

*Pharmacotherapy***Patient-reported adverse drug-related events from emergency department discharge prescriptions**

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ABSTRACT

Objective: The tolerability of drugs prescribed on emergency department (ED) discharge is unknown. Our objectives were to quantify and describe adverse drug-related events (ADREs) as reported by patients triaged as Canadian Emergency Department Triage and Acuity Scale scores 3, 4 or 5, discharged from the ED with prescriptions.

Methods: This prospective observational study was a planned substudy of a larger study on adherence to discharge prescriptions. This study was conducted in a tertiary care centre with an annual ED census of 69 000 visits. The primary outcome was the frequency of ADREs reported during a structured telephone questionnaire 2 weeks after ED discharge. An ADRE was deemed to have occurred if the patient reported a symptom consistent with a known ADRE that began and resolved within a plausible time frame after starting and stopping the drug, and if no alternative diagnosis was probable.

Results: Research assistants contacted 258/301 (85.7%) patients discharged from the ED with a prescription. An ADRE was reported by 54/258 patients (20.9%, 95% confidence interval [CI] 16.4%–26.3%). The most commonly reported ADREs were nausea, constipation and drowsiness. None required hospital admission or caused death. Participants reporting ADREs were not more likely to make an unplanned ED or clinic revisit (crude odds ratio [OR] 1.1, 95% CI 0.6–2.2; adjusted OR 1.2, 95% CI 0.6–2.4).

Conclusion: Approximately one-fifth of low-acuity patients prescribed medication on discharge from the ED report ADREs, but most of these are neither severe nor associated with an increase in use of health services. Attention to common preventable ADREs, such as opioid-associated constipation, could reduce the rate of ADREs in this population.

Keywords: adverse events, adverse drug-related events, emergency medicine, patient safety, medication

RÉSUMÉ

Objectif : On ignore quelle est la tolérabilité relative aux ordonnances remises aux patients qui reçoivent leur congé de l'urgence. Nos objectifs étaient de quantifier et de décrire les effets indésirables des médicaments (EIM) signalés par les patients qui avaient reçu un niveau de gravité 3, 4 ou 5, selon l'Échelle canadienne de triage et de gravité (ÉTg) pour les services d'urgence et qui avaient reçu une ordonnance à leur congé de l'urgence.

Méthodes : Cette étude prospective d'observation était une sous-étude planifiée, menée en marge d'une étude de plus grande envergure sur l'observance médicamenteuse pour les ordonnances remises au moment du congé. Cette étude a été réalisée dans un hôpital de soins tertiaires, dont les consultations à l'urgence se chiffraient annuellement à 69 000. Le principal critère d'évaluation était la fréquence des EIM signalés dans le cadre d'une entrevue téléphonique structurée deux semaines après le congé de l'urgence. On estimait qu'un EIM s'était produit si le patient signalait un symptôme concordant avec un EIM connu, ayant débuté et s'étant estompé dans des délais plausibles après le début et l'arrêt du médicament et en l'absence de tout autre diagnostic probable.

Résultats : Les adjoints de recherche ont communiqué avec 258 patients sur 301 (85,7 %) ayant reçu leur congé du service d'urgence avec une ordonnance. Cinquante-quatre patients sur 258 (20,9 %, intervalle de confiance [IC] à 95 %, de 16,4 à 26,3 %) ont signalé un EIM. Les EIM les plus souvent signalés étaient les nausées, la constipation et la somnolence. Aucun n'a nécessité d'hospitalisation ou provoqué le décès. Les participants ayant signalé des EIM n'étaient pas plus susceptibles de faire une visite non planifiée à l'urgence ou de retourner à la clinique (risque relatif approché de 1,1, IC à 95 %, de 0,6 à 2,2; risque relatif ajusté de 1,2, IC à 95 %, de 0,6 à 2,4).

