Health Insurance Review & Assessment (HIRA)

Under the National Health Insurance System (NHIS), most Koreans are covered by the national medical insurance as either an employee or a community member. Healthcare providers are required to submit reports to NHIS regularly on medical services provided under the health insurance policies. The Claims data of the Korean National Health Insurance Review & Assessment (HIRA) database contains information on all claims, including prescribed medications for approximately 50 million Koreans [24].

The HIRA database contains medical information of patients such as demographic characteristics, pharmaceuticals, and medical procedures, thus it is widely applied for various academic research [25]. In 2010, a study first applied the HIRA database to detect signals for rosuvastatin and made efforts in applying the HIRA database in the safety surveillance of marketed products [26]. Although previous studies

have tried to apply HIRA in safety signal detection, they did not verify the signals detected or make a comparison between HIRA and KAERS [27].

1.3 Adverse effects of Antidepressants

Antidepressants are medications used to treat major depressive disorder (MDD), some anxiety disorders, some chronic pain conditions, and to help manage some addictions [28]. There are different kinds of antidepressants: Tricyclic antidepressants, Monoamine oxidase inhibitors (MAOIs), Tricyclic antidepressants (TCAs), Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Serotonin modulator and stimulators (SMSs), Serotonin antagonist and reuptake inhibitors (SARIs), Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) and so on [29]. All of the antidepressants have a variety of adverse effects, which always leads to noncompliance.

1.3.1 Tricyclic antidepressants, Monoamine oxidase inhibitors (MAOIs)

MAOIs were introduced in the 1950s as the first drugs for depression. By inhibiting the activity of monoamine oxidase, MAOIs prevent the breakdown of monoamine neurotransmitters and thereby increase their availability. MAOIs mainly include Iproclozide, Iproniazide, Isocarboxazid, Moclobemide, Nialamide, Phenelzine, Toloxatone, Tranylcypromine. Due to severe adverse effects like hepatotoxicity and death due to hypertensive crises and intracranial haemorrhages, MAOIs have been seldom used in clinical practice. Currently, MAOIs are not first choice antidepressants and are usually used only when there is intolerance or lack of response to the newer drugs, refractory depression or when ECT is contraindicated [30].

1.3.2 Tricyclic antidepressants (TCAs)

TCAs are derived from antihistaminic compounds, which were the predecessors of phenothiazines. The first TCA imipramine was discovered in the 1950s and proved to

be effective in treating depression. TCAs mainly include Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Quinupramine, Trimipramine.

The TCAs were largely replaced by SSRIs in the 1990s, due to some studies showing that although SSRIs do not differ from TCAs in efficacy, they have fewer adverse effects [31]. Common adverse effects of TCAs include dry mouth, slight blurring of vision, constipation, problems passing urine, drowsiness, dizziness, weight gain, excessive sweating and heart rhythm problems.

A meta-analysis assessing the efficacy and safety of TCAs and other kinds of antidepressants identified 71 eligible RCTs and found that TCAs were more likely to cause adverse events than placebo (RR = 1.56; 95% CI 1.07-2.26) [32]. A meta-analysis containing 36 clinical trials of TCAs and SSRIs in a double-blind comparison showed that significantly more TCA-treated than SSRI-treated subjects dropped out due to either lack of efficacy or adverse reactions (30.0 vs. 24.7%, P = 0.01). Compared to SSRIs, TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms [33]. In children and adolescents, a network meta-analysis showed that TCAs imipramine (OR=0·23, 95% CI: 0·04-0·78) showed significantly less tolerability than SSRIs fluoxetine [34].

1.3.3 Selective serotonin reuptake inhibitors (SSRIs)

Dr Arvid Carlsson was the first one to develop the Zimelidine, which was the first SSRI [35]. SSRIs mainly include: Alaproclate, Citalopram, Escitalopram, Etoperidone, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Zimelidine. For depressive disorders, SSRIs are the most widely prescribed psychiatric drugs due to their relative safety in overdose and improved tolerability over other traditional antidepressants [29].

Common adverse effects of SSRIs include feeling agitated, feeling or being sick, indigestion, diarrhoea, weight loss, dizziness, blurred vision, dry mouth, excessive sweating and sexual dysfunction.

A study for 50,824 patients treated for major depressive disorder with SSRIs showed that the adverse effects mentioned most frequently were: "discomfort" of the digestive system (10%), sleep disorders (8.6%), and heart rhythm disorders (4%) [36]. Another study based on real-world data surveyed approximately 700 patients and found 38% of them reported having experienced an adverse effect of taking an SSRI. Only 25% of the adverse effects were considered "very bothersome" or "extremely bothersome" [37]. Although SSRIs seem to have fewer adverse effects than TCAs, a study showed that patients treated with SSRIs were more likely to suffer a sexual dysfunction than those treated with TCAs [38].

1.3.4 Serotonin-norepinephrine reuptake inhibitors (SNRIs)

The increasing knowledge of pathophysiological mechanisms of depression has led to the synthesis of SNRIs, which affect both serotonin and norepinephrine reuptake [35]. SNRIs mainly include Desvenlafaxine, Duloxetine, Levomilnacipran, Milnacipran, Nefazodone, Venlafaxine.

SNRIs had similar adverse effects as SSRIs. Common adverse effects of SNRIs include dizziness, nausea, dry mouth, headache, feeling agitated, feeling and being sick and sexual dysfunction.

Yet, SNRIs are especially associated with increased incidence of cardiovascular AEs, such as hypertension. A systematic review showed that the overall cardiovascular adverse reactions were higher for TCAs (0.15%) and SNRIs (0.14%) than SSRIs (0.08%). In terms of hypertension, SNRIs showed a significantly higher risk than other

antidepressants ($p < 0.001$). Among SNRIs, venlafaxine showed to have a significantly higher risk of hypertension ($p < 0.001$) [39].

1.3.5 Other antidepressants

New antidepressants including Serotonin modulator and stimulators (SMSs), Serotonin antagonist and reuptake inhibitors (SARIs), Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) and Serotonin receptor agonists (SRAs) also have been discovered and applied in the clinical treatment. Novel strategies, which mainly include monoamine targets, glutamatergic agents and peptidergic, remains to be seen the efficacy and adverse effect profile [40]. A review evaluating the literature on adverse events tolerability and safety of newer-generation antidepressants showed that main adverse events related to the use of newer-generation antidepressants include gastrointestinal, hepatotoxicity and hypersensitivity reactions, weight gain and metabolic disturbances, cardiovascular, genitourinary, sexual dysfunction, hyponatremia, osteoporosis and fractures, bleeding and central nervous system problems [41].

1.4 Objectives

Although widely applied for safety signal detection worldwide, SRS like KAERS has a limitation in detecting all safety signals because the reports do not come from all drug uses [28, 44]. On the other hand, the claims data of HIRA has information on drug-induced conditions for all insurance-covered patients along with their prior prescription records, which helps investigate the temporal association between drugs and ADRs. Therefore, complementing the HIRA to KAERS for drug safety signal detection would generate a more substantial list of safety signals than KAERS alone.

This study has the following objectives: 1) compare the profiles of the signals (signal classes, common ADR coverage (CAC), and labeling information coverage (LIC)) detected in HIRA and KAERS databases; 2) verify the validity of the signals detected but not covered by the labeling information with protopathic bias evaluation and relative risk (RR) assessment; 3) determine whether the signal profile depends on demographics (age and gender) and different time windows (4, 8, 12 weeks) used to define the prior drug exposure.

2. Methods

2.1 Signal detection and comparison

2.1.1 KAERS

2.1.1.1 Data source

Korea Adverse Event Reporting System (KAERS) data from 1st January 2017 to 31st December 2017 was provided by the Korea Institute of Drug Safety and Risk Management (KIDS). All the reports containing antidepressants were selected and outputted by KIDS, together with the information on demographics, reporters, drugs, ADRs and causality assessments. Drugs were recorded in the Anatomical Therapeutic Chemical (ATC) code, while ADRs were recorded in the World Health Organization-Adverse Reaction Terminology (WHO-ART), respectively.

2.1.1.2 Statistical analysis

(1) Description analysis

After data cleansing and selection, characteristics of the spontaneous reports, including age groups, genders, report sources and antidepressant types, were summarized.

(2) Signal Detection Algorithms (SDAs)

Two kinds of signal detection algorithms (SDAs) were used in the study: disproportionality and Bayesian methods. Data-mining indicators would be compared as follows:

1) Disproportionality methods: proportional reporting ratio (PRR), reporting odds ratio (ROR), confidence interval of proportional reporting ratio (PRRCI), and confidence interval of reporting odds ratio (RORCI).

2) Bayesian methods: Information component (IC), empirical Bayes geometric mean (EBGM) and the lower 5% point of empirical Bayes geometric mean (EB05).

As shown in Table 1b, based on the criteria applied in international and national SRS databases for defining a signal, the thresholds for each indicator would be chosen [2].

Table 1. Calculation and thresholds for data-mining indicators

(a) 2×2 contingency table

	Specific ADR	**All other ADRs**	**Total**
Specific drug	A (n11)	B (n12)	A+B (n10)
All other drugs	C (n21)	D (n22)	C+D (n20)
Total	A+C (n01)	B+D (n02)	A+B+C+D (n)

(b) Corresponding formulas

Signal detection indicators	**Calculation**	**Thresholds**
PRR	(n11 / n10) / (n21 / n20)	PRR≥2, χ^2 (ii)≥4, n11≥3
ROR	(n11 / n12) / (n21 / n22)	ROR≥2, χ^2≥4, n11≥3
PRRCI	(n11 / n10) / (n1 / n20)	PRR − 1.96SE > 1, n11≥3
RORCI	(n11 / n12) / (n21 / n22)	ROR - 1.96SE > 1, n11≥3
IC	$\mathrm{IC} = log_2 \frac{N_{ij}}{E_{ij}}$ (i)	IC - 2SD > 0, n11≥3
EBGM	See appendix 1	EBGM≥2.5, n11≥3
EB05	See appendix 1	EB05≥1.8, n11≥3

(i) N_{ij}: observed frequency of drug-ADR pairs; E_{ij}: expected frequency of drug-ADR pairs

(ii) χ^2: chi-square value

2.1.2 HIRA

2.1.2.1 Data source

Claims data of Korean National Health Insurance Review & Assessment (HIRA) are generated when healthcare service providers submit a claim to HIRA for reimbursement. The 2017 national patient data (HIRA-NPS) used in this study covered 3% of all the patients in Korea, which had been submitted by healthcare providers and extracted with the stratified random sampling method [42]. The database provided by HIRA concealed the individual identity and contained information including patients' ages, genders, diagnoses, and prescriptions. All the patients who received any type of antidepressants (see Appendix 2 for main ingredient codes) and reported to the HIRA system from 1st January 2017 to 31st December 2017 were included in this study.

2.1.2.2 Connection of drug use and specific ADR

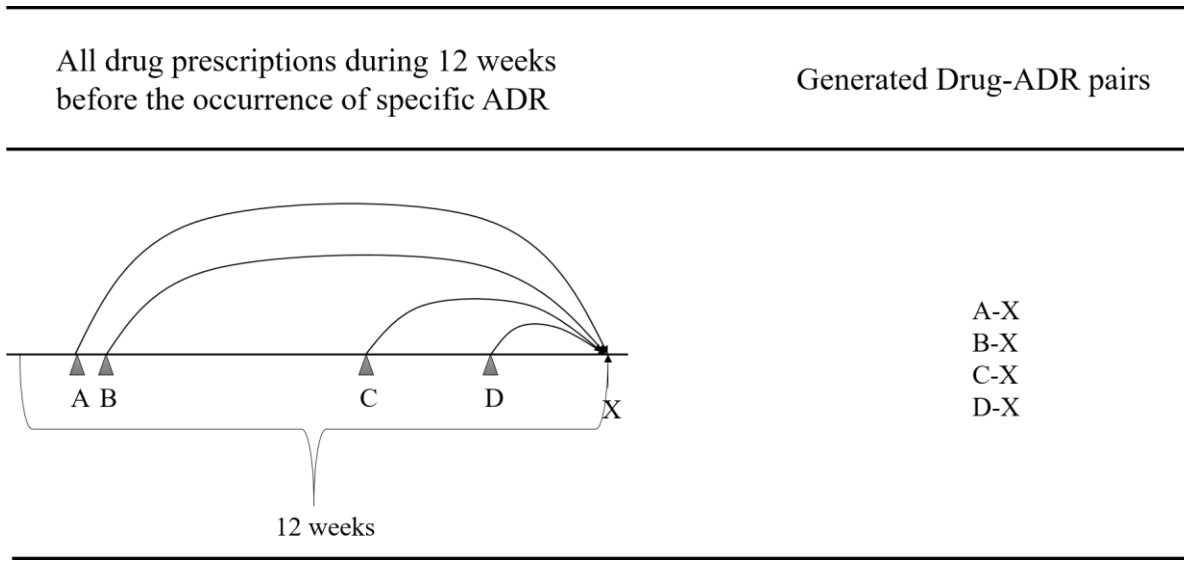
In the KAERS database, the ADRs were reported together with the drug usage. In contrast, in the HIRA database, ADRs had to be identified from the diagnoses, which were recorded with the Korean Standard Classification of Diseases (KCD) code (Appendix 3 shows the identified ADRs in the study). The drug usage needed to be determined from the prescriptions, which had been recorded with the main ingredient codes.

As one specific ADR can be induced by other drugs, the generation was implemented from the ADR perspective. First, after-antidepressant ADRs were exacted. If ADRs occurred within 12 weeks from the last prescription of antidepressants, the ADRs were considered after-antidepressant ADRs. Then, for each after-antidepressant ADR, the retrospective pairing was applied and all the drugs used in the previous 12 weeks were paired with the ADRs (Figure 4a). The generation followed the generation logic shown in Figure 4b. If ADRs occurred within 12 weeks from the last prescription of any drug, drug-ADR pairs were generated. Nevertheless, if a patient was diagnosed with an identical ADR

X twice, A-X_1 and A-X_2 would be kept. If a patient was diagnosed with different ADR X and Y within 12 weeks after taking drugs A and B, then the drug-ADR pairs A-X, A-Y, B-X, B-Y would be generated. Yet, if a patient had several identical drug-ADR pairs, these pairs were considered as one to reduce bias due to multiple repairing. The 12-week time window was decided based on the treatment pattern of antidepressants and previous studies concerning healthcare databases [26, 29].

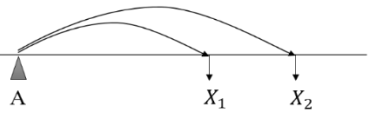
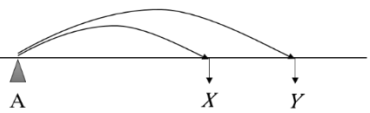
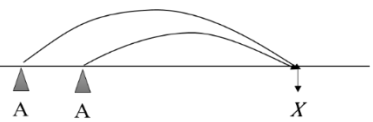
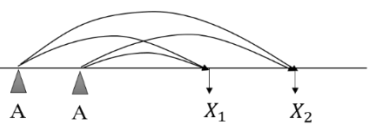
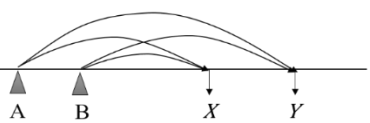
Figure 4. Generating algorithm for drug-ADR pairs

(a) ADR perspective pairing



**A, B, C, D: any prescription drugs; X: after-antidepressant ADR*

(b) Drug-ADR pairs generation logic

Drug prescriptions and occurrence of ADRs for one patient	Drug-ADR pairs	Drug-ADR pairs generated for one patient
1 	A-X_1 A-X_2	A-X_1 A-X_2
2 	A-X A-Y	A-X A-Y
3 	A-X A-X	A-X
4 	A-X_1 A-X_1 A-X_2 A-X_2	A-X_1 A-X_2
5 	A-X A-Y B-X B-Y	A-X A-Y B-X B-Y

**A, B: any kind of drugs; X, Y: any identified ADRs; X_1, X_2: the same ADR occurred at different times*

2.1.3 Comparison of the signals detected in the two systems

All the signals detected in KAERS and HIRA were classified and compared by the System Organ Class (SOC) level from the Medical Dictionary for Regulatory Activities [7] and types of antidepressants.

Also, all the signals detected were checked whether they were common ADRs for antidepressants according to the IBM Micromedex ® database [43], the Korea Pharmaceutical Information Center database [44] as well as the labeling information from both the FDA of the United States and the MFDS of South Korea. If the recorded incidence of a specific ADR for a particular antidepressant was found more significant than 1%, then the ADR was defined as a common ADR in this study. The proportion of

common ADRs among all signals detected was computed to measure the common ADR coverage (CAC).

The labeling information coverage (LIC) was represented by using the Mean Average Precision (mAP), which is a metric often used in the evaluation of object detection models in the field of information retrieval [45]. The mAP compares the ground-truth bounding box with the detected box and returns a score. The higher the score, the more accurate the model is in its detections. Although there was no gold standard determining whether the detected signals were valid or not, the labeling information collected from both the FDA of the United States and the MFDS of South Korea was regarded as truth in this study. The calculation of the mAP is exhibited in Table 2.

Table 2. The calculation of the mAP

Drug	ADR	Indicator value	Rank by indicator	Labeling information	Rank with labeling information	Precision
A	X	10	1	Yes	1	1/1=1
B	Y	9	2	No		
C	X	8	3	Yes	2	2/3=0.67
A	Z	7	4	No		
D	Y	6	5	Yes	3	3/5=0.6
mAP=(1+0.67+0.6)/3=0.76						

2.2 Validity of the unlabeled signals detected in HIRA

2.2.1 Protopathic bias evaluation

In the process of signal detection, false positive signals may appear because of protopathic bias, which occurs when a drug is prescribed to treat the disease itself or an early manifestation of a disease before the event is captured in the database. One of the advantages of a healthcare claims database over SRS is that the healthcare claims database contains more information to identify protopathic bias. Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD) was used to eliminate protopathic bias [46]. The method was based on comparing prescription numbers before and after the occurrence of a specific ADR in a fixed time window. For every drug-ADR combination, the number of prescriptions was supposed to diminish after the ADR event. If the number of prescriptions was found to increase after the ADR event, the drug might treat the ADR and not cause it. Therefore, an increase in the prescription number 12 weeks after an ADR relative to the one 12 weeks before the ADR is an indication of protopathic bias. A one-tailed binomial test was used to identify the protopathic bias with a 95% confidence level.

