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Original article

Investigation of the characteristics of medication errors and adverse drug reactions using pharmacovigilance data in China

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ABSTRACT

The aim of this study was to investigate the characteristics of medication errors (MEs) and adverse drug reactions (ADRs) using data from the spontaneous reporting system, which is helpful to understand the actual situation of MEs in China. Data from 2015 in a south distinct in Shanghai were gathered from the spontaneous reporting system and analyzed. The general information, cause of errors, severity, primary diseases, involved system and organs, symptoms, and suspected drugs were investigated. A total of 1290 adverse drug events (ADEs), including 1079 ADRs and 211 MEcs (MEs causing ADE), were reported. Older patients suffered from both ADRs and MEcs (age distribution and dosage form were different between ADRs and MEcs). The main causes of errors were inappropriate usage and dosage of drugs and inappropriate indication selection. Most ADR and MEc cases were mild; the possibility of developing a severe adverse event was quite low. The distribution of the top 10 system and organs, and symptoms involved was significantly different between ADRs and MEcs, with J01 drugs (antibacterials for systemic use) being the leading cause in both. Our results suggested that a direct analysis of data from the spontaneous reporting system is a reliable, and convenient method to investigate MEs and ADRs, despite the existing limitations, and contributes to further understanding the current situation of MEs and ADRs in China.

1. Introduction

An adverse drug event (ADE) is defined as an injury derived from medical intervention during clinical practice, which includes drug-related and drug usage-related harm (Dai et al., 2020). An ADE is the comprehensive result of many factors, such as drug quality flaws, drug standard flaws, adverse drug reactions (ADRs), inappropriate prescription. Globally, an ADE is classified as an ADR and a medication error (ME). An ADR is a harmful response that occurs with the administration of a normal drug dose, which is somewhat unintended and difficult to prevent (Edwards and Aronson, 2000). A ME has never been strictly defined. It is a "man-made" mistake that could be a wrong dose, a wrong administration, a wrong drug combination, etc., which could be prevented by perfecting the rules, improving medical education, and reinforcing the management of medications. As per the definition written by the National Coordinating Council for Medication Error Reporting and Prevention: "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use." (NAN, 2018). Similar to ADRs, MEs are also a cause of high morbidity, mortality, and economic burden worldwide (Segal et al., 2019).

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The data reported in previous reports show that up to 56% of ADEs were attributed to MEs (Bates et al., 1995a; Kunac and Tatley, 2011; Tanti et al., 2013). A Japanese study reported that of all the 103 ADE cases that received traditional Japanese Kampo medication in one hospital, 99 were MEs and only 4 were ADRs (Shimada et al., 2017). These studies prove the crucial role of MEs in ADEs. Recently, many authors have proposed the necessity of distinguishing MEs from ADRs with pharmacovigilance since many measures can be adopted to improve medication safety (Assiri et al., 2018; Kopp et al., 2006; Zhou et al., 2018). However, reliable data about ME are sensitive and sometimes difficult to obtain. Clinicians usually receive a penalty or have to make compensation because of a ME, and therefore, their incidence might be concealed. Moreover, in cases where a ME does not cause a harmful reaction (MEn), the data might be ignored. In 2006, Kopp et al., proposed a direct observation method to detect MEs (Kopp et al., 2006). Later, a number of reports used prospective (Ewig et al., 2017; Plank-Kiegele et al., 2017) or retrospective (Silva et al., 2011; Stultz and Nahata, 2015) methods to explore MEs; however, both these methods have limitations. A prospective study is usually costly and a large sample investigation is difficult to carry out. A retrospective study is limited to the cohort involved and the conclusions are not representative. Ayani et al., used a retrospective chart review to investigate MEs and ADRs in cases that were involved in the Japan Adverse Drug Events study (Ayani et al., 2016). This method is reliable, but costly, time consuming, and needs grant support.

