JOURNAL OF PHARMACEUTICAL POLICY AND PRACTICE
2025, VOL. 18, NO. 1, 2483419
https://doi.org/10.1080/20523211.2025.2483419

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RESEARCH ARTICLE

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Self-reporting of adverse drug reactions of nonsteroidal anti-inflammatory drugs in community pharmacies

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ABSTRACT

Background: Ibuprofen and diclofenac are nonsteroidal anti-inflammatory drugs widely used worldwide. Spontaneous reporting often results in an underestimation of the incidence of adverse drug reactions (ADRs), and a few studies have been conducted in community settings, particularly in community pharmacies. This study aimed to determine the frequency and characteristics of short-term ADRs associated with ibuprofen and diclofenac in community pharmacy patients.

Methods: This prospective cohort study was conducted in 15 community pharmacies. A questionnaire from a previous study was modified and tested for content validity. Community pharmacists distributed the questionnaire after dispensing ibuprofen or diclofenac and followed non-responders via telephone and online media platforms. The returned questionnaires were assessed for causality by a pharmacist and three researchers. Descriptive analyses and comparisons between reports on ibuprofen and diclofenac were performed using chi-square and independent t-tests for appropriate outcomes.

Results: Of the 590 distributed questionnaires, 279 were included in the analysis. The percentage of participants who reported ADRs to ibuprofen and diclofenac was 33.3%. Among participants with suspected ADRs, the average number of suspected ADRs from diclofenac was higher than from ibuprofen; however, no significant difference was observed (5.5 ± 8.9 and 3.1 ± 3.0, $p > 0.05$). Of the 347 self-reported ADRs, 45.2% were assessed as probable and

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20523211.2025.2483419.

possible ADRs. The highest rate of suspected ADRs was in Mental Health (14.4%), followed by the Nose, Throat, Neck, or Voice (9.8%), and the Stomach or Digestive Systems (8.9%), respectively.
Conclusions: Diclofenac showed more suspected ADRs than ibuprofen in a community setting. Almost half of the self-reported ADRs were assessed as probable or possible. Strategies for sustaining community pharmacists in monitoring patients and reporting ADRs should be supported.

ARTICLE HISTORY Received 6 September 2024; Accepted 18 March 2025

KEYWORDS Adverse drug reaction; community pharmacy; ibuprofen; diclofenac; NSAIDs; Thailand

Background

Pharmacovigilance plays an important role in the detection, assessment, understanding and prevention of adverse effects and any other medicine-related problems (WHO, n.d.). The spontaneous reporting of adverse drug reactions (ADRs) is an efficient and widely used method for detecting and monitoring drug safety. Nevertheless, the underreporting rate of ADRs is high (Hazell & Shakir, 2006). Several studies have reported that the factors involved include a lack of awareness of reporting systems and complicated reporting systems (Kitisopee et al., 2022; Worakunphanich et al., 2023).

Patient self-reporting provides the public with the opportunity to report, and is a feature of national pharmacovigilance schemes in many countries, such as the US and the UK (van Hunsel et al., 2012). The combination of patient self-reports and healthcare professional reports has generated signal detection (Härmark et al., 2015), new 'serious' reaction identification (Avery et al., 2011), and an increasingly accurate estimation of the true incidence of adverse effects (Morgan & Clark, 1998). However, the quality of these studies remains unclear. One study revealed that patient reports more commonly provided detailed descriptions of reactions than did health professional reports (Avery et al., 2011). The level of clinical information (Rolfes et al., 2017) and proportion of reports categorised as 'serious' under the Yellow Card Scheme (Avery et al., 2011) were similar between the patient and healthcare professional reports. A supportive suggestion for patient self-reporting is the robust reliability and validity of this questionnaire. Thus, these reports can be used in clinical practice and research to identify ADRs (Lim et al., 2021).

Several studies have shown that pharmacists are involved in the detection of ADRs, especially in hospitals (Christensen et al., 2011; Lobo et al., 2013). The involvement of pharmacists improves the detection of ADRs and promoted their prevention (Sánchez et al., 2014). Although information on reporting drug reactions through community pharmacies is limited (Thomson et al., 2010), a study that used the outreach role of community pharmacies

through pharmacy internship students identified 45 reports from 128 patients who received ibuprofen (Christensen et al., 2011). Nevertheless, the extent of pharmacist participation in reporting ADRs is largely unknown in both community and institutional settings (Kumar, 2017).

In clinical practice, ibuprofen and diclofenac are the most frequently prescribed NSAIDs for short-term use (Fosbøl et al., 2008). Given the balance between safety and therapeutic effects, ibuprofen is classified as over-the-counter medicine in both the UK and the US (Rainsford, 2007). However, ADRs involving ibuprofen may still occur, even with short-term use of seven days, the most frequent being dyspepsia (2.3%), minor gastrointestinal disorders (1.9%), and signs of overdose (1.7%) (Lanas et al., 2011). On the other hand, diclofenac is the only NSAID in the World Health Organization (WHO) database with at least 50 cases of fatal drug-induced liver disease (Björnsson & Olsson, 2006). Moreover, several cohort studies have revealed that diclofenac poses a greater risk to cardiovascular health than does ibuprofen (Schmidt et al., 2018). In clinical practice, appropriate NSAID use requires the consideration of all risks (Ho, 2020).

