

Documentation of Adverse Drug Reactions to Opioids in an Electronic Health Record

Running Title: Adverse Drug Reactions to Opioids

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Manuscript Word Count: 2764

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Keywords: opioids, drug allergy, electronic health records, adverse drug reaction

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/imj.15209](https://doi.org/10.1111/imj.15209)

Abstract

Introduction: Allergy to opioids is the second most common drug allergy label in electronic health records (EHR). Adverse drug reactions (ADRs) to opioids cause significant morbidity and contribute to healthcare costs, whilst incorrect opioid allergy labels may unnecessarily complicate patient management.

Aims: To examine the documentation of opioid ADRs in a large-scale hospital-based EHR.

Methods: A cross-sectional retrospective review of EHR documentation of opioid ADRs at four public hospitals in South Australia was conducted. Data was extracted from all ADR entries including the reported allergen, ADR category (allergy or intolerance) and reaction details. Expert criteria were used to determine consistency of ADR categorisation as allergy or intolerance.

Results: Of 86,727 unique ADR reports, there were 13,781 ADRs to opioids with most being entered as allergy (n=8913, 64.7%) rather than intolerance (n=4868, 35.3%). The most commonly documented reactions were nausea/vomiting (n=3912, 28%), rash (n=647, 5%), itch (n=642, 5%) and hallucinations (n=527, 4%). There were 362 (3%) ADR labels of anaphylaxis. Of those ADRs containing a reaction description (n=11,868), 89% of reports entered as allergy had a reaction description that was consistent with intolerance and 8% of the entered intolerances had descriptions consistent with allergy when assessed using pre-defined criteria.

Conclusions: This large EHR-based study demonstrates the high rate of opioid ADR labels in EHRs. The majority of these labels were for symptoms suggestive of pharmacological intolerance. Reactions consistent with true allergy were uncommon. Systematic review of ADRs by a dedicated clinical service would improve the accuracy of documentation.

Introduction

Adverse drug reactions (ADRs) cause significant morbidity for patients. Up to 35% of patients are reported to be allergic to one or more drugs.¹ Opioids are the second most common drug class giving rise to an allergy label after antibiotics¹. The majority of adverse reactions to opioids are gastrointestinal and neurological effects due to pharmacological intolerance. These reactions lead to patient discomfort, prolonged hospitalisation and increased healthcare costs.² Mitigating the risk of these ADRs is important given that opioids remain the cornerstone of acute pain management in the hospital setting.

In many large healthcare organisations, ADRs are being entered into electronic health records (EHRs). This provides an opportunity to improve documentation of ADRs, prevent predictable reactions and reduce prescribing errors. However, the benefits of EHRs depend on high quality documentation by clinicians based on accurate information from the patient history or previous records.³ EHRs have the advantage that the reaction can be recorded in a structured way, the information is retained without the need for repeated documentation and the data is used to generate prescribing alerts to assist clinicians.

Our previous work has shown a very high rate of penicillin ADRs in our EHR with poor documentation of the reaction type and misclassification as allergy or intolerance.⁴ In the case of opioids, true allergy (immunological reactivity) is exceedingly rare. Whilst reactions such as hyperemesis are obviously not caused by allergy, even allergy-like reactions such as pruritus and urticaria are usually mediated by the pharmacological histamine-releasing properties of opioids.⁵ It is difficult to distinguish true hypersensitivity reactions from

pharmacological intolerances even using skin testing.⁵ Given the rarity of true hypersensitivity reactions (anaphylaxis), patients are commonly prescribed opioids despite the presence of an opioid ADR label.⁶

Electronic prescribing alerts with forcing functions requiring clinician review have the potential to reduce predictable ADRs however, these alerts are often ignored due to poor specificity and alert fatigue.^{7, 8} Opioids were the most common trigger for prescribing alerts in large American study.⁹ However, drug allergy alerts for opioids were overridden by clinicians 90% of the time^{9, 10}. If prescribing alerts are routinely ignored, there is a risk that more serious alerts could be missed. Furthermore, most alerts were overridden because the patient had previously tolerated the medication, suggesting a failure of providers to remove the ADR label from the EHR.⁹ In order to improve the specificity and utility of prescribing alerts, it is necessary to understand the ADR labels within the EHR and update or remove labels where appropriate.