The spontaneous reporting system in the pharmacovigilance center, which was established by the administrative authority in a country, engages in the collection, monitoring, and evaluation of ADEs. Data reporting and collection are mandatory. As early as 2000, Crane made an appeal to improve the spontaneous reporting system to help distinguish between MEs and ADRs (Crane, 2000). Later, Zafar et al., established a streamlined interface design technique to improve the reporting rates of ADEs and MEs in the USA (Zafar et al., 2008). Currently, several studies use the spontaneous reporting system to investigate MEs and ADRs in ADE in New Zealand (Kunac and Tatley, 2011), Japan (Shimada et al., 2017), the USA (Carnovale et al., 2018), and Germany (Koberle et al., 2018). All these reports agreed that the direct use of data from the spontaneous reporting system in the pharmacovigilance center to detect MEs and ADRs is convenient method. Therefore, we believe that the spontaneous reporting system is the most important source of evidence to investigate MEs, and that distinguishing them from ADRs is the main task of the spontaneous reporting system. According to the World Health Organization's (WHO) "Monitoring Medicine" project, the development of tools and skills to distinguish between MEs and ADRs is required to improve the global spontaneous reporting system (WHO, 2014).

In addition, the occurrence of a ME is influenced by many complicated factors, such as the medical insurance system, the medical education level, the medical culture, and the medical laws. Therefore, investigating MEs in different populations and countries with different pharmacovigilance systems is extremely important. In China, a new version of the Provisions for Adverse Drug Reaction Monitoring and Reporting was issued in July 2011. Our previous study reported the improvements of the newer spontaneous reporting system (Fang et al., 2017). In the present paper, we conducted a study to investigate MEs and ADRs using data from an example year (2015, in a district in Shanghai) that was gathered from the newer spontaneous reporting system. The aim of this study was to investigate the characteristics of MEs and ADRs using data from the spontaneous reporting system in China. We believe that this study will be helpful to understand the actual situation of MEs, and improve the spontaneous reporting system as well as medication safety in China.

2. Materials and methods

2.1. Data sources

ADE data were acquired from the National Center for ADR Monitoring site for one district in south Shanghai. All the records from January 1, 2015 to December 31, 2015 were included. We selected the 2015 data from the spontaneous reporting system as our example to establish a novel approach to analyze ADRs and MEs because from 2015, a serial of rules and regulations were issued and implement by the Chinese government, which were believed to remarkably promote the rational and safe use of drug We used all records obtained from the database; hence no selection/exclusion criteria were applicable in this study. The experimental design of this study was shown in Fig. 1 (Fig. 1).

2.2. Standardized coding for ADR symptoms, system organ class, of ADRs and suspected drugs

The WHO Adverse Reactions Terminology dictionary was employed to code the symptoms and system organ class. In the event that one ADE case had more than one symptom or system organ class, each symptom or system organ class was coded separately. The suspected drug was coded with the WHO Guidelines for the Anatomical Therapeutic Chemical Classification System (WHO, 2019), and the code was positioned to the second class as was reported previously (Kunac and Tatley, 2011).

2.3. ADE classification approach

First, all the ADE cases were divided into MEs and ADEs without MEs according to the drug instructions, therapeutic guidelines, expert consensus, and related medical regulations. The original reports were examined independently and approved by three clinical pharmacologists (XT, DG, and HF). Further, the ME cases were classified into MEcs (MEs causing ADEs) and MEns (MEs not causing ADEs). Therefore, MEs = MEcs + MEns, and ADEs = MEcs + ADRs. All the data were cross-checked by the other pharmacologists (HF and TA) and discussed weekly to reach a final agreement.

2.4. Classification of MEs and MEcs

The second part of the Criteria of Assessing the Prescription Quality in Chinese Hospitals (The Trial Version) was used to classify the MEs and MEcs (Chen et al., 2010). It is a 9-item investigator-reported scale covering all types of MEs in China (2–1 Indication selection was inappropriate, 2–2 The selection of drugs is not appropriate, 2–3 The dosage form or route of administration is not appropriate, 2–4 National essential medicines are not preferred without good reason, 2–5 The usage and dosage of drugs is not appropriate, 2–6 The combination of medicine is not appropriate, 2–7 The situation of repeated medication, 2–8 Drug use has incompatibility or adverse interaction, 2–9 Other inappropriate situations of drug use).