In Thailand, community pharmacists have submitted only a few ADR reports to the pharmacovigilance centre. Because both diclofenac and ibuprofen are the only NSAIDs in the top 20 ADR reports (Health Product Vigilance Center, 2023) and are commonly dispensed through community pharmacies. Thus, these two NSAIDs were chosen for this study. The objective of this study was to determine the frequency and characteristics of ADRs associated with the short-term use of ibuprofen and diclofenac in community pharmacies.

Methods

This prospective cohort study involved 15 community pharmacies in northeastern Thailand between October 2012 and November 2013.

Questionnaire development and validation

A questionnaire for the detection and reporting of ADRs by Jarernsiripornkul et al. (2002) was modified for this study. Two community pharmacists assessed content validity. The 32-item questionnaire consisted of three parts as a guide for detecting of user experienced ADRs and functioned as a reporting form. The basic principle for the modification was to make it user-friendly and simple for respondents to use (see Supplemental Material 1).

First part: General and medication use information. One original item was excluded (Since you started taking … have you been in the hospital for any reason?). This study considered only the short-term use of NSAIDs, and pharmacists followed up and evaluated the respondents on the date they returned the questionnaire. Three additional items related to community

pharmacies, including education, prior use of NSAIDs, duration of NSAIDs use, and adherence, were added. Thus, this section contained 11 items.

Second part: ADR self-report questionnaire. This part consists of an extensive series of questions asking about the symptoms experienced, grouped by the body system following the System Body Classification (Jarernsiripornkul et al., 2002), to detect possible ADRs. It was slightly modified in three ways. First, two original systems were combined (Vision and Eyes, and Sexual function, and Reproductive System). Second, according to extensive reviews of known ADRs from ibuprofen and diclofenac, several symptoms were added to the Vision or Eyes Mouth or Gums, Breathing or Lungs, Rectum or Bowel Movements, Hearing or Ears, and Hair or Nails Systems. Finally, a pictorial symbol representing each body system was inserted to make the questionnaire friendly and easy for the respondents to use. In addition, there are two items in which suspected symptoms cause patient worry and bothersome severity. *Third part:* This part of the questionnaire focused on the reasons for stopping the index medication and the appearance or disappearance of reactions. We discarded one item (Have you told your doctor about any of these symptoms?). This study was performed only by pharmacists. The total number of items was three.

A checklist of known ADRs associated with ibuprofen and diclofenac was developed as a supplementary source for pharmacists for their reference. The information was gathered from Drug Information for the Health Care Professional (USP DI) (United States Pharmacopeial Convention, 2000), Drug Information Handbook (Lacy et al., 2011), computerised clinical information system (Micromedex®) (IBM Corporation, 2009), Drug Interaction Facts™ (Tatro, 2012), Meyler's Side Effects of Analgesics and Anti-inflammatory drugs (Aronson, 2006), and the Annual Report of Adverse Drug Reactions by the Health Product Vigilance Center (Health Product Vigilance Center, 2012). Information concerning symptoms and diseases was obtained from Davidson's Principles and Practice of Medicine (Boon et al., 2006) and Harrison's Principles of Internal Medicine (Kasper et al., 2005). After the checklist of known ADRs associated with ibuprofen, diclofenac, and potential interacting agents was completed, four researchers (CT, PT, WS, and PSO) reviewed the data for validation in the final steps.

Causality assessment

The ADR evaluation form consisted of two parts. The first part is a checklist for reviewing body systems. The second part was a guide for evaluating suspected symptoms related to ADRs, including medical history, concurrent medicines, symptom descriptions, ADR-related timing, descriptions of factors affecting better or worse symptoms, possible medical problems other than ADRs, known ADRs, and the need for referral. In the first part,

pharmacists reviewed body systems to identify suspected ADRs on the day the respondents returned the reports. The second part was for a pharmacist and three researchers (PSO, CT, PT, and WS) to evaluate causality according to the criteria.

The causality assessment comprised four criteria: (1) presenting suspected ADRs during the study period; (2) taking other medications and currently using them; (3) having other diseases; and (4) having known ADRs. Microsoft Excel Professional Plus 2019 was used to extract data, including participant IDs, suspected ADRs, four criteria, and assessments. Discrepancies were resolved by a third researcher (PP). The causality assessment in this study was divided into eight groups (Jarernsiripornkul et al., 2002), as shown in Supplemental Material 2.

