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TITLE PAGE

Learning from dosing errors with opioids: a post-hoc analysis of three Dutch adverse event studies.

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ABSTRACT

Objectives

Opioids are increasingly prescribed and frequently involved in adverse drug events (ADEs). The underlying nature of opioid related ADEs (ORADEs) is however understudied. This hampers our understanding of risks related to opioid use during hospitalization and when designing interventions. Therefore, we provided a description of the nature of ORADEs.

Methods

A post-hoc analysis of data collected during three Dutch retrospective patient record review studies in 32 hospitals (conducted in 2008, 2011/2012 and 2015/2016). Per identified ORADE, we described preventability, type of medication error, attributable factors and type of opioid involved. Moreover, characteristics of preventable and non-preventable ORADEs were compared to identify risk factors.

Results

Out of 10,917 patient records, 357 ADEs were identified of which 28 (8%) involved opioids. Eleven ORADEs were assessed as preventable. Of these, ten were caused by dosing errors and four probably contributed to the patients' death. Attributable factors identified were mainly on patient and organizational level. Morphine and oxycodone were the most frequently involved opioids. The risk for ORADEs was higher in elderly patients.

Conclusions

Only 8% of ADEs identified in our sample were related to opioids. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

Keywords Analgesia, Pain control, Adverse drug events, Hospitals, Drug Prescriptions, Opioids, ORADE

(225 words, without key-words)

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study was conducted during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016 within 32 Dutch hospitals.
- During all three studies, a broad and randomly selected sample of all hospital admissions of patients were reviewed to assess the nature and preventability of adverse drug events with opioids.
- Our study population was stratified, resulting in an overrepresentation of in-hospital deceased patients.
- The low frequency of ORADEs limited a comparison of events over time between the three study periods.

TEXT

INTRODUCTION

Over the past decades, prescription of opioids has substantially increased worldwide.[1,2] Moreover, the rise in addiction rates and deaths resulting from opioid overdoses have urged physicians to call out an opioid crisis.[3] In the Netherlands, the prescription of oxycodone has increased almost fivefold over ten years (from 96.000 users in 2008 to 485.000 users in 2018).[4] This increase may however not only lead to more addiction but may also affect the number of opioid related adverse drug events (ADEs) in hospitals.

Opioids are frequently involved in ADEs,[5-7] and approximately in 2-14% of all patients.[8-11] ADEs are unintended injuries from a medical intervention related to drugs.[12] Opioid related ADEs (ORADEs) occur frequently, specifically in pediatric,[7,13] palliative[14] and surgical patients.[10,11,15] ORADEs are often caused by errors such as omissions or incorrect dosing.[7,13,14,16] In addition, approximately 11% of ORADEs among hospitalized patients cause severe or even fatal patient harm,[17] also because of the fast therapeutic effects of opioids. Besides these severe consequences, ORADEs lead to significantly higher healthcare costs.[9,10,15]

Our current knowledge about the incidence of ORADEs and their underlying nature is mostly based on medication related incident reports.[7,13,14,16] However, a comprehensive patient chart review provides the most reliable information on ADEs in hospitals while incident reports suffer from severe underreporting.[18,19] Furthermore, ORADE studies based on incident reports were usually conducted at one point in time or within one hospital or at a specific department.[7,13,14,16] The few ORADE studies based on comprehensive patient chart review were mainly conducted within a surgical population.[10,11,15]

Therefore, and also motivated by the opioid crisis, we have conducted an in-depth analysis of ORADEs using data gathered during three consecutive national adverse event studies in the Netherlands in which patient record review was applied. To our knowledge, no such longitudinal multicenter study on ORADEs in a diverse inpatient population and using a comprehensive ADE detection method has been published. The aim of this study was to provide a detailed description of the underlying nature of ORADEs. By doing so, we hope to increase awareness and provide recommendations on how to prevent opioid related ADEs in future hospitalized patients.

METHODS

Design and setting

We conducted a post-hoc analysis of data that were collected during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016. The aim of these studies was to identify AEs and ADEs in Dutch hospitals. A detailed description of the methodology used in these studies was previously published.[20-22] In summary, for the 2008 and 2011/2012 studies, a random sample of 20 hospitals participated. In 2015/2016, a new random sample of 19 hospitals was selected, of which seven had previously participated in two of the earlier studies. Both samples were stratified for hospital type and representation of urban and rural area. In 2008 and 2011/2012, 200 patient records per hospital were randomly selected for review; 100 records of discharged patients and 100 records of in-hospital deceased patients. The 2015/2016 study was limited to 150 in-hospital deceased patients per hospital because the frequency of preventable AEs remained unchanged for in-hospital deceased patients in both the 2008 and the 2011/2012 measurement.[21,23,24] Records of patients younger than one year and of patients admitted at the departments of psychiatry and obstetrics were excluded because other expertise is necessary to

detect AEs in these patients. The medical ethical committee of the Amsterdam UMC, Vrije Universiteit Amsterdam waived the requirement of informed consent (protocol numbers: 2005.146, 2009.130, 2016.282) as they found the scope of the study outside the Dutch Medical Research (Human Subjects) Act.

Review procedure AE studies

During all three AE studies, selected patient records were reviewed for the occurrence of AEs, including ADEs. In Figure 1, a schematic overview of the review process in the national studies and this study is presented. In summary, the review process consisted of two phases. In phase one, the records were screened for potential AEs by trained independent nurses. When predefined triggers were found, indicating an AE might have occurred, the record was labelled for an in-depth review by a trained independent physician. Independent means that the physicians and nurses never had an employment contract in the participating hospitals. The physicians were highly experienced and specialized in surgery, internal medicine or neurology, and during the record review studies they had access to all information in the electronic patient record. Besides, 10% of all patient records were reviewed by two physicians to determine inter-rater reliability.

An AE was defined by three criteria: 1) an unintended physical or mental injury; 2) the injury resulted in prolongation of hospital stay, temporary or permanent disability or death; 3) the injury was caused by healthcare management rather than the patient's underlying disease.[20,21,25] An AE was scored as caused by the healthcare (causality) if the likelihood score was equal to or greater than 4 based on a 6-point Likert scale with (virtually) no evidence (1), slight to modest evidence (2), not likely, but borderline (3), more likely but borderline (4), moderate to strong evidence (5), or (virtually) certain evidence (6) of management causation. The scoring system was used in all three record review studies.

If an AE was identified, the independent physicians (hereafter: experts) assessed each AE on: cause (diagnostic, surgery, non-invasive procedure, medication, other clinical activities, admission, and other), preventability, possible contribution to death, and attributable factors (e.g. technical, care, organizational, patient related, violation and other). An AE was considered to be preventable when the care given fell below the current level of expected performance of practitioners or systems. Preventability was also assessed on a 6-point Likert scale with almost no evidence (1), slight to modest evidence (2), modest evidence, but borderline (3), modest to strong evidence (4), strong evidence (5) or almost certain evidence (6) of preventability. A score of 4-6 indicated that the reviewer assessed the AE as having a greater than 50% chance of being potentially preventable.

Furthermore, for each patient the following characteristics were registered: gender, age, length of hospital stay, urgency of admission, whether patients were terminally ill prior to the admission, the number of involved medical specialists, department of admission, type of procedure and co-morbidity. The latter was divided in no, minor, moderate and severe co-morbidity, and was assessed by the experts after careful review of the information in the patient record. Also, one organizational characteristic (type of hospital: university, tertiary teaching, or general) and one AE characteristic (weekend or holiday at the time of the AE) were registered.

When an AE was medication related (ADE), the following additional characteristics were registered by the experts: name and type of medication involved, medication phase, a description of the ADE, and whether the ADE possibly contributed to the patients' death. The medication phases were classified into ordering, transcribing, dispensing, administering and monitoring.[26,27] The possible

contribution to the patients' death was only registered for ORADEs with 'medication' as a main cause of the event and not for ADEs with 'medication' as a sub cause.

All data were entered into a national AE database, specifically designed for the AE studies.

Review procedure ORADEs

For our study, we used the national AE database to identify ORADEs (Figure 1). One researcher (BS) conducted the screening of the database and retrieved several pre-selected variables: (1) AEs with the main classification cause 'medication' as well as AEs with 'medication' as a sub cause and (2) AEs with 'analgesics' as involved medication. Furthermore, two free-text fields were selected: the summary of the AEs and the preventability assessment. A second researcher (MM) independently double checked the selection procedure.

All identified ORADEs, were then classified by BS on type of opioid involved using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification.[28] For the preventable ORADEs, the type of medication error was classified according to a data driven analysis of the free-text summaries of the ADEs. The classification of ORADEs was double checked by two senior researchers (JK & IJ) and any discrepancies were resolved by consensus.

Outcomes

To provide insight into the nature of the ORADEs, each ORADE case was summarized by gender, age of the patient (categorized in steps of 10 years for privacy reasons), type of opioid involved, attributable factors and preventability. When the ORADE was preventable, then the type of medication error and medication phase was also described. Besides, we conducted also a comparison between preventable and non-preventable ORADEs to identify risk factors.

Data analysis

Only descriptive statistics were used in this study. Descriptives are presented as median (age and length of hospital stay) or frequency (gender, comorbidity, type of opioid and attributable factor, etc.). Patient and hospital characteristics are presented on a patient level and ORADE characteristics are presented on AE level. Inter-rater reliability among nurses and physicians was addressed in terms of positive and negative agreement frequencies.[29] All analyses were conducted using STATA version 14.1 (StataCorp, TX) and double checked by a second researcher (MM) and a statistician (PS).

RESULTS

In total, 10,917 records were screened during the three AE studies. The patient records of discharged and deceased patients were equally distributed among male and female patients. Most patients were hospitalized for a non-elective procedure (Table 1). In 1150 patient records, at least one AE was detected, with a total of 1240 AEs. When detecting the adverse events, positive agreement between physicians varied between 53.4-63.3%, for assessing the preventability positive agreement between physicians varied between 71.4-73.3%. Overall, agreement frequencies were moderate. More detailed information about the inter-rater reliability is presented in Supplemental Table 1.

Opioid related ADEs

Of 1240 AEs, 357 (29%) were medication related (ADEs). In 28 (8%) ADEs, opioids were involved. These ADEs are summarized in detail in Box 1, and included 24 ADEs with 'medication' as a main cause and four ADEs with 'medication' as a sub cause. The ORADEs occurred in 27 patients; one

patient experienced two ORADEs. Most patients with ORADEs involved females (59%). Median age of the patients was 76 years (Inter Quartile Range (IQR): 66-83) and median length of hospital stay was 7 days (IQR: 4-16). Most patients had moderate to significant co-morbidity (70%) and had three medical specialists during the admission (78%) (Table 2).

Nature of opioid related ADEs: preventability

According to the experts, 11 (39%) out of the 28 ORADEs were considered as potentially preventable (Table 3). Non-preventable (31%) ORADEs occurred slightly more during weekends and holidays than preventable ADEs (18%). Moreover, most preventable and non-preventable ORADEs occurred during dayshifts (8am-5pm).

Nature of opioid related ADEs: medication errors & phase

Of the 11 potentially preventable ORADEs, 10 (91%) were caused by dosing errors of which six during the prescribing phase (cases #1, #3, #7, #8, #9, #10) and four during the administration phase (cases #2, #4, #5, #6) (Box 1). Of the ten dosing errors, six occurred in elderly patients (≥70 years) (cases #1, #3, #4, #5, #8, #9), and two around the patients' discharge (cases #2, #7). The remaining one preventable ORADE (#11) was related to incorrect decision making. Finally, as assessed by the experts, four preventable ORADEs possibly contributed to the death of the patient (cases #5, #6, #8, #9).

Nature of opioid related ADEs: attributable factors

The attributable factors involved in ORADEs were care (knowledge, skills, monitoring, verification, and coordination of care) and patient related (co-morbidity, age, a demanding patient or a patient with an intellectual disability) (Table 3). Of preventable ORADEs, 8 were care related and 6 were patient related. For non-preventable ORADEs, 3 were care related and 10 were patient related. However, in 3 of the cases of non-preventable ORADEs, the attributable factors could not be assessed by the experts due to insufficient information in the patient records.

Nature of opioid related ADEs: medication involved

Eight out of the eleven preventable ADEs occurred with opioids with ATC code N02AA which are morphine and oxycodone (Table 3). Non-preventable ORADEs occurred with opioids mainly with ATC code N02AA (morphine and oxycodone, 53%).

DISCUSSION

In three national patient record studies with 4 years intervals, we found 28 ADEs caused by opioids. These ADEs correspond with 8% of all identified ADEs and 0.3% of all studied patient records. Eleven of the 28 opioid related ADEs (ORADEs) (39%) were assessed as potentially preventable, involving mostly morphine and oxycodone. Dosing errors, during the prescription and administration phase were the most common cause of preventable ORADEs, and occurred most often in elderly patients. Four preventable ORADEs probably contributed to the patients' death. Finally, attributable factors for the ADEs were mostly care and patient related.

In this study, the percentage of ORADEs of all patient records (0.3%) was low, also in comparison with previously conducted ORADE studies that focused on large populations (11-14%).[10,11,15] However, two of these studies were based on large databases and all involved surgical patients who often receive opioids post-operative. We focused on a broad hospitalized patient

population, both surgical and non-surgical. Furthermore, the difference in ORADE occurrence might be explained by differences in the used ADE definition. For example, instead of using all ORADEs, i.e. including side-effects of opioids, in our study only ADEs that resulted in severe patient harm were included. This means that ADEs resulted in prolongation of hospital stay, temporary or permanent disability or death. Furthermore, only ADEs with a causality likelihood score of equal or greater than 4 were included, which means that the experts indicated an ADE as having a greater than 50% chance of being caused by healthcare. Should we have selected the cases with causality likelihood scores of 1-3 as well, then we could determine at least 2500 additional cases on whether medication and opioids were related.