Conclusion : Environ un cinquième des patients dont les cas étaient peu aigus et qui avaient reçu une ordonnance de

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médicaments au moment de leur congé du service d'urgence ont signalé des EIM dont la plupart n'étaient ni graves ni associés à une utilisation accrue des services de santé. En

portant une attention aux EIM courants évitables, comme la constipation associée aux opiacés, il serait possible de réduire le taux d'EIM dans cette population.

INTRODUCTION

In 2004, Baker and colleagues¹ estimated that up to 23 750 Canadians die annually from preventable adverse events (AEs) related to medical care. Adverse drug-related events (ADREs) are the most common type of preventable AEs in patients admitted to hospital, and cause up to 12% of visits to emergency departments (EDs) in Canadian tertiary care centres.¹⁻⁴ Efforts to reduce ADREs are therefore important.

Research on drug-related morbidity has predominantly focused on inpatient and community settings, largely ignoring the contribution of emergency physicians (EPs) to this problem. Emergency physicians practise in high-risk settings for medication errors and other AEs, treat high-acuity patients, work under time pressure, and treat patients based on incomplete information regarding medical history or medication consumption.⁵

Paradoxically, the lower-acuity ED patient may be more vulnerable to ADREs than the higher-acuity patient. Higher-acuity patients are more often admitted to hospital, are evaluated serially by nurses, physicians and pharmacists for the development of ADREs, and tend to receive closer follow-up after discharge from the hospital or ED. In contrast, lower-acuity patients are more likely to be discharged from the ED without specific follow-up plans or monitoring in place for ADREs even though they commonly receive prescriptions on discharge from the ED. The underlying assumption that these patients do not run into significant problems with the medications prescribed on discharge from the ED has not been tested. To our knowledge, this is the first study to evaluate and characterize the tolerability of prescriptions given on discharge from the ED.

The primary objective of this study was to determine the frequency of patient-reported ADREs in low-acuity patients discharged from the ED. Secondary objectives were to describe the nature of the ADREs identified, to examine medication and patient factors associated with these events, and to compare revisit rates in patients reporting an ADRE. Our hypothesis was that the occurrence of ADREs from prescriptions given on discharge

from the ED would be associated with additional use of health services. Our alternative hypothesis was that ADREs from prescriptions given on discharge from the ED are minor and not associated with additional use of health services.

METHODS

Study design

This prospective observational study enrolled patients discharged from the ED of Vancouver General Hospital between Jun. 13, 2005, and Aug. 2, 2005, and was an a priori planned substudy of a study examining adherence to prescriptions given on discharge from the ED.⁶ Vancouver General Hospital is an urban tertiary care centre in Canada with an annual census of 69 000 visits.

The institutional ethics review board approved the research protocol, and authorized the use of consent forms that partially concealed the study purpose. We told patients that we were interested in knowing whether or not they experienced "any problems with medications" but concealed the nature of the problems we were looking for. We felt that disclosing the exact study purpose to patients at that time of the ED visit may have caused patients to pay particular attention to any new symptoms between the time of discharge and follow-up, and may have led to overreporting of symptoms.

Study population

Patients who were over 18 years of age, spoke English and were discharged from the ED with a prescription written or cosigned by an attending EP were eligible for enrolment. We excluded patients who had been transferred from or to another health care facility, were triaged as acuity levels 1 or 2 (high acuity) on the Canadian Emergency Department Triage and Acuity Scale (CTAS),⁷ were in distress, presented with an intentional poisoning, were unable to sign their name, left against medical advice, had previously been enrolled, were seen by a consultant or admitted to hospital, had no telephone or lived outside of the study province.

Patient enrolment

We enrolled a convenience sample of patients who presented during data collection shifts scheduled 24 hours per day, 7 days per week in a predefined distribution that mirrored the discharge pattern of our ED. Data collection was performed 80 hours per week for 8 consecutive weeks.