2.2.2 Relative risk (RR) and the confidence interval

For evaluating the signal detection results, the RR and confidence interval were calculated for each drug-ADR combination with the complete prescription information contained in the HIRA database. First, data were arranged in Table 3. When the lower bond of RR was more significant than 1, then the risk of a specific drug causing a specific ADR was considered statistically significant.

Table 3. Data arrangement for RR calculation

	Occurrence of specific ADR	**Nonoccurrence of specific ADR**	**Total**
Patients who took a specific antidepressant	x1	n1-x1	n1
Patients who didn't take specific antidepressants	x2	n2-x2	n2

With arranged data, RR and confidence interval could be computed with

$$\mathrm{RR} = \frac{x1/n1}{x2/n2}$$

$$\mathrm{CI} = \exp\left[\ln\left(\widehat{RR}\right) \pm \mathrm{z}\sqrt{\frac{(n1-x1)/x1}{n1} + \frac{(n2-x2)/x2}{n2}}\right].$$

2.3 Demographics and time windows

For both HIRA and KAERS databases, age and gender variables were confounders while conducting signal detection; thus stratified analysis was used to adjust for the confounding variables.

In the HIRA database, as the durations of different kinds of ADRs are different, the length of the time window makes a significant contribution to the signal detection results. Different time windows (4, 8, 12 weeks) were used to show how the signal profiles change correspondingly.

All statistics were done with SAS® software (version 9.4) and R Statistical Software (version 4.0.3, R packages "PhViD" [47], "openEBGM" [48], and "RCOR" [49] were applied for signal detection and evaluation).

3. Results

3.1 Signal detected and comparison between KAERS and HIRA

3.1.1 KAERS

3.1.1.1 Characteristics of reports associated with antidepressants

A total of 3,957 KAERS reports containing antidepressants (ATC code: "N06A") from 1st January 2017 to 31st December 2017 were provided by KIDS. After data cleansing, 2,242 reports with 5,992 drug-ADR pairs were kept for signal detection (Figure 5).

Table 4 shows the characteristic of the reports containing antidepressants in 2017. Most of the reports (49.29%) were from the elderly who were older than 60. 65.7% of the reports were from females while 32.87% were from males. Only 2.81% of the reports were defined as critical cases. As for the types of antidepressants, most of the reports were related to SSRIs (39.47%), followed by TCAs (31.80%), NaSSAs (7.00%), SNRIs (6.47%), SARIs (5.44%) and SRAs (3.21%). Regarding the source of the reports, most of the reports were reported by pharmacists (39.16%), next followed by nurses (34.88%), doctors (18.55%) and customers (6.38%).

Among all the selected reports, the top 5 most frequently reported drugs, ADRs and drug-ADR pairs are listed in Table 5, namely duloxetine (N=444), amitriptyline (N=373), escitalopram (N=236), nortriptyline (N=215) and mirtazapine (N=157). Meanwhile, the most frequently reported ADRs were as follows: dizziness (N=362), nausea (N=300), somnolence (N=288), mouth dry (N=188) and constipation (N=169). As for drug-ADR pairs, top 5 were duloxetine-nausea (N=129), duloxetine-dizziness (N=103), amitriptyline-somnolence (N=99), duloxetine-vomiting (N=68) and amitriptyline- dizziness (N=68).

Figure 5. Selection of data in KAERS

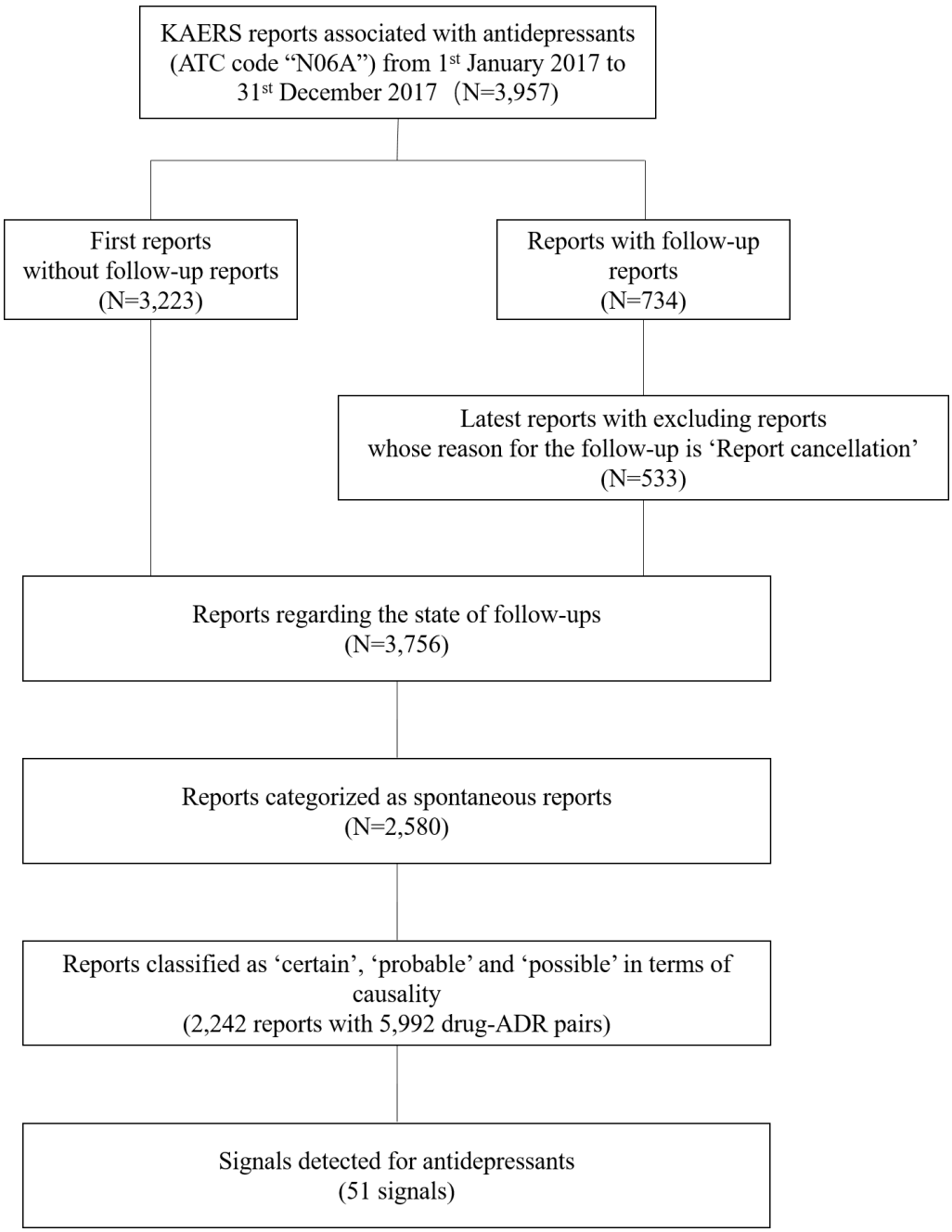


Table 4. Characteristics of reports associated with antidepressants

Characteristics	**Number of reports**	
Total	2,242	(100.00%)
Age		
0-19	52	(2.32%)
20-29	113	(5.04%)
30-39	161	(7.18%)
40-49	238	(10.62%)
50-59	441	(19.67%)
60-69	516	(23.02%)
70+	589	(26.27%)
unknwn	132	(5.89%)
Gender		
Male	737	(32.87%)
Female	1,473	(65.70%)
unknwn	32	(1.43%)
Critical case		
Yes	63	(2.81%)
No	2,179	(97.19%)
Types of antidepressants		
SSRI	885	(39.47%)
TCA	713	(31.80%)
NaSSA	157	(7.00%)
SNRI	145	(6.47%)
SARI	122	(5.44%)
SRA	72	(3.21%)
other	2	(0.09%)
Reporter information		
Pharmacist	878	(39.16%)
Nurse	782	(34.88%)
Doctor	416	(18.55%)
Consumer	143	(6.38%)
Missing value	13	(0.58%)
Others	10	(0.45%)

Table 5. Top5 most frequently reported drugs, ADRs, drug-ADR pairs

Top 5 most frequently reported antidepressants	**Counts (%)**
Duloxetine	444 (19.80%)
Amitriptyline	373 (16.64%)
Escitalopram	236 (10.53%)
Nortriptyline	215 (9.59%)
mirtazapine	157 (7.00%)
Top 5 most frequently reported ADRs	**Counts (%)**
Dizziness	362 (16.15%)
Nausea	300 (13.38%)
Somnolence	288 (12.85%)
Mouth dry	188 (8.39%)
Constipation	169 (7.54%)
Top 5 most frequently reported drug-ADR pairs	**Counts (%)**
Duloxetine-Nausea	129 (5.75%)
Duloxetine-Dizziness	103 (4.59%)
Amitriptyline-Somnolence	99 (4.42%)
Duloxetine-Vomiting	68 (3.03%)
Amitriptyline-Dizziness	68 (3.03%)

3.1.1.2 Signals detected in KAERS

With 5,992 drug-ADR pairs, 51 signals consisted of antidepressants were detected. Table 6 shows the signals detected, all of which were verified as labeled adverse effects of antidepressants according to both the FDA of the United States and the MFDS of South Korea. The number of detected signals that consisted of nortriptyline was the highest (8 signals), followed by those of amitriptyline and escitalopram (6 signals). PRRCI generated most of the signals (51 signals), while RORCI showed similar results (49 signals) with EBGM and EB05 generating fewer signals (4 and 2 signals).

Table 6. Detected signals of antidepressants in KAERS

(a) All signals detected

Drug	ADR	ADR count	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Somnolence	99	2.71	3.17	2.23	2.49	1.23	2.32	1.94
	Dizziness	68	1.29	1.34	1.03	1.03	0.33	1.23	1.01
	Mouth dry	51	1.90	2.01	1.43	1.47	0.80	1.66	1.31
	Weight increase	10	1.94	1.96	1.00	1.00	0.74	1.39	0.85
	Dysuria	6	2.45	2.47	1.02	1.02	0.88	1.42	0.77
	Cachexia	3	5.08	5.11	1.32	1.32	1.11	1.48	0.66
Amoxapine	Insomnia	5	13.10	19.82	6.38	6.57	2.08	3.61	1.37
Bupropion	Insomnia	7	3.57	3.85	1.74	1.74	1.39	2.09	1.04
	Palpitation	4	4.39	4.58	1.65	1.63	1.34	1.78	0.79
	Tremor	3	3.52	3.63	1.14	1.12	1.07	1.42	0.64
Desvenlafaxine	Constipation	6	2.44	2.66	1.15	1.12	0.98	1.50	0.80
	Anorexia	3	3.56	3.74	1.18	1.14	1.08	1.43	0.65
Doxepin	Headache	3	3.06	3.30	1.04	0.99	0.98	1.35	0.63
Duloxetine	Nausea	129	2.74	3.14	2.28	2.52	1.17	2.22	1.91
	Dizziness	103	1.33	1.38	1.09	1.10	0.35	1.25	1.06
	Vomiting	68	2.24	2.37	1.73	1.79	0.94	1.85	1.51
Escitalopram	Rash	10	2.22	2.25	1.16	1.16	0.91	1.54	0.93
	Urticaria	6	2.66	2.69	1.14	1.13	0.99	1.52	0.81
	Appetite increased	5	4.22	4.27	1.60	1.60	1.29	1.82	0.86
	Depression	4	6.45	6.51	2.06	2.06	1.43	1.95	0.83
	Hyponatraemia	4	3.73	3.77	1.28	1.27	1.13	1.55	0.73
	Cachexia	3	7.60	7.66	1.97	1.97	1.33	1.70	0.71
Fluoxetine	Anorexia	5	2.71	2.81	1.13	1.12	1.03	1.50	0.76
	Diarrhoea	5	4.11	4.28	1.70	1.69	1.38	1.93	0.89
	Depression	3	15.19	15.65	4.36	4.34	1.66	2.15	0.80
	Hypotension	3	20.26	20.87	5.57	5.56	1.72	2.26	0.82
Imipramine	Mouth dry	5	3.89	4.80	1.80	1.75	1.35	1.91	0.88
Milnacipran	Dyspepsia	7	2.42	2.58	1.19	1.17	1.00	1.56	0.85
	Dysuria	4	11.24	11.88	4.08	4.08	1.82	2.67	1.00
Mirtazapine	Somnolence	30	1.62	1.72	1.15	1.16	0.63	1.44	1.07
	Weight increase	7	2.97	3.03	1.38	1.37	1.16	1.74	0.92
	Apathy	6	4.07	4.16	1.74	1.74	1.39	2.03	0.97
Nortriptyline	Mouth dry	38	2.33	2.53	1.70	1.77	1.08	1.99	1.50
	Constipation	37	2.49	2.72	1.81	1.89	1.16	2.12	1.58
	Palpitation	8	2.29	2.33	1.11	1.11	0.92	1.51	0.86

	Temperature changed sensation	6	3.48	3.54	1.48	1.48	1.23	1.80	0.90
	Micturition disorder	5	4.23	4.29	1.63	1.63	1.32	1.85	0.87
	Tachycardia	5	9.24	9.39	3.23	3.24	1.74	2.69	1.09
	Oliguria	3	12.19	12.32	2.93	2.93	1.49	1.91	0.75
	Sleep disorder	3	4.69	4.73	1.34	1.34	1.15	1.50	0.67
Sertraline	Tremor	3	4.17	4.33	1.35	1.33	1.18	1.51	0.67
Tianeptine	Palpitation	6	4.02	4.18	1.78	1.78	1.42	2.08	0.98
	Myalgia	5	5.10	5.28	2.07	2.06	1.52	2.18	0.95
	Temperature changed sensation	5	6.80	7.05	2.71	2.72	1.70	2.56	1.05
	Fever	3	3.67	3.74	1.15	1.14	1.08	1.43	0.65
Trazodone	Delirium	3	4.98	5.06	1.50	1.49	1.23	1.57	0.68
	Hypotension	3	11.63	11.82	3.18	3.17	1.55	1.98	0.77
Venlafaxine	Asthenia	3	3.22	3.33	1.04	1.02	1.01	1.37	0.63
Vortioxetine	Nausea	14	1.73	1.85	1.06	1.04	0.69	1.41	0.92
	Pruritus	9	4.53	4.87	2.36	2.40	1.67	2.83	1.41
	Anorexia	5	2.60	2.69	1.09	1.07	1.00	1.47	0.75

3.1.2 HIRA

3.1.2.1 Characteristics of patients taking antidepressants

The HIRA database covering the information of 1,473,083 patients, consists of three datasets: basic information, outpatient prescription information and inpatient prescription information. First, patients who took antidepressants in 2017 were identified with 59,275 people taking 246,337 outpatient prescriptions and 58,354 people taking inpatient ones. After the data analysis and prescription date filtering, 90,228 patients in total were found with 536,597 antidepressant prescriptions from 1st Jan 2017 to 31st Dec 2017 (Figure 6).

Table 7 shows the characteristics of those receiving antidepressants. Among them, most patients (20.39%) came from the 50-59 age group, and 61.20% were female. Most of the patients got TCAs (51.82%) and SSRIs (48.32%) for prescriptions, while only a small part of the patients got MAOIs for prescriptions, occupying 0.03%. As for the frequency of ADRs, it was the highest in the patient group aged 60-69 (2.13%). Also, it was found that the frequencies of ADRs were similar for both males and females, with 1.87% and 1.73%, respectively. Regarding different types of antidepressants, for those who took NaSSAs, the frequency of ADRs was the highest, reaching 2.90%, followed by those of SNRIs (2.65%), SARIs (2.34%), SSRIs (1.92%), SRAs (1.63%), TCAs (1.61%), and MAOIs (0%).