2.5. Severity classification

The Common Terminology Criteria for Adverse Events (CTCAE v5.0) grading system was employed to assess the severity of the ADEs, serious ADEs, MEs, MEcs, and ADRs (Health and Services, 2017). It is a 5-grade investigator-reported grading system including: Grade 1: mild, asymptomatic or mild symptoms, no intervention required; Grade 2: Moderate; minimal, local symptoms, or noninvasive intervention required; Grade 3: Severe or medically significant but not immediately life-threatening symptoms; hospi-

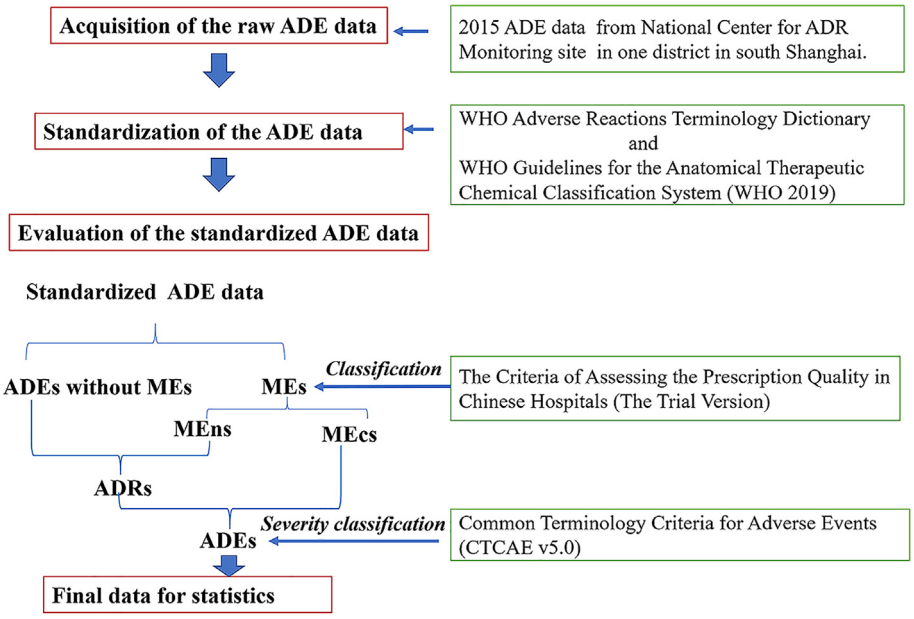

Fig. 1. The flowchart of the experimental design. ADEs: adverse drug events, ADRs: adverse drug reactions, MEs: medication errors, MEcs: medication errors causing ADE; MEns: medication errors without causing ADE; WHO: World Health Organization.

talization or prolongation of hospitalization required; Grade 4: Life-threatening consequences; urgent intervention required; and Grade 5: Death associated with ADE.

2.6. Statistics

SPSS software (v21.00, IBM, IL, USA) was used for the statistical analysis. A chi-squared test was used to compare the difference between the ADR and MEc groups. Fisher's exact test was used for comparisons containing expected frequencies < 5. A rank-sum test was employed for the rank data. $P < 0.05$ was considered a significant difference.

3. Results

3.1. General information

A total of 1290 ADEs were reported from January to December 2015, including 266 ME cases, with 211 MEc cases and 55 MEn cases. There was no significant difference in gender distribution between MEcs and ADRs. There were more cases of ADRs and MEcs in the population aged over 45 years, yet the distribution between ADRs and MEcs was different ($p < 0.05$). More ADR cases were involved in the over-45-year-old population. The dosage forms that were involved in MEs were oral medication and injection. The injection dosage form was predominant, and oral dosage was secondary (ME: 200 vs. 78; MEc: 161 vs. 61). The distribution of the dosage form between MEcs and ADRs was different ($p < 0.001$). Oral administration was the majority distribution form in ADRs and ADEs (62.09% in ADRs and 56.44% in ADEs); however, injection administration was the majority form in MEcs (Table 1).

3.2. Classification of errors involved in MEs and MEcs

The ME and MEc cases were clarified with the Criteria of Assessing the Prescription Quality in Chinese Hospitals. Most of the ME and MEc cases suffered from 2 to 1 errors (indication selection was inappropriate, ME: 75, 28.20%; MEc: 75, 35.55%), 2–5 errors (usage and dosage of drugs were inappropriate, ME: 109, 40.98%; MEc: 58, 27.49%), and 2–1 + 2–5 errors (ME: 48, 18.05%; MEc: 47, 22.27%) (Table 2).

3.3. Classification of the severity

The severity was classified according to the CTCAE v5.0 for serious ADEs, MEs, MEcs, and ADRs. The distribution of ADEs, MEs, MEcs, and ADRs in all five grades was analogous. Most of the cases (over 90%) were attributed to grades 1 and 2, which were represented as minimal and moderate severity. There was no significant difference of the distribution in the five grades between MEcs and ADRs ($p > 0.05$) (Table 3).