Pharmacist recruitment

Purposive sampling was conducted. Fifteen community pharmacies met the following inclusion criteria: (1) being a community pharmacy accredited by the Pharmacy Council of Thailand or serving as an experiential training site for final-year pharmacy students at Mahasarakham University; (2) located in four provinces (Khon Kaen, Roi-Et, Kalasin, and Maha Sarakham); and (3) willing to participate in this study. Pharmacy accreditation was granted by the Office of Pharmacy Accreditation of Thailand for community pharmacies that met the standard criteria (Pharmacy Council of Thailand, n.d.).

Participant recruitment

The study population included patients who received NSAIDs at one of the participating community pharmacies. The inclusion criteria were participants who (1) were aged at least 18 years; (2) had an indication and were able to use ibuprofen or diclofenac supplied from a community pharmacy; (3) were able to communicate through telephone and social media platforms; and (4) were willing to participate in the study. Participants who were unable to read or complete the self-report questionnaire or those taking more than one NSAIDs were excluded from the study. The study aimed to achieve a sufficient sample size with 80.0% power and 5.0% proportion of error based on the proportion of the population with gastritis (the most frequent ADR to NSAIDs) at 46.7% (Shi et al., 2004). The calculated required sample size was 382 participants, which was increased to 574 to allow for a 50.0% drop-out rate.

Questionnaire distribution

A set of materials was prepared and delivered to each community pharmacy. The set composed of six items; (1) a monitoring sheet for recording the date

of distribution and return of each questionnaire; (2) a flow chart describing the research process; (3) four cards of known ADRs of ibuprofen and diclofenac, a drug–drug interaction list, and a drug–disease interaction list; (4) patient information sheets explaining the objective of the study; (5) 32-item questionnaires; and (6) gift bags with a value of $0.75 USD for those who enrolled in the study.

Patients who had been dispensed with either diclofenac or ibuprofen for a short period of time, ranging from three to seven days, were invited to participate in the study. The pharmacists explained to them how to complete the questionnaire after finishing the medication or when experiencing any unusual symptoms. The participants were instructed to return the questionnaire to the community pharmacy within seven days of completing the course or earlier if they discontinued it because of ADRs. Participants were also instructed to keep empty packaging or unused ibuprofen or diclofenac in small plastic bags and attach them to the cover page of the questionnaire. This was performed to facilitate the identification of concomitant therapies by pharmacists. The pharmacists recorded the date of each administered questionnaire, medications provided, indications, and date of the returned questionnaire on the monitoring sheet. Telephone calls or communication via online platforms (LINE®, Facebook Messenger®, and e-mail) were also used to contact and follow-up the non-responders every week after they were dispensed with NSAIDs. If there were no responses after three attempts, they were excluded from the study.

When the questionnaires were returned, the pharmacists checked for any reactions identified by the participants and then assessed the causality of these symptoms by using the ADR evaluation form. Pharmacists provided any necessary information, counselling or referrals, as appropriate. Each participant was given a gift bag to recognise their time.

Statistical analysis

Descriptive analyses were performed using the IBM SPSS® (Statistics software) version 29.0 (IBM Corp., Armonk, NY, USA). For comparisons of proportions between groups, the chi-square test was used. The independent t-test was used for ratio scale variables. Missing values in the third part of the questionnaire (worry about symptoms and level of worry) were treated as negative results, with the assumption that participants did not have any symptoms of worry or no new symptoms after stopping medications.

Results

A total of 590 questionnaires were distributed to 15 accredited community pharmacies. There were 280 returned, with a response rate of 47.5%. One

respondent who did not meet the inclusion criteria was under 18 years of age. Therefore, 279 questionnaires were included in the final analysis. Most participants were female and more than 75% had no comorbidities, as shown in Table 1.

Most participants received ibuprofen (222 patients, 79.6%), whereas only 57 (20.4%) received diclofenac. Among 279 patients, 34.8% had prior experience with the medications. The participants' perception of the indication was inflammation, especially in the diclofenac group. Approximately 70% of the participants took medication every day, and less than 10% used other medications during the study period, as shown in Table 1.

Among the 279 participants, 33.3% reported suspected ADRs to either ibuprofen or diclofenac. The suspected ADRs included 347 reported events:

Table 1. Demographic data of participants who received ibuprofen or diclofenac.