In this study we examined the documentation of opioid ADRs in a state-wide EHR by different healthcare professionals including reaction type and appropriate categorisation as allergy or intolerance.

Methods

A cross-sectional retrospective review of EHR documentation of opioid ADRs at five public hospitals in South Australia, from August 2013 to September 2017, was conducted. These included four metropolitan hospitals (Royal Adelaide Hospital, Queen Elizabeth Hospital, Noarlunga Public Hospital and Repatriation General Hospital) and one regional hospital (Port Augusta Hospital and Regional Health Services). These hospitals use the Sunrise electronic health record, which is a modification of the Allscripts Sunrise product (Allscripts, Chicago, Illinois). Ethics approval for this study was obtained from the South Australian Health Ethics Committee.

ADR entry was prompted to healthcare workers at the time of placing any orders during a clinical interaction. A variety of healthcare professionals including doctors, nurses, pharmacists and allied health practitioners are able to enter ADRs. The ADR entry screen (Supplementary Figure 1) firstly requires users to choose between the reaction types 'allergy' and 'intolerance', following which they are required to enter an allergen which may be chosen from a list of specific agents or entered as free text. The type of reaction to the allergen is selected from predefined check boxes or entered as free text. The reaction types presented on the drop-down list correspond with the initial choice of 'allergy' or 'intolerance'. The documentation of the allergen and reaction are mandatory fields, although 'unknown' can be chosen, as well as 'other', in which case free text entries will be prompted. There are optional fields to provide a further description of the reaction, onset date, confidence level and information source. There is also an option to actively choose 'no known ADR'.

Clinicians are prompted to review patient ADRs prior to prescribing. In the event that an opioid is prescribed to someone with an opioid ADR label, a prescribing alert is shown which alerts the clinician to the potential reaction or cross-interaction (Supplementary Figure 2). This occurs irrespective of the reaction type (allergy or intolerance) and details that has been documented. In order to proceed, the clinician must acknowledge the alert and record their rationale.

Data was extracted from all documented ADR entries including the reported allergen, ADR category (allergy or intolerance), reaction details and occupation of the healthcare professional entering the information. Opioids were manually identified by their generic and trade names (Supplementary Table 1). Reaction descriptions entered as free text were manually aggregated. Optional fields in the ADR entry screen including onset date, confidence level and information source were rarely completed and this data was not examined.

In order to ascertain the consistency of the documented reaction with selection of allergy or intolerance, criteria were developed in consultation with an expert panel consisting of an immunologist and clinical pharmacologist (Supplementary Table 2). Reaction descriptions suggesting an immune-mediated mechanism (e.g. anaphylaxis or a reaction consistent with anaphylaxis such as rash with hypotension or respiratory symptoms) were considered to be consistent with allergy for the purpose of classification. Non-immunological ADRs (e.g. nausea, vomiting, headache) were consistent with intolerance. Allergy-like reactions such as itch, rash, urticaria or swelling were also considered to be pharmacological intolerance unless associated with systemic symptoms in which case they were classified as anaphylaxis.

Descriptive statistics (frequency and 95% confidence intervals) were used to describe the characteristics of opioid allergy documentation within the EHRs, and chi-square tests were used to examine the association between different healthcare professions and documentation of ADRs and consistency of ADR categorisation with our pre-set criteria. Probability values of $p < 0.05$ were considered statistically significant.

Results

Opioid ADR Entries

A total 231,623 patient EHR was examined, containing 86,727 unique ADR reports. Of these, 13,781 (15.9%) involved opioids (5.9% of patients), with the majority entered as allergy (n=8913, 64.7%) rather than intolerance (n=4868, 35.3%). The majority of these ADR reports used as the allergen specific drug names with the most common being codeine (n=5570, 40.4%), morphine (n=4130, 30.0%), oxycodone (n=1772, 12.9%), tramadol (n=1397, 10.1%), buprenorphine (n=363, 2.6%), fentanyl (n=345, 2.5%), methadone (n=39, 0.3%), hydromorphone (n=8, 0.1%) and butorphanol (n=1, 0.0%). A small number of ADRs used the general terms 'opioid-like analgesics' or 'narcotic analgesic' (n=156, 1.1%).