3.4. Comparison of primary diseases, system and organs, and symptoms between ADRs and MEcs

Table 4 shows the distribution of the number of primary diseases in ADRs and MEcs. After the removal of 22 cases with an unclear primary disease, all the cases were divided into 2 large groups according to the number of primary diseases, namely, primary disease = 1 and primary disease > 1. No significant difference was found in these groups between the ADR and MEc groups ($P > 0.05$) (Table 4).

Table 5 shows the top 10 system and organs and symptoms involved in ADRs and MEcs. They were similar for both groups, but the ranking order was different. The distribution of system and organs between MEcs and ADRs was significantly different ($p < 0.001$). The top 10 symptoms involved in ADRs and MEcs were different. If the frequency of symptoms of an ADR according to the top 10 symptoms in MEcs was calculated and compared with those in the MEcs, the difference was significant ($p < 0.001$) (Table 5).

3.5. Comparison of suspected drugs between ADRs and MEcs

Table 6 shows the top 10 suspected drugs involved in ADRs and MEcs. Antibacterials for systematic use (J01) were the most common cause of ADRs and MEcs. The order of the ranking between ADRs and MEcs was different. If the frequencies of the top 10

Table 1
General information on the ADEs.

General profile		Total ADEs (% of total ADEs)	Medication errors (% of MEs)	ME causing an ADE (% of MEcs)	ADR (% of total ADRs)	P (MEcs vs. ADRs)
Total		1290 (100%)	266 (100%)	211 (100%)	1079 (100%)	
Gender	Male	574 (44.50%)	123 (46.24%)	94 (44.55%)	480 (44.49%)	
	Female	713 (55.27%)	143(53.76%)	117 (55.45%)	596 (55.24%)	
	Unknown	3 (0.23%)	0	0	3 (0.28%)	
Age (years)	Over 45	1008 (78.14%)	193 (72.53%)	153 (72.51%)	855 (79.24%)	*
	Below 45	282 (21.86%)	73 (27.44%)	58 (27.49%)	224 (20.76%)	
Frequency of dosage forms	Injection preparations (suspected drug)	552 (40.62%)	200 (71.94%)	161 (72.52%)	391 (34.39%)	**
	Oral dosage forms (suspected drug)	767 (56.44%)	78 (28.06%)	61 (27.48%)	706 (62.09%)	
	Other administration methods (suspected drug)	40 (2.94%)	0	0	40 (3.52%)	

*means $p < 0.05$; ** means $p < 0.01$.

Table 2
ME and MEc cases and the dosage forms classified with the Criteria of Assessing the Prescription Quality in Chinese Hospitals.

Errors	Cases		ME		MEc	
	ME	MEc	Oral	Injection	Oral	Injection
2–1	75	75	23	53	23	51
2–2	12	11	6	6	6	5
2–3	2	2	0	2	0	2
2–5	109	58	40	71	24	36
2–6	3	1	1	3	0	2
2–7	2	2	3	0	3	0
2–1 + 2–2	3	3	0	3	0	3
2–1 + 2–5	48	47	4	46	4	46
2–2 + 2–5	7	7	0	8	0	8
2–1 + 2–6	1	1	1	0	1	0
2–2 + 2–5 + 2–6	2	2	0	4	0	4
2–5 + 2–6	2	2	0	4	0	4
Total	266	211	78	200	61	161

Table 3
Assessment of the severity of involved cases according to the CTCAE.

Grades	ADE cases (%)	ME cases (%)	MEc cases (%)	ADR cases (%)
1	947 (73.41%)	188 (70.68%)	147 (69.67%)	800 (74.14%)
2	274 (21.24%)	60 (22.56%)	47 (22.27%)	227 (21.04%)
3	40 (3.10%)	8 (3.01%)	8 (3.79%)	32 (2.97%)
4	28 (2.17%)	10 (3.76%)	9 (4.27%)	19 (1.76%)
5	1 (0.08%)	0 (0%)	0 (0%)	1 (0.09%)
Total	1290 (100%)	266 (100%)	211 (100%)	1079 (100%)

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3: severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4: life-threatening consequences; urgent intervention indicated. Grade 5: death related to an adverse event.

Table 4
Distribution of primary diseases in MEcs and ADRs.