In line with previous studies,[7,13,14,16] we found that dosing errors during prescribing and administering were the main cause of preventable ORADEs. Furthermore, 60% of the dosing errors in our study occurred in elderly patients (≥70 years). In general, prescribing medication for elderly patients is challenging since polypharmacy, multi-morbidity and altered pharmacokinetics and pharmacodynamics of drugs are often present. Besides, this population will rapidly increase in the upcoming years. Specifically related to opioids, physicians also need to be aware of the higher sensitivity of elderly patients to the effects of opioids,[30] and balancing between minimizing the risk of addiction and side-effects while effectively relieving pain.[31,32] Taking into account all these factors while prescribing, demands a lot from physicians during their busy daily hospital practice. A clinical decision support system (CDSS), can help physicians in this complex task by showing warnings and advices during prescribing, for example showing the most appropriate choice of medication for a given condition and/or by providing dosing recommendations. CDSS has shown to effectively reduce prescribing errors among hospitalized elderly patients[33,34] and errors with medications of which the therapeutic effects are fast, such as opiods.[35] Furthermore, a CDSS can also be effective in predicting which patients are at risk for ORADEs. Using retrospective data from gastro-intestinal surgical patients, Minkowitz et al. (2014) developed a risk-scoring model to identify patients with a high risk for experiencing an ORADE based on their clinical and demographic profiles.[36] If developed specifically for elderly inpatients, such a prediction model could help physicians in determining the most appropriate and safe pain management strategy for these vulnerable patients. Finally, a CDSS could also be used to identify patients who might be suitable for pre-emptive genotyping, which involves metabolic testing prior to prescribing.[37] Patients with high levels of pain despite using high doses of pain medication or patients that experience severe side-effects while using common dosing schedules may especially benefit from such an intervention.[38]

Administering opioids is a task usually conducted by nurses. The dosing errors in our study were mostly related to injectable opioids. Error prone activities, such as calculating the concentration and administration rate,[13,16] require that nurses have sufficient arithmetic knowledge and follow the protocol for safe preparation and administration of injectable medication. However, in daily practice, some nurses have math anxiety and on average arithmetic knowledge of nursing students seems moderate.[39,40] Besides, nurse compliance with protocols for safe administration of injectable medication is considered low (around 20%)[41,42] and needs further attention. An intervention which might help to reduce dosing errors during opioid administration is the use of smart infusion pumps. These pumps have integrated medication libraries which allow nurses to set the pump automatically to the right administration rate during administration. By doing so, the administration rate of smart pumps can be seen as a double check of the nurses' own calculation. Smart pumps seem also effective in reducing programming errors.[43] Furthermore, educational programs for nurses about

brand and generic names and pharmacology of opioids or side-effects might increase their knowledge and awareness of risks related to dosing during the administration of opioids.[44-46]

Overall, we think the ORADE frequency of 8% of all ADEs and 0.3% of all studied patient records found in our study is low and acceptable. However, although the frequency is low, the risk of serious consequences is high. Thus, new contributions to prevent ORADEs in future hospitalized patients need to be identified. Using the Safety-2 perspective may offer new opportunities to do so.[47] In order to understand what happened when an adverse (drug) event occurred, it is also necessary to understand how work is done when the process goes well.[48] Since healthcare processes have become more complex nowadays, it may be helpful to visualize the current variable practice of prescribing and administering opioids from a multi-stakeholder perspective.[49]

Strengths and limitations

Opioids are in the top ten of drug types that causes fatal medication errors.[8] Hence, focusing on the detailed description of the nature of ORADEs was important and necessary. Another strength of this study is that it was based on a comprehensive ADE detection method and conducted in a broad sample of all hospital admissions. Most previous studies, which described the nature of ORADEs, are based on medication related incident reports. Furthermore, data were gathered over an extended period of time within a randomly selected sample of one third of all Dutch hospitals.

This study also has some limitations. Firstly, in all three AE studies, the population consisted of relatively many older and deceased patients. Therefore, it is not possible to generalize the results to all Dutch hospital population. To make the study sample more representative for the Dutch hospital population, weighting the results (i.e. correcting for type of hospital, study period and discharge status) would be a solution which is used in previous studies of our research group. However, since the total amount of ORADEs was low, we chose not to weight our results as this had little effect and makes interpretation difficult. Secondly, due to this low number of ORADEs, it was not possible to compare the events over the three study periods. Therefore, we cannot conclude whether the low number is a positive finding, and if the occurrence of ORADEs increased or decreased over time. Thirdly, our post-hoc analysis was based on the information previously recorded by the experts in an AE database, and on the assessment conducted by these physicians. Therefore, interpreting the assessment of preventability was difficult for us in one case, resulting in a non-preventable ORADE. Besides, the retrospective interpretation can also be biased by temporal views. While the current opinion is that prescribing opioids should be minimized due to the harm of opioids, this changed throughout the years and may not have been recognized 15 years ago, when the focus was mainly on alleviating suffering of pain.

CONCLUSION

Only 8% of ADEs identified in our sample were related to opioids, 0.3% of all studied patient records. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

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Contributors BS, MM, JK, ML, MdB, and CW designed the study and developed the study protocol. BS and MM organized the selection and classification of ORADEs. JK and IJ double checked this classification. BS and MM performed statistical analyses and interpreted the analytical results. BS, JK, and IJ wrote the manuscript. MdB, and CW supervised the study. All authors made critical revisions and approved the final version of the manuscript.

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Table 1. Patient and hospital characteristics of all reviewed patient records, including adverse events per study period and discharge status.

	Study period and discharge status				
	2008		2011/2012		2015/2016
Hospital characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Number of patient records, n	2016	2007	2023	2025	2846
General hospital, n records (%)	1013 (50)	1015 (51)	794 (39)	813 (40)	1197 (42)
Tertiary teaching hospital, n records (%)	608 (30)	593 (30)	822 (41)	820 (40)	1052 (37)
Academic hospital, n records (%)	395 (20)	399 (20)	407 (20)	392 (19)	597 (21)
	2008		**2011/2012**		**2015/2016**
Patient characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Male sex, n (%)	999 (50)	1067 (53)	1027 (51)	1062 (52)	1524 (54)
Age (years), median (IQR)	62 (47-75)	77 (67-84)	63 (48-75)	77 (68-84)	77 (68-85)
Length of stay (days), median (IQR)	4 (2-8)	7 (3-14)	3 (2-7)	6 (2-13)	4 (1-11)
Non-elective admission, n (%)	1038 (51)	1708 (85)	1063 (53)	1775 (88)	2496 (88)
Admission department, n (%)					
Surgery	481 (24)	276 (14)	472 (23)	239 (12)	340 (12)
Cardiology	290 (14)	291 (15)	272 (13)	247 (12)	360 (13)
Internal medicine	364 (18)	599 (30)	365 (18)	597 (29)	876 (31)
Orthopaedics	226 (11)	33 (2)	225 (11)	26 (1)	29 (1)
Neurology	150 (7)	219 (11)	133 (7)	193 (10)	269 (9)
Lung diseases	117 (6)	259 (13)	126 (6)	300 (15)	347 (12)
Urology	109 (5)	18 (1)	111 (5)	28 (1)	23 (1)
Other	279 (14)	312 (16)	319 (16)	395 (20)	602 (21)
Underwent invasive procedure, n (%)	925 (46)	423 (21)	918 (45)	403 (20)	461 (16)
Adverse event occurrence §¶					
AE, n (%)	161 (8)	351 (16)	157 (8)	259 (12)	312 (10)
ADE, n (% within population)	37 (2)	93 (4)	40 (2)	76 (4)	111 (4)
ADE, n (% within adverse event)	37 (23)	93 (27)	40 (25)	76 (29)	111 (36)
ORADE, n (% within population)	1 (0)	7 (0)	2 (0)	8 (0)	10 (0)
ORADE, n (% within ADEs)	1 (3)	7 (8)	2 (5)	8 (11)	10 (9)

† Presented on patient record level.
§ Presented on AE level.
¶ Total number of AEs: 1240, total number of ADEs: 357, total number of opioid related ADEs: 28
AE = Adverse event, ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Table 2. Characteristics of patients (n=27) with ORADEs (n=28)†	
Patient characteristics	
Patients with an ADE, n	27
Male sex, n (%)	11 (41)
Age, median years (IQR)	76 (66-83)
Length of stay, median days (IQR)	7 (4-16)
Non-elective admission, n (%)	19 (70)
Terminally ill prior to admission, n (%)	6 (22)
Total number of medical specialists	
0, n (%)	0 (0)
1, n (%)	4 (15)
2, n (%)	2 (7)
3, n (%)	21 (78)
Primary specialisation during admission	
Surgical, n (%)	7 (26)
Non-surgical, n (%)	20 (74)
Underwent invasive procedure, n (%)	9 (33)
Co-morbidity§	
No co-morbidity, n (%)	0 (0)
Minor co-morbidity, n (%)	3 (11)
Moderate co-morbidity, n (%)	5 (19)
Significant co-morbidity, n (%)	19 (70)
† Presented on patient level. *§ The level of co-morbidity was assessed by the experts after careful review of the information in the patient record.* *ADE = Adverse drug event, ORADEs = Opioid related adverse drug events*	

Table 3. Clinical context of ORADEs (n=28)†		
Clinical context	**Non-preventable§ ADEs (n=17)**	**Preventable§ ADEs (n=11)**
Type of hospital		
University, n ADEs (%)	1 (6)	1 (9)
Tertiary teaching, n ADEs (%)	6 (35)	4 (36)
General, n ADEs (%)	10 (59)	6 (55)
Weekend or National holiday (yes), n (%)	5 (31)	2 (18)
Moment		
8am-5pm, n (%)	6 (35)	5 (45)
5pm-11pm, n (%)	3 (18)	0 (0)
11pm-8am, n (%)	2 (12)	3 (27)
Cannot be assessed, n (%)	6 (35)	3 (27)
Type of Opioid (ATC code)		
Opioid anesthetics (N01AH03), n (%)	2 (12)	1 (9)
Natural opium alkaloids (N02AA), n (%)	9 (53)	8 (73)
Natural opium alkaloids and Phenylpiperidine derivatives (N02AA/N02AB, combination), n (%)	1 (6)	1 (9)
Phenylpiperidine derivatives (N02AB), n (%)	2 (12)	0 (0)
Other opioids (N02AX), n (%)	1 (6)	0 (0)
Drugs used in opioid dependence (N07BC), n (%)	2 (12)	1 (9)
Attributable factors¶		
Technical, n (%)	0 (0)	0 (0)
Care related, n (%)	3 (19)	8 (80)
Organizational, n (%)	2 (13)	4 (40)
Patient related, n (%)	10 (63)	6 (60)
Violation, n (%)	0 (0)	1 (10)
Cannot be assessed, n (%)	3 (19)	1 (10)
Other, n (%)	1 (6)	0 (0)

† Presented on adverse event level.
§ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability. Not preventable ADEs were scored at 1-3, preventable ADEs were scored at 4-6.
¶ These variables were missing for 2 patients; one in the preventable group and one in the non-preventable group. Moreover, it was possible to select more than one option for this question.
ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Box 1. Descriptions of the 28 opioid related adverse drug events divided into preventable and non-preventable.		
Case	***Description*†**	***Preventability score (1-6)*‡§**
Preventable opioid related ADEs		
Cause: Dosing errors		
1	Male, 90-99 years, admitted with pain after a fall. Oxycodone for the pain was unintentionally prescribed twice instead of once and also administered twice. This resulted in drowsiness.	6
2	Male, 60-69 years, suffering from colon cancer and liver metastases, was admitted for optimizing his analgesics medication. On returning from his weekend leave, he was diagnosed with oxycodone intoxication. During hospital stay, he received a too high dose of the opioid antagonist naloxone (1 mg instead of 0,4 mg) which caused confusion and agitation.	6
3	Female, 70-79 years, admitted with a pelvic fracture after a fall. A too high dose of oxycodone was prescribed and administered resulting in hypotension and drowsiness. Consequently, she needed to be transferred to the intensive care unit.	5
4	Female, 80-89 years, admitted with malaise after a fall. During her admission she received a too high dose of morphine. In her patient record, the morphine was ordered as 'as needed'. In the medication list, the morphine was ordered '6 times a day'.	5
5	Female, 70-79 years, admitted for a plastic surgery. A high dose of administered anesthetic/pain medication (type unknown) caused hypoventilation and a myocardial infarct. The myocardial infarct was discovered too late. She was resuscitated and ventilated. Her death was possibly caused by a hospital acquired pneumonia.	5
6	Female, 50-59 years, admitted due to an aspiration pneumonia, was administered morphine. The pump mode was set at 13 instead of 8 as ordered. This possibly resulted in an epileptic insult requiring ventilation.	5
7	Male, 60-69 years, re-admitted to the hospital due to a collapse at home. He was previously hospitalized for treatment of rib fractures and COPD Gold IV. At discharge, the doses of fentanyl and oxycodone had been significantly increased. Monitoring the effects of increasing these opioid doses was not conducted.	4
8	Female, 80-89 years, admitted with osteoporosis, received at home 5 mg morphine twice daily for her back pain. The dosage was increased to 5 mg 4 times a day during hospital stay. Three days later, a paralytic ileus was discovered. A lower morphine dose was more appropriate for this elderly female.	4
9	Female, 80-89 years, admitted with abdominal pain due to a kidney bleeding. She received morphine injections daily, varying from 2-6 injections along with transdermal fentanyl 12 mcg hourly. Severe hypercapnia eventually caused her death.	4
10	Male, 0-9 years, with Down syndrome, was acutely ill due to a laryngitis. He was difficult to ventilate and received antibiotics and sedatives including opioids. He was transferred to another hospital following detubation. Here, his methadone intake was reduced resulting in a delirium. Initially he improved, but one day unexpectedly he was found dead. It is unclear why this patient received methadone, but reducing the methadone intake may have been the problem.	4
Cause: Incorrect decision making		
11	Female, 60-69 years, admitted for a laminectomy. Postoperatively she developed an ileus caused by severe constipation aggravated by administered morphine. Macrogol oral suspension instead of an enema was given as treatment, which was insufficient	4

	to resolve the ileus and colon perforation occurred. Untreatable abdominal septic complications followed.	
Non-preventable opioid related ADEs		
12	Female, 80-89 years, admitted due to a total knee replacement. Postoperatively, drowsiness, hypotension and oliguria occurred, possibly caused by the epidural medication sufentanil. This may have led to a small asymptomatic myocardial infarct.	3
13	Male, 80-89 years, admitted with a perforated stomach ulcer and known stomach cancer. His extreme, not previously known, sensitivity to morphine postoperatively resulted in recurrent apnea.	3
14	Female, 60-69 years, suffering from lung cancer, was admitted with severe back and limb pain related to bone metastases. She was treated with transdermal fentanyl 300 mcg per hour. This resulted in drowsiness and hypoventilation.	2
15	Female, 80-89 years, known with breast cancer and multiple lung metastases. She received tramadol for the pain which have been stopped due to drowsiness.	2
16	Male, 70-79 years, admitted with severe heart failure. He received morphine 2.5 mg for the pain. As a result of increased, not previously known, sensitivity to morphine, his saturation dropped.	2
17	Male, 90-99 years, admitted because of a stroke and a lot of pain. The nurse administered 10% of the prescribed dose of morphine on two occasions which caused unnecessary suffering.	2
18	Male, 60-69 years, admitted for surgery due to an ileus. Postoperative complications included an exacerbation COPD and a hospital acquired pneumonia after receiving morphine.	2
19	Female, 60-69 years, admitted with a reoccurrence of drowsiness, hypoventilation and difficult to wake up which was the result of a dose of methadone being administered in the hospital.	2
20	Female, 60-69 years, had a blood pressure drop following the administration of morphine in the recovery room.	1
21	Female, 70-79 years, admitted with pain related to severe Kahler disease. For the pain, she received opioids (unknown which type). The opioids caused drowsiness and because of the drowsiness, she choked once. This caused a pneumonia. The patient deceased during hospitalization.	1
22	Male, 70-79 years, received transdermal fentanyl and oxycodone daily up to 6 times due to metastases in the hip. This caused apraxia and confusion.	1
23	Female, 80-89 year, admitted for occlusion of an artery in her leg. She received a morphine infusion causing hypoventilation with a good response to naloxone.	1
24	Male, 80-89 years, admitted due to obstructive laryngeal cancer, was prescribed anticoagulants. This resulted in a hematoma along with severe abdominal pain for which he received morphine after which he deceased.	1
25	Male, 60-69 years, admitted with an acute respiratory insufficiency due to pneumonia. He received methadone, causing hypoventilation on two occasions. This needed to be treated with naloxone.	1
26	Female, 80-89 years, suffered from pain due to rib fractures caused by resuscitation. She received sufentanil, which led to bronchospasm.	1
27	Female, 70-79 years, admitted with pain related to breast cancer. During the admission, it became apparent that she had metastases along with femur and vertebral fractures. A high dose of morphine was necessary to relieve her pain which consequently resulted in a delirium.	1
28	Female, 80-89 years, admitted due to a hip fracture and pain. For her restlessness and pain she was administered morphine which probably caused a reduced level of consciousness.	1