Demographic data	Total (n,%) (n = 279)	Ibuprofen (n,%) (n = 222)	Diclofenac (n,%) (n = 57)	*p* value
Gender: female	183 (65.6)	150 (67.6)	33 (57.9)	0.170
Age (mean ± SD, years)	26.1 ± 11.1	24.8 ± 9.3	31.3 ± 15.4	<0.001
Education: Lower than bachelor's degree	46 (16.5)	33 (14.9)	13 (22.8)	0.137
Bachelor's degree	231 (82.7)	188 (84.7)	43 (75.4)	
Not specify	2 (0.7)	1 (0.5)	1 (1.8)	
Comorbidities				0.574
No	213 (76.3)	167 (75.2)	46 (80.7)	
Yes	50 (17.9)	41 (18.5)	9 (15.8)	
Asthma	2 (4.0)	2 (4.9)	0 (0.0)	
Gastric problems	8 (16.0)	7 (17.1)	1 (11.1)	
Hypertension	3 (6.0)	3 (7.3)	0 (0.0)	
Heart disease	2 (4.0)	1 (2.4)	1 (11.1)	
Others (thyroid, diabetes, anemia, migraine, gout, bone & joints pain, allergic rhinitis)	26 (52.0)	19 (46.3)	7 (77.8)	
Not specify	16 (5.7)	14 (6.3)	2 (3.5)	
History of using ibuprofen or diclofenac				
Previous use of ibuprofen or diclofenac	97 (34.8)	79 (35.6)	18 (33.3)	0.822
Current use of ibuprofen or diclofenac in the study				
Participant's perception of indication				n/a
Inflammation	126 (45.2)	84 (37.8)	42 (73.7)	
Sore throat from a cold	54 (19.4)	51 (23.0)	3 (5.2)	
Fever	38 (13.6)	36 (16.2)	2 (3.5)	
Migraine	6 (2.2)	6 (2.7)	0 (0.0)	
Not specify	55 (19.7)	45 (20.3)	10 (17.5)	
Adherence to the current medicines				0.106
Every day	210 (75.3)	168 (75.7)	42 (73.7)	
Alternate day	15 (5.4)	9 (4.1)	6 (10.5)	
Others (prn, one day)	42 (15.1)	33 (14.9)	9 (15.8)	
Not specify	12 (4.3)	12 (5.4)	0 (0.0)	
Taking other medicines (paracetamol (3), tolpersone (2), amoxycillin (1), antiplatelet (1), antihistamine (1), hemorrhoid medicine (1), serratiopeptidase (1), not specify (9))	19 (6.8)	14 (6.3)	5 (8.8)	0.552

Table 2. Numbers of suspected ADRs from ibuprofen and diclofenac.

	Total (n = 279) (n,%)	Ibuprofen (n = 222) (n,%)	Diclofenac (n = 57) (n,%)	*p* value
Total number of suspected ADRs (min–max)	347 (100.0) (0–39)	247 (71.2) (0–15)	100 (28.8) (0–39)	n/a
Frequency of ADRs				
0	186 (66.7)	147 (66.2)	39 (68.4)	0.949
1–5	78 (28.0)	63 (28.4)	15 (24.6)	
≥ 6	15 (5.4)	12 (5.4)	3 (5.3)	
Number of participants with suspected ADRs	93 (33.3)	75 (33.8)	18 (31.6)	0.753
Average suspected ADRs per person (mean ± SD)	1.2 ± 3.3	1.1 ± 2.3	1.7 ± 5.6	0.202
Average suspected ADRs per person among participants with suspected ADRs (mean ± SD)	3.7 ± 4.8	3.1 ± 3.0	5.5 ± 8.9	0.081

71.2% for ibuprofen and 28.8% for diclofenac. Interestingly, one participant reported 39 symptoms after diclofenac use as shown in Table 2.

The causality assessment of these 347 suspected ADRs revealed 'probable ADRs' (84, 24.2%), 'possible ADRs' (73, 21.0%), 'unlikely ADRs' (154, 44.4%), and 'unattributable ADRs' (36, 10.4%). The top suspected ADRs reported were in the Mental Health System (14.4%). Among the 247 suspected ADRs caused by ibuprofen, the highest number occurred in the Mental Health System (16.2%). Causality assessment revealed the highest percentage of probable and possible ADRs in the Stomach or Digestive System (probable ADRs 11.9% and possible ADRs 8.8%). Among the 100 suspected ADRs associated with diclofenac, the highest number was observed in the Stomach or Digestive System (12.0%). Causality assessment revealed that the most probable and possible ADRs were reported in the Skin System (probable ADRs 26.7 and possible ADRs 6.3%), as shown in Table 3.

The top four systems of suspected total ADRs according to participants' self-reports are shown in Figure 1(a). The most common suspected ADRs in the Mental Health, Nose, Throat, Neck, or Voice, Stomach or Digestive Systems, and Others were drowsiness, sore throat, feeling bloated, and fatigue, respectively. Causality assessment revealed that the most probable and possible ADRs in each system were a reduction in sleeping, sore throat, feeling bloated, and fatigue, respectively, as shown in Figure 1(b).

Among the 247 suspected ADRs in participants who took ibuprofen, the four most suspected ADRs by system were found in the Mental Health System, with the highest reporting of drowsiness; the Nose, Throat, Neck, or Voice System, with the highest reporting of sore throat; the Stomach or Digestive System, with the highest reporting of feeling bloated; and the Others, with the highest reporting of fatigue, as shown in Figure 2a. Considering the causality assessment, the highest probable and possible ADRs in the Mental Health System was a reduction in sleeping; in the Nose, Throat, Neck, or Voice system, sore throat; and in the Stomach or Digestive System, nausea; and in Others, fatigue, as shown in Figure 2b.