Figure 6. Selection of data in HIRA-NPS

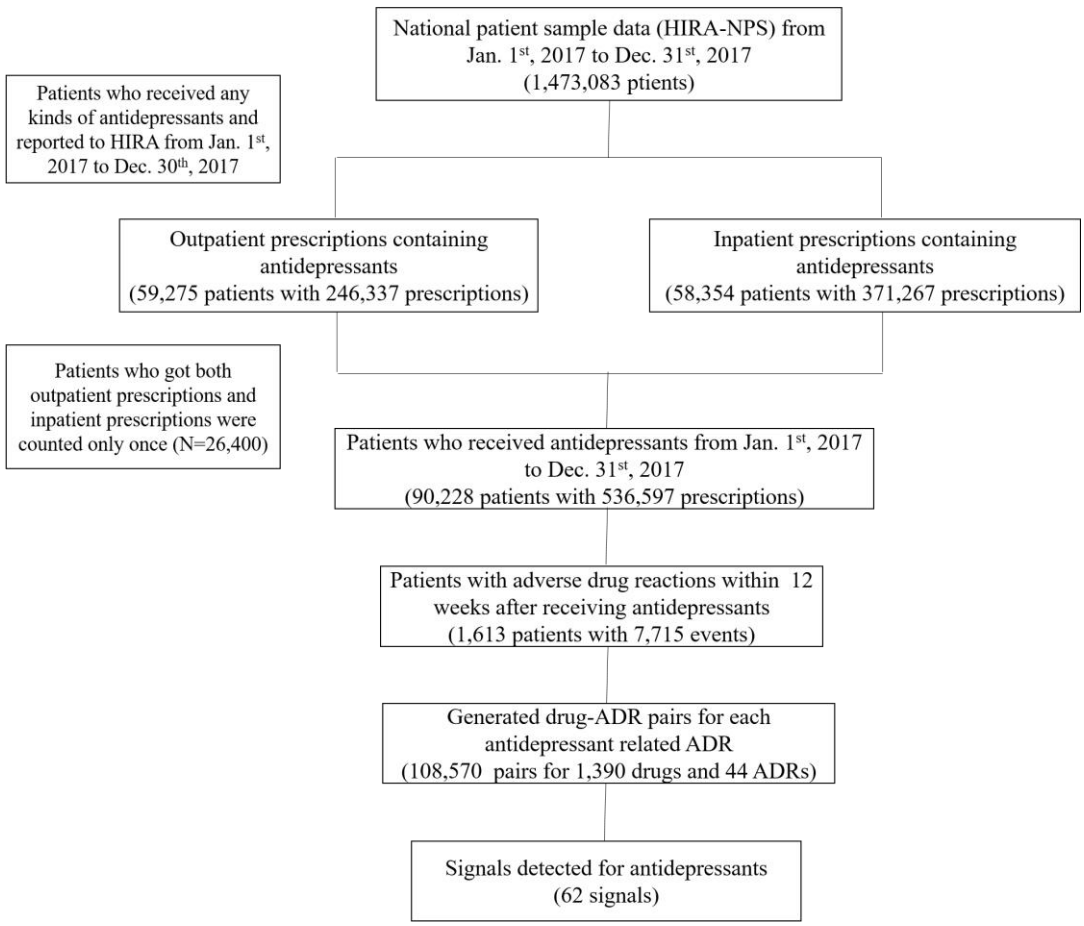


Table 7. Characteristics of patients receiving antidepressants in HIRA

Characteristics	Patients receiving antidepressants	Patients with ADRs	Frequency of ADRs
Total	**90,228**	**1,613**	**0.95%**
Age			
0-19	2,891 (3.20%)	33 (2.05%)	1.14%
20-29	6,015 (6.67%)	66 (4.09%)	1.10%
30-39	8,167 (9.05%)	124 (7.69%)	1.52%
40-49	12,473 (13.82%)	212 (13.14%)	1.70%
50-59	18,393 (20.39%)	364 (22.57%)	1.98%
60-69	17,886 (19.82%)	381 (23.62%)	2.13%
70+	24,403 (27.05%)	433 (26.84%)	1.77%
Gender			
Male	35,008 (38.80%)	656 (40.67%)	1.87%
Female	55,220 (61.20%)	957 (59.33%)	1.73%
Types of antidepressants			
NaSSA	4,447 (4.93%)	129 (5.73%)	2.90%
SNRI	5,140 (5.70%)	136 (6.04%)	2.65%
SARI	15,607 (17.30%)	365 (16.22%)	2.34%
SSRI	43,596 (48.32%)	837 (37.20%)	1.92%
SRA	1,958 (2.17%)	32 (1.42%)	1.63%
TCA	46,758 (51.82%)	751 (33.38%)	1.61%
MAOI	30 (0.03%)	0 (0.00%)	0.00%

After the linkage between the antidepressant usage and the ADRs occurrence, 7,715 antidepressant-ADR pairs were identified. As presented in Table 8, for individual drugs, most of the ADRs were related to trazodone (1347 pairs, 17.5%), amitriptyline (1288 pairs, 16.7%) and escitalopram (1108 pairs, 14.4%). When drug types were considered, most of the ADRs were connected to SSRIs (2817 pairs, 36.5%), TCAs (2618 pairs, 33.9%), SARIs (1347 pairs, 17.5%), SNRIs (410 pairs, 5.3%), NsSSAs (391 pairs, 5.1%), and SRAs (132 pairs, 1.7%). In addition, 2.76% of drug-ADR pairs were related to tremors (Table 9).

Table 8. The count of ADRs for antidepressants in HIRA-NPS

Drug	ADR count (% in total pairs)	Drug type	Total
Escitalopram	1108 (22.6%)	SSRI	2817 (57.5%)
Duloxetine	578 (11.8%)		
Fluoxetine	301 (6.1%)		
Sertraline	331 (6.8%)		
Paroxetine	368 (7.5%)		
Desvenlafaxine	65 (1.3%)		
Fluvoxamine	66 (1.3%)		
Amitriptyline	1288 (26.3%)	TCA	2618 (53.5%)
Tianeptine	573 (11.7%)		
Imipramine	573 (11.7%)		
Doxepin	146 (3.0%)		
Clomipramine	23 (0.5%)		
Amoxapine	15 (0.3%)		
Trazodone	1347 (27.5%)	SARI	1347 (27.5%)
Milnacipran	88 (1.8%)	SNRI	410 (8.4%)
Venlafaxine	201 (4.1%)		
Bupropion	121 (2.5%)		
Mirtazapine	391 (8.0%)	NaSSAs	391 (8.0%)
Vortioxetine	132 (2.7%)	SRA	132 (2.7%)

Table 9. Top5 most after-antidepressant ADRs, drug-ADR pairs

Top 5 most after-antidepressant ADRs	**Counts (%)**
Tremor	2996 (2.76%)
Unspecified toxic liver disease	1276 (1.18%)
Myoclonus	356 (0.33%)
Epileptic seizures	326 (0.30%)
Mental disorders	320 (0.29%)
Top 5 most drug-ADR pairs	**Counts (%)**
Trazodone-tremor	543 (0.50%)
Amitriptyline- tremor	504 (0.46%)
Imipramine- tremor	403 (0.37%)
Escitalopram- tremor	390 (0.36%)
Tianeptine-toxic liver disease	177 (0.16%)

3.1.2.2 Signals detected in HIRA

For each after-antidepressant ADR, all the drugs used in the previous 12 weeks were paired with the ADRs. Altogether, 108,570 drug-ADR pairs were generated and used to conduct signal detection. Bayesian and non-Bayesian methods were used, and 7 data mining indicators were calculated. In total, 62 signals that consisted of antidepressants were detected. Table 10 exhibits all the signals detected. The number of detected signals that consisted of duloxetine was the highest with 7 signals, followed by those of tianeptine (6 signals) and amitriptyline (5 signals).

Like KAERS, PRRCI and RORCI generated most of the signals (62 signals), while IC showed similar results with 57 signals. The indicators PRR and ROR were found to have similar results with 43 and 45 signals, respectively. EBGM and EB05 generated fewer signals than other indicators, only 28 and 22 signals were detected. In all the signals detected, 57 of them were labeled according to the FDA of the United States and the MFDS of South Korea. However, the other 5 ADRs have not been labeled yet with signals in red.

Table 10. Detected signals of antidepressants in HIRA-NPS

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05	RR	RRlower	ADR incidence (*)
Amitriptyline	Tremor	504	1.52	1.86	1.42	1.66	0.59	1.51	1.40	0.58	0.42	0.20%
	Myoclonus	**103**	**1.38**	**1.42**	**1.15**	**1.16**	**0.45**	**1.36**	**1.15**	**1.42**	**0.92**	**0.13%**
	Toxic liver disease	29	1.85	1.87	1.29	1.29	0.83	1.70	1.25	0.90	0.36	0.03%
	Analgesic nephropathy	16	8.77	8.87	5.25	5.28	2.50	7.51	4.75	Inf	NA	0.00%
	Headache	14	1.98	1.99	1.17	1.17	0.88	1.68	1.08	2.37	0.72	0.02%
Amoxapine	Other disorders of liver	9	28.52	69.79	18.83	24.82	2.90	22.48	12.47	5.50	0.76	0.24%
Bupropion	Dystonia	29	15.33	19.85	11.13	13.04	3.35	14.40	10.49	2.02	0.27	0.05%
	Mental disorders	24	6.46	7.81	4.51	4.99	2.39	6.12	4.20	3.31	1.03	0.16%
	Epileptic seizures	11	2.62	2.78	1.49	1.49	1.19	2.04	1.22	2.02	0.49	0.11%
	Pancreatitis	4	16.52	17.05	6.25	6.24	2.00	10.22	2.47	97.15	8.81	0.11%
Clomipramine	Tremor	13	2.19	3.73	1.53	1.63	0.96	1.82	1.14	3.60	1.35	1.07%
	Hepatitis	6	5.71	7.37	2.87	2.90	1.74	3.65	1.47	3.34	0.46	0.27%
Desvenlafaxine	Tremor	33	1.96	2.96	1.55	1.82	0.91	1.83	1.37	2.95	1.22	0.88%
	Hepatic necrosis	9	3.19	3.54	1.74	1.75	1.37	2.29	1.28	6.28	2.32	0.70%
	Localized skin eruption	8	7.79	8.74	4.06	4.16	2.14	6.32	2.70	4.91	0.67	0.18%
Doxepin	Generalized skin eruption	26	3.17	3.64	2.24	2.38	1.54	2.79	1.97	1.92	0.84	0.17%
	Mental disorders	9	2.00	2.06	1.06	1.05	0.85	1.59	0.92	2.93	1.16	0.14%
Duloxetine	Toxic liver disease	149	1.35	1.47	1.17	1.22	0.42	1.33	1.16	1.39	1.06	0.61%
	Epileptic seizures	56	2.81	3.00	2.19	2.28	1.43	2.62	2.09	1.12	0.48	0.06%
	Polyneuropathy	28	4.05	4.20	2.81	2.86	1.85	3.60	2.52	12.30	4.38	0.09%
	Myelopathy	**22**	**3.56**	**3.66**	**2.35**	**2.38**	**1.66**	**3.03**	**2.06**	**8.88**	**4.05**	**0.13%**
	Other disorders of liver	20	1.64	1.67	1.07	1.07	0.67	1.50	1.03	1.74	0.77	0.07%
	Chronic lobular hepatitis	5	4.60	4.63	1.90	1.90	1.50	2.54	1.08	12.30	2.06	0.03%
	Unspecified contact dermatitis	5	4.69	4.73	1.94	1.94	1.52	2.59	1.10	8.20	1.16	0.02%
Escitalopram	Tremor	390	1.37	1.57	1.26	1.38	0.44	1.36	1.25	1.67	1.30	0.43%
	Irritant contact dermatitis	41	1.72	1.75	1.27	1.28	0.75	1.63	1.25	1.08	0.22	0.01%
	Folate deficiency anaemia	20	5.67	5.76	3.63	3.65	2.16	4.97	3.17	16.21	1.89	0.02%
	Cholestasis	9	4.72	4.75	2.42	2.43	1.74	3.30	1.67	Inf	NA	0.01%
Fluoxetine	Tremor	159	2.05	3.22	1.84	2.57	1.02	2.01	1.76	1.78	1.24	0.51%
	Epileptic seizures	40	3.85	4.28	2.88	3.07	1.83	3.55	2.66	1.82	0.77	0.10%
Fluvoxamine	Tremor	35	2.05	3.24	1.63	2.00	0.97	1.91	1.44	1.69	0.63	0.51%
	Gastroenteritis and colitis	10	8.02	9.27	4.52	4.72	2.28	6.98	3.53	11.31	3.46	0.38%
Imipramine	Tremor	403	2.74	6.88	2.60	5.75	1.43	2.70	2.48	3.20	2.22	0.88%
	Epileptic seizures	46	2.32	2.44	1.76	1.80	1.16	2.17	1.69	2.08	0.75	0.11%

Milnacipran	Tremor	31	1.36	1.56	1.03	1.01	0.41	1.30	0.97	2.27	1.13	0.67%
	Hepatitis	10	2.49	2.68	1.39	1.38	1.12	1.92	1.13	3.20	1.01	0.25%
	Osteoporosis	8	5.02	5.42	2.59	2.62	1.78	3.55	1.67	9.33	2.81	0.25%
	Myopathy	4	4.96	5.15	1.90	1.88	1.46	2.46	0.95	3.11	0.42	0.08%
Mirtazapine	Tremor	127	1.26	1.38	1.09	1.12	0.32	1.24	1.07	2.13	1.44	0.61%
	Mental disorders	48	4.02	4.44	3.08	3.28	1.90	3.76	2.89	6.61	3.44	0.27%
	Irritant contact dermatitis	30	3.57	3.79	2.53	2.60	1.71	3.19	2.29	6.43	1.30	0.04%
	Folate deficiency anaemia	6	4.66	4.72	2.09	2.09	1.60	2.83	1.26	3.86	0.45	0.02%
Paroxetine	Tremor	174	1.83	2.58	1.65	2.10	0.86	1.80	1.59	1.36	0.89	0.40%
	Chronic active hepatitis	10	14.93	15.31	7.97	8.04	2.69	12.51	7.14	13.95	0.87	0.02%
Sertraline	Tremor	175	2.05	3.23	1.85	2.60	1.02	2.01	1.78	2.34	1.62	0.65%
	Mental disorders	17	1.67	1.70	1.05	1.04	0.68	1.50	1.00	2.55	1.09	0.12%
Tianeptine	Toxic liver disease	177	1.62	1.90	1.43	1.59	0.68	1.60	1.41	0.80	0.62	0.38%
	Ulcer of oesophagus	**42**	**2.23**	**2.33**	**1.66**	**1.70**	**1.11**	**2.08**	**1.60**	**1.57**	**0.89**	**0.09%**
	Hepatic necrosis	41	1.65	1.70	1.23	1.24	0.69	1.57	1.21	1.20	0.76	0.13%
	Other disorders of liver	29	2.41	2.49	1.69	1.71	1.19	2.17	1.59	2.80	1.49	0.09%
	Gastroenteritis and colitis	**25**	**2.32**	**2.38**	**1.57**	**1.59**	**1.13**	**2.06**	**1.47**	**0.52**	**0.18**	**0.02%**
	Osteomalacia	**7**	**7.72**	**7.80**	**3.64**	**3.65**	**2.04**	**5.68**	**2.21**	**Inf**	**NA**	**0.01%**
Trazodone	Tremor	543	1.57	1.95	1.47	1.75	0.64	1.55	1.45	1.73	1.32	0.46%
	Mental disorders	76	1.85	1.90	1.48	1.50	0.85	1.77	1.46	4.58	2.59	0.15%
	Irritant contact dermatitis	42	1.45	1.46	1.07	1.07	0.51	1.39	1.07	1.59	0.32	0.01%
	Cholestasis	6	2.54	2.55	1.13	1.13	1.03	1.71	0.87	2.39	0.22	0.01%
Venlafaxine	Tremor	112	2.16	3.62	1.91	2.74	1.09	2.10	1.80	3.65	2.40	1.03%
	Mental disorders	20	3.23	3.48	2.13	2.19	1.54	2.74	1.84	4.47	1.77	0.21%
	Allergic contact dermatitis	11	5.55	5.81	3.11	3.15	1.99	4.51	2.30	3.63	1.11	0.13%
Vortioxetine	Tremor	86	2.52	5.37	2.23	3.76	1.30	2.43	2.03	2.27	1.30	0.66%
	Mental disorders	13	3.20	3.44	1.91	1.94	1.45	2.51	1.53	2.00	0.49	0.10%
	Unspecified contact dermatitis	4	16.43	16.91	6.20	6.19	2.00	10.15	2.44	15.03	1.56	0.05%

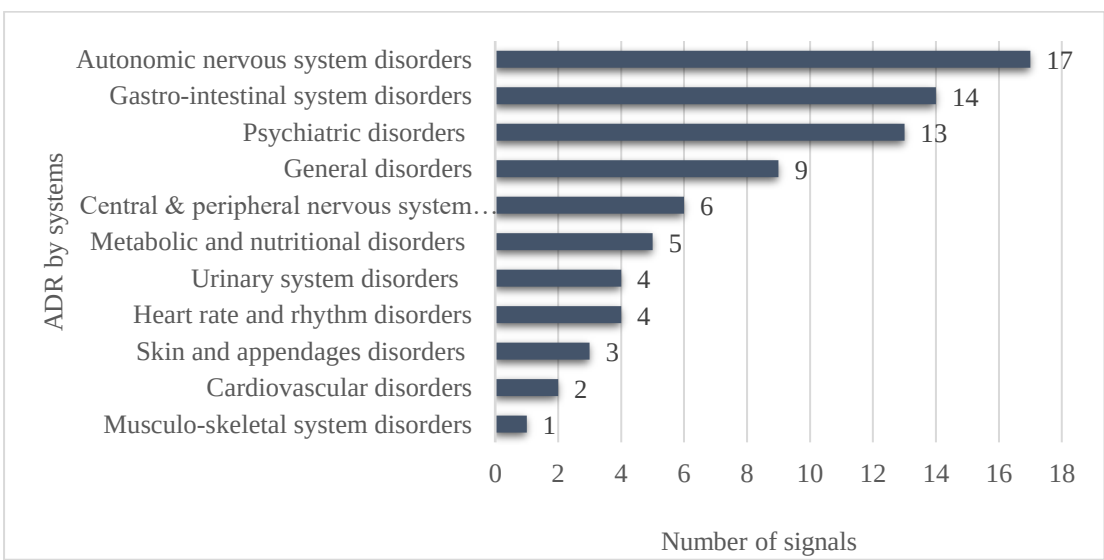
$$*Incidence = \frac{Number\ of\ patients\ who\ took\ specific\ antidepressants\ and\ had\ the\ occurance\ of\ specific\ ADR}{Number\ of\ patients\ who\ took\ the\ specific\ antidepressants}$$

3.1.3 Comparison

Figure 7 exhibits the characteristics of the signals detected in KAERS. Most of them consisted of autonomic nervous system disorders (N=17, 33.3%), followed by gastrointestinal system disorders (N=14, 27.5%), and psychiatric disorders (N=13, 25.5%). Figure 7c displays all the EBGM values for all the drug-ADR combinations that consist of antidepressants, where each large rectangle corresponds to a particular system organ class. The size of the rectangle corresponds to the number of drug-ADR pairs, whereas the shade of blue depends on the EBGM value. As for drug types, TCAs showed most signals (N=21, 41.2%), followed by SSRIs (N=16, 31.4%), SNRIs (N=6, 11.8%), NaSSAs (N=3, 5.9%), SRA (N=3, 5.9%), and SARI (N=2, 3.9%).