† Patients were categorized in age groups of ten years to avoid traceability.
‡ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability.
§ For the judgment on preventability, the experts had access to all information in the electronic patient record and therefore to the whole context in which ADEs occurred.

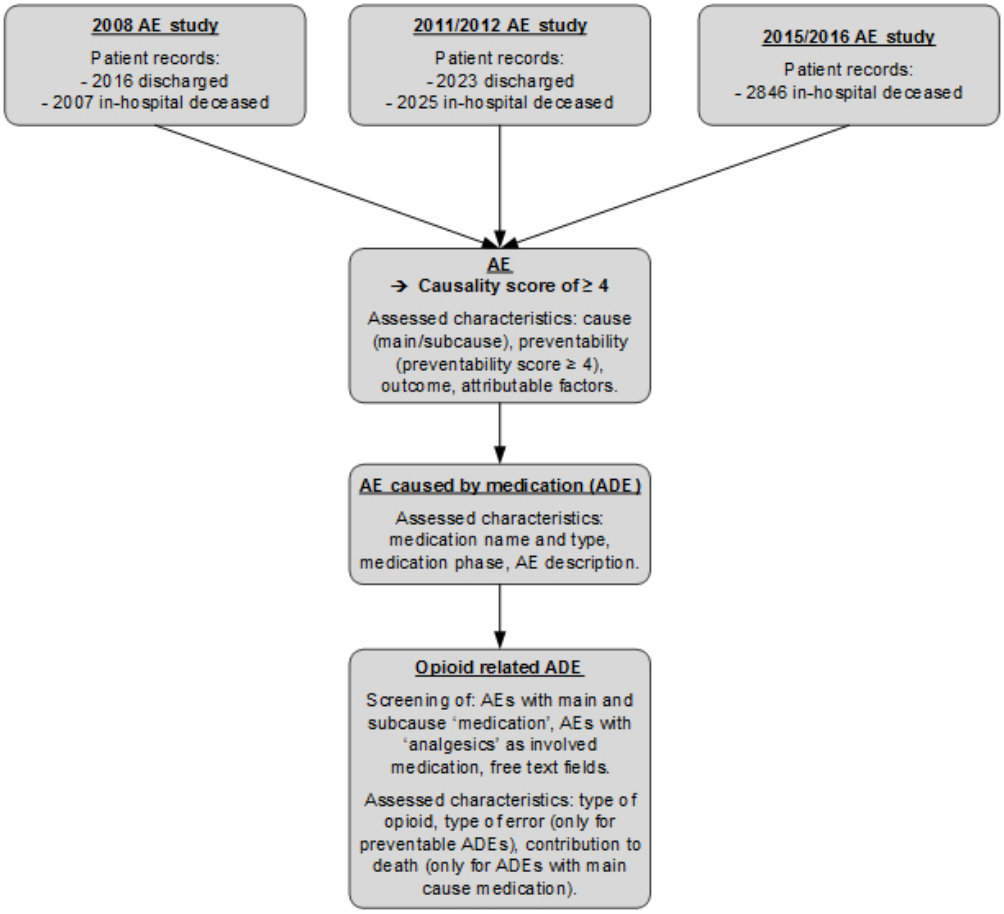

Figure 1: Overview of the three Dutch adverse event studies and our study.

Supplemental Table 1: Positive and negative agreement (%) between nurses and physicians during the adverse events studies.†‡						
	Nurses		**Physicians – adverse event**		**Physicians - preventability**	
Study	Positive agreement	Negative agreement	Positive agreement	Negative agreement	Positive agreement	Negative agreement
2008	76.0	89.0	63.3	86.9	n/a	n/a
2011/2012	85.8	63.3	56.9	82.9	73.3	83.3
2015/2016	91.5	68.9	54.3	80.9	71.4	81.0

† All frequencies are separately calculated by a 2x2 table:

		Nurse / Physician 1	
		Positive agreement	Negative agreement
Nurse / Physician 2	Positive agreement	A	B
	Negative agreement	C	D

Positive agreement = (2xA) / ((2xA)+B+C) and negative agreement = (2xD) / ((2xD)+B+C).

‡ The interpretation of the Kappa is not straightforward, and it is influenced by the number of categories of each variable and the prevalence of the given scores. It is therefore possible that despite a high agreement, the Kappa is low. This occurs in studies with few adverse events. For this reason we chose to present positive and negative agreement frequencies. It helps to answer questions such as: 'if one expert finds a preventable adverse event, what is the probability that another expert will also find a preventable adverse event?'

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TITLE PAGE

The nature of adverse events with opioids in hospitalized patients: a post-hoc analysis of three patient record review studies.

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ABSTRACT

Objectives

Opioids are increasingly prescribed and frequently involved in adverse drug events (ADEs). The underlying nature of opioid related ADEs (ORADEs) is however understudied. This hampers our understanding of risks related to opioid use during hospitalization and when designing interventions. Therefore, we provided a description of the nature of ORADEs.

Design

A post-hoc analysis of data collected during three retrospective patient record review studies (in 2008, 2011/2012 and 2015/2016).

Setting

The three record review studies were conducted in 32 Dutch hospitals.

Participants

A total of 10,917 patient records were assessed by trained nurses and physicians.

Outcome measures

Per identified ORADE, we described preventability, type of medication error, attributable factors and type of opioid involved. Moreover, characteristics of preventable and non-preventable ORADEs were compared to identify risk factors.

Results

Out of 10,917 patient records, 357 ADEs were identified of which 28 (8%) involved opioids. Eleven ORADEs were assessed as preventable. Of these, ten were caused by dosing errors and four probably contributed to the patients' death. Attributable factors identified were mainly on patient and organizational level. Morphine and oxycodone were the most frequently involved opioids. The risk for ORADEs was higher in elderly patients.

Conclusions

Only 8% of ADEs identified in our sample were related to opioids. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

Keywords Analgesia, Pain control, Adverse drug events, Hospitals, Drug Prescriptions, Opioids, ORADE

(248 words, without key-words)

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study was based on data gathered during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016 within 32 Dutch hospitals.
- During all three studies, a broad and randomly selected sample of all hospital admissions of patients were reviewed to assess the nature and preventability of adverse drug events with opioids.
- Our study population was stratified, resulting in an overrepresentation of in-hospital deceased patients.
- The low frequency of ORADEs limited a comparison of events over time between the three study periods.

TEXT

INTRODUCTION

Over the past decades, prescription of opioids has substantially increased worldwide.[1,2] Moreover, the rise in addiction rates and deaths resulting from opioid overdoses have urged physicians to call out an opioid crisis.[3] In the Netherlands, the prescription of oxycodone has increased almost fivefold over ten years (from 96.000 users in 2008 to 485.000 users in 2018).[4] This increase may however not only lead to more addiction but may also affect the number of opioid related adverse drug events (ADEs) in hospitals.

Opioids are frequently involved in ADEs,[5-7] and approximately in 2-14% of all patients.[8-12] ADEs are unintended injuries from a medical intervention related to drugs.[13] Opioid related ADEs (ORADEs) occur frequently, specifically in pediatric,[7,14] palliative[15] and surgical patients.[10,11,16] ORADEs are often caused by errors such as omissions or incorrect dosing.[7,14,15,17] In addition, approximately 11% of ORADEs among hospitalized patients cause severe or even fatal patient harm,[18] also because of the fast therapeutic effects of opioids. Besides these severe consequences, ORADEs lead to significantly higher healthcare costs.[9,10,16]

Our current knowledge about the incidence of ORADEs and their underlying nature is mostly based on medication related incident reports.[7,14,15,17] However, a comprehensive patient chart review provides the most reliable information on ADEs in hospitals while incident reports suffer from severe underreporting.[19,20] Furthermore, ORADE studies based on incident reports were usually conducted at one point in time or within one hospital or at a specific department.[7,14,15,17] The few ORADE studies based on comprehensive patient chart review were mainly conducted within a surgical population.[10,11,16]

Therefore, and also motivated by the opioid crisis, we have conducted an in-depth analysis of ORADEs using data gathered during three consecutive national adverse event studies in the Netherlands in which patient record review was applied. To our knowledge, no such longitudinal multicenter study on ORADEs in a diverse inpatient population and using a comprehensive ADE detection method has been published. The aim of this study was to provide a detailed description of the underlying nature of ORADEs. By doing so, we hope to increase awareness and provide recommendations on how to prevent opioid related ADEs in future hospitalized patients.

METHODS

Design and setting

We conducted a post-hoc analysis of data that were collected during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016. The aim of these studies was to identify AEs and ADEs in Dutch hospitals. A detailed description of the methodology used in these studies was previously published and comparable to other international AEs studies.[21,22] In summary, for the 2008 and 2011/2012 studies, a random sample of 20 hospitals participated. In 2015/2016, a new random sample of 19 hospitals was selected, of which seven had previously participated in two of the earlier studies. Both samples were stratified for hospital type and representation of urban and rural area. In 2008 and 2011/2012, 200 patient records per hospital were randomly selected for review; 100 records of discharged patients and 100 records of in-hospital deceased patients. The 2015/2016 study was limited to 150 in-hospital deceased patients per hospital because the frequency of preventable AEs remained unchanged for in-hospital deceased patients in both the 2008 and the 2011/2012 measurement.[23-25] Records of patients younger than one year and of patients admitted at the departments of psychiatry and obstetrics were excluded

because other expertise is necessary to detect AEs in these patients. The random selection of patient records was conducted by the participating hospitals with clear instructions of the researchers. The medical ethical committee of the Amsterdam UMC, Vrije Universiteit Amsterdam waived the requirement of informed consent (protocol numbers: 2005.146, 2009.130, 2016.282) as they found the scope of the study outside the Dutch Medical Research (Human Subjects) Act.

Review procedure AE studies

During all three AE studies, selected patient records were reviewed for the occurrence of AEs, including ADEs. In Figure 1, a schematic overview of the review process in the national studies and this study is presented. In summary, the review process consisted of two phases. In phase one, the records were screened for potential AEs by trained independent nurses. When predefined triggers were found, indicating an AE might have occurred, the record was labelled for an in-depth review by a trained independent physician. Independent means that the physicians and nurses never had an employment contract in the participating hospitals. The physicians were highly experienced and specialized in surgery, internal medicine or neurology, and during the record review studies they had access to all information in the electronic patient record. Besides, 10% of all patient records were reviewed by two physicians to determine inter-rater reliability. Validity of this scoring system has not been tested, but it has been used widely in AE studies for over 20 years and the ratings of the system did not change in that time.[21-23,26-29] Prior to the study, both nurses and physicians had training sessions in which cases were discussed to enhance the quality and standardization of the review process.

An AE was defined by three criteria: 1) an unintended physical or mental injury; 2) the injury resulted in prolongation of hospital stay, temporary or permanent disability or death; 3) the injury was caused by healthcare management rather than the patient's underlying disease.[23,27,28] An AE was scored as caused by the healthcare (causality) if the likelihood score was equal to or greater than 4 based on a 6-point Likert scale with (virtually) no evidence (1), slight to modest evidence (2), not likely, but borderline (3), more likely but borderline (4), moderate to strong evidence (5), or (virtually) certain evidence (6) of management causation. The scoring system was used in all three record review studies and the physicians made the judgments about causality and preventability based on all the available information of the patient's condition and taking into account the guidelines.

If an AE was identified, the independent physicians (hereafter: experts) assessed each AE on: cause (diagnostic, surgery, non-invasive procedure, medication, other clinical activities, admission, and other), preventability, possible contribution to death, and attributable factors. The attributable factors were based on the taxonomy of the Eindhoven Classification Model and consisted of the main categories: technical, care, organizational, patient related, violation and other.[30] An AE was considered to be preventable when the care given fell below the current level of expected performance of practitioners or systems. Before the physicians answered the question about preventability, they were required to respond to 13 questions to add more structure to the review process. For example, if there was a complex medical history, if the patient had co-morbidity and whether another physician would repeat this treatment. Preventability was also assessed on a 6-point Likert scale with almost no evidence (1), slight to modest evidence (2), modest evidence, but borderline (3), modest to strong evidence (4), strong evidence (5) or almost certain evidence (6) of preventability. A score of 4-6 indicated that the reviewer assessed the AE as having a greater than 50% chance of being potentially preventable.