Primary diseases number	MEc	ADR
1	190	947
2	15	72
3	2	22
4	3	8
5	0	6
6	1	1
9	0	1
Uncertain	1	21
Primary disease = 1	190	947
Primary disease > 1	21	110

MEc drugs in ADR cases was calculated and compared with those in MEc cases, the difference was significant ($p < 0.001$) (Table 6).

Once the top 10 drugs of MEcs were analyzed with the CAPQCH, we found that drugs in items 2–1 and 2–5 were involved in more errors than others, particularly J01 (47 cases in 2–1, 45 cases in 2–1 and 2–5) and N06 (16 cases in 2–5). In addition, R05 and V03 were also contributors in 2–2 (Table 7).

When the top 10 suspected drugs in cases (CTCAE grade ≥ 3) were listed, only three drugs (J01, B01, and J05) existed simultaneously in both ADRs and MEcs, which indicated that J01, B01, and J05 tend to cause serious injuries in both MEcs and ADRs (Table 8).

4. Discussion

In the present study, we analyzed data from one year in a district where MEs have been distinguished from ADRs in the newer spontaneous reporting system (2011 version) (Fang et al., 2017). The general information, medication errors involved, severity, clinical manifestations, and involved suspected drugs were analyzed and compared between MEs and ADRs. To the best of our knowledge, this is the first report showing the actual situation of MEs

Table 5
Top 10 system and organs and symptoms involved in ADRs and MEcs.

Ranking	System and organs (frequency)		Symptoms (frequency)		Frequency of top 10 ADR symptoms in MEcs
	ADR	MEc	ADR	MEc	
1	Gastrointestinal system disorders (348)	Skin and appendage disorders (65)	Nausea (178)	Rash (49)	Nausea (178)
2	Skin and appendage disorders (253)	Gastrointestinal system disorders (58)	Rash (155)	Nausea (33)	Rash (155)
3	Body as a whole-general disorder (209)	Body as a whole-general disorder (45)	Leucopenia neonatal (116)	Leucopenia neonatal (26)	Leucopenia neonatal (116)
4	Central & peripheral nervous system disorders (183)	Central & peripheral nervous system disorders (31)	Dizziness (111)	Dizziness (22)	Dizziness (111)
5	Vascular (extracardiac) disorders (87)	Application site disorders (24)	Vomiting (89)	Malaise (19)	Vomiting (89)
6	Heart rate and rhythm disorders (46)	Vascular(extracardiac) disorders (8)	Malaise (74)	Injection site pain (18)	Malaise (74)
7	Respiratory system disorders (42)	Heart rate and rhythm disorders (7)	Diarrhea (71)	Vomiting (13)	Abdominal pain (53)
8	Application site disorders (40)	Liver and biliary system disorders (6)	Edema (66)	Headache (11)	Headache (51)
9	Liver and biliary system disorders (35)	Respiratory system disorders (4)	Flushing (54)	Abdominal pain (8)	Palpitation (35)
10	Psychiatric disorders (25)	Psychiatric disorders (4)	Abdominal pain (53)	Palpitation (7)	Injection site pain (13)

Table 6
Top 10 suspected drugs in ADRs and MEcs.

Ranking	ADR (frequency)	MEc (frequency)	Frequencies of top 10 MEc drugs in ADR cases
1	J01 (292)	J01 (117)	J01 (292)
2	C08 (113)	N06 (18)	C08 (113)
3	C09 (88)	R05 (16)	C09 (88)
4	V03 (75)	V03 (15)	V03 (75)
5	M01 (59)	B01 (7)	M01 (59)
6	N05 (58)	A05 (6)	B01 (52)
7	B01 (52)	C08 (4)	R05 (51)
8	R05 (51)	M01 (4)	C01 (16)
9	J05 (29)	C01 (4)	N06 (13)
10	N02 (17)	C09 (3)	A05 (5)

and ADRs that has been acquired from the spontaneous reporting system in China. This study proved that using the data from the existing spontaneous reporting system in the pharmacovigilance center is a reliable and convenient method to investigate the ME and ADR situation. The findings of this study will contribute to the prevention of MEs during clinical practice, and provides evidence to improve the spontaneous reporting system in the future.