A systematic enrolment algorithm, described in detail elsewhere, was used to generate a representative sample of low-acuity ED patients discharged with a prescription.⁶ Briefly, at the beginning of each data collection shift, research assistants (RAs) used the hospital's computerized patient tracking system to identify patients in the ED, and approached patients after they had been triaged according to the time of presentation. Research assistants collected signed consent forms at the end of the ED visit.

Measurements

Data collection forms using explicit terms and definitions were pilot-tested, and used to collect data on potential predictor variables. These included demographic data (age, sex), socio-economic status (income level, insurance coverage, employment status and availability of transportation to a pharmacy), illicit drug use, access to a family physician, and complementary and alternative medication use. The total number of discharge prescriptions, medication names, medication class and dosing schedules were identified before patients left the ED and were verified with the treating EP. The patient's CTAS category, chief complaint and discharge diagnosis were abstracted from the patient's chart.

Two weeks after the ED encounter, an RA attempted to contact patients by telephone up to 5 times before deeming them lost to follow-up. A pilot-tested algorithm was used to determine whether or not the patient had experienced an ADRE to a discharge medication (Fig. 1⁸). We developed this algorithm by modifying the only validated ADRE causality algorithm, the Naranjo Adverse Drug Reactions Probability Scale.⁹ We incorporated the most important questions from the scale for determining causality: known response pattern, temporal plausibility for both the onset and resolution of symptoms, and absence of an alternative explanation for the development of new symptoms (Appendix 1).^{9,10} All these criteria had to be satisfied for the event to be deemed an ADRE. Therefore, all events we deemed ADREs would have been rated a score of 6/10, or a

“probable” ADRE on the Naranjo Adverse Drug Reactions Probability Scale.⁹ An investigator (C.M.H.) reviewed all suspected ADRE cases with an RA (G.T., a trained pharmacist), and had to reach consensus for an event to be deemed an ADRE.

Unplanned ED revisits and admissions to the study hospital were identified using the hospital's computerized admission, discharge and transfer database. During the telephone interview, patients were also asked to report any unplanned ED or clinic visits and admissions to other institutions.

Definitions

A “patient-reported ADRE” was defined as an unfavourable medical event related to the use or misuse of medication.^{11,12} To be considered an ADRE, the self-reported symptom had to be consistent with one of the known toxic effects, drug interactions or withdrawal reactions of the medication as listed in the *Compendium of Pharmaceuticals and Specialties*,⁸ or consistent with nonadherence.¹¹

ADREs were classified as severe if the patient required admission to hospital for treatment, or died as a result of the ADRE.¹³

An “unplanned visit” was defined as any return to an ED, clinic or physician's office within 2 weeks that had not been planned at the time of ED discharge. An “admission” was defined as any return to hospital resulting in a bed request by an admitting service that occurred within 2 weeks of the index ED visit.

Outcome measures

The primary outcome measure was the proportion of patients who reported an ADRE from a medication prescribed on discharge from the ED. Secondary measures included descriptions of the patient-reported ADREs, and the association between ADREs and unplanned revisits.

Data analysis

Data were entered into a Microsoft Excel database by a single RA and verified by a second RA. We generated univariate associations between the previously described a priori-defined potential predictor variables using odds ratios (ORs) to measure each variable's association with ADREs. Then, we performed bivariate analyses between potential predictor variables using χ^2 statistics

with a *p* value cutoff of ≤ 0.05 to identify and exclude collinear variables. We then fit 2 logistic regression models (one using a patient-level analysis, the other using a medication-level analysis) between the remaining potential predictor variables and the occurrence of an ADRE. An additional regression model was fit to evaluate the association between ADREs and unplanned visits. All regression models were fit with a minimum of 10 events of interest per covariate. Data

were analyzed using SAS, version 9.1.3 for Windows.