Furthermore, for each patient the following characteristics were registered: gender, age, length of hospital stay, urgency of admission, whether patients were terminally ill prior to the admission, the number of involved medical specialists, department of admission, type of procedure and co-morbidity. The latter was divided in no, minor, moderate and severe co-morbidity, and was assessed by the experts after careful review of the information in the patient record. Also, one organizational characteristic (type of hospital: university, tertiary teaching, or general) and one AE characteristic (weekend or holiday at the time of the AE) were registered.

When an AE was medication related (ADE), the following additional characteristics were registered by the experts: name and type of medication involved, medication phase, a description of the ADE, and whether the ADE possibly contributed to the patients' death. The medication phases were classified into ordering, transcribing, dispensing, administering and monitoring.[31,32] The possible contribution to the patients' death was only registered for ORADEs with 'medication' as a main cause of the event and not for ADEs with 'medication' as a sub cause.

All data were entered into a national AE database, specifically designed for the AE studies.

Review procedure ORADEs

For our study, we used the national AE database to identify ORADEs (Figure 1). One researcher (BS) conducted the screening of the database and retrieved several pre-selected variables: (1) AEs with the main classification cause 'medication' as well as AEs with 'medication' as a sub cause and (2) AEs with 'analgesics' as involved medication. Furthermore, two free-text fields were selected: the summary of the AEs and the preventability assessment. A second researcher (MM) independently double checked the selection procedure.

All identified ORADEs, were then classified by BS on type of opioid involved using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification.[33] For the preventable ORADEs, the type of medication error was classified according to a data driven analysis of the free-text summaries of the ADEs. The classification of ORADEs was double checked by two senior researchers (JK & IJ) and any discrepancies were resolved by consensus.

Outcomes

To provide insight into the nature of the ORADEs, each ORADE case was summarized by gender, age of the patient (categorized in steps of 10 years for privacy reasons), type of opioid involved, attributable factors and preventability. When the ORADE was preventable, then the type of medication error and medication phase was also described. Furthermore, in order to identify risk factors, we compared the outcome variables between preventable and non-preventable ORADEs.

Data analysis

Only descriptive statistics were used in this study. Descriptives are presented as median (age and length of hospital stay) or frequency (gender, comorbidity, type of opioid and attributable factor, etc.). Patient and hospital characteristics are presented on a patient level and ORADE characteristics are presented on AE level. Inter-rater reliability among nurses and physicians was addressed in terms of positive and negative agreement frequencies.[34] All analyses were conducted using STATA version 14.1 (StataCorp, TX) and double checked by a second researcher (MM) and a statistician (PS).

RESULTS

In total, 10,917 records were screened during the three AE studies. The patient records of discharged and deceased patients were equally distributed among male and female patients. Most patients were hospitalized for a non-elective procedure (Table 1). In 1150 patient records, at least one AE was detected, with a total of 1240 AEs. When detecting the predefined triggers, positive agreement between nurses varied between 76.0-91.5%. When detecting the adverse events, positive agreement between physicians varied between 53.4-63.3%. For assessing the preventability positive agreement between physicians varied between 71.4-73.3%. Overall, agreement frequencies were moderate. More detailed information about the inter-rater reliability is presented in Supplemental Table 1.

Opioid related ADEs

Of 1240 AEs, 357 (29%) were medication related (ADEs). In 28 (8%) ADEs, opioids were involved. These ADEs are summarized in detail in Box 1, and included 24 ADEs with 'medication' as a main cause and four ADEs with 'medication' as a sub cause. The ORADEs occurred in 27 patients; one patient experienced two ORADEs. Most patients with ORADEs involved females (59%). Median age of the patients was 76 years (Inter Quartile Range (IQR): 66-83) and median length of hospital stay was 7 days (IQR: 4-16). Most patients had moderate to significant co-morbidity (70%) and had three medical specialists during the admission (78%) (Table 2).

Nature of opioid related ADEs: preventability

According to the experts, 11 (39%) out of the 28 ORADEs were considered as potentially preventable (Table 3). Non-preventable (31%) ORADEs occurred slightly more during weekends and holidays than preventable ADEs (18%). Moreover, most preventable and non-preventable ORADEs occurred during dayshifts (8am-5pm).

Nature of opioid related ADEs: medication errors & phase

Of the 11 potentially preventable ORADEs, 10 (91%) were caused by dosing errors of which six during the prescribing phase (cases #1, #3, #7, #8, #9, #10) and four during the administration phase (cases #2, #4, #5, #6) (Box 1). Of the ten dosing errors, six occurred in elderly patients (≥70 years) (cases #1, #3, #4, #5, #8, #9), and two around the patients' discharge (cases #2, #7). The remaining one preventable ORADE (#11) was related to incorrect decision making. Finally, the experts assessed the consequences of the ORADEs (multiple options possible). In eight ORADEs, an intervention or extra treatment was needed, in two ORADEs the patients had a prolonged hospital stay and four preventable ORADEs possibly contributed to the death of the patient (cases #5, #6, #8, #9).

Nature of opioid related ADEs: attributable factors

The attributable factors involved in ORADEs were care (knowledge, skills, monitoring, verification, and coordination of care) and patient related (co-morbidity, age, a demanding patient or a patient with an intellectual disability) (Table 3). Of preventable ORADEs, 8 were care related and 6 were patient related. For non-preventable ORADEs, 3 were care related and 10 were patient related. However, in 3 of the cases of non-preventable ORADEs, the attributable factors could not be assessed by the experts due to insufficient information in the patient records.

Nature of opioid related ADEs: medication involved

Eight out of the eleven preventable ADEs occurred with opioids with ATC code N02AA which are morphine and oxycodone (Table 3). Non-preventable ORADEs occurred with opioids mainly with ATC code N02AA (morphine and oxycodone, 53%).

DISCUSSION

In three national patient record studies with 4 years intervals, we found 28 ADEs caused by opioids. These ADEs correspond with 8% of all identified ADEs and 0.3% of all studied patient records. Eleven of the 28 opioid related ADEs (ORADEs) (39%) were assessed as potentially preventable, involving mostly morphine and oxycodone. Dosing errors, during the prescription and administration phase were the most common cause of preventable ORADEs, and occurred most often in elderly patients. Four preventable ORADEs probably contributed to the patients' death. Finally, attributable factors for the ADEs were mostly care and patient related.

In this study, the percentage of ORADEs of all patient records (0.3%) was low, also in comparison with previously conducted ORADE studies that focused on large populations (11-14%).[10,11,16] However, two of these studies were based on large databases and all involved surgical patients who often receive opioids post-operative. We focused on a broad hospitalized patient population, both surgical and non-surgical. Furthermore, the difference in ORADE occurrence might be explained by differences in the used ADE definition. For example, instead of using all ORADEs, i.e. including side-effects of opioids, in our study only ADEs that resulted in severe patient harm were included. This means that ADEs resulted in prolongation of hospital stay, temporary or permanent disability or death. Furthermore, only ADEs with a causality likelihood score of equal or greater than 4 were included, which means that the experts indicated an ADE as having a greater than 50% chance of being caused by healthcare. Should we have selected the cases with causality likelihood scores of 1-3 as well, then we could determine at least 2500 additional cases on whether medication and opioids were related. However, we did not determine these 2500 cases, since we wanted to stay true to the definition of an AE (at least 4 on the 6-point Likert scale) and we did not consider it ethical to change the method of the study afterwards.

In line with previous studies,[7,14,15,17] we found that dosing errors during prescribing and administering were the main cause of preventable ORADEs. Furthermore, 60% of the dosing errors in our study occurred in elderly patients (≥70 years). In general, prescribing medication for elderly patients is challenging since polypharmacy, multi-morbidity and altered pharmacokinetics and pharmacodynamics of drugs are often present. Besides, this population will rapidly increase in the upcoming years. Specifically related to opioids, physicians also need to be aware of the higher sensitivity of elderly patients to the effects of opioids,[35] and balancing between minimizing the risk of addiction and side-effects while effectively relieving pain.[36,37] Taking into account all these factors while prescribing, demands a lot from physicians during their busy daily hospital practice. A clinical decision support system (CDSS), can help physicians in this complex task by showing warnings and advices during prescribing, for example showing the most appropriate choice of medication for a given condition and/or by providing dosing recommendations. CDSS has shown to effectively reduce prescribing errors among hospitalized elderly patients[38,39] and errors with medications of which the therapeutic effects are fast, such as opiods.[40] Furthermore, a CDSS can also be effective in predicting which patients are at risk for ORADEs. Using retrospective data from gastro-intestinal surgical patients, Minkowitz et al. (2014) developed a risk-scoring model to identify patients with a high risk for experiencing an ORADE based on their clinical and demographic profiles.[41] If developed

specifically for elderly inpatients, such a prediction model could help physicians in determining the most appropriate and safe pain management strategy for these vulnerable patients. Finally, a CDSS could also be used to identify patients who might be suitable for pre-emptive genotyping, which involves metabolic testing prior to prescribing.[42] Patients with high levels of pain despite using high doses of pain medication or patients that experience severe side-effects while using common dosing schedules may especially benefit from such an intervention.[43]

Administering opioids is a task usually conducted by nurses. The dosing errors in our study were mostly related to injectable opioids. Error prone activities, such as calculating the concentration and administration rate,[14,17] require that nurses have sufficient arithmetic knowledge and follow the protocol for safe preparation and administration of injectable medication. However, in daily practice, some nurses have math anxiety and on average arithmetic knowledge of nursing students seems moderate.[44,45] Besides, nurse compliance with protocols for safe administration of injectable medication is considered low (around 20%)[46,47] and needs further attention. An intervention which might help to reduce dosing errors during opioid administration is the use of smart infusion pumps. These pumps have integrated medication libraries which allow nurses to set the pump automatically to the right administration rate during administration. By doing so, the administration rate of smart pumps can be seen as a double check of the nurses' own calculation. Smart pumps seem also effective in reducing programming errors.[48] Furthermore, educational programs for nurses about brand and generic names and pharmacology of opioids or side-effects might increase their knowledge and awareness of risks related to dosing during the administration of opioids.[49-51]

Overall, we think the ORADE frequency of 8% of all ADEs and 0.3% of all studied patient records found in our study is low and acceptable. However, although the frequency is low, the risk of serious consequences is high. Thus, new contributions to prevent ORADEs in future hospitalized patients need to be identified. Using the Safety-2 perspective may offer new opportunities to do so.[52] In order to understand what happened when an adverse (drug) event occurred, it is also necessary to understand how work is done when the process goes well.[53] Since healthcare processes have become more complex nowadays, it may be helpful to visualize the current variable practice of prescribing and administering opioids from a multi-stakeholder perspective.[54]

Strengths and limitations

Opioids are in the top ten of drug types that causes fatal medication errors.[8] Hence, focusing on the detailed description of the nature of ORADEs was important and necessary. Another strength of this study is that it was based on a comprehensive ADE detection method and conducted in a broad sample of all hospital admissions. Most previous studies, which described the nature of ORADEs, are based on medication related incident reports. Furthermore, data were gathered over an extended period of time within a randomly selected sample of one third of all Dutch hospitals.

This study also has some limitations. Firstly, in all three AE studies, the population consisted of relatively many older and deceased patients. Therefore, it is not possible to generalize the results to all Dutch hospital population. To make the study sample more representative for the Dutch hospital population, weighting the results (i.e. correcting for type of hospital, study period and discharge status) would be a solution which is used in previous studies of our research group. However, since the total amount of ORADEs was low, we chose not to weight our results as this had little effect and makes interpretation difficult. Secondly, overall agreement frequencies between physicians were moderate. This could have led to different assessments or different scores if other experts were involved. This should be taken into account when interpreting our results. However, a

previous review of studies focusing on assessing AEs showed also moderate to substantial inter-rater reliability.[55] For this reason, patient records in all Dutch AE studies have been assessed by the same experts as much as possible and over the years these experts have not become stricter or lenient in their judgment of AEs and their preventability.[56] Thirdly, due to this low number of ORADEs, it was not possible to compare the events over the three study periods. Therefore, we cannot conclude whether the low number is a positive finding, and if the occurrence of ORADEs increased or decreased over time. Fourthly, our post-hoc analysis was based on the information previously recorded by the experts in an AE database, and on the assessment conducted by these physicians. Therefore, some information could be missing and interpreting the assessment of preventability was difficult for us in one case, resulting in a non-preventable ORADE. Furthermore, this was also the reason that the harm could not be further categorized according to the NCCMERP Index for Categorizing Medication Errors.[57] Besides, the retrospective interpretation can also be biased by temporal views. The current opinion is that prescribing opioids should be minimized due to the harm of opioids, which is supported by updated guidelines.[58] This view changed throughout the years and may not have been recognized 15 years ago, when the focus was mainly on alleviating suffering of pain. This change in opinion may have increased alertness when prescribing or administering opioids, which could have led to less ORADEs. However, our study showed that ORADEs still occur and publishing about them could serve as a method of increasing awareness.

CONCLUSION

Only 8% of ADEs identified in our sample were related to opioids, 0.3% of all studied patient records. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

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Contributors BS, MM, JK, ML, MdB, and CW designed the study and developed the study protocol. BS and MM organized the selection and classification of ORADEs. JK and IJ double checked this classification. BS and MM performed statistical analyses and interpreted the analytical results. BS, JK, and IJ wrote the manuscript. MdB, and CW supervised the study. All authors made critical revisions and approved the final version of the manuscript.

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Table 1. Patient and hospital characteristics of all reviewed patient records, including adverse events per study period and discharge status.