The general information of the involved ADEs showed that age distribution exhibited a significant difference between ADRs and MEcs ($p < 0.05$), with ADRs having a greater proportion than MEcs (79.24% vs. 72.51%) (Table 1). We found that the component ratio of ADRs in the population over 45 years was significantly higher than in that below 45 years (79.24% vs. 20.76%, respectively) and this agrees with previous studies in different countries (Khan et al., 2012; Pourseyed et al., 2009; Sauer et al., 2007). It is easy to understand that the incidence of ADR increases with age. Our data of MEcs also showed the same tendency. The component ratio of MEcs was higher in the older population (72.51% vs. 27.49%), which was similar to the data in a 2011 study in New Zealand (Kunac and Tatley, 2011). This result indicates that MEcs occur more in the older population. The cause of this phenomenon is unclear. One possibility is that the older population suffers from several simultaneous diseases, which increases the difficulty of prescribing medication and makes it easier to make mistakes. It is also possible that younger patients receive more attention, and this could be a possible explanation for the high incidence of MEcs in aging patients. It is noteworthy that the incidence of MEcs was 16.36% (211/1290), which was remarkably higher than the 2.9% that was reported in a population in Germany in 2015 (Kuklik et al., 2019). This might be caused by the difference in the level of medical development between Germany and China. With respect to the dosage forms, our data show that injection, rather than oral administration, contributed to more cases of MEcs (72.52% vs 34.39%, $p < 0.001$, MEcs vs. ADRs, respectively). These data indicate that an injection can easily cause a MEc; therefore, more attention should be paid to the administration of injections. Our data did not show that gender influenced the occurrence of MEcs and ADRs. These data are in accordance with a previous study

Table 7
Classification of suspected drugs in MEcs according to the Criteria of Assessing the Prescription Quality in Chinese Hospitals.

	J01	N06	R05	V03	B01	A05	C08	M01	C01	C09	Total
2–1	47	2	1	6	5	5	0	0	0	0	66
2–2	1	0	4	3	0	0	0	0	1	0	9
2–3	0	0	0	0	0	0	0	0	1	0	1
2–5	8	16	7	4	1	1	4	4	2	3	50
2–6	0	0	0	0	0	0	0	0	0	0	0
2–7	0	0	3	0	0	0	0	0	0	0	3
2–1 + 2–2	0	0	0	2	0	0	0	0	0	0	2
2–1 + 2–5	45	0	1	0	1	0	0	0	0	0	47
2–2 + 2–5	7	0	0	0	0	0	0	0	0	0	7
2–1 + 2–6	1	0	0	0	0	0	0	0	0	0	1
2–2 + 2–6	0	0	0	0	0	0	0	0	0	0	0
2–5 + 2–6	4	0	0	0	0	0	0	0	0	0	4
2–2 + 2–5 + 2–6	4	0	0	0	0	0	0	0	0	0	4
Total	117	18	16	15	7	6	4	4	4	3	194

Table 8
Classification of suspected drugs in severe cases (CTCAE grade ≥ 3).

Ranking	ADR (%)	MEc (%)
1	J01 (1.32%)	J01 (4.05%)
2	B01 (0.70%)–	R05 (0.90%)
3	J05 (0.62%)	A02 (0.45%)
4	*L*01 (0.62%)	A12 (0.45%)
5	A10 (0.44%)	B01 (0.45%)
6	C10 (0.35%)	C03 (0.45%)
7	J02 (0.35%)	J05 (0.45%)
8	C02 (0.18%)	M01 (0.45%)
9	J04 (0.18%)	N02 (0.45%)
10	V03 (0.18%)	A11 (0.45%)

(Schmiedl et al., 2018), which confirmed that gender is not a risk factor of MEcs.

We identified the main cause of MEcs and clarified them with the CAPQCH. Error 2–5 (usage and dosage of drugs were inappropriate) was the top error. A total of 109 cases involved a ME, including 58 cases that developed an adverse event (MEc) and 51 cases that did not develop an adverse event (MEn). Error 2–1 (indication selection was inappropriate) was the second most common error. All these cases developed an adverse event. An error with both 2–5 and 2–1 was the third most common, and 47 of 48 of such cases developed an adverse event, with only one case being a MEn. Our results are in agreement with previous studies (Bates et al., 1995b; Seidling et al., 2010), which confirm that errors in the prescription process are the predominate cause of MEs (Table 2). Our results cannot be compared directly with the previous studies, which indicate that dosage errors were the majority, because we used a different assessment system (Ewig et al., 2017; Mekonnen et al., 2018). However, dosage errors are attributed to error 2–5 in the Criteria of Assessing the Prescription Quality in Chinese Hospitals, and we believe that our results do not contradict the previous results.