Opioid ADR Entry by Occupation

Over half of the opioid ADR reports were entered by nurses (n=7483, 54.3%) followed by doctors (4259 30.9%), pharmacists (n=1798 13.0%), allied health (n=108, 0.8%), students (n=105, 0.8%) and administrative staff (n=28, 0.2%) (Table 1).

Aggregation of Reaction Types

The most common reaction types were nausea/vomiting (n= 3912, 28%), rash (n=647, 5%), itch (n=642, 5%), hallucinations (n=527, 4%), anaphylaxis (n=362, 3%), abdominal pain

(n=352, 3%), GI upset (n=282, 2%), confusion (n=217, 2%), itch and rash (n=174, 1%) (Table 2).

ADRs without Documented Reactions

A significant proportion of ADR entries (n=1913, 14%) did not include a reaction description and are represented as 'unknown'. (Table 1). ADRs entered by doctors omitted a reaction description in 21% (95% CI 19.8-22.2) of cases. By comparison, allied health practitioners were more likely than doctors to document an ADR without a reaction description (35%, 95% CI 26.1-44.8, P=0.0005). Conversely, nurses and pharmacists were significantly less likely than doctors to omit the reaction description (10%, 95% CI 9.3-10.7, P < 0.0001 and 11%, 95% CI 9.6-12.5, P<0.0001 respectively).

Aggregation of Reaction Types by ADR Classification

These entries were aggregated based on the reaction type selected by the healthcare professional on entering the ADR. The most common documented reactions entered as allergy were nausea/vomiting (n=1843), unknown (n=1749), rash (n=571), itch (n=453) and hallucinations (n=352). The most commonly documented reactions entered as intolerance were nausea/vomiting (n=2069), gastrointestinal upset (n=202), itch (n=189), confusion (n=181), hallucinations (n=175) (Table 3). The categorisation of the 10 most commonly documented reaction types are shown in Figure 1. As an example, of the 3912 ADR entries for nausea/vomiting, 1843 (47%) were entered as intolerance and 2069 (53%) were entered as allergy. Conversely, for the 362 entries of anaphylaxis, 350 (97%) were entered as allergy and 12 (3%) were entered as intolerance.

Consistency of ADR Classification

The 11,868 ADR entries that included a reaction description were evaluated for consistency of reporting as allergy or intolerance using pre-defined criteria (Supplementary Table 2). Of the 7164 ADRs entered as allergy that included a reaction description, 823 (11%) had a description that was consistent with allergy while 6341 (89%) were consistent with intolerance. Of the 4704 ADRs entered as intolerance, 4323 (92%) had a reaction description that was consistent with intolerance while 381 (8%) were consistent with allergy.

The classification of ADRs for each occupation was compared to doctors (reference group), whose categorisation was consistent with our expert criteria in 42% of cases (95% CI 40.3-43.7). Pharmacists were significantly more likely to enter the correct classification than doctors (53%, 95% CI 50.52-55.47, $P < 0.0001$). There was no significant difference between the remaining professions when compared to doctors (Table 1).

Discussion

This large EHR-based study demonstrates high rates of opioid ADR labels (5.9% of all patients), comparable to international studies. A recent US study reported that of 1,766,328 individual patient medical records, 6.8% had a recorded drug allergy to opioids.¹ In our study the most frequently documented reactions were nausea/vomiting (28%) followed by rash (5%), while only 3% reported anaphylaxis, potentially reflective of true allergy. This is consistent with another large US study of hospitalised surgical patients that also showed nausea/vomiting to be the most common opioid ADR followed by dermatological manifestations.¹¹ We also found there was incomplete documentation with 14% recording unknown reactions and the categorisation of allergy and intolerance was used inconsistently. Despite the majority of opioid ADRs being suggestive of intolerance, over half of opioid ADR labels were entered as allergy.