Table 3. Causality assessment of suspected ADRs from ibuprofen and diclofenac.

No	Body systems	Total ADRs (n = 347) (n,%)	Suspected ADRs from Ibuprofen (n,%)					Suspected ADRS from Diclofenac (n,%)				
			Total (n = 247)	Probable (n = 69)	Possible (n = 57)	Unlikely (n = 104)	Unattributable (n = 17)	Total (n = 100)	Probable (n = 15)	Possible (n = 16)	Unlikely (n = 49)	Unattributable (n = 20)
1.	Mental Health	50 (14.4)	40 (16.2)	1 (1.5)	3 (5.3)	31 (29.8)	5 (29.4)	10 (10.0)	0 (0.0)	0 (0.0)	6 (12.2)	4 (20.0)
2.	Nose, Throat, Neck, or Voice	34 (9.8)	30 (12.1)	8 (11.6)	5 (8.8)	13 (12.5)	4 (23.5)	4 (4.0)	2 (13.3)	1 (6.3)	1 (2.0)	0 (0.0)
3.	Stomach or Digestive System	31 (8.9)	19 (7.7)	9 (13.0)	6 (10.5)	2 (1.9)	2 (11.8)	12 (12.0)	0 (0.0)	3 (18.8)	8 (16.3)	1 (5.0)
4.	Muscles, Bones or Joints	25 (7.2)	15 (6.1)	5 (7.3)	7 (12.3)	3 (2.9)	0 (0.0)	10 (10.0)	0 (0.0)	1 (6.3)	7 (14.3)	2 (10.0)
5.	Mouth or Gums	23 (6.6)	18 (7.3)	9 (13.0)	5 (8.8)	4 (3.9)	0 (0.0)	5 (5.0)	3 (20.0)	1 (6.3)	0 (0.0)	1 (5.0)
6.	Breathing or Lungs	21 (6.1)	17 (6.9)	3 (4.4)	5 (8.8)	9 (8.7)	0 (0.0)	4 (4.0)	1 (6.7)	0 (0.0)	3 (6.1)	0 (0.0)
7.	Nervous System	20 (5.8)	9 (3.6)	1 (1.5)	4 (7.0)	4 (3.9)	0 (0.0)	11 (11.0)	2 (13.3)	1 (6.3)	4 (8.2)	4 (20.0)
8.	Head	20 (5.8)	15 (6.1)	1 (1.5)	4 (7.0)	10 (9.6)	0 (0.0)	5 (5.0)	0 (0.0)	2 (12.5)	3 (6.1)	0 (0.0)
9.	Vision or Eyes	18 (5.2)	12 (4.9)	4 (5.8)	4 (7.0)	4 (3.9)	0 (0.0)	6 (6.0)	1 (6.7)	1 (6.3)	4 (8.2)	0 (0.0)
10.	Rectum or Bowel Movements	17 (4.9)	14 (5.7)	8 (11.6)	3 (5.3)	3 (2.9)	0 (0.0)	3 (3.0)	0 (0.0)	1 (5.3)	2 (4.1)	0 (0.0)
11.	Skin	15 (4.3)	7 (2.8)	3 (94.4)	2 (3.5)	1 (1.0)	1 (5.9)	8 (8.0)	4 (26.7)	1 (6.3)	1 (2.0)	2 (10.0)
12.	Heart or Circulation	11 (3.2)	7 (2.8)	4 (5.8)	2 (3.5)	1 (1.0)	0 (0.0)	4 (4.0)	1 (6.7)	0 (0.0)	3 (6.1)	0 (0.0)
13.	Kidneys, Bladder or Urinary System	11 (3.2)	8 (3.2)	6 (8.7)	0 (0.0)	1 (1.9)	0 (0.0)	3 (3.0)	1 (6.7)	0 (0.0)	1 (2.0)	1 (5.0)
14.	Hearing and Ears	8 (2.3)	5 (2.0)	2 (2.9)	2 (3.5)	1 (1.0)	0 (0.0)	3 (3.0)	0 (0.0)	0 (0.0)	2 (4.1)	1 (5.0)
15.	Reproductive System	6 (1.7)	3 (1.2)	0 (0.0)	0 (0.0)	2 (1.9)	1 (5.9)	3 (3.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (10.0)
16.	Hair, or Nails	4 (1.2)	2 (0.8)	1 (1.5)	0 (0.0)	0 (0.0)	1 (5.9)	2 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (5.0)
17.	Other ADRs[a] (sweating (5), fatigue (11), thirsty (10), having body aches (3), fever (2), body shaking (1), edema (1))	33 (9.5)	26 (10.5)	4 (5.8)	5 (8.8)	14 (13.5)	3 (17.6)	7 (7.0)	0 (0.0)	5 (25.0)	2 (4.1)	1 (5.0)

[a]*Other ADRs* were classified based on systematic symptoms (Jarernsiripornkul et al, 2002)