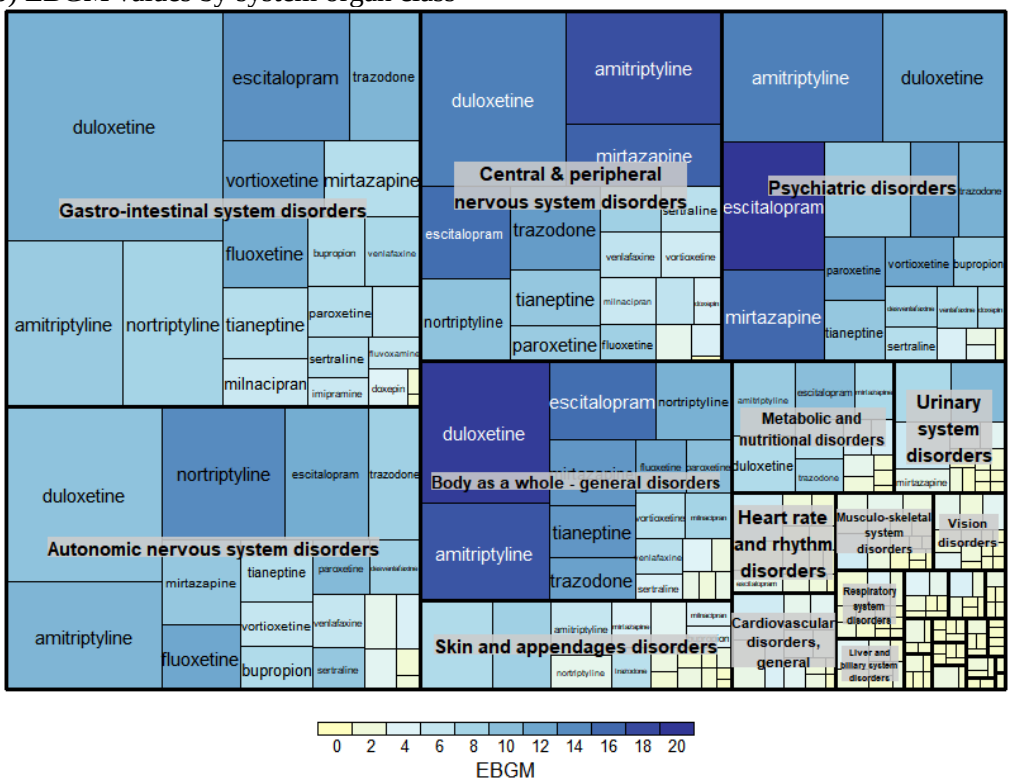
Figure 7. Characteristics of signals detected in KAERS

(a) Number of signals by system organ class



** One ADR can belong to more than one organ systems*

(b) EBGM values by system organ class



** The size of the rectangle corresponds to the number of drug-ADR pairs, whereas the shade of blue depends on the EBGM value.*

(c) Number of signals by drug type

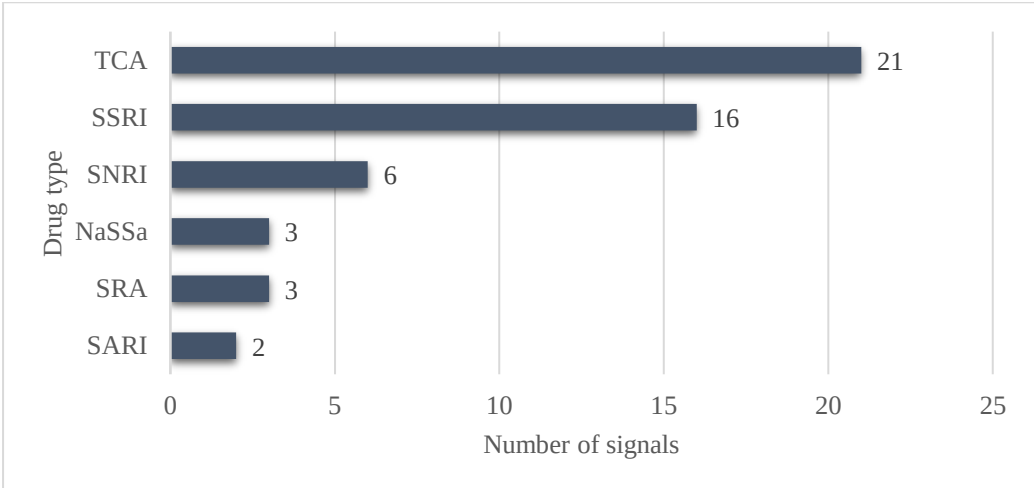
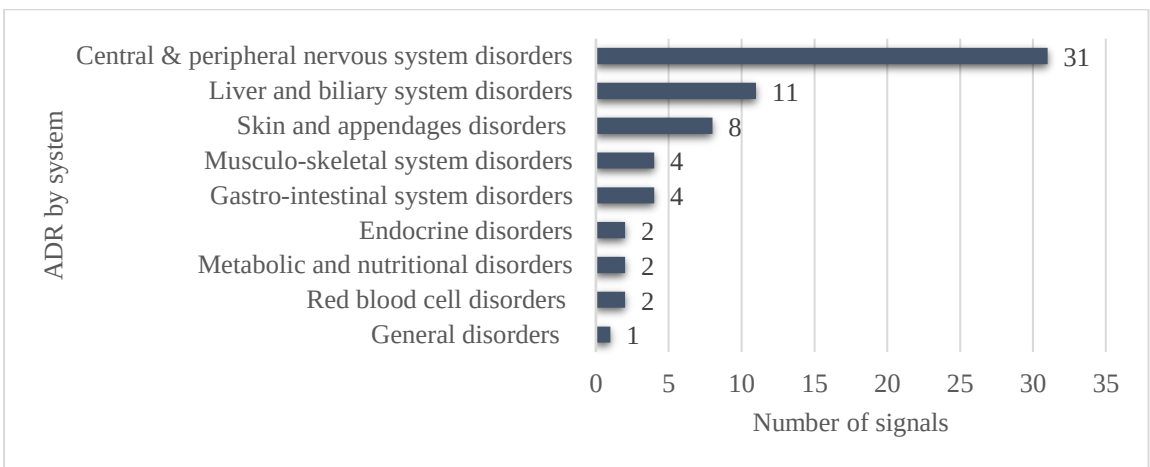


Figure 8 shows the characteristics of the signals detected in HIRA. Most of the detected signals were central & peripheral nervous system disorders (N=31, 50%), then liver and biliary system disorders (N=11, 17.7%), skin and appendages disorders (N=8, 12.9%), musculoskeletal system disorders (N=4, 6.5%) and Gastro-intestinal system disorders (N=4, 6.5%). Figure 8c displays all the EBGM values for all drug-ADR combinations that consist of antidepressants, where each large rectangle corresponds to a particular system organ class. Regarding drug types, SSRIs showed most signals (N=22, 35.5%), followed by TCAs (N=18, 29.0%), SNRIs (N=11, 17.7%), SARIs (N=4, 6.5%), NaSSAs (N=4, 6.5%) and SRAs (N=3, 4.8%).

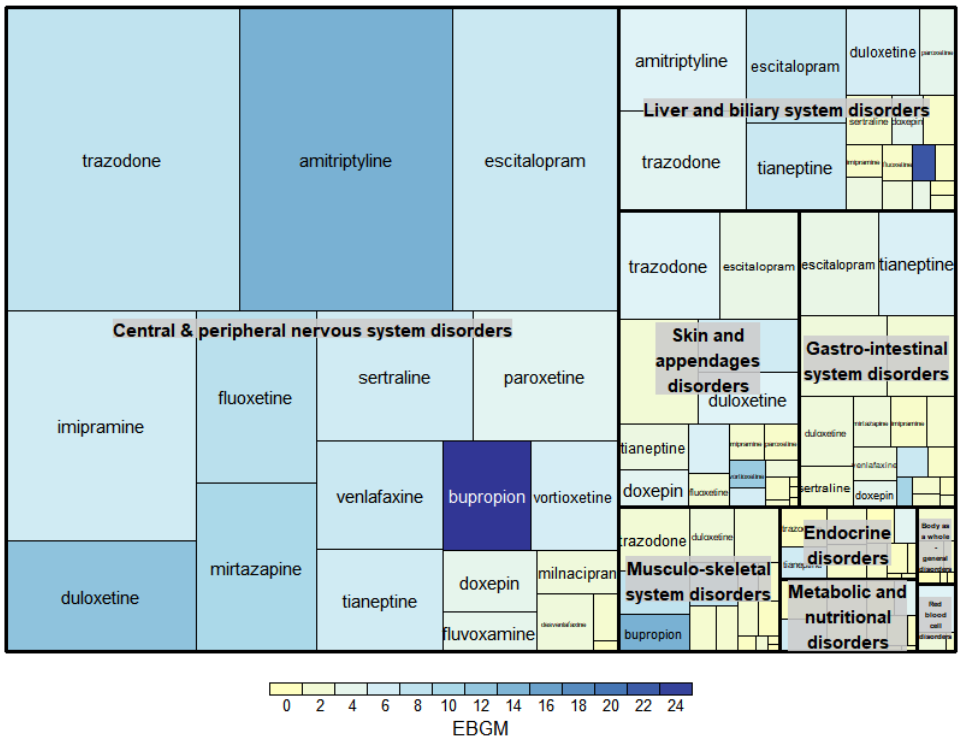
Figure 8. Characteristics of signals detected in HIRA

(a) Number of signals by systems



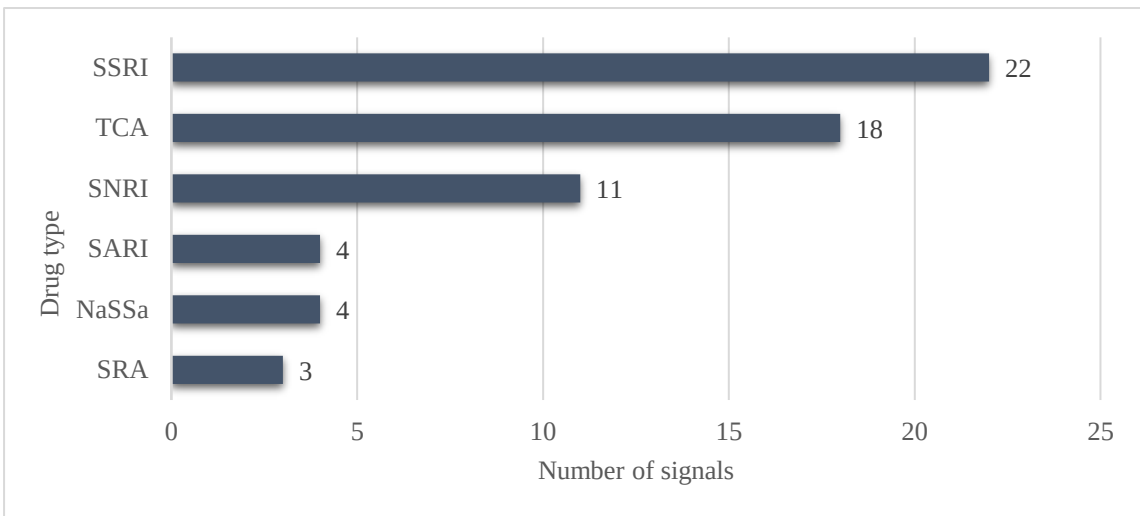
** One ADR can belong to more than one organ systems*

(b) EBGM values by system organ class



* The size of the rectangle corresponds to the number of drug-ADR pairs, whereas the shade of blue depends on the EBGM value.

(c) Number of signals by drug type



For the two systems, the common ADR coverage (CAC) of signals detected was checked according to the IBM Micromedex ® database, the Korea Pharmaceutical Information Center database and the collected labeling information. In the 51 signals detected in KAERS, 35 signals (68.63%) were associated with common ADRs (recorded incidence > 1%). While in HIRA, only 29.03% of the signals (18 in 62 signals) were concerned with common ADRs.

Table 11 shows the comparison of labeling information coverage (LIC) between the two databases. For both the two databases, PRRCI generated most of the signals, and thus, more unlabeled signals were detected via PRRCI. In KAERS, no unlabeled signals were detected; therefore, the mAP was 1.00 for all indicators. In HIRA, EB05 produced the least of the signals, but the accuracy was higher (mAP=0.983).

Table 11.Comparison of labeling information coverage between KAERS and HIRA

Database		**KAERS**	**HIRA**
Number of signals detected (unlabeled)	**PRR**	36 (0)	43 (4)
	ROR	37 (0)	45 (4)
	PRRCI	51 (0)	62 (5)
	RORCI	49 (0)	62 (5)
	IC	24 (0)	57 (5)
	EBGM	4 (0)	28 (2)
	EB05	2 (0)	22 (2)
mAP	**PRR**	1.00	0.944
	ROR	1.00	0.955
	PRRCI	1.00	0.936
	RORCI	1.00	0.947
	IC	1.00	0.933
	EBGM	1.00	0.951
	EB05	1.00	0.983

3.2 Verification of the signals detected

3.2.1 Protopathic bias evaluation

Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD) was used to eliminate protopathic bias. As shown in Table 12, for every unlabeled drug-ADR combination, the number of prescriptions 12 weeks before the first occurrence of the ADR and 12 weeks after the ADR were counted and tested with the one-tailed binomial test.

The combination of duloxetine and myelopathy is likely due to protopathic bias. After data processing, 34 prescriptions of duloxetine were initiated 12 weeks before myelopathy, and 44 created 12 weeks later. There is a significant increase ($P<0.05$) of prescription before and after the ADR, which indicates that the signal is probably caused by protopathic bias.

Table 12. LEOPARD and reporting situation for unlabeled signals

Drug	ADR	Number of patients	Prescriptions before ADR	Prescriptions after ADR	P-value
Amitriptyline	Myoclonus	30	54	65	0.1797
Duloxetine	Myelopathy	13	34	44	0.01026
Tianeptine	Ulcer of oesophagus	17	24	27	0.3899
	Gastroenteritis and colitis	4	4	3	0.7734
	Osteomalacia	2	3	1	0.9375

**Oesophageal haemorrhage(1), oesophagitis(3)*

3.2.2 Relative risk (RR)

For each drug-ADR combination, the RR and the confidence interval were also calculated. Two of the five unlabeled signals showed statistically significant risk compared to other antidepressants: duloxetine-myelopathy and tianeptine-osteomalacia. All drug-ADR combinations with a lower bond greater than 1 are listed in Table 13.

Table 13. Drug-ADR combinations with lower bonds greater than 1

Drug	ADR	Number of patients	RR	RR lower	RR upper	ADR incidence
Amitriptyline	Nephropathy	4	5.68	1.04	31.01	0.02%
	Osteonecrosis	8	3.25	1.18	8.95	0.03%
Bupropion	Acute pancreatitis	2	97.15	8.81	1070.97	0.11%
	Hypotension	1	48.58	3.04	776.34	0.05%
	Mental disorders	3	3.31	1.03	10.66	0.16%
	Tremor	13	2.45	1.40	4.26	0.71%
Clomipramine	Tremor	4	3.60	1.35	9.61	1.07%
Desvenlafaxine	Mental disorders	2	6.98	1.70	28.70	0.35%
	Hepatic necrosis	4	6.28	2.32	17.00	0.70%
	Mucositis	3	5.68	1.80	17.90	0.53%
	Tremor	5	2.95	1.22	7.12	0.88%
Doxepin	Acute pancreatitis	1	12.30	1.12	135.60	0.03%
	Fever	1	12.30	1.12	135.60	0.03%
	Chronic persistent hepatitis	2	8.20	1.66	40.61	0.06%
	Toxic liver disease	3	3.35	1.00	11.20	0.09%
	Mental disorders	5	2.93	1.16	7.40	0.14%
Duloxetine	Polyneuropathy	9	12.30	4.38	34.55	0.09%
	Chronic lobular hepatitis	3	12.30	2.06	73.61	0.03%
	Myelopathy	13	8.88	4.05	19.46	0.13%
	Unspecified contact dermatitis	2	8.20	1.16	58.21	0.02%
	Mucositis	16	1.87	1.09	3.23	0.16%
	Unspecified toxic liver disease	60	1.39	1.06	1.83	0.61%
Escitalopram	Folate deficiency anaemia	5	16.21	1.89	138.73	0.02%
	Mental disorders	17	1.84	1.01	3.33	0.08%
	Tremor	92	1.67	1.30	2.14	0.43%
Fluoxetine	Tremor	32	1.78	1.24	2.58	0.51%
Fluvoxamine	Osteomalacia	1	113.07	7.08	1806.17	0.13%
	Unspecified contact dermatitis	1	37.69	3.92	361.95	0.13%

	Gastroenteritis and colitis	3	11.31	3.46	36.97	0.38%
Imipramine	Osteoporosis	1	11.95	1.08	131.79	0.03%
	Fever	1	11.95	1.08	131.79	0.03%
	Myopathy	4	4.55	1.56	13.26	0.11%
	Tremor	32	3.20	2.22	4.62	0.88%
	Mucositis	9	2.79	1.40	5.57	0.25%
Milnacipran	Osteomalacia	1	74.63	4.67	1192.53	0.08%
	Systemic lupus erythematosus	1	37.32	3.39	411.26	0.08%
	Osteoporosis	1	37.32	3.39	411.26	0.08%
	Fever	1	37.32	3.39	411.26	0.08%
	Unspecified contact dermatitis	1	24.88	2.59	238.99	0.08%
	Nephropathy	1	14.93	1.75	127.67	0.08%
	Irritant contact dermatitis	1	10.66	1.31	86.59	0.08%
	Osteoporosis	3	9.33	2.81	30.94	0.25%
	Hepatitis	3	3.20	1.01	10.14	0.25%
	Tremor	8	2.27	1.13	4.58	0.67%
Mirtazapine	Mental disorders	12	6.61	3.44	12.73	0.27%
	Irritant contact dermatitis	2	6.43	1.30	31.85	0.04%
	Localized skin eruption	5	3.44	1.33	8.92	0.11%
	Osteoporosis	4	3.35	1.16	9.70	0.09%
	Epileptic seizures	6	2.63	1.12	6.17	0.13%
	Generalized skin eruption	9	2.35	1.18	4.68	0.20%
	Tremor	27	2.13	1.44	3.17	0.61%
Sertraline	Osteoporosis	4	3.04	1.05	8.78	0.08%
	Mental disorders	6	2.55	1.09	6.02	0.12%
	Tremor	32	2.34	1.62	3.38	0.65%
Tianeptine	Other disorders of liver	17	2.80	1.49	5.23	0.09%
Trazodone	Mental disorders	23	4.58	2.59	8.12	0.15%
	Dystonia	10	3.19	1.43	7.09	0.06%
	Epileptic seizures	20	3.19	1.81	5.61	0.13%
	Allergic contact dermatitis	13	2.96	1.48	5.91	0.08%
	Tremor	72	1.73	1.32	2.26	0.46%
Venlafaxine	Mental disorders	5	4.47	1.77	11.29	0.21%
	Mucositis	8	3.85	1.86	7.96	0.34%
	Tremor	24	3.65	2.40	5.54	1.03%
	Allergic contact dermatitis	3	3.63	1.11	11.88	0.13%
	Epileptic seizures	4	3.26	1.18	9.06	0.17%
Vortioxetine	Unspecified contact dermatitis	1	15.03	1.56	144.41	0.05%
	Nephropathy	1	9.02	1.05	77.14	0.05%
	Tremor	13	2.27	1.30	3.96	0.66%

3.3 Signal profiles change depending on demographics and time windows

While signal detection was conducted in subgroups of patients with different demographic characteristics, the HIRA database showed lower CACs and LICs than the KAERS database. The change of signal profiles by demographics is illustrated in Table 14. In KAERS, drug-ADR pairs from the females were much more than those from the males, and more signals were found in the female group than the male one with 50 and 22 signals, respectively. Also, the signals detected in the female group showed a higher CAC (72.00% VS 68.18%).