The sample size calculation was based on the desired precision of the primary end point of the primary study, which suggested that 320 patients would be required.⁶

RESULTS

During the study period, 301 patients were discharged with a prescription during data collection hours and consented

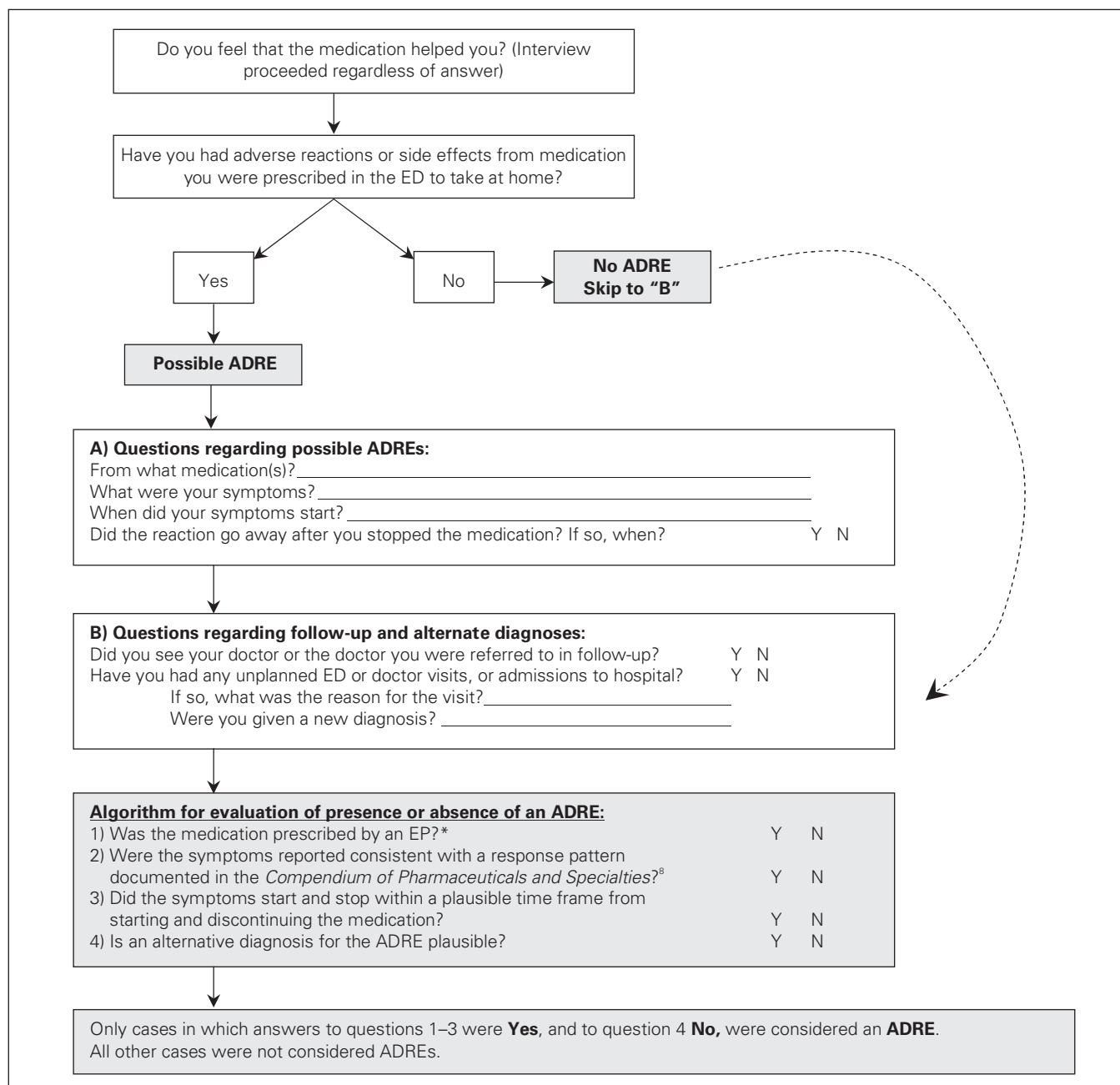


Fig. 1. Telephone interview (white boxes) and evaluation algorithm for adverse drug-related effects (ADREs) (grey boxes). *Research assistant verified the prescribing physician using emergency department (ED) records and PharmaNet data. EP = emergency physician.