Many EHRs require an obligatory categorisation of an ADR as allergy or intolerance before documentation of the reaction type. There was significant misclassification of opioid ADRs when this dichotomy is used in the initial entry of reactions, similar to that which has been demonstrated in penicillin ADRs⁴. This distinction is challenging when limited history is available and given immunological testing is not in widespread use for suspected opioid hypersensitivity.⁵ Previous studies have shown that healthcare professionals have a poor ability to discriminate between allergy and intolerance in real-life scenarios and tend to select the default option when entering reactions into the EHR.^{12, 13} Less than half of all ADRs were categorised consistently with the criteria set out by the expert panel. For these reasons, entering ADRs as allergy or intolerance is probably not a useful dichotomy for generalist healthcare professionals. However, we acknowledge that the ADR module is also used to record non-drug intolerances, such as dietary requirements, where the distinction between allergy and intolerance has different implications.

The quality of documentation of opioid ADRs in the EHR was suboptimal. There were high rates of incomplete documentation with missing reaction types being a common occurrence. This is consistent with studies of penicillin ADRs demonstrating that this is a limitation of the paradigm for entering patient ADRs⁴. Furthermore, the majority of ADR entry is being performed by nursing staff which is in contrast to more traditional situation where this task fell to prescribers. The paradigm of retrospective reporting of ADRs with a reliance on patient recollection is a potential contributor to the poor quality of ADR documentations.¹⁴ Many reactions may have occurred decades prior to the clinical encounter in which they were recorded. There would be merit in prospective and contemporaneous recording of

ADRs into a universal EHR, such as the Australian Government's My Health Record system, where they would be retained for future reference.

Systematic review of ADR labels would improve the completeness of documentation and information available to frontline clinicians. The availability of a complete reaction description is necessary for prescribers to distinguish drug allergy from intolerance. The date of reaction, despite being rarely completed, is also likely to assist with clinical decision making since immunological responses (other than severe cutaneous T-cell mediated reactions) are thought to wane over time.¹⁵ The high rate of alert overrides due to patients previously tolerating the agent suggests that clinicians are more likely to dismiss alerts rather than update the patient's recorded ADRs.⁹

Pharmacist-led initiatives have shown promise in improving the completeness of ADR documentation and identifying discrepancies between the patient's medical records.^{16 17} While pharmacists outperformed other health professionals in terms of entering a reaction type and categorisation of an ADR consistent with our pre-set criteria, they still only correctly classified 53% of ADRs in our study. This clearly highlights the need for additional training and support from specialist clinicians for all health professionals involved in ADR documentation. Further research is also needed to define the acceptable standard for ADR classification which may form an audit standard.

There are opportunities for a dedicated clinical service to manage the documentation of ADRs in the hospital setting. We envisage a multifaceted strategy with both prospective and retrospective components to combat the accumulation of ADR labels over a patient's lifetime.¹⁸ Prospective and contemporaneous recording of ADRs into the EHR will allow

them to be retained for future reference. A prospective approach is necessary, as details of the suspected ADR often cannot be elicited to guide further evaluation, long after the index reaction. Ideally the allergy module would articulate with the nationwide My Health Record system. This should be coupled with educational initiatives directed towards all healthcare professionals who enter ADRs. The provision of feedback to clinical staff has been shown to improve performance in medication management which would likely extend to ADR documentation.^{19, 20} Retrospective review of ADR labels could be employed to identify those most likely to benefit from further evaluation or delabelling. For instance, a report of anaphylaxis should generate an immunology referral for further evaluation in order to identify alternative agents that the patient will tolerate when analgesics are next required.

These findings have implications for the design of the ADR modules. We propose abandoning the requirement for ADRs be entered as allergy or intolerance. The selection of allergy or intolerance has no operational significance when it comes to the generation of prescribing alerts. Furthermore, it is nonsensical to classify an unknown reaction as either allergy or intolerance. Prescribing alerts should be generated based on reaction description rather than the often inaccurate categorisation as allergy or intolerance. We propose that the terms allergy and intolerance should be reserved for use after the ADR has been evaluated by an appropriately trained healthcare professional. Ideally this would occur through a dedicated clinical service that manages the documentation of ADRs in the hospital setting. Our proposal is consistent with others who have suggested that the ADR module be redesigned to preserve the meaning of an allergy label.²¹

There is also an opportunity to tailor prescribing alerts for opioid analgesics in order to reduce alert fatigue and improve specificity. Clinicians could be nudged to prescribe in a

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manner that reduces the occurrence of opioid ADRs. This approach would be acceptable given that most opioid ADRs warrant pre-medication, dose reduction or opioid rotation rather than outright avoidance.²² For instance, if the reaction is nausea and vomiting, then a tailored alert might prompt the clinician to co-prescribe an antiemetic. If the previous reaction is hallucinations then the alert might suggest starting at the low end of the dose range or consider opioid rotation. Anaphylaxis however would signify an absolute contraindication to that particular opioid, with a requirement for testing and cautious trial of an alternative.