Our data also suggested that most of the ADR and MEc cases were mild (grade 1 in the CTCAE), and there were fewer moderate cases (grade 2; 22.27% in MEc and 21.04% in ADR). No significant difference was found between ADRs and MEcs. Despite a severe adverse reaction event being quite low (8.06% in MEcs and 4.82% in ADRs), these reactions must be noticed and avoided (Table 3).

Most cases involving MEcs and ADRs in this study suffered from one primary disease (Table 4). The distribution of the top 10 involved system and organs, and symptoms was significantly different between ADRs and MEcs (Table 5). These differences require further investigation.

Our results for suspected drugs indicated that J01 drugs (antibacterials for systemic use) were the leading cause in both MEcs and ADRs. J01 drugs were also the most involved type in MEs in a previous report (Kuklik et al., 2019). However, the distribution of the top 10 suspected drugs was different in MEcs and ADRs. In addition to J01, C08 (Ca^{++} channel blockers), and C09 drugs (drugs for the renin–angiotensin system) tend to induce ADRs, but seldom are the cause of MEcs. Conversely, N06 drugs (psychoanaleptics) tend to be the cause of MEcs, but seldom cause ADRs (Table 6). The fact that N06 drugs are seldom prescribed might be the potential cause for this and requires further investigation. When the suspected drugs in MEcs were evaluated by the Criteria of Assessing the Prescription Quality in Chinese Hospitals, errors 2–1 and 2–5 were the cause in the majority of cases (Table 7). For the top 10 suspected drugs in severe cases (CTCAE grade ≥ 3), we found that three drugs (J01, B01, and J05) existed simultaneously in both ADRs and MEcs. Therefore, more attention should be paid to the application of J01, B01, and J05 to prevent severe adverse reactions (Table 8).

The present study has several potential limitations. The data for this study were acquired from the local spontaneous reporting system. It is known that not all MEs cause a harmful reaction (Goedecke et al., 2016). MEs that cause a harmful reaction (MEcs) might be reported routinely to the pharmacovigilance center; however, the MEs that do not cause a harmful reaction (MEns) might be omitted. Also, MEs might result in a penalty or need to make compensation, which could also potentially keep clinicians from reporting an existing ME as an ADR to avoid potential trouble. Moreover, the potential of under-reporting, which is a common flaw of the spontaneous reporting system, might lead to a biased result. Additionally, the present study only used the 2015 data from the spontaneous reporting system in a south district in China, which might lack representativeness. We are now planning a subsequent study using data involving several years and more locations.

The present study verified a method to investigate the distribution of MEs and ADRs in all ADE cases using example data from one year from the spontaneous reporting system from the pharmacovigilance center in China. Although using the data directly from the spontaneous reporting system has several limitations, it is a stable, and convenient method to investigate MEs and ADRs. The value of this method depends on the reliability of the data from the spontaneous reporting system, which can be improved through education to reduce the under-reporting rate, perfect the spontaneous reporting system, and encourage the clinicians (Fang et al., 2017).

5. Conclusions

We analyzed the difference between MEcs and ADRs using data from a local spontaneous reporting system in China. Our results showed similarities in gender distribution, the severity of distribution, the leading cause of the suspected drug (J01), and the drugs that cause severe adverse events (J01, B01, and J05) between MEcs and ADRs. Significant differences in age distribution, distribution of the dosage form, distribution of the system and organs, symptoms, and top 10 suspected drugs were also identified. These results provided evidence that MEs are different from ADRs, which should be distinguished in the spontaneous reporting system. The findings contribute to further understanding the current situation of MEs and ADRs in China, and are helpful in preventing MEs during clinical practice. A more reliable spontaneous reporting system that may reduce the under-reporting of MEs, especially MEns, is expected in the future.

Author contributions

Conceptualization, X.T., H.F., and T.A; methodology, X.T., D.G., X. L., H.F., and T.A; software, X.T., D.G., X.L., and H.F., validation: H.F., and T.A; writing—original draft preparation, X.T., H.F., and T.A; writing—review and editing, X.T., D.G., X.L., H.F., and T.A; visualization, H.F., and T.A; supervision, J H.F., and T.A.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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