to follow-up. Details of the patient flow for this study have been published in the primary study.⁶ Telephone follow-up was successful in 258 patients (85.7%), who received a total of 344 prescriptions. The most commonly prescribed medications were acetaminophen with codeine, ciprofloxacin and cephalexin (Table 1).

Sixty-five of 258 patients (25.2%, 95% confidence interval [CI] 20.3%–30.8%) reported symptoms they believed were due to an ADRE. Of those, 6 were excluded because the timeline was not plausible, and 5 were excluded because the symptoms were not consistent with a known ADRE. Fifty-four of 258 patients (20.9%,

95% CI 16.4%–26.3%) reported symptoms that met our definition of a patient-reported ADRE. The most commonly reported symptoms were nausea (14/258, 5.4%, 95% CI 3.3%–8.9%), constipation (12/258, 4.7%, 95% CI 2.7%–8.0%) and drowsiness (8/258, 3.1%, 95% CI 1.6%–6.0%), consistent with the pattern of the most commonly prescribed drug classes (Table 2).

The only significant predictor of an ADRE was the type of medication prescribed, with opioid-containing analgesics significantly increasing the likelihood of an ADRE (crude OR 3.3, 95% CI 1.4–8.0; adjusted OR 3.3, 95% CI 1.4–8.0). Age, sex, socio-economic factors,

Table 1. Baseline characteristics of 301 patients discharged from the emergency department with a prescription, by follow-up status

Characteristic	No. (%) of patients*			
	Follow-up successful, <i>n</i> = 258		Lost to follow-up, <i>n</i> = 43	
Mean (SD) age, yr	46.3	(17.7)	44.7	(19.1)
Female sex	123	(47.7)	19	(44.2)
Highest level of education achieved				
No formal education	10	(4.0)	0	(0.0)
Primary school	17	(6.7)	2	(4.8)
High school	93	(36.8)	15	(35.7)
Diploma program	57	(22.5)	12	(28.6)
University	76	(30.0)	13	(31.0)
Annual income, Can\$				
0–10 000	40	(16.7)	14	(36.8)
10 000–25 000	63	(26.3)	8	(21.1)
25 000–50 000	71	(29.6)	9	(23.7)
> 50 000	66	(27.5)	7	(18.4)
Employed	148	(57.6)	22	(52.4)
Insurance coverage for medications	107	(41.6)	17	(40.5)
Illicit drug use in past month	8	(3.1)	5	(12.5)
Availability of family physician	205	(79.5)	32	(76.2)
Transportation available	199	(77.4)	30	(71.4)
Use of herbal remedies	75	(29.1)	12	(30.0)
Most common discharge diagnosis				
Cellulitis/abscess		(13.2)	Abdominal pain NYD	(14.0)
Back pain NYD		(12.0)	Back pain NYD	(11.6)
Urinary tract infection		(7.0)	Urinary tract infection	(9.3)
Abdominal pain NYD		(5.4)	Cellulitis/abscess	(7.0)
Soft-tissue injury		(4.7)	Dental pain/infection	(7.0)
Median (IQR) no. of discharge medications prescribed	1.0	(1.0–2.0)	1.0	(1.0–2.0)
Most common medications prescribed				
Acetaminophen/codeine		(27.0)	Acetaminophen/codeine	(27.9)
Ciprofloxacin		(7.9)	Ciprofloxacin	(9.8)
Cephalexin		(6.4)	Cephalexin	(4.9)
Hydromorphone		(4.7)	Naproxen	(4.9)
Naproxen		(4.7)	Prednisone	(4.9)
Most common medication classes prescribed				
Opioid-containing analgesics		(34.3)	Opioid-containing analgesics	(34.4)
Anti-infectives		(34.0)	Anti-infectives	(32.8)
Miscellaneous agents		(9.0)	Nonopioid analgesics	(13.1)

IQR = interquartile range; NYD = not yet diagnosed; SD = standard deviation.