Our study is limited by the retrospective design and the inability to confirm the entered ADR details with the patient's recollection, the medical records or the original source of ADR (e.g. transcribed from GP documentation, medical history by treating doctor). Furthermore, in assessing the differences in documentation performance between different professionals, we were not able to further classify individuals based on the seniority and specialty of medical professionals (e.g. medical intern, physician or immunologist).

In conclusion, there is a high rate of opioid ADR labels in EHRs. The majority of labels were suggestive of intolerance rather than allergy but the categorisation of allergy and intolerance was used inconsistently. Tailoring prescribing alerts to the reaction type would improve their specificity and utility to frontline clinicians. Systematic review of ADR labels and tailored prescribing alerts requires further research.

Acknowledgements

None

Funding Sources

None

Trial Registration

Not applicable

Disclosures

None to declare

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Table 1: Documentation of opioid ADR in EHR by health profession

	Health Profession N (% , 95% CI) p-value*						
	Allied Health (n=108)	Doctor (n=4259)	Nurse (n=7483)	Administrative Staff (n=28)	Pharmacist (n=1798)	Student (n=105)	Total (n=13781)
Reaction Not Documented	38 (35, 26.1-44.8) P = 0.0005	914 (21, 19.8-22.3)	742 (10, 9.3-10.7) P < 0.0001	7 (25, 10.7-44.9) P = 0.6047	199 (11, 9.6-12.5) P < 0.0001	13 (12, 6.5-19.8) P = 0.0248	1913
Correct Classification	26 (37, 22.8-49.4) P = 0.4015	1415 (42, 40.3-43.7)	2816 (42, 40.1-43.2) P = 1.0000	6 (29, 11.6-52.6) P = 0.2288	844 (53, 50.5-55.5) P < 0.0001	39 (42, 31.8-52.8) P = 1.0000	5146

*p-value by comparison to Doctors, those in bold are statistically significant (p<0.05)