In HIRA, both the male and female groups showed 51 signals, while 16 signals were found in both groups (Appendix 5). However, the female group exhibited a lower CAC than the male group (25.49% VS. 33.3%). More signals were detected in the elderly group than the young group (55 and 46 signals, respectively). Compared to the young group, the signals detected in the elderly group presented a lower CAC (18.18% VS. 31.91%).

Table 15 illustrates the change of signal profiles by different time windows (4, 8, 12 weeks) in HIRA and Appendix 6 shows all the signals detected. With a shorter time window, the number of drug-ADR pairs and signals detected decreased, CACs declined (29.03%, 27.87%, 27.27%), while LIC increased (0.983, 1.0, 1.0).

Table 14. Signal profiles change by demographics (HIRA & KAERS)

	Demographics	Patients receiving antidepressants	Patients with ADRs	ADR events	Drug-ADR pairs	Signals detected	CAC	LIC
KAERS	Full	NA	NA	2,242	5,992	51	68.63%	1.0
	Male			737	1,866	22	68.18%	1.0
	Female			1,473	4,014	50	72.00%	1.0
	Young (< 60)			1,005	2,685	34	72.73%	1.0
	Elderly (≥ 60)			1,105	3,051	29	72.41%	1.0
HIRA	Full	90,228	1,613	4,771	108,570	62	29.03%	0.983
	Male	35,008	656	1,787	41,903	51	33.33%	0.883
	Female	55,220	957	2,984	66,667	51	25.49%	0.975
	Young (< 60)	47,939	799	2,635	50,865	46	31.91%	0.986
	Elderly (≥ 60)	42,289	814	2,136	57,705	55	18.18%	0.996

**CAC: common ADR coverage; LIC: labeling information coverage (mAP for EB05)*

**Appendix 4 & Appendix 5 shows all the signals detected for different demographic subgroups*

Table 15. Signal profiles change by time windows (HIRA)

Time windows	Patients with ADRs	After-antidepressant ADRs	Drug-ADR pairs	Signals detected	CAC	LIC
12 weeks	1,613	4,771	108,570	62	29.03%	0.983
8 weeks	1,467	4,342	81,598	61	27.87%	1.0
4 weeks	1,160	3,292	45,638	55	27.27%	1.0

**CAC: common ADR coverage; LIC: labeling information coverage (mAP for EB05)*

**Appendix 6 shows all the signals detected for different time windows*

5. Discussion

5.1 Signals detected

For both HIRA and KAERS, most of the signals detected were nervous system disorders. Although various kinds of antidepressants have different mechanisms, most act on neurotransmitters or receptors, possibly leading to nervous system disorders [50]. Antidepressants also showed several disorders related to the liver and biliary system, skin and appendages, musculoskeletal system, gastro-intestinal system, urinary system, endocrine system, respiratory system, and reproductive disorders. A previous meta-analysis showed similar results. The authors found that antidepressants were associated with an increased risk for several physical diseases, including obesity, dyslipidemia, diabetes mellitus, thyroid disorders, hyponatremia, cardiovascular, respiratory tract, gastrointestinal, haematological, musculoskeletal and renal diseases, as well as movement and seizure disorders. Also, the elderly suffered greater absolute risk for most of these physical diseases [51]. Some previous studies showed that antidepressants are associated with suicidality [52-54], whereas no evidence was found in this study. In HIRA, drug-induced suicide could not be identified with diagnosis information, while in KAERS, only 4 reports were related to suicide attempts. Therefore, no signal related to suicide was detected.

5.2 Comparison between HIRA and KAERS

In this study, with the same research time, HIRA and KAERS presented different signal detection results. The numbers of signals detected in the KAERS and HIRA databases were 51 and 62, respectively. Most of the signals detected in KAERS consisted of autonomic nervous system disorders of SOC (N=17, 33.3%) and TCA (N=21, 41.2%) antidepressants while those in HIRA consisted of central & peripheral nervous system disorders of SOC (N=31, 50%) and SSRI (N=22, 35.5%) antidepressants.

With only 2017 data, HIRA had 5 of the signals detected that are not found in the drug labeling information while KAERS had 0. A previous study got similar results that the healthcare database EU-ADR was possible to identify a strong signal concerning rofecoxib and AMI since Q3 2000 (RR LGPS = 4.5 [95% CI: 2.84-6.72]) and the signal peaked to 4.8 in Q4 2000, whereas the SRS WHO-VigiBase was to identify the signal in the Q4 2004 (EB05 = 2.94) [55]. Also, HIRA showed a lower CAC than KAERS (29.03% [H] VS. 68.63% [K]). Therefore, we can infer that HIRA might have a more significant potential for detecting signals for the ADRs that are commonly not considered as antidepressants induced ones in some situations.

Table 16 demonstrates the differences of contained information between KAERS and HIRA databases. KAERS is an SRS, which focuses on the spontaneously reported ADR only; thus, only small sections of the subject's medical history are available. HIRA, however, contains more information not directly connected with the actual ADR. With extra information, more methods can be applied to the HIRA database. Protopathic bias elimination and risk assessment are only available in HIRA.

Table 16. Difference of contained data between KAERS and HIRA

	HIRA (Healthcare claims database)	KAERS (SRS)
Subjects	Patients with & without ADRs	Patients with ADRs
Data source	Claims data submitted by healthcare service providers	Spontaneous ADR reports
Drugs	Drugs covered by national insurance only	All drugs reported
ADRs	ADRs recorded with KCD code only	All ADRs reported
Information available	More information not directly connected with the actual ADR	Focus on the ADR only
Relationship of drug and ADR	Require generation of drug-ADR pairs	ADRs were reported together with the drug usage
Methods available	Disproportionality methods: PRR, ROR, PRRCI, RORCI Bayesian methods: IC, EBGM Cohort methods: RR Case-control methods: OR	Disproportionality methods: PRR, ROR, PRRCI, RORCI Bayesian methods: IC, EBGM
Elimination of protopathic bias	LEOPARD can be used to eliminate protopathic bias	Lack of information
Risk assessment	Available	Unavailable

KAERS is designed expressly for pharmacovigilance; thus, more drugs and ADRs can be detectable. WHO-ART codes are used to record the ADRs, including 2085 preferred and principal terms for describing ADRs [7]. However, KCD codes are used to describe ADRs in HIRA. KCD code was developed from the ICD code, which was primarily used for recording conditions, and only a limited number of codes can be used to describe ADRs [56]. Also, HIRA consists of the claims data, which exclude ADRs that would not affect daily life. In addition, some drugs not covered by insurance, such as hyperici herba, can only be monitored in KAERS.

Meanwhile, KAERS, as an SRS, bears a list of limitations. First, as the ADRs are spontaneously reported by pharmacists, physicians, patients, consumers, and even pharmaceutical companies, they inherently carry a considerable ratio of under-reporting. The situations for varied drugs are different, and thus the under-reporting proportion is

hard to estimate. At the same time, SRS also has the potential for over-reporting. Not all the ADRs were verified by experts, and the reports of ADRs could be influenced by many external factors, including the media, society and environment. For example, media coverage of a specific ADR for a drug may increase the number of spontaneous reports dramatically within a period. As discussed above, the KAERS database contains much less information than the HIRA database, leading to restricted research. Also, there may exist a delay in reporting in KAERS.

5.3 Validity of the unlabeled signals

Table 17. Summary of unlabeled signals detected in HIRA

Drug	ADR	Number of patients	Drug-ADR pairs	PRRCI	RORCI	IC	EB05	RR	ADR incidence	LEOPARD P-value
Amitriptyline	Myoclonus	30	103	1.15	1.16	0.45	1.15	1.42	0.13%	0.1797
Duloxetine	Myelopathy	13	22	2.35	2.38	1.66	2.06	8.88	0.13%	0.01026
Tianeptine	Ulcer of oesophagus	17	42	1.66	1.70	1.11	1.60	1.57	0.09%	0.3899
	Gastroenteritis and colitis	4	25	1.57	1.59	1.13	1.47	0.52	0.02%	0.7734
	Osteomalacia	2	7	3.64	3.65	2.04	2.21	Inf	0.01%	0.9375

All the signals detected in KAERS were labeled according to the Food and Drug Administration (FDA) of the United States and the Ministry of Food and Drug Safety (MFDS) of South Korea, while five unlabeled signals were detected in HIRA: amitriptyline-myoclonus, duloxetine-myelopathy, tianeptine-ulcer of oesophagus, tianeptine-gastroenteritis and colitis, and tianeptine-osteomalacia. Some previous studies or case reports related to the unlabeled signals were found. A study shows that 30 in 98 patients who had taken cyclic antidepressant therapy experienced clinically insignificant drug-associated myoclonus [57]. A case of myoclonus presenting as an adverse effect of amitriptyline was reported in Korea in 2006 [58]. Ulcer of oesophagus, gastroenteritis and colitis, as well as osteomalacia, were found related to tianeptine, which was not approved by the FDA for medical use within the United States. Thus, only Korean labeling information was available and verified. Although tianeptine-ulcer of oesophagus and tianeptine-gastroenteritis and colitis could not be found in the labeling information, gastrointestinal adverse effects were frequently observed in patients who had consumed antidepressants [58-60]. Osteomalacia is a rare adverse effect, which is a result of bone loss. Some previous studies showed that antidepressants are related to bone disorders. An analysis based on the French and Spanish pharmacovigilance databases consistently shows

that bone loss is relevant to antidepressants [61]. Other studies show that antidepressants are supposed to impair bone strength [62, 63].

For the combination duloxetine-myelopathy, duloxetine was found to be used to treat neuropathic pain, which may be caused by myelopathy [64, 65]. After valuation with LEOPARD, duloxetine-myelopathy was supposed to be caused by protopathic bias. However, even though LEOPARD has a positive effect on the signal detection performance, it cannot be used to rule out drug safety signals, but as an indication that protopathic bias might be present [66]. In the actual use of drugs, sometimes drugs possibly continue to be prescribed despite the occurrence of some ADRs.

5.4 Gender differences

In both KAERS and HIRA databases, more females turned out to report or be diagnosed with ADRs after taking antidepressants. A large number of epidemiological studies have suggested that females are more likely to be diagnosed with depression than males [67-69]; thus more females take antidepressants than males [70, 71].

In KAERS, higher CAC in the female group (female: 73.00%; male: 68.18%) suggests that the females suffer common ADRs more than males. Some previous studies using SRS databases support that being a female can increase the risk of common ADRs [72-74]. However, in HIRA, the male group has a higher CAC than the female group (female: 25.49%; male: 33.33%). The limited KCD codes used to identify ADRs in the HIRA database can explain the lower CACs compared to KAERS, but the reversed outcomes for gender in the two databases need to be investigated with further research.

Some other studies investigated the gender differences in antidepressant drug response and showed that there may be no significant difference between males and females [75, 76]. One of the studies based on a survey from France, Italy and Spain found that although there was a higher number of reports of ADRs in females, ADR reporting rates might be similar in males and females [75]. The other study reviewed the literature regarding the differences in the pharmacokinetics and pharmacodynamics of antidepressants in males and females and the impact of the differences on the occurrence of ADRs in clinical trials. It shows that there is no strong support for the gender differences in ADRs of antidepressants [76]. Further studies are needed to clarify the gender differences in antidepressant drug response.

5.5 Limitations

There were some limitations in this study. First, although the scale of the HIRA database was large, the research period was restricted to 12 months. Thus only 12-month of KAERS data was used for comparison. As the data provided by KIDS were only the reports containing antidepressants, only 2,242 reports with 5992 pairs were used for signal detection in the KAERS database. Whereas Ola et al recommended the minimum size of 500 reports for national databases in signal detection [77], the reports used in this study were not numerous. Also, the subjects of the two systems were a bit different. For the KAERS database, as the reports were reported anonymously, not all the drugs used before the occurrence of ADR were paired with the ADR. Second, in HIRA, ADRs were identified with the diagnosis information while the drug usages were identified with the prescription information, which might differ from patients' actual diagnosis and drug usage. However, previous studies which had used HIRA for signal detection showed relative high PPV [26, 78]. When generating the drug-ADR pairs, identical drug-ADR pairs were considered as ones to reduce bias to avoid multiple repairing. Therefore, the effect of the repeated use of drugs was not considered in this study. Third, for both systems, although some confounders were adjusted in the study, other factors might still influence the results. Furthermore, although the labeling information was collected and compared with the signals detected in the study, there is no gold standard for determining which system gets more accurate results; it is hard to measure the performance of each system fairly. However, as the signals detected could be evaluated separately, the two systems even with different signal results, are valuable in the post-market vigilance of drugs. Further research is needed to evaluate the signals detected for antidepressants.

6. Conclusion

The safety signals detected for antidepressants in HIRA (healthcare claims database) and KAERS (SRS) databases exhibited different signal profiles. The signals detected but not covered by drug labeling information, which were only detected in HIRA, need to be verified with further research. Safety signal detection in both healthcare claims and SRS databases would provide additional regulatory insight for pharmacovigilance. As healthcare claims databases have not been widely used for safety signal detection, in the future, healthcare claims databases could be applied more in post-market safety surveillance.

7. Appendix

Appendix 1. Formulas for Bayesian methods

1) Information component (IC)

Information component (IC) can be expressed as

$$IC_{ij} = log_2 \frac{N_{ij}}{E_{ij}}$$

where N_{ij} is the observed frequency of drug-ADR pairs and E_{ij} is the expected frequency of drug-ADR pairs.

Resulting from the Bayesian Confidence Propagation Neural Network analysis (BCPNN) [79-81], the expectation and variance of IC can be expressed as

$$E(IC_{ij}) = log_2 \frac{(n11 + \gamma_{ij})(N + \alpha)(N + \beta)}{(N + \gamma)(n10 + \alpha_i)(n01 + \beta_j)}$$

$$V(IC_{ij}) = \frac{\frac{N - n11 + \gamma - \gamma_{ij}}{(n11 + \gamma_{ij})(1 + N + \gamma)} + \frac{N - n10 + \alpha - \alpha_i}{(n10 + \alpha_i)(1 + N + \alpha)} + \frac{N - n01 + \beta - \beta_i}{(n01 + \beta_j)(1 + N + \beta)}}{(\log 2)^2}$$

where $\gamma = \gamma_{ij} \frac{(N+\alpha)(N+\beta)}{(n10+\alpha_i)(n10+\beta_j)}$, $\gamma_{ij} = \alpha_i = \beta_j = 1, \alpha = \beta = 2$, N is the total number of reports in the database [3].

The lower bound of an approximate 95% credible interval (IC - 2SD) was used for the signal indicator.

2) Empirical Bayes geometric mean (EBGM)

Assume that n_{ij} is a draw from a Poisson distribution, and $\mathrm{E}(N_{ij}) = u_{ij}$, then $\lambda_{ij} = \frac{u_{ij}}{E_{ij}}$, where λ_{ij} is a draw from a common prior distribution. The prior probability density of λ can be expressed as

$$\lambda \sim \pi(\lambda; \alpha_1, \beta_1, \alpha_2, \beta_2, \mathrm{P}) = Pg(\lambda; \alpha_1, \beta_1) + (1-P)g(\lambda; \alpha_2, \beta_2)$$

where $g(\lambda; \alpha, \beta)$ means gamma distribution with mean=α/β and variance= α/β^2.

Assume the distribution of N_{ij} is

$$\mathrm{P}(N = n) = Pf(n; \alpha_1, \beta_1, E) + (1-P)f(n; \alpha_2, \beta_2, E)$$

where

$$\mathrm{f}(\mathrm{n}; \alpha, \beta, \mathrm{E}) = (1 + \beta/\mathrm{E})^{-n}(1 + \mathrm{E}/\beta)^{-\alpha} \times \frac{\Gamma(\alpha + n)}{\Gamma(\alpha) n!}$$

Then according to the Bayes rule, the posterior probability Q_n that λ came from the first component of the mixture can be expressed as

$$Q_n = \frac{Pf(n; \alpha_1, \beta_1, E)}{Pf(n; \alpha_1, \beta_1, E) + (1-P)f(n; \alpha_2, \beta_2, E)}.$$

The posterior distribution can be expressed as

$$\lambda | \mathrm{N} = \mathrm{n} \sim \pi(\lambda; \alpha_1 + n, \beta_1 + E, \alpha_2 + n, \beta_2 + E, Q_n),$$

and

$$\mathrm{E}(\lambda | \mathrm{N} = \mathrm{n}) = Q_n(\alpha_1 + n)/(\beta_1 + E) + (1 - Q_n)(\alpha_2 + n)/(\beta_2 + E)$$

then

$$\mathrm{E}[\log(\lambda) | \mathrm{N} = \mathrm{n}] = Q_n[\Psi((\alpha_1 + n) - \log(\beta_1 + E)] + (1 - Q_n)[(\alpha_2 + n) - \log(\beta_2 + E)$$

$$\text{EBlog2} = (log2)^{-1}Q_n[\Psi((\alpha_1 + n) - \log(\beta_1 + E)] + (1 - Q_n)[(\alpha_2 + n) - \log(\beta_2 + E)$$

$$\text{EBGM} = 2^{EBlog2}.[8]$$

For a reasonably large sample, EBlog2 reduces to

$$\text{EBlog2} = \log[(1 + n11)/(1 + \frac{n10 \times n01}{n})]$$

When $Q_n = 1$ and $\alpha_1 = \beta_1 = 1$. Also, for a reasonably large sample, the expectation of IC showed above reduces to

$$\text{E(IC)} = \log[(1 + n11)/(1 + \frac{n10 \times n01}{n})] + \log[\frac{(2 + n)^2(1 + \frac{n10 \times n01}{n})}{(1 + n10)(1 + n01)(4 + n)}].$$

The second term of this expression can be written as

$$\log\left[\frac{(2 + n)^2\left(1 + \frac{n10 \times n01}{n}\right)}{(1 + n10)(1 + n01)(4 + n)}\right] \approx 1$$

for large n. In conclusion, EBlog2 and E(IC) have the same value when n is large and EBGM is the special case of IC.