	Study period and discharge status				
	2008		2011/2012		2015/2016
Hospital characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Number of patient records, n	2016	2007	2023	2025	2846
General hospital, n records (%)	1013 (50)	1015 (51)	794 (39)	813 (40)	1197 (42)
Tertiary teaching hospital, n records (%)	608 (30)	593 (30)	822 (41)	820 (40)	1052 (37)
Academic hospital, n records (%)	395 (20)	399 (20)	407 (20)	392 (19)	597 (21)
	2008		**2011/2012**		**2015/2016**
Patient characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Male sex, n (%)	999 (50)	1067 (53)	1027 (51)	1062 (52)	1524 (54)
Age (years), median (IQR)	62 (47-75)	77 (67-84)	63 (48-75)	77 (68-84)	77 (68-85)
Length of stay (days), median (IQR)	4 (2-8)	7 (3-14)	3 (2-7)	6 (2-13)	4 (1-11)
Non-elective admission, n (%)	1038 (51)	1708 (85)	1063 (53)	1775 (88)	2496 (88)
Admission department, n (%)					
Surgery	481 (24)	276 (14)	472 (23)	239 (12)	340 (12)
Cardiology	290 (14)	291 (15)	272 (13)	247 (12)	360 (13)
Internal medicine	364 (18)	599 (30)	365 (18)	597 (29)	876 (31)
Orthopaedics	226 (11)	33 (2)	225 (11)	26 (1)	29 (1)
Neurology	150 (7)	219 (11)	133 (7)	193 (10)	269 (9)
Lung diseases	117 (6)	259 (13)	126 (6)	300 (15)	347 (12)
Urology	109 (5)	18 (1)	111 (5)	28 (1)	23 (1)
Other	279 (14)	312 (16)	319 (16)	395 (20)	602 (21)
Underwent invasive procedure, n (%)	925 (46)	423 (21)	918 (45)	403 (20)	461 (16)
Adverse event occurrence §¶					
AE, n (%)	161 (8)	351 (16)	157 (8)	259 (12)	312 (10)
ADE, n (% within population)	37 (2)	93 (4)	40 (2)	76 (4)	111 (4)
ADE, n (% within adverse event)	37 (23)	93 (27)	40 (25)	76 (29)	111 (36)
ORADE, n (% within population)	1 (0)	7 (0)	2 (0)	8 (0)	10 (0)
ORADE, n (% within ADEs)	1 (3)	7 (8)	2 (5)	8 (11)	10 (9)

† Presented on patient record level.
§ Presented on AE level.
¶ Total number of AEs: 1240, total number of ADEs: 357, total number of opioid related ADEs: 28
AE = Adverse event, ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Table 2. Characteristics of patients (n=27) with ORADEs (n=28)†	
Patient characteristics	
Patients with an ADE, n	27
Male sex, n (%)	11 (41)
Age, median years (IQR)	76 (66-83)
Length of stay, median days (IQR)	7 (4-16)
Non-elective admission, n (%)	19 (70)
Terminally ill prior to admission, n (%)	6 (22)
Total number of medical specialists	
0, n (%)	0 (0)
1, n (%)	4 (15)
2, n (%)	2 (7)
3, n (%)	21 (78)
Primary specialisation during admission	
Surgical, n (%)	7 (26)
Non-surgical, n (%)	20 (74)
Underwent invasive procedure, n (%)	9 (33)
Co-morbidity§	
No co-morbidity, n (%)	0 (0)
Minor co-morbidity, n (%)	3 (11)
Moderate co-morbidity, n (%)	5 (19)
Significant co-morbidity, n (%)	19 (70)
† Presented on patient level. *§ The level of co-morbidity was assessed by the experts after careful review of the information in the patient record.* *ADE = Adverse drug event, ORADEs = Opioid related adverse drug events*	

Table 3. Clinical context of ORADEs (n=28)†		
Clinical context	**Non-preventable§ ADEs (n=17)**	**Preventable§ ADEs (n=11)**
Type of hospital		
University, n ADEs (%)	1 (6)	1 (9)
Tertiary teaching, n ADEs (%)	6 (35)	4 (36)
General, n ADEs (%)	10 (59)	6 (55)
Weekend or National holiday (yes), n (%)	5 (31)	2 (18)
Moment		
8am-5pm, n (%)	6 (35)	5 (45)
5pm-11pm, n (%)	3 (18)	0 (0)
11pm-8am, n (%)	2 (12)	3 (27)
Cannot be assessed, n (%)	6 (35)	3 (27)
Type of Opioid (ATC code)		
Opioid anesthetics (N01AH03), n (%)	2 (12)	1 (9)
Natural opium alkaloids (N02AA), n (%)	9 (53)	8 (73)
Natural opium alkaloids and Phenylpiperidine derivatives (N02AA/N02AB, combination), n (%)	1 (6)	1 (9)
Phenylpiperidine derivatives (N02AB), n (%)	2 (12)	0 (0)
Other opioids (N02AX), n (%)	1 (6)	0 (0)
Drugs used in opioid dependence (N07BC), n (%)	2 (12)	1 (9)
Attributable factors¶		
Technical, n (%)	0 (0)	0 (0)
Care related, n (%)	3 (19)	8 (80)
Organizational, n (%)	2 (13)	4 (40)
Patient related, n (%)	10 (63)	6 (60)
Violation, n (%)	0 (0)	1 (10)
Cannot be assessed, n (%)	3 (19)	1 (10)
Other, n (%)	1 (6)	0 (0)

† Presented on adverse event level.
§ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability. Not preventable ADEs were scored at 1-3, preventable ADEs were scored at 4-6.
¶ These variables were missing for 2 patients; one in the preventable group and one in the non-preventable group. Moreover, it was possible to select more than one option for this question.
ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Box 1. Descriptions of the 28 opioid related adverse drug events divided into preventable and non-preventable.		
Case	***Description*†**	***Preventability score (1-6)*‡ and type of error§**
Preventable opioid related ADEs		
Cause: Dosing errors		
1	Male, 90-99 years, admitted with pain after a fall. Oxycodone for the pain was unintentionally prescribed twice instead of once and also administered twice (dose unknown). This resulted in drowsiness.	6 (prescribing error)
2	Male, 60-69 years, suffering from colon cancer and liver metastases, was admitted for optimizing his analgesics medication. On returning from his weekend leave, he was diagnosed with oxycodone intoxication. During hospital stay, he received a too high dose of the opioid antagonist naloxone (1 mg instead of the ordered 0,4 mg) which caused confusion and agitation.	6 (administration error)
3	Female, 70-79 years, admitted with a pelvic fracture after a fall. A too high dose (dose unknown) of oxycodone was prescribed and administered resulting in hypotension and drowsiness. Consequently, she needed to be transferred to the intensive care unit.	5 (prescribing error)
4	Female, 80-89 years, admitted with malaise after a fall. During her admission she received a too high dose of morphine. In her patient record, the morphine was ordered as 'as needed' (PRN). In the medication list, the morphine was ordered '6 times a day' (dose unknown). This resulted in drowsiness.	5 (prescribing error)
5	Female, 70-79 years, admitted for a plastic surgery. A high dose of intravenous administered anesthetic/pain medication (dose and medication type unknown) caused hypoventilation and a myocardial infarct. The myocardial infarct was discovered too late. She was resuscitated and ventilated. Her death was possibly caused by a hospital acquired pneumonia.	5 (administration error)
6	Female, 50-59 years, admitted due to an aspiration pneumonia, was administered morphine. The pump mode was set at 13 ml/hour instead of 8 ml/hour as ordered. This possibly resulted in an epileptic insult requiring ventilation.	5 (administration error)
7	Male, 60-69 years, re-admitted to the hospital due to a collapse at home. He was previously hospitalized for treatment of rib fractures and COPD Gold IV. At discharge, the doses of fentanyl and oxycodone had been significantly increased to 20 mg 4 to 6 times a day. Monitoring the effects of increasing these opioid doses was not conducted.	4 (prescribing error)
8	Female, 80-89 years, admitted with osteoporosis, received at home 5 mg morphine twice daily for her back pain. The dosage was increased to subcutaneous of 5 mg 4 times a day during hospital stay. Three days later, a paralytic ileus was discovered. A lower morphine dose was more appropriate for this elderly female.	4 (prescribing error)
9	Female, 80-89 years, admitted with abdominal pain due to a kidney bleeding. She received morphine injections daily, varying from 2-6 subcutaneous injections of 2,5 mg per day along with transdermal fentanyl 12 mcg hourly. Severe hypercapnia eventually caused her death.	4 (prescribing error)
10	Male, 0-9 years, with Down syndrome, was acutely ill due to a laryngitis. He was difficult to ventilate and received antibiotics and sedatives including opioids. He was transferred to another hospital following detubation. Here, his methadone intake was reduced resulting in a delirium (dose unknown). Initially he improved, but one day unexpectedly he was found dead. It is unclear why this	4 (unknown)

	patient received methadone, but reducing the methadone intake may have been the problem.	
Cause: Incorrect decision making		
11	Female, 60-69 years, admitted for a laminectomy. Postoperatively she developed an ileus caused by severe constipation aggravated by administered morphine. Macrogol oral suspension (dose unknown) instead of an enema was given as treatment, which was insufficient to resolve the ileus and colon perforation occurred. Untreatable abdominal septic complications followed.	4 (unknown)
Non-preventable opioid related ADEs		
12	Female, 80-89 years, admitted due to a total knee replacement. Postoperatively, drowsiness, hypotension and oliguria occurred, possibly caused by the epidural medication sufentanil (dose unknown). This may have led to a small asymptomatic myocardial infarct.	3 (administration error)
13	Male, 80-89 years, admitted with a perforated stomach ulcer and known stomach cancer. His extreme, not previously known, sensitivity to morphine postoperatively (dose unknown) resulted in recurrent apnea.	3 (other error)
14	Female, 60-69 years, suffering from lung cancer, was admitted with severe back and limb pain related to bone metastases. She was treated with transdermal fentanyl 300 mcg per hour. This resulted in drowsiness and hypoventilation.	2 (prescribing error)
15	Female, 80-89 years, known with breast cancer and multiple lung metastases. She received tramadol (dose unknown) for the pain which have been stopped due to drowsiness.	2 (unknown)
16	Male, 70-79 years, admitted with severe heart failure. He received morphine 2.5 mg for the pain. As a result of increased, not previously known, sensitivity to morphine, his saturation dropped.	2 (other error)
17	Male, 90-99 years, admitted because of a stroke and a lot of pain. The nurse administered 10% of the prescribed dose (dose unknown) of morphine on two occasions which caused unnecessary suffering.	2 (administration error)
18	Male, 60-69 years, admitted for surgery due to an ileus. Postoperative complications included an exacerbation COPD and a hospital acquired pneumonia after receiving morphine (dose unknown).	2 (unknown)
19	Female, 60-69 years, admitted with a reoccurrence of drowsiness, hypoventilation and difficult to wake up which was the result of a dose of 5 mg of methadone being administered in the hospital.	2 (prescribing and administration error)
20	Female, 60-69 years, had a blood pressure drop following the administration of morphine (dose unknown) in the recovery room.	1 (other error)
21	Female, 70-79 years, admitted with pain related to severe Kahler disease. For the pain, she received opioids (unknown which type and dose). The opioids caused drowsiness and because of the drowsiness, she choked once. This caused a pneumonia. The patient deceased during hospitalization.	1 (other error)
22	Male, 70-79 years, received transdermal fentanyl and oxycodone 5 mg daily up to 6 times due to metastases in the hip. This caused apraxia and confusion.	1 (unknown)
23	Female, 80-89 year, admitted for occlusion of an artery in her leg. She received a morphine infusion (0.5-1.0 mg/hour) causing hypoventilation with a good response to naloxone.	1 (administration error)
24	Male, 80-89 years, admitted due to obstructive laryngeal cancer, was prescribed anticoagulants. This resulted in a hematoma along with severe abdominal pain for which he received morphine (dose unknown) after which he deceased.	1 (other error)
25	Male, 60-69 years, admitted with an acute respiratory insufficiency due to pneumonia. He received methadone 20 mg 2 times a day, causing hypoventilation on two occasions. This needed to be treated with naloxone.	1 (prescribing error)

26	Female, 80-89 years, suffered from pain due to rib fractures caused by resuscitation. She received sufentanil (dose unknown), which led to bronchospasm.	1 (unknown)
27	Female, 70-79 years, admitted with pain related to breast cancer. During the admission, it became apparent that she had metastases along with femur and vertebral fractures. A high dose of morphine (dose unknown) was necessary to relieve her pain which consequently resulted in a delirium.	1 (prescribing error)
28	Female, 80-89 years, admitted due to a hip fracture and pain. For her restlessness and pain she was administered 1 mg morphine which probably caused a reduced level of consciousness.	1 (other error)

† Patients were categorized in age groups of ten years to avoid traceability.
‡ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability.
§ For the judgment on preventability and type of error, the experts had access to all information in the electronic patient record and therefore to the whole context in which ADEs occurred. The types of error were: prescribing error, administration error, other error (e.g. side-effects) or unknown.

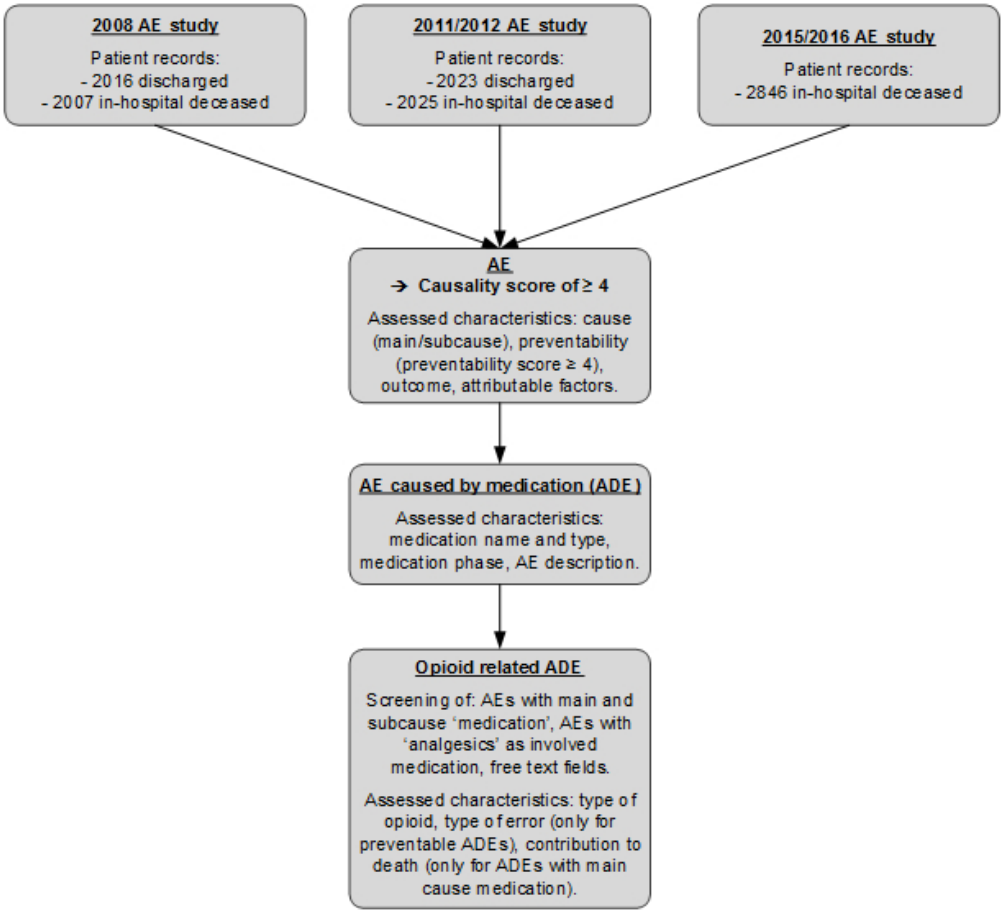

Figure 1: Overview of the three Dutch adverse event studies and our study.