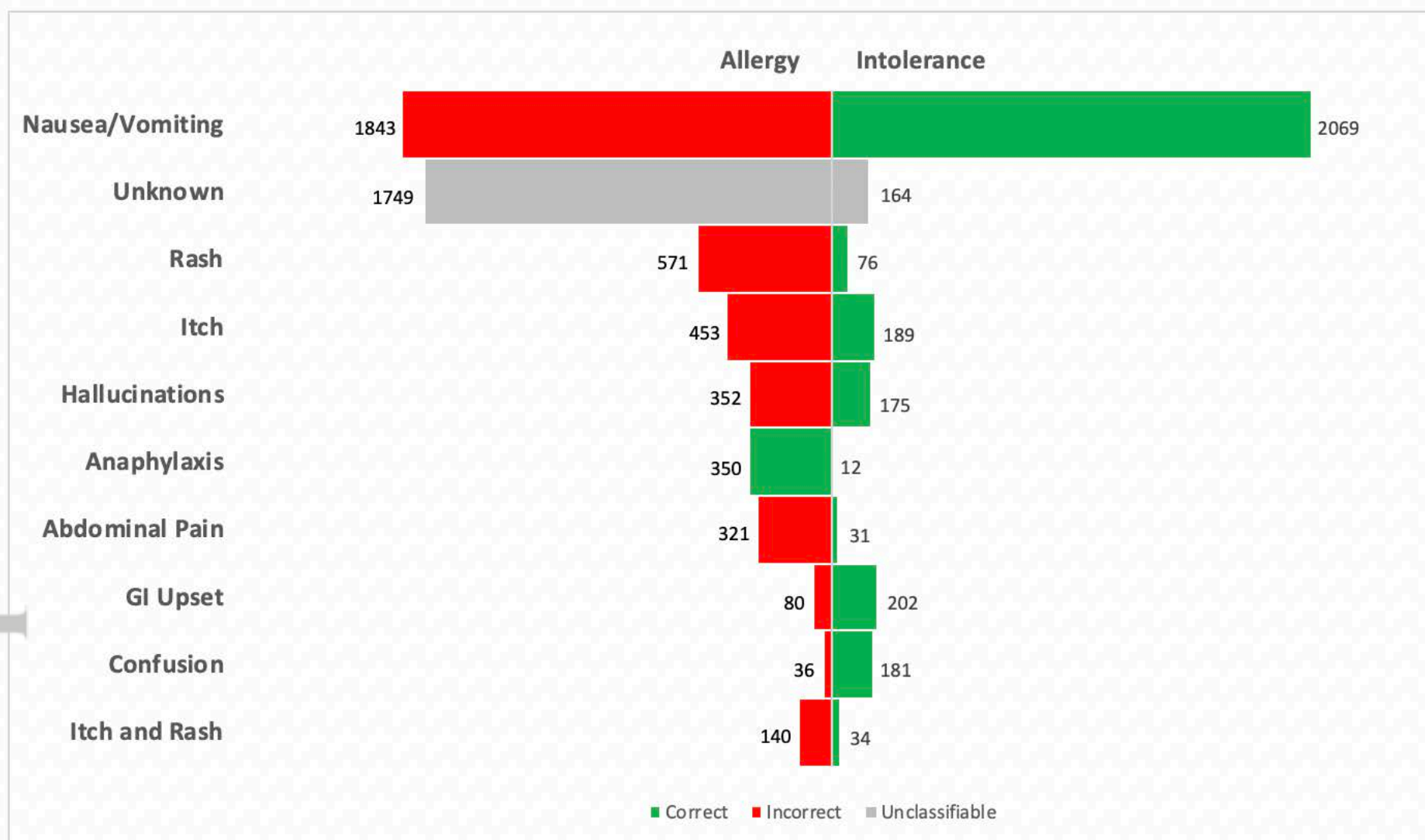
Table 2: Documentation of 10 most common reactions to opioids

Reaction Type	Number of Documented ADRs (Percentage)
Nausea/Vomiting	3912 (28%)
Unknown	1913 (14%)
Rash	647 (5%)
Itch	642 (5%)
Hallucinations	527 (4%)
Anaphylaxis	362 (3%)
Abdominal Pain	352 (3%)
GI Upset	282 (2%)
Confusion	217 (2%)
Itch and Rash	174 (1%)

Table 3: Categorisation of 20 most commonly documented reaction types

Documented as allergy (n=8913)		Documented as intolerance (n=4868)	
Aggregated reaction type	Number of ADRs (n)	Aggregated reaction type	Number of ADRs (n)
Nausea/Vomiting	1843	Nausea/Vomiting	2069
Unknown	1749	Gastrointestinal Upset	202
Rash	571	Itch	189
Itch	453	Confusion	181
Hallucinations	352	Hallucinations	175
Anaphylaxis	350	Unknown	164
Abdominal Pain	321	Chest Pain	122
Gastrointestinal Upset	80	Constipation	95
Confusion	36	Rash	76
Itch; Rash	140	Dizziness; Nausea/Vomiting	71
Chest Pain	39	Dizziness	61
Constipation	41	Drowsiness	52
Dizziness; Nausea/Vomiting	64	Cramps	49
Dizziness	56	Nausea/Vomiting; Gastrointestinal Upset	41
Swelling	96	Nausea/Vomiting; Dizziness	38
Short of Breath	93	Itch; Rash	34
Respiratory Distress	85	Abdominal Pain	31
Drowsiness	26	Collapse	30
Abdominal Pain; Nausea/Vomiting	63	Migraine	27

Figure 1: Categorisation of the 10 most commonly documented reaction types



Supplementary Table 2: Pre-Set Criteria for Opioid ADR Categorisation

<u>Categorisation</u>	<u>Criteria</u>	<u>Examples</u>
Allergy	Reaction descriptions consistent with an immune-mediated mechanism	Anaphylaxis Reaction consistent with anaphylaxis - Rash with hypotension - Rash with respiratory symptoms Allergy-like reactions (i.e. itch, rash, urticarial or swelling) with systemic symptoms
Intolerance	Reaction descriptions consistent with a non-immunological mechanism	Nausea Vomiting Headache
	Allergy-like reactions without systemic symptoms	Isolated itch Isolated rash Isolated urticaria Isolated swelling
Unclassifiable	Unable to make a determination	Unknown reaction No reaction type documented