3) The lower 5% point of empirical Bayes geometric mean (EBGM05)

The 95% posterior probability interval of λ is given by

$$EBGM_{ij} \exp\left\{-\frac{2}{\sqrt{N_{ij} + 1}}\right\} < \lambda_{ij} < EBGM_{ij} \exp\left\{\frac{2}{\sqrt{N_{ij} + 1}}\right\}$$

$$\text{EB05}=EBGM_{ij} \exp\left\{-\frac{2}{\sqrt{N_{ij}+1}}\right\}.$$

Appendix 2. Main ingredient codes in HIRA-NPS

Drug type	Drug name	Main ingredient codes	Drug type	Drug name	Main ingredient codes
SSRI	Fluoxetine	161501ACH	TCA	Tianeptine	229601ATB
		161501ATB		Imipramine	173701ATB
		161502ACH		Clomipramine	136301ACH
		161502ATB			136302ACH
	Citalopram	428301ATB		Amitriptyline	107501ATB
	Paroxetine	209301ATB			107502ATB
		209302ATB			107504ATB
		209304ATR		Doxepin	149203ATB
		209305ATR			149204ATB
	Sertraline	227001ATB		Amoxapine	108002ATB
		227002ATB	SNRI	Venlafaxine	247502ACR
		227003ATB			247504ACR
	Fluvoxamine	162501ATB		Milnacipran	355801ACH
		162502ATB			355802ACH
	Escitalopram	474801ATB			355803ACH
		474802ATB		Bupropion	428101ATB
		474803ATB			428102ATR
		474804ATB			428103ATR
	Duloxetine	495501ACE	SARI	Trazodone	242901ACH
		495501ATE			242901ATB
		495502ACE			242902ATB
		495502ATE			242903ATR
	Desvenlafaxine	626401ATR	NaSSA	Mirtazapine	196201ATB
		626402ATR			196202ATB
		687601ATR			196204ATB
		687602ATR	SRA	Vortioxetine	628501ATB
		687701ATR			628502ATB
		687702ATR			628504ATB

Appendix 3. Identified ADRs in HIRA-NPS

KCD	ADR
D521	Drug-induced folate deficiency anaemia
D590	Drug-induced autoimmune haemolytic anaemia
D592	Drug-induced nonautoimmune haemolytic anaemia
D592	Drug-induced enzyme deficiency anaemia
D611	Drug-induced aplastic anaemia
D642	Secondary sideroblastic anaemia due to drugs and toxins
E064	Drug-induced thyroiditis
F106	Amnestic disorder, alcohol- or drug-induced
F116	Amnestic disorder, opioids- or drug-induced
F126	Amnestic disorder, cannabinoids- or drug-induced
F136	Amnestic disorder, sedatives or hypnotics- or drug-induced
F146	Amnestic disorder, cocaine- or drug-induced
F156	Amnestic disorder, other stimulants, including caffeine- or drug-induced
F166	Amnestic disorder, hallucinogens- or drug-induced
F176	Amnestic disorder, tobacco- or drug-induced
F186	Amnestic disorder, volatile solvents- or drug-induced
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
G240	Drug-induced dystonia
G251	Drug-induced tremor
G253	Drug-induced myoclonus
G254	Drug-induced chorea
G256	Drug-induced tics and other tics of organic origin
G258	Akathisia (drug-induced) (treatment-induced)
G405	Epileptic seizures related to drugs
G444	Drug-induced headache, NEC
G620	Drug-induced polyneuropathy
G711	Drug-induced myotonia
G720	Drug-induced myopathy
G958	Drug-induced myelopathy
I427	Cardiomyopathy due to drugs and other external agents
I952	Hypotension due to drugs
J702	Acute drug-induced interstitial lung disorders
J703	Chronic drug-induced interstitial lung disorders
J704	Drug-induced interstitial lung disorder, unspecified
K123	Drug-induced mucositis (oral)(oropharyngeal)
K221	Ulcer of oesophagus due to ingestion of drugs and medicaments
K521	Drug-induced gastroenteritis and colitis

K71	Drug-induced idiosyncratic (unpredictable) liver disease
K710	Toxic liver disease
K711	Toxic liver disease with cholestasis
K712	Toxic liver disease with hepatic necrosis
K713	Toxic liver disease with chronic persistent hepatitis
K714	Toxic liver disease with chronic lobular hepatitis
K715	Toxic liver disease with chronic active hepatitis
K716	Toxic liver disease with hepatitis, NEC
K717	Toxic liver disease with fibrosis and cirrhosis of liver
K718	Toxic liver disease with other disorders of liver
K719	Toxic liver disease, unspecified
K853	Drug-induced acute pancreatitis
L105	Drug-induced pemphigus
L233	Allergic contact dermatitis due to drugs in contact with skin
L244	Irritant contact dermatitis due to drugs in contact with skin
L251	Unspecified contact dermatitis due to drugs in contact with skin
L270	Generalized skin eruption due to drugs and medicaments
L271	Localized skin eruption due to drugs and medicaments
L640	Drug-induced androgenic alopecia
M102	Drug-induced gout
M320	Drug-induced systemic lupus erythematosus
M342	Systemic sclerosis induced by drugs and chemicals
M804	Drug-induced osteoporosis with patho- logical fracture
M814	Drug-induced osteoporosis
M835	Other drug-induced osteomalacia in adults
M871	Osteonecrosis due to drugs
N14	Drug-and heavy-metal- induced tubulo-interstitial and tubular condition
N140	Analgesic nephropathy
N141	Nephropathy induced by other drugs, medicaments and biological substances
N142	Nephropathy induced by unspecified drug, medicament or biological substance
N144	Toxic nephropathy, NEC
R502	Drug-induced fever
R832	Abnormal level of other drugs, medicaments and biological substances in cerebrospinal fluid
R842	Abnormal level of other drugs, medicaments and biological substances in specimens from respiratory organs and thorax
R852	Abnormal level of other drugs, medicaments and biological substances in specimens from digestive organs and abdominal
R862	Abnormal level of other drugs, medicaments and biological substances in specimens from male genital organs

R872	Abnormal level of other drugs, medicaments and biological substances in specimens from female genital organs
R892	Abnormal level of other drugs, medicaments and biological substances in specimens from other organs, systems and tissues
T886	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T887	Unspecified adverse effect of drug or medicament

Appendix 4. Stratified analysis for KAERS

(1) By age

a. Patients less than 60 years old

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Somnolence	58	2.92	3.63	2.27	2.61	1.29	2.53	1.87
	Mouth dry	18	1.64	1.70	1.02	1.02	0.59	1.56	0.96
	Micturition disorder	3	3.83	3.87	1.04	1.04	0.97	3.12	0.65
Bupropion	Insomnia	5	4.13	4.50	1.74	1.73	1.37	3.91	0.91
	Palpitation	4	6.60	7.12	2.44	2.42	1.56	6.01	0.88
Duloxetine	Nausea	60	3.14	3.73	2.40	2.69	1.32	2.57	1.90
	Dizziness	48	1.59	1.71	1.20	1.22	0.56	1.50	1.13
	Vomiting	33	2.82	3.07	1.95	2.03	1.18	2.38	1.57
Escitalopram	Pruritus	8	2.18	2.25	1.06	1.06	0.85	2.05	0.88
	Rash	8	3.65	3.80	1.73	1.74	1.33	3.18	1.09
	Urticaria	5	2.64	2.70	1.04	1.04	0.94	2.42	0.77
	Anorexia	5	3.38	3.46	1.31	1.31	1.13	2.98	0.83
	Cachexia	3	16.90	17.22	3.44	3.45	1.52	8.95	0.77
Fluoxetine	Anorexia	3	3.76	3.88	1.17	1.15	1.07	3.49	0.67
	Hypotension	3	14.52	15.06	3.83	3.82	1.60	10.46	0.79
	Palpitation	3	2.90	2.98	0.91	0.90	0.91	2.75	0.63
Milnacipran	Dyspepsia	6	4.36	4.86	2.00	2.00	1.48	4.12	1.02
Mirtazapine	Somnolence	17	1.96	2.20	1.26	1.27	0.84	1.90	1.10
	Weight increase	4	3.75	3.89	1.36	1.35	1.18	3.46	0.77
	Tremor	3	3.72	3.82	1.14	1.13	1.06	3.42	0.66
Nortriptyline	Constipation	16	2.27	2.45	1.39	1.41	0.99	2.14	1.17
	Insomnia	9	2.68	2.80	1.36	1.36	1.08	2.47	1.02
	Palpitation	5	2.88	2.96	1.14	1.14	1.02	2.64	0.80
	Tachycardia	4	9.52	9.78	2.90	2.91	1.60	6.68	0.90
	Hypotonia	3	19.04	19.45	3.88	3.89	1.57	10.02	0.79
	Micturition disorder	3	6.35	6.47	1.74	1.73	1.28	5.01	0.71
Tianeptine	Dizziness	13	2.39	2.90	1.48	1.52	1.06	2.33	1.15
	Palpitation	3	4.71	4.96	1.50	1.47	1.23	4.42	0.70
Trazodone	Hypotension	3	15.12	15.72	3.99	3.98	1.61	10.89	0.79
Vortioxetine	Nausea	10	2.70	3.19	1.54	1.56	1.17	2.63	1.11
	Pruritus	7	6.52	7.54	3.16	3.24	1.85	5.97	1.29
	Vomiting	7	3.21	3.62	1.59	1.58	1.27	3.09	1.00
	Dyspepsia	4	2.90	3.08	1.11	1.08	1.02	2.81	0.73

b. Patients more than 60 years old

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Somnolence	39	2.34	2.60	1.71	1.79	1.03	2.12	1.47
	Mouth dry	33	2.15	2.33	1.52	1.57	0.93	1.97	1.34
	Tremor	7	2.41	2.45	1.08	1.08	0.89	2.17	0.82
	Dysuria	4	3.35	3.39	1.11	1.11	1.00	2.83	0.69
	Fever	4	3.35	3.39	1.11	1.11	1.00	2.83	0.69
	Cachexia	3	35.14	35.57	3.67	3.69	1.52	9.53	0.71
Amoxapine	Insomnia	3	11.40	15.86	4.32	4.03	1.62	11.03	0.72
Bupropion	Mouth dry	4	3.05	3.60	1.27	1.18	1.06	3.02	0.70
Desvenlafaxine	Constipation	3	2.86	3.23	1.01	0.93	0.91	2.83	0.59
Duloxetine	Nausea	64	2.54	2.85	1.95	2.09	1.06	2.13	1.63
	Vomiting	32	1.86	1.94	1.28	1.29	0.71	1.68	1.16
	Sweating increased	11	2.69	2.74	1.36	1.36	0.98	2.23	1.03
Escitalopram	Insomnia	8	2.42	2.51	1.19	1.18	0.98	2.28	0.90
	Diarrhoea	5	4.04	4.17	1.59	1.58	1.29	3.58	0.84
	Abdominal pain	4	4.77	4.89	1.65	1.64	1.31	4.11	0.76
	Weight increase	4	3.78	3.86	1.33	1.32	1.16	3.38	0.72
	Hyponatraemia	3	4.53	4.61	1.33	1.32	1.15	3.94	0.63
Fluvoxamine	Dizziness	5	3.10	4.27	1.52	1.42	1.13	3.07	0.80
	Mouth dry	4	3.63	4.51	1.54	1.44	1.19	3.58	0.73
Mirtazapine	Dizziness	21	1.55	1.67	1.04	1.03	0.55	1.52	0.96
Nortriptyline	Mouth dry	22	2.65	3.00	1.77	1.85	1.21	2.48	1.44
	Constipation	18	2.56	2.82	1.63	1.67	1.15	2.40	1.31
	Face oedema	5	2.50	2.56	1.01	1.00	0.92	2.36	0.72
	Temperature changed sensation	5	5.76	5.95	2.20	2.20	1.52	4.80	0.91
Tianeptine	Myalgia	4	8.11	8.54	2.86	2.85	1.64	6.97	0.84
	Palpitation	3	3.76	3.88	1.18	1.16	1.09	3.53	0.62
Trazodone	Delirium	3	7.86	8.11	2.28	2.27	1.42	6.58	0.69
Vortioxetine	Anorexia	4	4.23	4.61	1.63	1.59	1.31	4.07	0.76

(2) By gender

a. Male

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM
Amitriptyline	Dizziness	23	1.62	1.76	1.09	1.09	0.59	1.56
	Somnolence	22	2.29	2.55	1.51	1.56	0.99	2.10
	Mouth dry	11	2.09	2.19	1.14	1.13	0.83	1.94
	Fatigue	3	4.38	4.46	1.20	1.19	1.06	3.53
Bupropion	Insomnia	5	10.26	12.27	4.32	4.39	1.92	9.01
Duloxetine	Nausea	41	3.16	3.62	2.24	2.43	1.25	2.49
	Vomiting	22	3.25	3.48	2.00	2.06	1.23	2.53
	Sweating increased	6	5.95	6.08	2.02	2.03	1.34	3.66
	Chest pain	4	5.55	5.63	1.50	1.50	1.14	3.53
Escitalopram	Pruritus	7	2.88	3.00	1.31	1.31	1.08	2.58
	Urticaria	5	4.48	4.64	1.68	1.68	1.31	3.69
	Tremor	3	3.05	3.10	0.89	0.88	0.88	2.70
Imipramine	Mouth dry	3	5.55	6.92	2.01	1.87	1.32	5.38
Milnacipran	Dysuria	4	16.41	18.98	5.86	5.91	1.92	13.33
Mirtazapine	Somnolence	10	1.86	2.00	1.02	1.00	0.72	1.80
Nortriptyline	Mouth dry	9	3.20	3.52	1.67	1.68	1.28	2.96
	Dysuria	3	4.46	4.61	1.34	1.32	1.15	3.94
	Oliguria	3	25.28	26.35	5.19	5.22	1.66	13.14
Paroxetine	Dyspepsia	3	3.10	3.44	1.06	1.00	0.97	3.03
Tianeptine	Dizziness	8	2.52	3.10	1.38	1.36	1.04	2.46
Trazodone	Delirium	3	16.16	17.02	4.15	4.14	1.62	11.11
Vortioxetine	Diarrhoea	3	4.90	5.29	1.58	1.54	1.24	4.58

b. Female

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Somnolence	73	2.79	3.32	2.22	2.49	1.25	2.44	1.89
	Mouth dry	39	1.82	1.93	1.32	1.35	0.74	1.71	1.23
	Weight increase	9	2.11	2.15	1.05	1.04	0.80	1.94	0.90
	Dysuria	5	5.75	5.83	1.98	1.98	1.39	4.17	0.94
	Micturition disorder	5	3.03	3.06	1.14	1.13	1.00	2.61	0.80
	Cachexia	3	11.50	11.60	2.33	2.33	1.36	6.25	0.74
Amoxapine	Insomnia	4	15.21	26.58	7.17	7.05	1.94	14.74	0.99
Bupropion	Mouth dry	6	2.75	3.17	1.33	1.29	1.09	2.72	0.89
	Rash	3	8.76	9.59	2.87	2.81	1.53	8.26	0.77
Desvenlafaxine	Constipation	4	2.80	3.05	1.11	1.06	1.00	2.76	0.73
	Anorexia	3	5.93	6.44	1.96	1.91	1.37	5.70	0.73
Duloxetine	Nausea	88	2.63	3.02	2.11	2.31	1.12	2.22	1.77
	Dizziness	68	1.31	1.37	1.04	1.04	0.33	1.27	1.02
	Vomiting	45	1.92	2.02	1.41	1.43	0.77	1.74	1.28
	Drug hypersensitivity syndrome	3	5.82	5.85	1.31	1.31	1.06	3.76	0.68
Escitalopram	Insomnia	11	1.86	1.91	1.02	1.01	0.73	1.78	0.92
	Diarrhoea	6	3.10	3.16	1.32	1.32	1.13	2.80	0.90
	Anxiety	3	3.98	4.03	1.15	1.15	1.06	3.46	0.67
	Appetite increased	3	3.28	3.31	0.97	0.96	0.95	2.94	0.65
	Hyponatraemia	3	4.65	4.70	1.32	1.32	1.14	3.92	0.69
Fluoxetine	Diarrhoea	4	6.40	6.75	2.35	2.34	1.55	5.88	0.88
	Anorexia	3	2.89	2.98	0.93	0.91	0.93	2.81	0.64
	Hypotension	3	30.38	31.80	7.76	7.78	1.78	20.58	0.82
	Palpitation	3	2.80	2.89	0.90	0.88	0.91	2.72	0.63
Fluvoxamine	Dizziness	5	2.87	3.80	1.39	1.29	1.06	2.85	0.83
	Mouth dry	3	2.83	3.28	1.02	0.92	0.90	2.81	0.64
Milnacipran	Dyspepsia	6	3.73	4.21	1.75	1.74	1.37	3.63	1.00
Mirtazapine	Somnolence	20	1.54	1.63	1.01	1.00	0.55	1.51	0.97
	Constipation	12	1.92	2.01	1.10	1.09	0.79	1.86	0.97
	Weight increase	7	3.74	3.88	1.73	1.73	1.37	3.41	1.06
	Apathy	5	4.54	4.67	1.79	1.79	1.40	4.04	0.93
	Micturition disorder	3	3.90	3.96	1.18	1.17	1.08	3.53	0.67
	Fever	3	2.92	2.96	0.90	0.89	0.90	2.74	0.63

Nortriptyline	Mouth dry	29	2.08	2.25	1.45	1.49	0.92	1.97	1.31
	Constipation	27	3.20	3.53	2.18	2.29	1.42	2.88	1.73
	Insomnia	13	2.21	2.30	1.27	1.27	0.94	2.08	1.08
	Palpitation	8	2.45	2.51	1.19	1.18	0.98	2.28	0.94
	Temperature changed sensation	6	3.15	3.22	1.34	1.34	1.14	2.84	0.91
	Sleep disorder	3	5.52	5.58	1.53	1.52	1.21	4.47	0.70
	Tachycardia	3	7.88	7.98	2.05	2.05	1.35	5.82	0.73
	Oedema peripheral	3	2.90	2.93	0.87	0.86	0.87	2.64	0.63
Tianeptine	Palpitation	6	4.37	4.62	1.94	1.94	1.48	4.07	1.04
	Temperature changed sensation	5	6.27	6.59	2.52	2.52	1.64	5.63	1.01
	Abdominal pain	3	3.56	3.66	1.12	1.11	1.06	3.38	0.67
Trazodone	Dizziness	20	1.56	1.69	1.04	1.03	0.57	1.54	0.98
	Hypotension	3	17.58	18.04	4.45	4.45	1.65	12.05	0.79
Vortioxetine	Nausea	12	2.20	2.48	1.31	1.31	0.97	2.16	1.07
	Pruritus	6	5.88	6.38	2.64	2.66	1.71	5.45	1.13
	Dyspepsia	6	2.31	2.45	1.06	1.04	0.92	2.27	0.83
	Anorexia	3	2.94	3.03	0.95	0.93	0.94	2.85	0.64