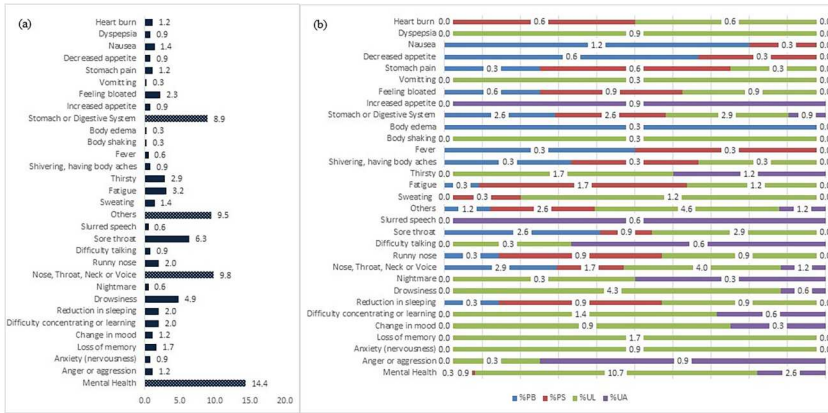

Figure 1. Percentage of the top four suspected ADRs by systems from patient self-reports and the causality assessment.

Among the 100 suspected ADRs reported by the participants who took diclofenac, the highest number of ADRs involved feeling bloated in the Stomach or Digestive System, dizziness in the Nervous System, bone or joint pain in the Muscles, Bones or Joints, anger or aggression, anxiety, loss of memory, and drowsiness in the Mental Health System, as shown in Figure 3a. The highest number of probable and possible ADRs in the Stomach or Digestive System was feeling bloated, and in the Nervous System was experiencing dizziness, as shown in Figure 3b.

Among the 93 participants (75 who used ibuprofen and 18 who used diclofenac) who reported suspected ADRs, worried symptoms were mostly

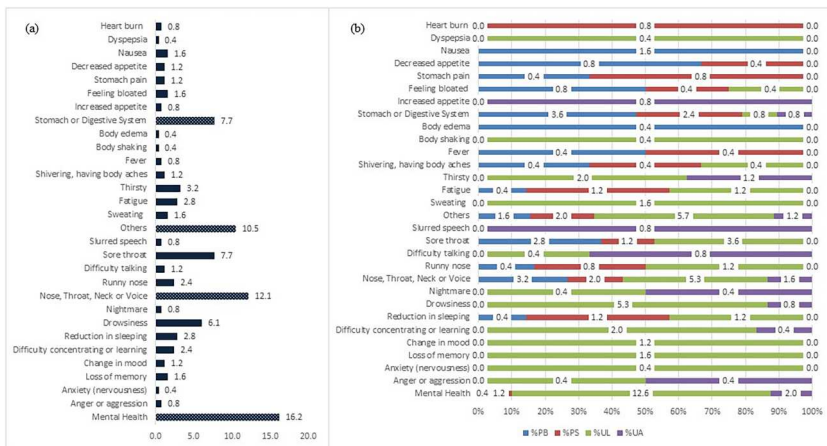

Figure 2. Percentage of the top four suspected ADRs by systems and causality assessment of the ADRs from ibuprofen.

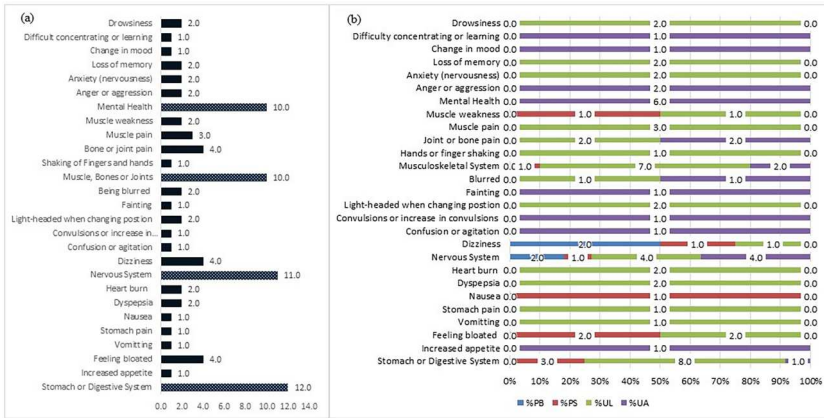

Figure 3. Percentage of the top four suspected ADRs by systems and causality assessment of the ADRs from diclofenac.

minimal for ibuprofen (16.0%) and moderate (27.8%) for diclofenac. Four participants who reported severely worried symptoms were administered ibuprofen. Two worried symptoms were from insomnia and the other was from difficulty concentrating. No other symptoms were reported. The main reason for discontinuation of ibuprofen and diclofenac was cure or improvement (73.9% and 71.9%, respectively). Discontinuation of medications due to suspected ADRs was found in 4.1% (nine) of the patients treated with ibuprofen and 5.3% (three) of those treated with diclofenac, as shown in Table 4.