Supplemental Table 1: Positive and negative agreement (%) between nurses and physicians during the adverse events studies.†‡						
	Nurses		**Physicians – adverse event**		**Physicians - preventability**	
Study	Positive agreement	Negative agreement	Positive agreement	Negative agreement	Positive agreement	Negative agreement
2008	76.0	89.0	63.3	86.9	n/a	n/a
2011/2012	85.8	63.3	56.9	82.9	73.3	83.3
2015/2016	91.5	68.9	54.3	80.9	71.4	81.0

† All frequencies are separately calculated by a 2x2 table:

		Nurse / Physician 1	
		Positive agreement	Negative agreement
Nurse / Physician 2	Positive agreement	A	B
	Negative agreement	C	D

Positive agreement = (2xA) / ((2xA)+B+C) and negative agreement = (2xD) / ((2xD)+B+C).

‡ The interpretation of the Kappa is not straightforward, and it is influenced by the number of categories of each variable and the prevalence of the given scores. It is therefore possible that despite a high agreement, the Kappa is low. This occurs in studies with few adverse events. For this reason we chose to present positive and negative agreement frequencies. It helps to answer questions such as: 'if one expert finds a preventable adverse event, what is the probability that another expert will also find a preventable adverse event?'

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8

		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

n.a. = not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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TITLE PAGE

The nature of adverse events with opioids in hospitalized patients: a post-hoc analysis of three patient record review studies.

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ABSTRACT

Objectives

Opioids are increasingly prescribed and frequently involved in adverse drug events (ADEs). The underlying nature of opioid related ADEs (ORADEs) is however understudied. This hampers our understanding of risks related to opioid use during hospitalization and when designing interventions. Therefore, we provided a description of the nature of ORADEs.

Design

A post-hoc analysis of data collected during three retrospective patient record review studies (in 2008, 2011/2012 and 2015/2016).

Setting

The three record review studies were conducted in 32 Dutch hospitals.

Participants

A total of 10,917 patient records were assessed by trained nurses and physicians.

Outcome measures

Per identified ORADE, we described preventability, type of medication error, attributable factors and type of opioid involved. Moreover, characteristics of preventable and non-preventable ORADEs were compared to identify risk factors.

Results

Out of 10,917 patient records, 357 ADEs were identified of which 28 (8%) involved opioids. Eleven ORADEs were assessed as preventable. Of these, ten were caused by dosing errors and four probably contributed to the patients' death. Attributable factors identified were mainly on patient and organizational level. Morphine and oxycodone were the most frequently involved opioids. The risk for ORADEs was higher in elderly patients.

Conclusions

Only 8% of ADEs identified in our sample were related to opioids. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

Keywords Analgesia, Pain control, Adverse drug events, Hospitals, Drug Prescriptions, Opioids, ORADE

(248 words, without key-words)

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This study was based on data gathered during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016 within 32 Dutch hospitals.
- During all three studies, a broad and randomly selected sample of all hospital admissions of patients were reviewed to assess the nature and preventability of adverse drug events with opioids.
- Our study population was stratified, resulting in an overrepresentation of in-hospital deceased patients.
- The low frequency of ORADEs limited a comparison of events over time between the three study periods.

TEXT

INTRODUCTION

Over the past decades, prescription of opioids has substantially increased worldwide.[1,2] Moreover, the rise in addiction rates and deaths resulting from opioid overdoses have urged physicians to call out an opioid crisis.[3] In the Netherlands, the prescription of oxycodone has increased almost fivefold over ten years (from 96.000 users in 2008 to 485.000 users in 2018).[4] This increase may however not only lead to more addiction but may also affect the number of opioid related adverse drug events (ADEs) in hospitals.

Opioids are frequently involved in ADEs,[5-7] and approximately in 2-14% of all patients.[8-12] ADEs are unintended injuries from a medical intervention related to drugs.[13] Opioid related ADEs (ORADEs) occur frequently, specifically in pediatric,[7,14] palliative[15] and surgical patients.[10,11,16] ORADEs are often caused by errors such as omissions or incorrect dosing.[7,14,15,17] In addition, approximately 11% of ORADEs among hospitalized patients cause severe or even fatal patient harm,[18] also because of the fast therapeutic effects of opioids. Besides these severe consequences, ORADEs lead to significantly higher healthcare costs.[9,10,16]

Our current knowledge about the incidence of ORADEs and their underlying nature is mostly based on medication related incident reports.[7,14,15,17] However, a comprehensive patient chart review provides the most reliable information on ADEs in hospitals while incident reports suffer from severe underreporting.[19,20] Furthermore, ORADE studies based on incident reports were usually conducted at one point in time or within one hospital or at a specific department.[7,14,15,17] The few ORADE studies based on comprehensive patient chart review were mainly conducted within a surgical population.[10,11,16]

Therefore, and also motivated by the opioid crisis, we have conducted an in-depth analysis of ORADEs using data gathered during three consecutive national adverse event studies in the Netherlands in which patient record review was applied. To our knowledge, no such longitudinal multicenter study on ORADEs in a diverse inpatient population and using a comprehensive ADE detection method has been published. The aim of this study was to provide a detailed description of the underlying nature of ORADEs. By doing so, we hope to increase awareness and provide recommendations on how to prevent opioid related ADEs in future hospitalized patients.

METHODS

Design and setting

We conducted a post-hoc analysis of data that were collected during three national retrospective patient record review studies conducted in 2008, 2011/2012 and 2015/2016. The aim of these studies was to identify AEs and ADEs in Dutch hospitals. A detailed description of the methodology used in these studies was previously published and comparable to other international AEs studies.[21,22] In summary, for the 2008 and 2011/2012 studies, a random sample of 20 hospitals participated. In 2015/2016, a new random sample of 19 hospitals was selected, of which seven had previously participated in two of the earlier studies. Both samples were stratified for hospital type and representation of urban and rural area. In 2008 and 2011/2012, 200 patient records per hospital were randomly selected for review; 100 records of discharged patients and 100 records of in-hospital deceased patients. The 2015/2016 study was limited to 150 in-hospital deceased patients per hospital because the frequency of preventable AEs remained unchanged for in-hospital deceased patients in both the 2008 and the 2011/2012 measurement.[23-25] Records of patients younger than one year and of patients admitted at the departments of psychiatry and obstetrics were excluded

because other expertise is necessary to detect AEs in these patients. The random selection of patient records was conducted by the participating hospitals with clear instructions of the researchers. The medical ethical committee of the Amsterdam UMC, Vrije Universiteit Amsterdam waived the requirement of informed consent (protocol numbers: 2005.146, 2009.130, 2016.282) as they found the scope of the study outside the Dutch Medical Research (Human Subjects) Act.

Review procedure AE studies

During all three AE studies, selected patient records were reviewed for the occurrence of AEs, including ADEs. In Figure 1, a schematic overview of the review process in the national studies and this study is presented. In summary, the review process consisted of two phases. In phase one, the records were screened for potential AEs by trained independent nurses. When predefined triggers were found, indicating an AE might have occurred, the record was labelled for an in-depth review by a trained independent physician. Independent means that the physicians and nurses never had an employment contract in the participating hospitals. The physicians were highly experienced and specialized in surgery, internal medicine or neurology, and during the record review studies they had access to all information in the electronic patient record. Besides, 10% of all patient records were reviewed by two physicians to determine inter-rater reliability. Validity of this scoring system has not been tested, but it has been used widely in AE studies for over 20 years and the ratings of the system did not change in that time.[21-23,26-29] Prior to the study, both nurses and physicians had training sessions in which cases were discussed to enhance the quality and standardization of the review process.

An AE was defined by three criteria: 1) an unintended physical or mental injury; 2) the injury resulted in prolongation of hospital stay, temporary or permanent disability or death; 3) the injury was caused by healthcare management rather than the patient's underlying disease.[23,27,28] An AE was scored as caused by the healthcare (causality) if the likelihood score was equal to or greater than 4 based on a 6-point Likert scale with (virtually) no evidence (1), slight to modest evidence (2), not likely, but borderline (3), more likely but borderline (4), moderate to strong evidence (5), or (virtually) certain evidence (6) of management causation. The scoring system was used in all three record review studies and the physicians made the judgments about causality and preventability based on all the available information of the patient's condition and taking into account the guidelines.

If an AE was identified, the independent physicians (hereafter: experts) assessed each AE on: cause (diagnostic, surgery, non-invasive procedure, medication, other clinical activities, admission, and other), preventability, possible contribution to death, and attributable factors. The attributable factors were based on the taxonomy of the Eindhoven Classification Model and consisted of the main categories: technical, care, organizational, patient related, violation and other.[30] An AE was considered to be preventable when the care given fell below the current level of expected performance of practitioners or systems. Before the physicians answered the question about preventability, they were required to respond to 13 questions to add more structure to the review process (see Supplemental Table 1). For example, if there was a complex medical history, if the patient had co-morbidity and whether another physician would repeat this treatment. Preventability was also assessed on a 6-point Likert scale with almost no evidence (1), slight to modest evidence (2), modest evidence, but borderline (3), modest to strong evidence (4), strong evidence (5) or almost certain evidence (6) of preventability. A score of 4-6 indicated that the reviewer assessed the AE as having a greater than 50% chance of being potentially preventable.

Furthermore, for each patient the following characteristics were registered: gender, age, length of hospital stay, urgency of admission, whether patients were terminally ill prior to the admission, the number of involved medical specialists, department of admission, type of procedure and co-morbidity. The latter was divided in no, minor, moderate and severe co-morbidity, and was assessed by the experts after careful review of the information in the patient record. Also, one organizational characteristic (type of hospital: university, tertiary teaching, or general) and one AE characteristic (weekend or holiday at the time of the AE) were registered.

When an AE was medication related (ADE), the following additional characteristics were registered by the experts: name and type of medication involved, medication phase, a description of the ADE, and whether the ADE possibly contributed to the patients' death. The medication phases were classified into ordering, transcribing, dispensing, administering and monitoring.[31,32] The possible contribution to the patients' death was only registered for ORADEs with 'medication' as a main cause of the event and not for ADEs with 'medication' as a sub cause.

All data were entered into a national AE database, specifically designed for the AE studies.

Review procedure ORADEs

For our study, we used the national AE database to identify ORADEs (Figure 1). One researcher (BS) conducted the screening of the database and retrieved several pre-selected variables: (1) AEs with the main classification cause 'medication' as well as AEs with 'medication' as a sub cause and (2) AEs with 'analgesics' as involved medication. Furthermore, two free-text fields were selected: the summary of the AEs and the preventability assessment. A second researcher (MM) independently double checked the selection procedure.

All identified ORADEs, were then classified by BS on type of opioid involved using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification.[33] For the preventable ORADEs, the type of medication error was classified according to a data driven analysis of the free-text summaries of the ADEs. The classification of ORADEs was double checked by two senior researchers (JK & IJ) and any discrepancies were resolved by consensus.

Outcomes

To provide insight into the nature of the ORADEs, each ORADE case was summarized by gender, age of the patient (categorized in steps of 10 years for privacy reasons), type of opioid involved, attributable factors and preventability. When the ORADE was preventable, then the type of medication error and medication phase was also described. Furthermore, in order to identify risk factors, we compared the outcome variables between preventable and non-preventable ORADEs.

Data analysis

Only descriptive statistics were used in this study. Descriptives are presented as median (age and length of hospital stay) or frequency (gender, comorbidity, type of opioid and attributable factor, etc.). Patient and hospital characteristics are presented on a patient level and ORADE characteristics are presented on AE level. Inter-rater reliability among nurses and physicians was addressed in terms of positive and negative agreement frequencies.[34] All analyses were conducted using STATA version 14.1 (StataCorp, TX) and double checked by a second researcher (MM) and a statistician (PS).

Patient and Public Involvement statement Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

In total, 10,917 records were screened during the three AE studies. The patient records of discharged and deceased patients were equally distributed among male and female patients. Most patients were hospitalized for a non-elective procedure (Table 1). In 1150 patient records, at least one AE was detected, with a total of 1240 AEs. When detecting the predefined triggers, positive agreement between nurses varied between 76.0-91.5%. When detecting the adverse events, positive agreement between physicians varied between 53.4-63.3%. For assessing the preventability positive agreement between physicians varied between 71.4-73.3%. Overall, agreement frequencies were moderate. More detailed information about the inter-rater reliability is presented in Supplemental Table 2.

Opioid related ADEs

Of 1240 AEs, 357 (29%) were medication related (ADEs). In 28 (8%) ADEs, opioids were involved. These ADEs are summarized in detail in Box 1, and included 24 ADEs with 'medication' as a main cause and four ADEs with 'medication' as a sub cause. The ORADEs occurred in 27 patients; one patient experienced two ORADEs. Most patients with ORADEs involved females (59%). Median age of the patients was 76 years (Inter Quartile Range (IQR): 66-83) and median length of hospital stay was 7 days (IQR: 4-16). Most patients had moderate to significant co-morbidity (70%) and had three medical specialists during the admission (78%) (Table 2).

Nature of opioid related ADEs: preventability

According to the experts, 11 (39%) out of the 28 ORADEs were considered as potentially preventable (Table 3). Non-preventable (31%) ORADEs occurred slightly more during weekends and holidays than preventable ADEs (18%). Moreover, most preventable and non-preventable ORADEs occurred during dayshifts (8am-5pm).

Nature of opioid related ADEs: medication errors & phase

Of the 11 potentially preventable ORADEs, 10 (91%) were caused by dosing errors of which six during the prescribing phase (cases #1, #3, #7, #8, #9, #10) and four during the administration phase (cases #2, #4, #5, #6) (Box 1). Of the ten dosing errors, six occurred in elderly patients (≥70 years) (cases #1, #3, #4, #5, #8, #9), and two around the patients' discharge (cases #2, #7). The remaining one preventable ORADE (#11) was related to incorrect decision making. Finally, the experts assessed the consequences of the ORADEs (multiple options possible). In eight ORADEs, an intervention or extra treatment was needed, in two ORADEs the patients had a prolonged hospital stay and four preventable ORADEs possibly contributed to the death of the patient (cases #5, #6, #8, #9).