Appendix 5. Stratified analysis for HIRA

(1) By age

a. Patients less than 60 years old

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Tremor	418	1.64	2.66	1.55	2.28	0.70	1.62	1.50
	Headache	13	3.24	3.29	1.87	1.88	1.44	2.47	1.51
Bupropion	Dystonia	29	13.04	18.10	9.56	11.69	3.18	12.21	8.89
	Mental disorders	24	5.28	6.66	3.72	4.20	2.15	4.89	3.28
	Myoclonus	9	2.57	2.73	1.38	1.37	1.14	1.91	1.10
Clomipramine	Tremor	13	1.51	2.17	1.05	0.95	0.49	1.35	0.86
	Hepatitis	6	5.75	7.43	2.89	2.93	1.74	3.69	1.47
Desvenlafaxine	Tremor	29	1.68	2.85	1.35	1.56	0.69	1.57	1.16
	Localized skin eruption	8	16.37	19.60	8.67	9.10	2.58	13.46	7.13
Doxepin	Generalized skin eruption	24	4.69	5.95	3.31	3.74	2.01	4.26	2.84
Duloxetine	Unspecified toxic liver disease	98	2.12	2.70	1.80	2.11	1.05	2.04	1.73
	Generalized skin eruption	24	1.53	1.58	1.04	1.04	0.58	1.43	1.02
	Polyneuropathy	13	4.20	4.35	2.45	2.48	1.75	3.28	1.89
	Myelopathy	9	6.58	6.76	3.42	3.44	2.05	5.15	2.34
	Gastroenteritis and colitis	9	3.79	3.88	1.98	1.98	1.55	2.64	1.42
Escitalopram	Tremor	307	1.32	1.62	1.22	1.39	0.39	1.31	1.19
	Hepatitis	41	1.45	1.49	1.08	1.08	0.51	1.39	1.08
Fluoxetine	Tremor	148	1.54	2.27	1.39	1.77	0.61	1.52	1.32
	Epileptic seizures	40	3.06	3.43	2.29	2.45	1.52	2.78	2.11
Fluvoxamine	Tremor	31	2.36	12.94	2.10	4.57	1.14	2.15	1.59
Imipramine	Tremor	280	1.97	4.63	1.85	3.69	0.96	1.94	1.75
	Epileptic seizures	46	2.36	2.55	1.80	1.87	1.18	2.19	1.71
Milnacipran	Osteoporosis	6	6.76	7.39	3.15	3.17	1.87	4.56	1.68
	Myopathy	4	10.68	11.36	4.11	4.10	1.85	6.15	1.55
	Other disorders of liver	3	4.87	5.07	1.61	1.58	1.30	2.06	0.76
Mirtazapine	Mental disorders	30	3.09	3.45	2.22	2.34	1.52	2.74	1.99
	Myoclonus	19	2.55	2.71	1.66	1.68	1.23	2.17	1.47
	Headache	4	3.20	3.24	1.20	1.20	1.14	1.76	0.79
Paroxetine	Tremor	143	1.45	1.98	1.30	1.55	0.52	1.43	1.24
	Chronic active hepatitis	10	9.73	10.07	5.21	5.27	2.40	8.26	4.46
	Toxic liver disease	7	5.73	5.86	2.73	2.74	1.82	3.87	1.64
Sertraline	Tremor	142	1.67	2.77	1.51	2.11	0.72	1.64	1.42
Tianeptine	Unspecified toxic liver disease	101	2.46	3.42	2.11	2.66	1.26	2.36	2.00
	Ulcer of oesophagus	23	4.52	4.87	3.05	3.16	1.95	4.01	2.65
	Hepatic necrosis	21	2.01	2.10	1.33	1.34	0.93	1.78	1.24
	Other disorders of liver	9	3.54	3.63	1.85	1.86	1.48	2.48	1.36
	Myelopathy	6	4.88	4.97	2.19	2.19	1.63	2.95	1.29
	Chronic persistent hepatitis	4	3.27	3.30	1.23	1.22	1.15	1.78	0.79
Trazodone	Tremor	417	1.32	1.63	1.23	1.42	0.39	1.31	1.21
	Mental disorders	67	1.71	1.77	1.35	1.38	0.74	1.64	1.34
	Toxic liver disease	8	2.03	2.04	1.01	1.00	0.84	1.56	0.88
Venlafaxine	Tremor	92	1.59	2.44	1.39	1.77	0.64	1.55	1.30
	Mental disorders	20	2.77	3.04	1.84	1.89	1.34	2.35	1.60
	Allergic contact dermatitis	10	6.05	6.40	3.30	3.35	2.03	4.88	2.35
Vortioxetine	Tremor	57	1.75	3.17	1.50	2.04	0.77	1.68	1.35
	Mental disorders	13	3.21	3.59	1.94	1.99	1.45	2.50	1.53

b. Patients more than 60 years old

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Myoclonus	78	1.67	1.77	1.36	1.40	0.72	1.62	1.34
	Generalized skin eruption	47	1.36	1.39	1.03	1.03	0.42	1.31	1.03
	Toxic liver disease	28	2.49	2.56	1.72	1.74	1.22	2.21	1.61
	Analgesic nephropathy	16	9.95	10.19	5.98	6.05	2.62	8.48	5.44
	Myopathy	14	1.98	2.00	1.17	1.17	0.88	1.69	1.08
Amoxapine	Other disorders of liver	9	20.98	56.94	14.16	19.06	2.77	16.99	9.41
Bupropion	Tremor	7	1.95	2.37	1.05	0.97	0.75	1.50	0.81
	Epileptic seizures	6	13.01	17.24	6.52	6.79	2.24	10.00	4.15
	Hepatic necrosis	6	5.77	7.46	2.90	2.94	1.75	3.78	1.51
Desvenlafaxine	Hepatic necrosis	8	9.33	15.38	5.50	6.18	2.24	7.79	3.62
Doxepin	Tremor	19	2.34	3.12	1.64	1.77	1.11	2.04	1.38
Duloxetine	Epileptic seizures	53	9.39	11.25	7.31	8.30	2.97	8.83	7.00
	Other disorders of liver	16	1.79	1.83	1.11	1.10	0.76	1.58	1.04
	Polyneuropathy	15	3.96	4.12	2.41	2.44	1.72	3.23	1.96
	Osteoporosis	15	2.43	2.51	1.48	1.49	1.15	2.03	1.31
	Myelopathy	13	2.80	2.88	1.64	1.65	1.29	2.23	1.38
	Unspecified contact dermatitis	4	6.19	6.26	2.30	2.30	1.58	3.11	1.08
	Chronic lobular hepatitis	3	5.00	5.04	1.60	1.59	1.30	2.13	0.75
Escitalopram	Irritant contact dermatitis	41	2.11	2.21	1.57	1.60	1.02	1.97	1.51
	Folate deficiency anaemia	20	8.30	8.61	5.32	5.42	2.56	7.41	4.97
	Cholestasis	8	7.51	7.62	3.69	3.71	2.08	5.69	2.46
Fluoxetine	Myoclonus	10	2.93	3.50	1.70	1.73	1.29	2.21	1.28
Fluvoxamine	Unspecified toxic liver disease	13	1.94	2.62	1.28	1.28	0.82	1.65	1.04
	Gastroenteritis and colitis	10	11.48	16.47	6.88	7.74	2.53	10.03	5.64
Imipramine	Tremor	123	4.17	9.90	3.75	7.36	2.00	4.05	3.47
	Mucositis	13	1.72	1.77	1.02	1.01	0.70	1.50	0.95
	Myopathy	8	3.57	3.69	1.81	1.81	1.46	2.48	1.30
	Mental disorders	7	2.18	2.22	1.05	1.04	0.91	1.62	0.87
Milnacipran	Hepatitis	5	4.03	4.71	1.82	1.78	1.39	2.34	1.03
Mirtazapine	Tremor	48	1.69	1.94	1.33	1.40	0.73	1.62	1.28
	Irritant contact dermatitis	29	3.97	4.53	2.84	3.04	1.83	3.58	2.54
	Mental disorders	18	5.95	6.49	3.82	3.98	2.22	5.39	3.37
	Folate deficiency anaemia	6	6.34	6.52	2.86	2.87	1.83	4.19	1.62
Paroxetine	Unspecified toxic liver disease	40	1.78	2.27	1.39	1.53	0.79	1.69	1.30
	Tremor	31	1.91	2.30	1.42	1.51	0.88	1.78	1.32
	Dystonia	8	8.28	8.89	4.23	4.30	2.18	6.73	2.97
Sertraline	Tremor	33	2.06	2.56	1.55	1.69	0.98	1.91	1.42
	Mucositis	10	2.46	2.61	1.36	1.36	1.10	1.91	1.12
	Ulcer of oesophagus	9	1.98	2.07	1.06	1.04	0.83	1.59	0.92
Tianeptine	Gastroenteritis and colitis	25	2.80	2.95	1.92	1.96	1.37	2.46	1.74
	Other disorders of liver	20	2.05	2.12	1.34	1.34	0.95	1.81	1.25
	Osteomalacia	7	7.36	7.51	3.49	3.50	2.01	5.38	2.15
Trazodone	Tremor	126	1.62	1.83	1.39	1.50	0.68	1.59	1.37
	Irritant contact dermatitis	42	2.09	2.19	1.56	1.59	1.01	1.95	1.51
	Hepatitis	39	1.70	1.76	1.26	1.27	0.73	1.61	1.23
	Osteoporosis	20	1.90	1.93	1.23	1.23	0.85	1.69	1.17
	Myelopathy	14	1.75	1.78	1.04	1.04	0.73	1.53	0.98
	Allergic contact dermatitis	9	1.98	2.00	1.03	1.03	0.84	1.58	0.91
	Cholestasis	6	5.36	5.42	2.38	2.38	1.69	3.31	1.39
	Unspecified contact dermatitis	5	4.54	4.58	1.87	1.86	1.48	2.54	1.08
Venlafaxine	Tremor	20	2.79	4.17	2.01	2.33	1.33	2.40	1.63
	Generalized skin eruption	7	2.64	2.94	1.34	1.31	1.11	1.87	0.99
Vortioxetine	Tremor	29	4.14	9.83	3.33	5.34	1.88	3.79	2.67
	Epileptic seizures	5	5.53	6.10	2.42	2.40	1.64	3.23	1.25
	Unspecified contact dermatitis	4	40.36	44.20	15.59	15.60	2.18	19.91	7.51

(2) By gender

a. Male

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Myoclonus	42	1.85	1.96	1.39	1.42	0.85	1.77	1.36
	Toxic liver disease	27	3.32	3.49	2.29	2.35	1.58	2.94	2.11
	Hepatic necrosis	22	1.65	1.69	1.10	1.10	0.67	1.54	1.07
	Myopathy	14	3.01	3.09	1.79	1.80	1.38	2.49	1.56
	Myelopathy	9	2.08	2.11	1.09	1.08	0.89	1.71	0.97
	Headache	6	4.29	4.34	1.91	1.91	1.51	2.76	1.29
Bupropion	Tremor	14	3.44	9.12	2.58	3.50	1.51	2.85	1.77
Clomipramine	Tremor	11	2.84	5.37	1.94	2.16	1.24	2.30	1.36
	Hepatitis	6	4.74	6.46	2.44	2.45	1.58	3.11	1.40
Desvenlafaxine	Tremor	25	3.41	8.89	2.74	4.37	1.61	3.06	2.15
	Localized skin eruption	8	11.79	14.88	6.37	6.76	2.40	9.61	4.71
Doxepin	Mental disorders	4	4.71	5.07	1.84	1.81	1.42	2.58	1.01
Duloxetine	Epileptic seizures	46	7.18	9.18	5.55	6.56	2.62	6.80	5.26
	Polyneuropathy	17	3.70	3.97	2.34	2.40	1.66	3.13	2.02
	Myelopathy	11	5.15	5.41	2.88	2.92	1.91	4.06	2.23
	Mucositis	11	2.12	2.19	1.19	1.19	0.94	1.79	1.08
	Other disorders of liver	8	3.60	3.72	1.82	1.82	1.46	2.61	1.38
Escitalopram	Tremor	155	1.83	2.32	1.61	1.90	0.85	1.79	1.57
	Irritant contact dermatitis	40	1.80	1.88	1.33	1.35	0.80	1.71	1.31
	Folate deficiency anaemia	5	3.61	3.64	1.49	1.49	1.30	2.24	1.01
Fluoxetine	Tremor	54	2.86	5.43	2.40	3.60	1.45	2.71	2.15
	Myoclonus	11	1.96	2.09	1.12	1.11	0.84	1.68	1.01
	Dystonia	7	5.27	5.62	2.57	2.59	1.76	3.66	1.70
	Epileptic seizures	7	2.15	2.25	1.05	1.04	0.90	1.68	0.89
Fluvoxamine	Tremor	28	2.99	6.09	2.37	3.37	1.45	2.72	1.97
	Gastroenteritis and colitis	7	5.50	6.30	2.77	2.81	1.79	3.86	1.77
Imipramine	Tremor	119	3.45	9.04	3.12	6.52	1.73	3.33	2.86
	Myopathy	7	3.29	3.39	1.59	1.58	1.34	2.34	1.20
Milnacipran	Osteoporosis	7	7.72	9.19	3.94	4.05	2.05	5.77	2.43
Mirtazapine	Tremor	86	2.01	2.70	1.70	2.05	0.98	1.95	1.63
	Irritant contact dermatitis	29	2.59	2.84	1.84	1.91	1.28	2.37	1.73
	Mental disorders	15	3.89	4.12	2.38	2.42	1.70	3.22	2.01
Paroxetine	Tremor	38	1.45	1.63	1.11	1.12	0.50	1.40	1.06
	Hepatic necrosis	16	3.51	3.87	2.21	2.29	1.59	2.96	1.89
	Chronic active hepatitis	10	16.44	17.74	8.92	9.16	2.74	13.27	7.55
	Dystonia	8	4.35	4.57	2.21	2.22	1.65	3.13	1.60
	Osteonecrosis	3	3.89	3.95	1.26	1.25	1.16	1.95	0.71
Sertraline	Tremor	52	2.67	4.63	2.22	3.10	1.35	2.53	2.00
	Mental disorders	5	2.82	2.92	1.20	1.19	1.10	1.89	0.88
Tianeptine	Gastroenteritis and colitis	24	4.19	4.61	2.86	3.00	1.87	3.71	2.56
	Hepatic necrosis	17	2.30	2.42	1.45	1.47	1.09	2.03	1.34
	Other disorders of liver	13	5.31	5.60	3.12	3.17	1.99	4.36	2.51
	Allergic contact dermatitis	8	3.81	3.92	1.92	1.92	1.52	2.74	1.44
Trazodone	Tremor	170	1.61	1.90	1.42	1.58	0.66	1.58	1.39
	Irritant contact dermatitis	42	1.51	1.55	1.13	1.13	0.56	1.45	1.12
	Dystonia	18	2.43	2.48	1.53	1.54	1.15	2.12	1.42
	Mental disorders	17	1.77	1.80	1.10	1.10	0.75	1.60	1.07
Venlafaxine	Tremor	31	2.77	5.06	2.19	2.97	1.37	2.55	1.88
	Mental disorders	5	4.93	5.33	2.13	2.12	1.56	2.99	1.25
Vortioxetine	Tremor	29	3.03	6.31	2.42	3.50	1.48	2.77	2.01
	Epileptic seizures	5	3.04	3.29	1.33	1.30	1.16	2.00	0.92

b. Female

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Tremor	434	1.64	2.22	1.53	1.95	0.70	1.62	1.49
	Analgesic nephropathy	16	7.60	7.72	4.56	4.59	2.36	6.49	4.02
Amoxapine	Other disorders of liver	9	22.43	54.57	14.80	19.40	2.81	18.40	10.20
Bupropion	Dystonia	29	17.52	24.17	12.81	15.64	3.47	16.24	11.83
	Mental disorders	24	6.19	7.81	4.36	4.93	2.34	5.86	4.02
	Epileptic seizures	11	3.15	3.41	1.80	1.82	1.40	2.34	1.38
Desvenlafaxine	Hepatic necrosis	9	6.43	8.87	3.73	4.03	2.03	5.19	2.32
Doxepin	Generalized skin eruption	21	3.72	4.45	2.54	2.75	1.71	3.18	2.10
	Gastroenteritis and colitis	4	2.99	3.07	1.14	1.13	1.09	1.66	0.75
Duloxetine	Unspecified toxic liver disease	124	1.63	1.92	1.41	1.55	0.69	1.60	1.38
	Osteoporosis	15	2.61	2.67	1.58	1.59	1.23	2.11	1.36
	Polyneuropathy	11	6.85	7.02	3.78	3.81	2.17	5.75	2.90
	Myelopathy	11	2.74	2.79	1.52	1.53	1.24	2.07	1.24
	Unspecified contact dermatitis	5	6.07	6.14	2.50	2.50	1.69	3.36	1.25
	Chronic lobular hepatitis	4	5.07	5.12	1.89	1.88	1.46	2.41	0.94
Escitalopram	Tremor	235	1.17	1.25	1.05	1.07	0.22	1.16	1.04
	Mental disorders	39	1.47	1.50	1.08	1.08	0.53	1.40	1.08
	Hepatitis	35	1.57	1.60	1.13	1.14	0.62	1.48	1.12
	Folate deficiency anaemia	15	7.01	7.14	4.17	4.20	2.28	6.06	3.60
	Headache	9	1.99	2.00	1.03	1.03	0.84	1.56	0.91
	Cholestasis	6	11.05	11.14	4.76	4.77	2.12	7.69	2.66
Fluoxetine	Tremor	105	1.73	2.47	1.51	1.88	0.77	1.69	1.43
	Epileptic seizures	33	4.62	5.31	3.37	3.65	2.04	4.30	3.08
Fluvoxamine	Gastroenteritis and colitis	3	11.22	13.02	3.94	3.81	1.64	4.78	1.07
Imipramine	Tremor	284	2.43	5.88	2.28	4.74	1.26	2.38	2.16
	Epileptic seizures	40	2.90	3.11	2.16	2.24	1.45	2.63	2.00
Milnacipran	Hepatitis	6	3.77	4.16	1.78	1.77	1.41	2.27	1.09
	Myopathy	4	11.62	12.56	4.52	4.50	1.88	6.87	1.63
Mirtazapine	Mental disorders	33	4.79	5.64	3.51	3.86	2.09	4.49	3.22
	Myelopathy	7	3.77	3.88	1.82	1.82	1.47	2.40	1.20
	Folate deficiency anaemia	6	10.36	10.68	4.66	4.68	2.13	7.77	2.70
	Headache	4	3.37	3.43	1.27	1.27	1.18	1.78	0.79
Paroxetine	Tremor	136	1.95	3.20	1.74	2.48	0.94	1.90	1.65
	Toxic liver disease	5	3.43	3.48	1.43	1.43	1.27	1.95	0.92
Sertraline	Tremor	123	1.79	2.66	1.59	2.06	0.82	1.75	1.51
	Epileptic seizures	16	1.97	2.04	1.22	1.23	0.89	1.70	1.12
Tianeptine	Unspecified toxic liver disease	129	1.82	2.27	1.58	1.83	0.84	1.78	1.53
	Ulcer of oesophagus	38	3.39	3.67	2.50	2.62	1.66	3.06	2.29
	Other disorders of liver	16	1.64	1.67	1.01	1.01	0.65	1.46	0.97
	Osteomalacia	7	7.46	7.58	3.53	3.54	2.01	5.45	2.08
	Chronic persistent hepatitis	4	3.45	3.48	1.29	1.29	1.20	1.80	0.80
Trazodone	Tremor	373	1.56	2.02	1.44	1.76	0.62	1.54	1.41
	Mental disorders	59	1.87	1.94	1.46	1.48	0.87	1.78	1.43
	Cholestasis	6	9.22	9.28	3.97	3.97	2.02	6.14	2.07
Venlafaxine	Tremor	81	1.90	3.02	1.64	2.18	0.90	1.84	1.53
	Mental disorders	15	2.67	2.86	1.65	1.67	1.26	2.16	1.39
	Epileptic seizures	11	2.18	2.27	1.23	1.23	0.98	1.74	1.06
	Allergic contact dermatitis	9	6.37	6.72	3.37	3.41	2.03	5.06	2.27
Vortioxetine	Tremor	57	2.29	4.93	1.97	3.13	1.15	2.17	1.74
	Mental disorders	13	3.97	4.51	2.40	2.49	1.69	3.10	1.80
	Unspecified contact dermatitis	4	22.22	23.27	8.42	8.41	2.07	13.54	4.02