Discussion

In our study, 33.8% and 31.6% of the participants reported suspected ADRs from ibuprofen and diclofenac, respectively. Among the 347 suspected ADRs, the highest number of reports were in the Mental Health System. The causality assessment for both NSAIDs revealed 45.2% probable and possible or true ADRs. The main reason for discontinuing medication was a cure or an improvement rate greater than 70.0%.

This study reported a 47.5% response rate, which was comparable to the 42% response rate for self-reported NSAIDs in the outpatient department of a hospital (Jarernsiripornkul, Chaisrisawadsuk, et al., 2009). The rate of suspected ADRs in this study was 33.3%, which was higher than that reported in a study conducted in nine community pharmacies (25.8%) (Christensen et al., 2011). In this study, the gastrointestinal adverse effects of ibuprofen were reported to be 7.7%, which is lower than that reported in one study (19.3%) that used a dose of 1,200 mg for 10 consecutive days (Doyle et al., 1999). There were some differences between the studies; for example, the

Table 4. Worries about symptoms, levels of worry, reasons to stop treatment of ibuprofen and diclofenac.

Questions	Ibuprofen (n = 222) (n,%)	Diclofenac (n = 57) (n,%)
Worries about symptoms ($n_{ib} = 75$, $n_{di} = 18$) *	12 (16.0)	5 (27.8)
Difficult concentrating and irritability	1	0
Insomnia	1	1
Red spots on the palms	1	0
Constipation	1	0
Irritating eyes	0	1
Very thirsty	1	0
Palpitation	0	2
Sore throat	1	0
No information	6	1
Severity of symptoms in participants who had suspected ADRs ($n_{ib} = 75$, $n_{di} = 18$)		
Very minimal	17 (22.7)	6 (33.3)
Minimal	12 (16.0)	2 (11.1)
Moderate	8 (10.7)	5 (27.8)
Severe	4 (5.3)	0 (0.0)
Reasons for stopping the medication		
Cure or improving	164 (73.9)	41 (71.9)
Pharmacist instructed to stop due to completion	23 (10.4)	7 (12.3)
Pharmacist instructed to stop because of suspected ADRs	1 (0.5)	0 (0.0)
Self-stop because of suspected ADRs	9 (4.1)	3 (5.3)
Self-stop because of no improvement	11 (5.0)	0 (0.0)
Finished the medications	9 (4.1)	4 (7.0)
No opinion	62 (27.9)	2 (3.5)

participants in this study were younger (25 years old) than those in another study (44 years old). Moreover, the course of treatment was shorter in this study (3–7 d), and monitoring was less intensive (e.g. no occult blood test) than that in the earlier study.

The most frequently reported suspected ADRs were in the Mental Health System, with the most common symptom being drowsiness. Central nervous system (CNS) side effects (e.g. drowsiness to coma) related to ibuprofen administration have been reported (Auriel et al., 2014). However, NSAIDs may disrupt sleep, which may be related to the direct and indirect consequences of inhibiting prostaglandin synthesis, including a decrease in prostaglandin D2 and suppression of nighttime melatonin levels (Murphy et al., 1994).

The most suspected ADRs in the Nose, Throat, Neck, or Voice System showed the highest symptom of sore throat due to the use of ibuprofen. A possible mechanism of action is that ibuprofen has an excitatory effect on some mucosal nociceptors or may produce throat irritation by stimulating a class of epithelial pH-sensitive receptors that mediate stinging/pricking sensations and a subset of sensitive receptors that generate a tickle and cough. Administering ibuprofen with sodium bicarbonate to increase pH helps to reduce ibuprofen irritation in the throat (Breslin, 2001). However, more information about the characteristics of sore throats may be required to exclude

heartburn, which can cause a burning sensation in the throat (Informed-Health.org [Internet], 2021).

The most common symptoms in the Stomach or Digestive System, the highest symptom was bloating. As NSAIDs are harmful to the gastrointestinal system, feeling bloated is one of the symptoms of dyspepsia (epigastric discomfort, bloating, postprandial nausea, early satiety, and belching). However, dyspepsia symptoms were not predictive of mucosal injury. Serious peptic ulcer complications (such as bleeding and perforation) can occur without prior warning symptoms (Tai & McAlindon, 2021).

Pharmacists have a potential role in reducing adverse medication events. In this study, the pharmacists' role was to counsel and monitor participants, especially those concerned with adverse events such as face edema, red spots on the hands, and a rash on the face. According to the research protocol, the pharmacist instructed the patients to contact their pharmacist immediately if abnormal symptoms occurred. One participant returned to the pharmacy and reported experiencing facial edema and swollen eyes approximately 30 minutes after taking one dose of ibuprofen. During the first exposure, a pharmacist recommended discontinuation of ibuprofen. Fortunately, the symptoms disappeared. A pharmacist delivered a written card containing the medication name and symptoms to the participant. This study provides additional evidence for pharmacist-led pharmacovigilance in community pharmacies, which involves providing education to patients to ensure patient safety and encouraging them to perceive the benefits of reporting adverse effects (Kitisopee et al., 2022).