Supplementary Table 1: Opioid Generic and Trade Names

Drug Name
buprenorphine
Buprenorphine Hydrochloride
buprenorphine-naloxone
Butorphanol Tartrate
CODAPANE FORTE
codeine
Codeine Linctus
Codeine Phosphate
Codeine Phosphate-Guaifenesin
Codeine Sulfate
codeine-pseudoephedrine
codeine/dexchlorpheniramine/phenylephrine
codeine/pseudoephedrine/triprolidine
FENPATCH
fentanyl
Fentanyl Citrate
Fentanyl Matrix
fentanyl-ropivacaine
HYDROMORPHONE
KAPANOL
methadone
Methadone Hydrochloride
morphine
morphine liposomal
Morphine Sulfate
Morphine Sulfate ADD-Vantage
Morphine Sulfate ER
Morphine Sulfate SR
MS Contin
narcotic analgesics
NORSPAN
opioid-like analgesics
oxycodone
oxycodone - naloxone
Oxycodone Hydrochloride
Oxycodone Hydrochloride ER
OxyContin
OXYNORM
PANADEINE
PANADEINE FORTE
paracetamol - codeine
paracetamol - codeine - doxylamine
TARGIN
tramadol
TraMADOL Hydrochloride
Tramal
Tramal SR

Supplementary Figure 2. Prescribing Alert

Alert Detail

morphine injection

Alert Summary

Ack...	View...	Doc...	Alert	Priority	Type	Comment	Scope
☒	☒		Patient Allergy	HIGH	WARNING		Chart

Alert:

Patient Allergy

Message:

[Expand](#)

[References](#)

ALLERGY ALERT - oxycodone

This patient is allergic to oxycodone, which is a(n) phenanthrene derivative. morphine is also a(n) phenanthrene derivative. The extent to which allergic cross-reactivity occurs among phenanthrene derivatives is unknown.

Order/Additive Name: **morphine injection**

Reaction: Rash to oxycodone

Confidence Level: <N/A>

INTOLERANCE ALERT - morphine

This patient has intolerance to morphine.

Order/Additive Name: **morphine injection**

Reaction: Other reaction (Unknown); Short of breath (Unknown) to morphine

Description: Lumps, hallucinations, shortness of breath as per patient

Confidence Level: <N/A>

Acknowledgement Comment:

A comment must be added before clicking Proceed.

☒ Acknowledge when seen

Unacknowledge

<< Previous

Alert 1 of 1

Next >>

To view suggested actions for the morphine injection order click View Action

To continue with the morphine injection unchanged click Proceed.

To return to the morphine injection and discard alerts click Go Back.

View Actions...

Proceed

Go Back

Help

Supplementary Figure 1. ADR Entry within the EHR

Allergy/Intolerance(Adding New)

Allergy/Intolerance Details

Category: ☒ Allergy ☐ Intolerance

Type:

Drug

Status:

Active

Allergen:

Reaction:

Add Reaction

Description:

Onset Date:

☐ M/Y

/

☒ Full Date

Confidence Level:

Info Source:

Confirmed By:

Me

Add New

Apply

Reason:

Entered:

Last Modified:

Attachments...

OK

Cancel

Discontinue

Delete

Reaction Details

Reaction Details

☐ Unknown

☒ Select all reactions that apply

	Reaction	Severity
☐	Anaphylaxis	
☐	Angioedema	
☐	Congestion	
☐	Contact Derm	
☐	Coughing	
☐	Dysrhythmia	
☐	Erythema	
☐	Fever	
☐	Flushing	
☐	Hay fever	

OK

Cancel

Reaction Details

Reaction Details

☐ Unknown

☒ Select all reactions that apply

	Reaction	Severity
☐	Akathisia	
☐	Anaemia	
☐	Bleeding	
☐	Cardiac Arrest	
☐	Confusion	
☐	Congestion	
☐	Constipation	
☐	Contact Derm	
☐	Coughing	
☐	Cramps	

OK

Cancel