Appendix 6. Signal detection with different time windows

(1) 8 weeks

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Tremor	478	1.55	1.94	1.44	1.73	0.62	1.53	1.42
	Myoclonus	93	1.41	1.44	1.16	1.17	0.48	1.38	1.16
	Toxic liver disease	27	1.88	1.90	1.29	1.29	0.85	1.72	1.25
	Analgesic nephropathy	16	9.11	9.22	5.43	5.46	2.52	7.63	4.78
Amoxapine	Other disorders of liver	5	25.80	56.80	14.36	15.24	2.30	17.72	7.55
Bupropion	Dystonia	29	16.40	22.28	11.98	14.48	3.41	15.35	11.18
	Mental disorders	17	4.97	5.74	3.21	3.41	2.01	4.27	2.60
	Epileptic seizures	10	2.75	2.93	1.52	1.53	1.23	2.10	1.23
	Acute pancreatitis	4	15.37	15.94	5.82	5.81	1.98	9.30	2.17
Clomipramine	Tremor	9	1.83	2.66	1.15	1.06	0.69	1.51	0.87
	Hepatitis	6	7.74	11.10	4.02	4.17	1.94	5.33	1.91
Desvenlafaxine	Tremor	29	1.80	2.58	1.39	1.55	0.79	1.68	1.23
	Hepatic necrosis	9	3.55	4.01	1.95	1.97	1.48	2.53	1.39
	Localized skin eruption	8	9.85	11.23	5.16	5.32	2.30	8.21	3.69
Doxepin	Generalized skin eruption	24	3.30	3.84	2.30	2.46	1.58	2.87	2.00
Duloxetine	Unspecified toxic liver disease	134	1.52	1.73	1.31	1.41	0.59	1.50	1.30
	Epileptic seizures	35	2.16	2.26	1.57	1.60	1.06	2.00	1.51
	Polyneuropathy	22	4.54	4.72	3.00	3.06	1.95	3.92	2.60
	Other disorders of liver	19	1.89	1.92	1.21	1.21	0.84	1.69	1.15
	Myelopathy	12	2.88	2.93	1.64	1.64	1.31	2.24	1.37
	Chronic lobular hepatitis	5	5.80	5.86	2.39	2.39	1.66	3.17	1.25
	Unspecified contact dermatitis	5	5.37	5.42	2.22	2.21	1.61	2.92	1.20
Escitalopram	Tremor	344	1.31	1.48	1.20	1.30	0.38	1.30	1.19
	Irritant contact dermatitis	34	1.77	1.80	1.27	1.27	0.78	1.66	1.24
	Folate deficiency anaemia	20	5.93	6.03	3.78	3.81	2.19	5.10	3.24
	Headache	9	1.94	1.95	1.00	1.00	0.81	1.56	0.90
	Cholestasis	9	5.12	5.15	2.62	2.62	1.81	3.53	1.78
Fluoxetine	Tremor	153	2.03	3.30	1.83	2.61	1.00	1.99	1.74
	Epileptic seizures	37	3.88	4.33	2.87	3.06	1.83	3.53	2.63
	Tremor	33	2.16	3.83	1.74	2.25	1.04	2.00	1.50
	Gastroenteritis and colitis	7	7.09	7.96	3.54	3.60	1.99	5.14	2.05
Imipramine	Tremor	361	2.62	6.54	2.47	5.40	1.37	2.57	2.36
	Epileptic seizures	45	2.57	2.72	1.94	2.00	1.29	2.38	1.85
Milnacipran	Hepatitis	9	2.61	2.82	1.41	1.41	1.15	1.97	1.12
	Osteoporosis	8	5.75	6.28	2.98	3.02	1.90	4.12	1.88
	Myopathy	4	5.53	5.77	2.12	2.11	1.53	2.69	1.01
Mirtazapine	Tremor	112	1.21	1.31	1.04	1.04	0.26	1.20	1.02
	Mental disorders	38	3.45	3.76	2.55	2.68	1.68	3.13	2.35
	Irritant contact dermatitis	26	3.85	4.09	2.65	2.73	1.78	3.37	2.35
	Myelopathy	7	2.30	2.33	1.10	1.10	0.98	1.69	0.91
	Folate deficiency anaemia	6	4.84	4.91	2.17	2.17	1.63	2.90	1.30
Paroxetine	Tremor	167	1.83	2.64	1.64	2.13	0.85	1.80	1.58
	Chronic active hepatitis	10	13.00	13.37	6.94	7.01	2.60	10.99	6.18
Sertraline	Tremor	161	1.97	3.08	1.77	2.45	0.96	1.93	1.69
	Epileptic seizures	17	1.63	1.67	1.03	1.02	0.65	1.48	0.99
Tianeptine	Unspecified toxic liver disease	156	1.74	2.09	1.53	1.73	0.78	1.71	1.49
	Hepatic necrosis	37	1.81	1.88	1.32	1.34	0.81	1.70	1.30
	Ulcer of oesophagus	35	2.44	2.55	1.77	1.80	1.21	2.23	1.68
	Other disorders of liver	26	2.54	2.63	1.74	1.77	1.25	2.26	1.62
	Gastroenteritis and colitis	19	2.26	2.32	1.45	1.46	1.08	1.97	1.34

	Myelopathy	9	2.11	2.13	1.10	1.10	0.91	1.67	0.96
	Osteomalacia in adults	6	7.71	7.80	3.42	3.42	1.95	5.04	1.84
Trazodone	Tremor	503	1.52	1.88	1.42	1.68	0.59	1.50	1.40
	Mental disorders	70	1.77	1.82	1.41	1.42	0.79	1.70	1.39
	Cholestasis	6	2.63	2.64	1.17	1.16	1.06	1.76	0.90
Venlafaxine	Tremor	104	2.05	3.39	1.81	2.54	1.01	2.00	1.70
	Mental disorders	19	3.14	3.38	2.04	2.10	1.49	2.64	1.77
	Allergic contact dermatitis	10	5.98	6.26	3.26	3.30	2.03	4.69	2.30
Vortioxetine	Tremor	71	2.37	4.86	2.06	3.29	1.20	2.27	1.86
	Mental disorders	13	3.62	3.97	2.17	2.23	1.59	2.83	1.71
	Unspecified contact dermatitis	4	18.29	18.94	6.90	6.90	2.03	11.18	2.69

(2) 4 week

Drug	ADR	Drug-ADR pairs	PRR	ROR	PRRCI	RORCI	IC	EBGM	EB05
Amitriptyline	Tremor	430	1.67	2.33	1.56	2.04	0.72	1.64	1.52
	Myoclonus	67	1.33	1.35	1.05	1.05	0.39	1.29	1.05
	Analgesic nephropathy	16	9.49	9.65	5.59	5.63	2.51	7.61	4.80
Amoxapine	Other disorders of liver	3	43.25	106.64	21.06	17.79	1.88	16.68	3.24
Bupropion	Dystonia	28	19.22	30.81	14.29	19.10	3.52	17.59	12.74
	Mental disorders	8	3.49	3.81	1.81	1.82	1.43	2.42	1.28
	Acute pancreatitis	3	15.69	16.33	5.11	5.07	1.74	6.85	1.33
Clomipramine	Hepatitis	5	12.60	24.19	6.77	7.00	2.06	8.86	2.71
Desvenlafaxine	Tremor	19	1.67	2.33	1.21	1.24	0.65	1.52	1.04
Desvenlafaxine	Localized skin eruption	8	13.64	17.01	7.34	7.77	2.48	11.36	5.87
Doxepin	Generalized skin eruption	20	3.70	4.44	2.50	2.70	1.69	3.15	2.09
Doxepin	Gastroenteritis and colitis	5	3.12	3.24	1.33	1.31	1.19	1.90	0.89
Duloxetine	Unspecified toxic liver disease	103	1.90	2.36	1.62	1.86	0.90	1.84	1.56
	Hepatic necrosis	19	1.58	1.62	1.02	1.02	0.61	1.45	0.99
	Epileptic seizures	17	1.67	1.71	1.05	1.04	0.67	1.50	1.00
	Polyneuropathy	16	4.06	4.23	2.50	2.54	1.75	3.29	2.05
	Mucositis	16	1.78	1.82	1.10	1.10	0.75	1.57	1.04
	Myelopathy	6	2.25	2.28	1.01	1.01	0.92	1.60	0.82
Escitalopram	Tremor	239	1.16	1.25	1.05	1.06	0.21	1.15	1.04
Escitalopram	Irritant contact dermatitis	32	1.78	1.81	1.26	1.27	0.78	1.65	1.23
	Folate deficiency anaemia	15	9.70	9.90	5.67	5.72	2.53	7.96	4.95
	Cholestasis	7	3.91	3.94	1.83	1.83	1.47	2.47	1.24
Escitalopram	Headache	6	2.56	2.58	1.14	1.14	1.04	1.73	0.88
Fluoxetine	Tremor	105	1.78	2.67	1.56	2.02	0.81	1.74	1.48
	Epileptic seizures	24	3.66	4.03	2.51	2.62	1.70	3.17	2.19
Fluvoxamine	Tremor	21	2.00	3.50	1.53	1.78	0.90	1.80	1.25
	Gastroenteritis and colitis	5	8.31	9.53	3.68	3.69	1.89	5.26	1.68
Imipramine	Tremor	288	2.40	5.84	2.25	4.71	1.23	2.35	2.13
	Epileptic seizures	40	2.98	3.20	2.21	2.30	1.48	2.71	2.06
Milnacipran	Osteoporosis	5	6.17	6.67	2.66	2.65	1.71	3.56	1.33
	Myopathy	4	7.98	8.50	3.08	3.06	1.72	4.15	1.26
Mirtazapine	Tremor	88	1.28	1.46	1.09	1.12	0.35	1.26	1.06
Mirtazapine	Mental disorders	23	3.18	3.42	2.15	2.22	1.52	2.74	1.90
Mirtazapine	Irritant contact dermatitis	11	1.82	1.86	1.02	1.01	0.76	1.54	0.93
Mirtazapine	Headache	3	3.81	3.85	1.23	1.22	1.15	1.76	0.68
Paroxetine	Tremor	151	1.79	2.71	1.61	2.14	0.82	1.76	1.54
	Chronic active hepatitis	10	13.63	14.09	7.22	7.31	2.61	11.12	6.28
	Toxic liver disease	7	2.52	2.56	1.21	1.20	1.07	1.80	0.96
Sertraline	Tremor	125	1.84	2.88	1.64	2.21	0.86	1.80	1.55
	Hepatic necrosis	16	1.78	1.84	1.11	1.11	0.76	1.58	1.04
	Epileptic seizures	15	1.97	2.04	1.21	1.21	0.88	1.71	1.11
Sertraline	Osteoporosis	7	2.17	2.20	1.04	1.03	0.91	1.62	0.87
Tianeptine	Unspecified toxic liver disease	125	2.14	2.85	1.87	2.28	1.07	2.08	1.79
	Ulcer of oesophagus	24	2.70	2.84	1.83	1.86	1.32	2.36	1.67
	Hepatic necrosis	20	1.55	1.58	1.01	1.00	0.58	1.43	0.98
	Other disorders of liver	16	3.58	3.71	2.20	2.23	1.61	2.89	1.83
	Gastroenteritis and colitis	14	2.50	2.57	1.49	1.50	1.17	2.05	1.31
Trazodone	Tremor	387	1.37	1.63	1.27	1.43	0.44	1.36	1.25
	Mental disorders	52	1.75	1.79	1.34	1.35	0.76	1.66	1.32
Venlafaxine	Tremor	80	1.92	3.18	1.67	2.27	0.91	1.86	1.55
	Mental disorders	17	3.86	4.26	2.47	2.56	1.72	3.20	2.03
	Allergic contact dermatitis	5	3.96	4.07	1.67	1.66	1.39	2.26	1.01
Vortioxetine	Tremor	52	2.07	3.80	1.75	2.45	1.00	1.97	1.56
	Mental disorders	12	4.50	5.09	2.66	2.75	1.81	3.53	1.98
	Unspecified contact dermatitis	4	19.72	20.66	7.44	7.44	2.04	11.69	3.01

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국문 초록

자발적부작용보고 시스템 (spontaneous reporting systems, SRS)에 비해 국민건강보험공단 청구자료 (HIRA)는 모든 피보험자의 진단 및 처방 정보가 포함되어 있지만, 약물 안전 감시에 적용되는 경우가 많이 없었다. 본 연구의 목적은 건강보험청구자료 (HIRA)와 자발적부작용보고자료 (KAERS)를 이용하여 항우울제 사용으로 인한 실마리정보를 탐색하고, 두 시스템에서 발견한 실마리정보의 특징을 비교하는 것이다.

본 연구에 사용된 자료는 2017 년 HIRA 와 KAERS 데이터이다. HIRA 데이터의 경우는 실마리정보를 탐색하기 전에 모든 약물과 약물이상반응 (ADR)을 후향적 페어링하고 약물-이상반응 조합 (drug-ADR pair)을 추출했다. 두 시스템의 약물-이상반응 조합에 대하여 여러 가지 실마리정보 지표를 계산한 뒤 실마리정보의 중류 (class), 부작용일반성지표 (common ADR coverage, CAC)또는 허가상항내재지표 (labeling information coverage, LIC)측면에서 두 시스템을 비교 분석해 보았다. 부작용일반성지표는 흔한 ADR 의 비율로 측정하고 허가상항내재지표는 mAP (Mean Average Precision)로 측정했다. 또한, 제약회사의 제품설명서 및 허가사항에 포함되지 않은 실마리정보는 protopathic bias 평가또는 RR (Relative risk)평가로 확인되었다. Protopathic bias 평가할때 LEOPARD (Observational Profiles of Adverse Events Related to Drug)를 이용했다. 그리고 성별, 나이, 시간대에 따라 실마리정보 분포의 변화를 관측하였다.

KAERS 데이터베이스에서 총 5,992 건의 약물-이상반응 조합을 이용하여 총 51 개 실마리정보를 발견했다. 제약회사의 제품설명서 및 허가사항에 포함되지 않은 실마리정보는 없었다. HIRA 데이터베이스에서 총 108,570 건의

약물-이상반응 조합 만들어 총 62 개 실마리정보를 발견했다. 이 중 5 개는 제약회사의 제품설명서 및 허가사항에 포함되지 않은 실마리정보였다. KAERS 에서 항우울제가 더 많은 장기 시스템의 장애와 관련이 있음을 보였다. KAERS 에서 더 높은 mAP (EB05 의 mAP : 1.00 [K] VS. 0.983 [H])를 보였지만 일반적인 부작용과 관련된 실마리정보는 HIRA 보다 더 많이 발견되었다 (68.63 % [K] VS. 29.03 % [H]). 실마리정보를 확인할 때 LEOPARD 를 통해 duloxetine 과 myelopathy 의 조합은 protopathic bias 때문에 생기는 것으로 확인되었다 (P-value=0.01026). 각 연령 및 성별 그룹에서 실마리정보 탐색시 HIRA 는 항상 KAERS 보다 낮은 CAC 와 LIC 를 보였다. HIRA 에서 시간대가 단축함에 따라 CAC 는 감소하고 (29.03%, 27.87%, 27.27%) LIC 는 증가했다 (0.983, 1.0, 1.0).

본 연구를 통해 실마리정보 탐색할 때 건강보험청구자료와 자발적부작용보고자료에서 발견한 실마리정보는 서로 다른 프로파일을 보였다. 건강보험청구자료를 통해 허가사항에 포함되지 않은 실마리정보를 발견되었으며 추가 연구를 통해 확인해야 한다. 앞으로 약물감시 업무에서 실마리정보 탐색 시 HIRA 같은 건강보험청구자료를 더 많이 적용해야 할 것이다.

주요어: 실마리정보 탐색, 약물감시, 데이터 마이닝, 건강보험청구자료, 자발적부작용보고자료, 항우울제

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