Nature of opioid related ADEs: attributable factors

The attributable factors involved in ORADEs were care (knowledge, skills, monitoring, verification, and coordination of care) and patient related (co-morbidity, age, a demanding patient or a patient with an intellectual disability) (Table 3). Of preventable ORADEs, 8 were care related and 6 were patient related. For non-preventable ORADEs, 3 were care related and 10 were patient related. However, in 3 of the cases of non-preventable ORADEs, the attributable factors could not be assessed by the experts due to insufficient information in the patient records.

Nature of opioid related ADEs: medication involved

Eight out of the eleven preventable ADEs occurred with opioids with ATC code N02AA which are morphine and oxycodone (Table 3). Non-preventable ORADEs occurred with opioids mainly with ATC code N02AA (morphine and oxycodone, 53%).

DISCUSSION

In three national patient record studies with 4 years intervals, we found 28 ADEs caused by opioids. These ADEs correspond with 8% of all identified ADEs and 0.3% of all studied patient records. Eleven of the 28 opioid related ADEs (ORADEs) (39%) were assessed as potentially preventable, involving mostly morphine and oxycodone. Dosing errors, during the prescription and administration phase were the most common cause of preventable ORADEs, and occurred most often in elderly patients. Four preventable ORADEs probably contributed to the patients' death. Finally, attributable factors for the ADEs were mostly care and patient related.

In this study, the percentage of ORADEs of all patient records (0.3%) was low, also in comparison with previously conducted ORADE studies that focused on large populations (11-14%).[10,11,16] However, two of these studies were based on large databases and all involved surgical patients who often receive opioids post-operative. We focused on a broad hospitalized patient population, both surgical and non-surgical. Furthermore, the difference in ORADE occurrence might be explained by differences in the used ADE definition. For example, instead of using all ORADEs, i.e. including side-effects of opioids, in our study only ADEs that resulted in severe patient harm were included. This means that ADEs resulted in prolongation of hospital stay, temporary or permanent disability or death. Furthermore, only ADEs with a causality likelihood score of equal or greater than 4 were included, which means that the experts indicated an ADE as having a greater than 50% chance of being caused by healthcare. Should we have selected the cases with causality likelihood scores of 1-3 as well, then we could determine at least 2500 additional cases on whether medication and opioids were related. However, we did not determine these 2500 cases, since we wanted to stay true to the definition of an AE (at least 4 on the 6-point Likert scale) and we did not consider it ethical to change the method of the study afterwards.

In line with previous studies,[7,14,15,17] we found that dosing errors during prescribing and administering were the main cause of preventable ORADEs. Furthermore, 60% of the dosing errors in our study occurred in elderly patients (≥70 years). In general, prescribing medication for elderly patients is challenging since polypharmacy, multi-morbidity and altered pharmacokinetics and pharmacodynamics of drugs are often present. Besides, this population will rapidly increase in the upcoming years. Specifically related to opioids, physicians also need to be aware of the higher sensitivity of elderly patients to the effects of opioids,[35] and balancing between minimizing the risk of addiction and side-effects while effectively relieving pain.[36,37] Taking into account all these factors while prescribing, demands a lot from physicians during their busy daily hospital practice. A clinical decision support system (CDSS), can help physicians in this complex task by showing warnings and advices during prescribing, for example showing the most appropriate choice of medication for a given condition and/or by providing dosing recommendations. CDSS has shown to effectively reduce prescribing errors among hospitalized elderly patients[38,39] and errors with medications of which the therapeutic effects are fast, such as opiods.[40] Furthermore, a CDSS can also be effective in predicting which patients are at risk for ORADEs. Using retrospective data from gastro-intestinal surgical patients, Minkowitz et al. (2014) developed a risk-scoring model to identify patients with a high risk for experiencing an ORADE based on their clinical and demographic profiles.[41] If developed

specifically for elderly inpatients, such a prediction model could help physicians in determining the most appropriate and safe pain management strategy for these vulnerable patients. Finally, a CDSS could also be used to identify patients who might be suitable for pre-emptive genotyping, which involves metabolic testing prior to prescribing.[42] Patients with high levels of pain despite using high doses of pain medication or patients that experience severe side-effects while using common dosing schedules may especially benefit from such an intervention.[43]

Administering opioids is a task usually conducted by nurses. The dosing errors in our study were mostly related to injectable opioids. Error prone activities, such as calculating the concentration and administration rate,[14,17] require that nurses have sufficient arithmetic knowledge and follow the protocol for safe preparation and administration of injectable medication. However, in daily practice, some nurses have math anxiety and on average arithmetic knowledge of nursing students seems moderate.[44,45] Besides, nurse compliance with protocols for safe administration of injectable medication is considered low (around 20%)[46,47] and needs further attention. An intervention which might help to reduce dosing errors during opioid administration is the use of smart infusion pumps. These pumps have integrated medication libraries which allow nurses to set the pump automatically to the right administration rate during administration. By doing so, the administration rate of smart pumps can be seen as a double check of the nurses' own calculation. Smart pumps seem also effective in reducing programming errors.[48] Furthermore, educational programs for nurses about brand and generic names and pharmacology of opioids or side-effects might increase their knowledge and awareness of risks related to dosing during the administration of opioids.[49-51]

Overall, we think the ORADE frequency of 8% of all ADEs and 0.3% of all studied patient records found in our study is low and acceptable. However, although the frequency is low, the risk of serious consequences is high. Thus, new contributions to prevent ORADEs in future hospitalized patients need to be identified. Using the Safety-2 perspective may offer new opportunities to do so.[52] In order to understand what happened when an adverse (drug) event occurred, it is also necessary to understand how work is done when the process goes well.[53] Since healthcare processes have become more complex nowadays, it may be helpful to visualize the current variable practice of prescribing and administering opioids from a multi-stakeholder perspective.[54]

Strengths and limitations

Opioids are in the top ten of drug types that causes fatal medication errors.[8] Hence, focusing on the detailed description of the nature of ORADEs was important and necessary. Another strength of this study is that it was based on a comprehensive ADE detection method and conducted in a broad sample of all hospital admissions. Most previous studies, which described the nature of ORADEs, are based on medication related incident reports. Furthermore, data were gathered over an extended period of time within a randomly selected sample of one third of all Dutch hospitals.

This study also has some limitations. Firstly, in all three AE studies, the population consisted of relatively many older and deceased patients. Therefore, it is not possible to generalize the results to all Dutch hospital population. To make the study sample more representative for the Dutch hospital population, weighting the results (i.e. correcting for type of hospital, study period and discharge status) would be a solution which is used in previous studies of our research group. However, since the total amount of ORADEs was low, we chose not to weight our results as this had little effect and makes interpretation difficult. Secondly, overall agreement frequencies between physicians were moderate. This could have led to different assessments or different scores if other experts were involved. This should be taken into account when interpreting our results. However, a

previous review of studies focusing on assessing AEs showed also moderate to substantial inter-rater reliability.[55] For this reason, patient records in all Dutch AE studies have been assessed by the same experts as much as possible and over the years these experts have not become stricter or lenient in their judgment of AEs and their preventability.[56] Thirdly, due to this low number of ORADEs, it was not possible to compare the events over the three study periods. Therefore, we cannot conclude whether the low number is a positive finding, and if the occurrence of ORADEs increased or decreased over time. Fourthly, our post-hoc analysis was based on the information previously recorded by the experts in an AE database, and on the assessment conducted by these physicians. Therefore, some information could be missing and interpreting the assessment of preventability was difficult for us in one case, resulting in a non-preventable ORADE. Furthermore, this was also the reason that the harm could not be further categorized according to the NCCMERP Index for Categorizing Medication Errors.[57] Besides, the retrospective interpretation can also be biased by temporal views. The current opinion is that prescribing opioids should be minimized due to the harm of opioids, which is supported by updated guidelines.[58] This view changed throughout the years and may not have been recognized 15 years ago, when the focus was mainly on alleviating suffering of pain. This change in opinion may have increased alertness when prescribing or administering opioids, which could have led to less ORADEs. However, our study showed that ORADEs still occur and publishing about them could serve as a method of increasing awareness.

CONCLUSION

Only 8% of ADEs identified in our sample were related to opioids, 0.3% of all studied patient records. Although the frequency is low, the risk of serious consequences is high. We recommend to use our findings to increase awareness among physicians and nurses. Future interventions should focus on safe dosing of opioids when prescribing and administering, especially in elderly patients.

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Contributors BS, MM, JK, ML, MdB, and CW designed the study and developed the study protocol. BS and MM organized the selection and classification of ORADEs. JK and IJ double checked this classification. BS and MM performed statistical analyses and interpreted the analytical results. BS, JK, and IJ wrote the manuscript. MdB, and CW supervised the study. All authors made critical revisions and approved the final version of the manuscript.

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Table 1. Patient and hospital characteristics of all reviewed patient records, including adverse events per study period and discharge status.

	Study period and discharge status				
	2008		2011/2012		2015/2016
Hospital characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Number of patient records, n	2016	2007	2023	2025	2846
General hospital, n records (%)	1013 (50)	1015 (51)	794 (39)	813 (40)	1197 (42)
Tertiary teaching hospital, n records (%)	608 (30)	593 (30)	822 (41)	820 (40)	1052 (37)
Academic hospital, n records (%)	395 (20)	399 (20)	407 (20)	392 (19)	597 (21)
	2008		**2011/2012**		**2015/2016**
Patient characteristics †	**Discharged**	**Deceased**	**Discharged**	**Deceased**	**Deceased**
Male sex, n (%)	999 (50)	1067 (53)	1027 (51)	1062 (52)	1524 (54)
Age (years), median (IQR)	62 (47-75)	77 (67-84)	63 (48-75)	77 (68-84)	77 (68-85)
Length of stay (days), median (IQR)	4 (2-8)	7 (3-14)	3 (2-7)	6 (2-13)	4 (1-11)
Non-elective admission, n (%)	1038 (51)	1708 (85)	1063 (53)	1775 (88)	2496 (88)
Admission department, n (%)					
Surgery	481 (24)	276 (14)	472 (23)	239 (12)	340 (12)
Cardiology	290 (14)	291 (15)	272 (13)	247 (12)	360 (13)
Internal medicine	364 (18)	599 (30)	365 (18)	597 (29)	876 (31)
Orthopaedics	226 (11)	33 (2)	225 (11)	26 (1)	29 (1)
Neurology	150 (7)	219 (11)	133 (7)	193 (10)	269 (9)
Lung diseases	117 (6)	259 (13)	126 (6)	300 (15)	347 (12)
Urology	109 (5)	18 (1)	111 (5)	28 (1)	23 (1)
Other	279 (14)	312 (16)	319 (16)	395 (20)	602 (21)
Underwent invasive procedure, n (%)	925 (46)	423 (21)	918 (45)	403 (20)	461 (16)
Adverse event occurrence §¶					
AE, n (%)	161 (8)	351 (16)	157 (8)	259 (12)	312 (10)
ADE, n (% within population)	37 (2)	93 (4)	40 (2)	76 (4)	111 (4)
ADE, n (% within adverse event)	37 (23)	93 (27)	40 (25)	76 (29)	111 (36)
ORADE, n (% within population)	1 (0)	7 (0)	2 (0)	8 (0)	10 (0)
ORADE, n (% within ADEs)	1 (3)	7 (8)	2 (5)	8 (11)	10 (9)

† Presented on patient record level.
§ Presented on AE level.
¶ Total number of AEs: 1240, total number of ADEs: 357, total number of opioid related ADEs: 28
AE = Adverse event, ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Table 2. Characteristics of patients (n=27) with ORADEs (n=28)†	
Patient characteristics	
Patients with an ADE, n	27
Male sex, n (%)	11 (41)
Age, median years (IQR)	76 (66-83)
Length of stay, median days (IQR)	7 (4-16)
Non-elective admission, n (%)	19 (70)
Terminally ill prior to admission, n (%)	6 (22)
Total number of medical specialists	
0, n (%)	0 (0)
1, n (%)	4 (15)
2, n (%)	2 (7)
3, n (%)	21 (78)
Primary specialisation during admission	
Surgical, n (%)	7 (26)
Non-surgical, n (%)	20 (74)
Underwent invasive procedure, n (%)	9 (33)
Co-morbidity§	
No co-morbidity, n (%)	0 (0)
Minor co-morbidity, n (%)	3 (11)
Moderate co-morbidity, n (%)	5 (19)
Significant co-morbidity, n (%)	19 (70)
† Presented on patient level. *§ The level of co-morbidity was assessed by the experts after careful review of the information in the patient record.* *ADE = Adverse drug event, ORADEs = Opioid related adverse drug events*	

Table 3. Clinical context of ORADEs (n=28)†		
Clinical context	**Non-preventable§ ADEs (n=17)**	**Preventable§ ADEs (n=11)**
Type of hospital		
University, n ADEs (%)	1 (6)	1 (9)
Tertiary teaching, n ADEs (%)	6 (35)	4 (36)
General, n ADEs (%)	10 (59)	6 (55)
Weekend or National holiday (yes), n (%)	5 (31)	2 (18)
Moment		
8am-5pm, n (%)	6 (35)	5 (45)
5pm-11pm, n (%)	3 (18)	0 (0)
11pm-8am, n (%)	2 (12)	3 (27)
Cannot be assessed, n (%)	6 (35)	3 (27)
Type of Opioid (ATC code)		
Opioid anesthetics (N01AH03), n (%)	2 (12)	1 (9)
Natural opium alkaloids (N02AA), n (%)	9 (53)	8 (73)
Natural opium alkaloids and Phenylpiperidine derivatives (N02AA/N02AB, combination), n (%)	1 (6)	1 (9)
Phenylpiperidine derivatives (N02AB), n (%)	2 (12)	0 (0)
Other opioids (N02AX), n (%)	1 (6)	0 (0)
Drugs used in opioid dependence (N07BC), n (%)	2 (12)	1 (9)
Attributable factors¶		
Technical, n (%)	0 (0)	0 (0)
Care related, n (%)	3 (19)	8 (80)
Organizational, n (%)	2 (13)	4 (40)
Patient related, n (%)	10 (63)	6 (60)
Violation, n (%)	0 (0)	1 (10)
Cannot be assessed, n (%)	3 (19)	1 (10)
Other, n (%)	1 (6)	0 (0)