*Unless otherwise indicated.

number of medications prescribed simultaneously, complementary and alternative medication use, and illicit drug use were not found to be associated with ADREs.

Of the 258 patients, 62 had an unplanned visit (24.0%, 95% CI 19.2%–29.6%), of which 5 were felt to be related to an ADRE by the patient (8.1%, 95% CI 3.6%–17.6%). Reporting an ADRE did not appear to be associated with a greater risk of incurring an unplanned visit (crude OR 1.1, 95% CI 0.6–2.2). There was no change in the estimate after adjustment for age, sex, compliance status, number of medications prescribed, shift of presentation and socio-economic status (adjusted OR 1.2, 95% CI 0.6–2.4). No hospital admissions or deaths were associated with an ADRE (0%, 95% CI 0.5%–6.5%).

DISCUSSION

This study examined the incidence and nature of patient-

reported ADREs from medications prescribed on discharge from the ED. One in 5 lower-acuity patients reported symptoms consistent with an ADRE related to a discharge prescription, but most ADREs were minor and represented expected side-effects of analgesics and antibiotics.

We were unable to identify any ADREs that had any significant impact on patient outcome. Five patients reported returning to the ED because of an ADRE. However, none of these patients were admitted to hospital and no deaths were identified. Therefore, our data suggest that severe ADREs from ED discharge medications are rare. This finding is reassuring, yet it is important to note that, because of our small sample size, our data are consistent with the proportion of patients experiencing a severe ADRE (admission or death) being as high as 1.4% (0/258, 95% CI 0%–1.4%), the upper limit of the CI of the proportion we estimated. Also, our results should not be generalized to higher-acuity (CTAS 1 and 2) patients.

Table 2. Culprit medication classes, medications and descriptions of adverse drug-related events reported

Culprit medication class (no. of ADREs/ no. of prescriptions in the medication class)	Culprit medication (no. of ADREs/ no. of prescriptions of the medication)	Description of ADRE (no.)		
Opioid-containing analgesics (28/118)	Acetaminophen with codeine (22/93)	Constipation (10)		
		Drowsiness (7)		
		Nausea (4)		
		Dizziness (1)		
		Constipation (2)		
	Hydromorphone (5/16)	Nausea (2)		
		Drowsiness (1)		
		Withdrawal reaction when discontinued (1)		
		Anti-infectives (17/117)	OxyContin (1/19)	Nausea (2)
				Rash (1)
Joint pain (1)				
Dizziness (1)				
Ciprofloxacin (5/27)	Nausea (3)			
	Rash (1)			
Nitrofurantoin (4/4)	Rash (1)			
	Diarrhea (1)			
Clindamycin (2/14)	Rash (1)			
	Diarrhea (1)			
	Cephalexin (2/22)	Nausea (1)		
		Nausea (2)		
Steroids (4/14)	Penicillin (2/3)	Yeast infection (1)		
		Headache (1)		
	Amoxicillin/clavulanic acid (1/3)	Agitation (3)		
		Prednisone (4/14)	Increased appetite (1)	
Cardiovascular drugs (2/9)	Metoprolol (2/3)	Weakness (1)		
		Dizziness (1)		
Nonopioid analgesics (2/28)	Diclofenac (1/4)	Diarrhea (1)		
		Naproxen (1/16)	Epigastric pain (1)	
Gastrointestinal agents (1/12)	Ranitidine (1/6)		Headache (1)	

ADRE = adverse drug-related event.