In the international context, the formal evaluation of patient reports has been extensive. One study that comparing physician and patient reports found that physicians reported fewer suspected ADRs (13) than patients (249 symptoms). Of these, 190 (76.3%) were assessed by a hospital pharmacist as probable or possible ADRs (Jarernsiripornkul, Kakaew, et al., 2009). Other studies have shown differences between patients and healthcare professionals reports in terms of a significantly greater number of suspected ADRs (Avery et al., 2011; McLernon et al., 2010). However, no difference was observed in the proportion of reports considered serious by the healthcare professionals and patients. The study showed similar proportions of reports contained at least one reaction term that was classified as 'serious' by the Medicines and Healthcare products Regulatory Agency (MHRA) (58.5% for patients vs 58.8% for healthcare professionals; $p = 0.58$) (McLernon et al., 2010). Although our study did not show serious ADRs due to the short-term use of NSAIDs, it supports the findings of previous studies that patient self-reports increase spontaneous reporting and provide more causal evidence. In our study, 45.2% of the patients were assessed as having probable and possible or true ADRs.

One systematic review revealed 12 patient-reported side effect questionnaires used to report ADRs (Lim et al., 2021). Four general questionnaires

were developed for this study. The causality assessment method developed by Jarernsiripornkul et al. (2002) was validated and translated into Thai. This questionnaire was modified and used in this study. Compared to Naranjo's algorithm, which is designed for controlled trials rather than routine clinical practice, several criteria in Naranjo's algorithm cannot be applied in community pharmacies, such as detection in any body fluid at toxic concentrations and re-administration of the medication (Naranjo et al., 1981). Thus, the study questionnaire was considered practical and user-friendly. However, the assessment criteria for the study questionnaire did not include 'definite ADR'.

The strengths of this study are, first, the incorporation of community pharmacists into drug surveillance. Second, the self-report questionnaire was previously validated, and this study modified it to help the participants report it back to the pharmacists. Finally, the causality assessment was practical for community pharmacists in a clinical setting.

However, the present study has several limitations including: (1) the response rate during the first two visits by four researchers to 15 community pharmacies was very low. To address this, the researchers visited the pharmacies five times and shortened the follow-up schedule with participants to 5, 10, and 15 d, using both online communication and telephone. Thus, a low response rate could introduce a bias with an overestimated proportion of reported ADRs; however, when comparing the response with the estimated sample size of 382, this was not a critical issue as the response rate was over 70% (ScienceDirect. (n.d.). Moreover, we initially proposed that all accredited community pharmacies (a total of 13 in four provinces at that time), participated in our study. However, owing to the low response rate observed during the first two visits, the researchers decided to include two additional community pharmacies, which were our experiential training sites. This adjustment increased the possibility of obtaining estimated number of reports, which was 25 reports from each pharmacy. (2) Several phone numbers could not be contacted; therefore, follow-up was impossible. (3) Self-reporting revealed symptoms that might not be related to the study medications (e.g. related current sickness), which led to higher reporting rates than expected, despite the researchers' efforts to provide a detailed explanation. One patient (out of 279, 0.4%) who received diclofenac reported experiencing 39 ADRs, which was the highest number of ADR reported in our study. This could be an example of overreporting in patient reports; however, it is a typical pattern of a few report loads. A similar pattern was reported by Jarernsiripornkul et al. (2002). Using the same questionnaire, it was found that the greater the number of symptoms reported, the greater the likelihood that some were classified as unlikely to be an ADR or not attributable ($p < 0.001$) (Jarernsiripornkul, Kakaew, et al., 2009). (4) Due to the long distance between the 15 community pharmacies, researchers were delayed in receiving self-

reports, which caused a delay in checking the questionnaires and helping pharmacists perform causality assessments. (5) Participants expressed concerns about the use of ibuprofen and diclofenac, as monitoring led to anxiety regarding the use of these medications. However, a thorough explanation was provided and pamphlets were created in addition to the questionnaire and consent forms.

Health care professionals, including community pharmacists, should be encouraged to report ADRs to increase the efficiency of the national pharmacovigilance system. In addition, updating the checklist of symptoms from contemporary literature reviews and using questionnaire in comparison studies would increase the validity and ability to detect changes over time. Further research on validated and customised tools for reporting ADRs to both patients and healthcare professionals is necessary to increase awareness and maximise the effectiveness of the national pharmacovigilance system.

Conclusion

In conclusion, 33.3% of the participants perceived suspected ADRs from ibuprofen and diclofenac, with 45.2% of the suspected ADRs categorised as probable or possible. Diclofenac users reported more suspected ADRs than did ibuprofen users. Community pharmacists' monitoring helps patients become aware of their safety. Community pharmacies should be encouraged to continue their role in pharmacovigilance and to actively encourage patients to report ADRs.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Mahasarakham University: [Grant Number 5601045].

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