† Presented on adverse event level.
§ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability. Not preventable ADEs were scored at 1-3, preventable ADEs were scored at 4-6.
¶ These variables were missing for 2 patients; one in the preventable group and one in the non-preventable group. Moreover, it was possible to select more than one option for this question.
ADE = Adverse drug event, ORADE = Opioid related adverse drug event, IQR = Interquartile range

Box 1. Descriptions of the 28 opioid related adverse drug events divided into preventable and non-preventable.		
Case	***Description*†**	***Preventability score (1-6)*‡ and type of error§**
Preventable opioid related ADEs		
Cause: Dosing errors		
1	Male, 90-99 years, admitted with pain after a fall. Oxycodone for the pain was unintentionally prescribed twice instead of once and also administered twice (dose unknown). This resulted in drowsiness.	6 (prescribing error)
2	Male, 60-69 years, suffering from colon cancer and liver metastases, was admitted for optimizing his analgesics medication. On returning from his weekend leave, he was diagnosed with oxycodone intoxication. During hospital stay, he received a too high dose of the opioid antagonist naloxone (1 mg instead of the ordered 0,4 mg) which caused confusion and agitation.	6 (administration error)
3	Female, 70-79 years, admitted with a pelvic fracture after a fall. A too high dose (dose unknown) of oxycodone was prescribed and administered resulting in hypotension and drowsiness. Consequently, she needed to be transferred to the intensive care unit.	5 (prescribing error)
4	Female, 80-89 years, admitted with malaise after a fall. During her admission she received a too high dose of morphine. In her patient record, the morphine was ordered as 'as needed' (PRN). In the medication list, the morphine was ordered '6 times a day' (dose unknown). This resulted in drowsiness.	5 (prescribing error)
5	Female, 70-79 years, admitted for a plastic surgery. A high dose of intravenous administered anesthetic/pain medication (dose and medication type unknown) caused hypoventilation and a myocardial infarct. The myocardial infarct was discovered too late. She was resuscitated and ventilated. Her death was possibly caused by a hospital acquired pneumonia.	5 (administration error)
6	Female, 50-59 years, admitted due to an aspiration pneumonia, was administered morphine. The pump mode was set at 13 ml/hour instead of 8 ml/hour as ordered. This possibly resulted in an epileptic insult requiring ventilation.	5 (administration error)
7	Male, 60-69 years, re-admitted to the hospital due to a collapse at home. He was previously hospitalized for treatment of rib fractures and COPD Gold IV. At discharge, the doses of fentanyl and oxycodone had been significantly increased to 20 mg 4 to 6 times a day. Monitoring the effects of increasing these opioid doses was not conducted.	4 (prescribing error)
8	Female, 80-89 years, admitted with osteoporosis, received at home 5 mg morphine twice daily for her back pain. The dosage was increased to subcutaneous of 5 mg 4 times a day during hospital stay. Three days later, a paralytic ileus was discovered. A lower morphine dose was more appropriate for this elderly female.	4 (prescribing error)
9	Female, 80-89 years, admitted with abdominal pain due to a kidney bleeding. She received morphine injections daily, varying from 2-6 subcutaneous injections of 2,5 mg per day along with transdermal fentanyl 12 mcg hourly. Severe hypercapnia eventually caused her death.	4 (prescribing error)
10	Male, 0-9 years, with Down syndrome, was acutely ill due to a laryngitis. He was difficult to ventilate and received antibiotics and sedatives including opioids. He was transferred to another hospital following detubation. Here, his methadone intake was reduced resulting in a delirium (dose unknown). Initially he improved, but one day unexpectedly he was found dead. It is unclear why this	4 (unknown)

	patient received methadone, but reducing the methadone intake may have been the problem.	
Cause: Incorrect decision making		
11	Female, 60-69 years, admitted for a laminectomy. Postoperatively she developed an ileus caused by severe constipation aggravated by administered morphine. Macrogol oral suspension (dose unknown) instead of an enema was given as treatment, which was insufficient to resolve the ileus and colon perforation occurred. Untreatable abdominal septic complications followed.	4 (unknown)
Non-preventable opioid related ADEs		
12	Female, 80-89 years, admitted due to a total knee replacement. Postoperatively, drowsiness, hypotension and oliguria occurred, possibly caused by the epidural medication sufentanil (dose unknown). This may have led to a small asymptomatic myocardial infarct.	3 (administration error)
13	Male, 80-89 years, admitted with a perforated stomach ulcer and known stomach cancer. His extreme, not previously known, sensitivity to morphine postoperatively (dose unknown) resulted in recurrent apnea.	3 (other error)
14	Female, 60-69 years, suffering from lung cancer, was admitted with severe back and limb pain related to bone metastases. She was treated with transdermal fentanyl 300 mcg per hour. This resulted in drowsiness and hypoventilation.	2 (prescribing error)
15	Female, 80-89 years, known with breast cancer and multiple lung metastases. She received tramadol (dose unknown) for the pain which have been stopped due to drowsiness.	2 (unknown)
16	Male, 70-79 years, admitted with severe heart failure. He received morphine 2.5 mg for the pain. As a result of increased, not previously known, sensitivity to morphine, his saturation dropped.	2 (other error)
17	Male, 90-99 years, admitted because of a stroke and a lot of pain. The nurse administered 10% of the prescribed dose (dose unknown) of morphine on two occasions which caused unnecessary suffering.	2 (administration error)
18	Male, 60-69 years, admitted for surgery due to an ileus. Postoperative complications included an exacerbation COPD and a hospital acquired pneumonia after receiving morphine (dose unknown).	2 (unknown)
19	Female, 60-69 years, admitted with a reoccurrence of drowsiness, hypoventilation and difficult to wake up which was the result of a dose of 5 mg of methadone being administered in the hospital.	2 (prescribing and administration error)
20	Female, 60-69 years, had a blood pressure drop following the administration of morphine (dose unknown) in the recovery room.	1 (other error)
21	Female, 70-79 years, admitted with pain related to severe Kahler disease. For the pain, she received opioids (unknown which type and dose). The opioids caused drowsiness and because of the drowsiness, she choked once. This caused a pneumonia. The patient deceased during hospitalization.	1 (other error)
22	Male, 70-79 years, received transdermal fentanyl and oxycodone 5 mg daily up to 6 times due to metastases in the hip. This caused apraxia and confusion.	1 (unknown)
23	Female, 80-89 year, admitted for occlusion of an artery in her leg. She received a morphine infusion (0.5-1.0 mg/hour) causing hypoventilation with a good response to naloxone.	1 (administration error)
24	Male, 80-89 years, admitted due to obstructive laryngeal cancer, was prescribed anticoagulants. This resulted in a hematoma along with severe abdominal pain for which he received morphine (dose unknown) after which he deceased.	1 (other error)
25	Male, 60-69 years, admitted with an acute respiratory insufficiency due to pneumonia. He received methadone 20 mg 2 times a day, causing hypoventilation on two occasions. This needed to be treated with naloxone.	1 (prescribing error)

26	Female, 80-89 years, suffered from pain due to rib fractures caused by resuscitation. She received sufentanil (dose unknown), which led to bronchospasm.	1 (unknown)
27	Female, 70-79 years, admitted with pain related to breast cancer. During the admission, it became apparent that she had metastases along with femur and vertebral fractures. A high dose of morphine (dose unknown) was necessary to relieve her pain which consequently resulted in a delirium.	1 (prescribing error)
28	Female, 80-89 years, admitted due to a hip fracture and pain. For her restlessness and pain she was administered 1 mg morphine which probably caused a reduced level of consciousness.	1 (other error)

† Patients were categorized in age groups of ten years to avoid traceability.
‡ Preventability was scored on a 6-point Likert scale: 1 = (almost) no evidence of preventability; 2 = small indications for preventability; 3 = preventability not very likely, less than 50% but 'close call'; 4 = Preventability more than likely, more than 50% but 'close call'; 5 = strong indications for preventability; 6 = (almost) certain indications of preventability.
§ For the judgment on preventability and type of error, the experts had access to all information in the electronic patient record and therefore to the whole context in which ADEs occurred. The types of error were: prescribing error, administration error, other error (e.g. side-effects) or unknown.

Figure legend

Figure 1: Overview of the three Dutch adverse event studies and our study.

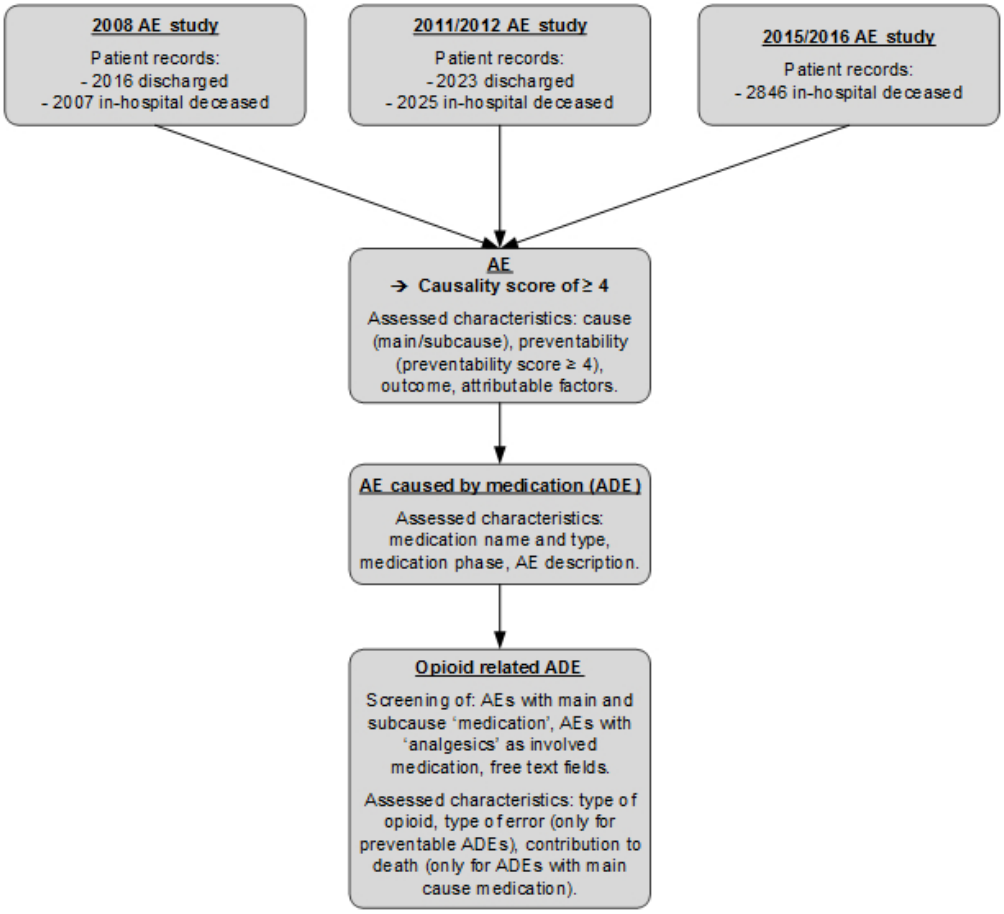

Figure 1: Overview of the three Dutch adverse event studies and our study.

Supplemental Table 1: Preventability, preparatory and judgment questions for physicians.	
Question	**Answer options**
1. How complex was this case?	Very complex/Moderately complex/Somewhat complex/Not complex/Unable to determine
2. Was the management of the primary illness (not the adverse event) appropriate?	Definitely appropriate/Possibly appropriate/Probably appropriate/Definitely not appropriate
3. What was the degree of deviation of management of the primary illness (not the adverse event) from the accepted norm?	Severe/Moderate/Little/None
4. What was the comorbidity of the patient?	Significant comorbidity/Moderate comorbidity/Mild comorbidity/No comorbidity
5. What was the degree of emergency in management of the primary illness (not the adverse event) prior to the occurrence of adverse event?	Very urgent/Moderately urgent/Not urgent
6. What potential benefit was associated with the management of the illness which led to the Adverse Event?	Lifesaving/Curing/Life prolonging/Symptom relief/Palliation/No potential benefit
7. What was the chance of benefit associated with the management of the illness which led to the adverse event?	High/Moderate/Low/Not applicable
8. What was the risk of an adverse event related to the management?	High/Moderate/Low/Not applicable
9. Is the injury/complication a recognised complication?	No/Yes/Not applicable
10. What percentage of patients like this would be expected to have this complication?	Unable to determine (UTD)/Not applicable/<1/1%–9%/10%–24%/>=25%
11. On reflection, would a reasonable doctor or health professional repeat this healthcare management strategy again?	Definitely/Probably/Probably not/Definitely not
12. Was there a comment in the medical records indicating a need for follow-up as a result of this adverse event? (select all that apply)	No/Counselling/Psychiatric/Rehabilitation/Routine clinical/Other/UTD
13. Did the patient have any follow-up as a result of this adverse event?	No/Counselling/Psychiatric/Rehabilitation/Routine clinical/Other/UTD
Final judgment Please indicate to what extent there are indications that the event was preventable:	1. (Virtually) no evidence for preventability 2. Slight to modest evidence of preventability 3. Preventability not quite likely (less than 50/50, but 'close call') 4. Preventability more than likely (more than 50/50, but 'close call') 5. Strong evidence of preventability 6. (Virtually) certain evidence of preventability

Supplemental Table 2: Positive and negative agreement (%) between nurses and physicians during the adverse events studies.†‡						
	Nurses		**Physicians – adverse event**		**Physicians - preventability**	
Study	Positive agreement	Negative agreement	Positive agreement	Negative agreement	Positive agreement	Negative agreement
2008	76.0	89.0	63.3	86.9	n/a	n/a
2011/2012	85.8	63.3	56.9	82.9	73.3	83.3
2015/2016	91.5	68.9	54.3	80.9	71.4	81.0

† All frequencies are separately calculated by a 2x2 table:

		Nurse / Physician 1	
		Positive agreement	Negative agreement
Nurse / Physician 2	Positive agreement	A	B
	Negative agreement	C	D

Positive agreement = (2xA) / ((2xA)+B+C) and negative agreement = (2xD) / ((2xD)+B+C).

‡ The interpretation of the Kappa is not straightforward, and it is influenced by the number of categories of each variable and the prevalence of the given scores. It is therefore possible that despite a high agreement, the Kappa is low. This occurs in studies with few adverse events. For this reason we chose to present positive and negative agreement frequencies. It helps to answer questions such as: 'if one expert finds a preventable adverse event, what is the probability that another expert will also find a preventable adverse event?'

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8

		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

n.a. = not applicable

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.