We found that the prescription of opioid-containing analgesics tripled the odds of patients experiencing an ADRE. Although the provision of adequate and appropriate analgesia is a cornerstone of good practice in emergency medicine, future studies on opioid-induced ADREs should investigate the optimal use of alternative analgesics, the titration of opioids to minimize side effects and coprescription of laxatives.

An expanded role for clinical pharmacists in the ED with the goal of minimizing ADREs from discharge medications may be warranted. Interventions such as discharge medication reconciliation, patient counselling before discharge, liaison with outpatient health care providers and postdischarge follow-up by pharmacists have been successful in reducing avoidable ADREs in other patient care areas.¹⁴ Targeting opioid analgesics for pharmacist services to improve titration of analgesics after ED discharge may be warranted.

This study has several limitations. Because of our sample size, the ability of this study to detect rare ADREs, or ADREs leading to ED revisits, hospital admission or death was limited.

A second limitation stems from our a priori decision to restrict enrolment to patients with lower-acuity CTAS scores (CTAS 3–5). Most higher-acuity patients are admitted to hospital, and including these discharged patients would have introduced heterogeneity in our patient sample. In addition, many higher-acuity patients required urgent attention by emergency nurses and EPs, precluding the use of our enrolment algorithm that relied on consenting patients before being seen by an EP. As a result, our findings apply only to lower-acuity patients.

Because we followed up with patients by telephone, we were unable to perform complete causality assessments on patient-reported symptoms attributed to ADREs.⁸ However, to enhance the reliability of our assessments, we used a structured interview algorithm that incorporated the most important elements of the validated Naranjo causality algorithm and retained only “probable” ADREs.⁹ The Naranjo algorithm has been shown to have good interrater and intrarater agreement and face validity,¹⁰ and to be superior to ADRE evaluation without the algorithm.⁹

A further limitation arose from the fact that we were unable to record information on patients who received consent forms but were not eligible for participation at the end of their visit (i.e., did not receive a prescription) or declined participation. We could not ask EPs and nurses to detain patients in the ED after discharge to complete study procedures, including consent. As a

result, we were unable to provide exclusion criteria and demographic information on missed patients, and cannot exclude the possibility that systematic differences exist between the 2 groups.

We followed up with patients by telephone 2 weeks after the index visit. It is possible that patients recalled their symptoms in a different way than had they been evaluated earlier. However, by waiting 2 weeks, we were able to assess resolution after discontinuation of the medication, a necessary element of all causality algorithms for ADREs. To minimize under- or overreporting of symptoms, trained RAs uninvolved in the patient’s care conducted the follow-up telephone interview.

Finally, we used a broad classification scheme for ADRE severity that did not allow us to distinguish between minor ADREs presenting with symptoms only and moderate events that required a change in medication, a diagnostic procedure or follow-up. This limitation arose because we were unable to obtain accurate data by telephone on medical interventions after the ED visit.

CONCLUSION

Patient-reported ADREs from ED discharge medications are common but are generally not severe, and do not appear to be associated with an increase in use of health services. Preventive efforts should target common ADREs, such as constipation with opioid prescription.

Competing interests: None declared.

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Appendix 1. Modified Naranjo Adverse Drug Reactions Probability Scale*

Question	Yes	No	Do not know
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered/withdrawn?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued/readministered or a <i>specific</i> antagonist/treatment was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered/withdrawn again?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the event?	-1	+2	0
6. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
7. Was the reaction more severe when the dose was increased/decreased, or less severe when the dose was decreased/increased?	+1	0	0
8. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure/withdrawal?	1	0	0
9. Was the adverse event confirmed by any objective evidence?	+1	0	0

*Each clinical scenario suspicious for an adverse drug-related event (ADRE) was evaluated using this scale. The ADRE probability score was calculated by answering the 9 questions for each scenario and adding the points obtained. Scores of 5 or greater are considered ADRE scenarios. Modified with permission from Naranjo et al.⁹