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Review Paper

Understanding how medications contribute to clinical deterioration and are used in rapid response systems: A comprehensive scoping review

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ABSTRACT

Background: In hospitals, rapid response systems (RRSs) identify patients who deteriorate and provide critical care at their bedsides to stabilise and escalate care. Medications, including oral and parenteral pharmaceutical preparations, are the most common intervention for hospitalised patients and the most common cause of harm. This connection between clinical deterioration and medication safety is poorly understood.

Objectives: To inform improvements in prevention and management of clinical deterioration, this review aimed to examine how medications contributed to clinical deterioration and how medications were used in RRSs.

Review methods: A scoping review was undertaken of medication data reported in studies of clinical deterioration or RRSs in diverse hospital settings between 2005 and 2017. Bibliographic database searches used permutations of "rapid response system," "medical emergency team," and keyword searching with medication-related terms. Independent selection, quality assessment, and data extraction informed mapping against four medication themes: causes of deterioration, predictors of deterioration, RRS use, and management.

Results: Thirty articles were reviewed. Quality was low: limited by small samples, observational, single-centre designs and few primary medication-related outcomes. Adverse drug reactions and potentially preventable medication errors, involving sedatives, analgesics, and cardiovascular agents, contributed to clinical deterioration. While sparsely reported, outcomes included death and escalation of care. In children, administration of antibiotics or nebulised medications appeared to predict subsequent deterioration. Cardiovascular medications, sedatives, and analgesics commonly were used to manage deterioration but further detail was lacking. Despite reported potential for patient harm, evaluation of medication management systems was limited.

Conclusions: Medications contributed to potentially preventable clinical deterioration, with considerable harm, and were common interventions for its management. When assessing deteriorating patients or caring for patients who require escalation to critical care, clinicians should consider medication errors

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and adverse reactions. Studies with more specific medication-related, patient-centred end points could reduce medication-related deterioration and refine RRS medication use and management.

1. Introduction

Acute clinical deterioration of patients during hospital admission is associated with increased morbidity and mortality.[1] The rapid response system (RRS) is a hospital-wide approach to improve recognition and response to such deterioration, with the aim of preventing adverse events such as cardiac arrest.[2] Embodying the idea of critical care without walls,[3] RRSs are described as having four components: an afferent limb which involves nurses monitoring patients and detecting deterioration; an efferent limb which brings critical care expertise to deteriorating patients outside the intensive care unit (ICU); and quality improvement and governance limbs.[2] The responding arm is a team of critical care clinicians, usually nurses and doctors, variably termed the rapid response team (RRT) and medical emergency team (MET).[2,4] The landmark MERIT study was equivocal on the benefits of RRS.[5] Subsequent analyses have suggested reductions in in-hospital cardiac arrest[6–8] and all cause hospital mortality.[8] Internationally, healthcare safety agency mandates have led to exponential uptake of RRSs.[9,10]

The mortality of deteriorating patients remains high prompting further investigation and refinement of RRSs.[11] Current research seeks to prevent deterioration through appreciation of its epidemiology and causes.[1] These efforts are complicated by the heterogeneity of RRSs and RRTs. The methods and criteria used to define, detect, and respond to deterioration continue to be refined. Similarly, there is a diversity in the membership of the teams, their skills and knowledge requirements, and the interventions they provide to rescue or stabilise patients.[8,12]

Medications, including oral and parenteral pharmaceuticals, are ubiquitous in acute care but are not without risks and harm.[13] Adverse drug events include harms from adverse reactions to medications and errors at any step of the medication management process from prescribing to dispensing to administration to monitoring.[14–16] The risks of adverse drug events are higher in critically ill patients in the ICU.[17,18] Similar to clinical deterioration, medication safety is a priority in health care.[10,19] However, there is limited exploration of how medications contribute to clinical deterioration or critical illness outside the ICU and the RRS more broadly. A better understanding of these relationships would benefit all clinicians, especially critical care clinicians who are members of RRTs and involved in the escalated care for deteriorating patients.

Conceptually, there are four potential links between medications and clinical deterioration. First, clinical deterioration that activates the RRS may represent a manifestation of harm associated with an adverse drug event. In addition, the administration of certain medications may contribute to prediction of impending deterioration. Furthermore, medications are likely to be common RRT interventions for the management of deteriorating patients. Finally, safe and effective rescue of RRT patients is likely to require reliable and efficient access to the most appropriate medications. Using these four themes, this review aimed to scope the current understanding of how medications contribute to clinical deterioration and are used in RRSs. With the objective of guiding clinical practice and research in medication safety and management for clinical deterioration and RRSs, specifically it aimed to explore how medications may cause clinical deterioration, whether use of medications in certain scenarios could predict impending clinical deterioration, which medications were used by the RRT, and the role of medication management systems in RRSs.

2. Methods

Scoping reviews have been developed to allow detailed exploration of the breadth, depth, and range of research activity on a topic.[20,21] This contrasts with systematic reviews and meta-analyses which address focused questions and limit the type or quality of studies reviewed.[20,21] Through the prescribed processes of defining a research question, identifying and selecting relevant studies as well as charting the data, collating, summarising, and reporting results, often with input from stakeholders, scoping reviews can be used to disseminate findings and identify gaps in the existing literature.[20,21] The technique is particularly useful in novel fields of enquiry and where there is diversity in research methodologies.[21] Given the emerging nature and potential breadth of the topic of medications and RRSs, a scoping review allowed exploration of the full extent of available evidence from a range of study types. The methodology also allowed for the available evidence to be summarised for clinicians to guide rapidly developing RRSs as well as identification and prioritisation of partially or unanswered research questions in the field.

2.1. Identification of studies

A structured, comprehensive literature search, as recently described for scoping reviews,[21] was undertaken. Bibliographic databases were searched: Medline (Ovid), EMBASE (Ovid), Cochrane CENTRAL, and CINAHL plus. Owing to the maturity of RRS practice and research in Australia, manual searches were conducted of Anaesthesia and Intensive Care, Critical Care and Resuscitation, Australian Critical Care, and Journal of Pharmacy Practice and Research along with the reference lists of the included papers (Fig. 1). Searches were limited to January 2005 to December 2017 inclusive to ensure currency as well as capture the period of rapid growth in RRSs surrounding publication of the MERIT study.[5,22] Database-specific subject headings for “rapid response system” and “medical emergency team” and related keywords were used as search terms (Supplementary File 1). Search hedges were used to identify clinical studies.[23] Subsequent keyword searching of titles and abstracts for intervention and medication-related terms (drug, medicine, medication, therapy, intervention, treatment, pharmac*) was conducted because of the limited indexing of these as subject headings.

2.2. Study selection

Abstract selection was undertaken by two independent reviewers (BJL & GB) with any disagreement resolved by discussion. Full texts were reviewed for studies assessed as potentially meeting the inclusion criteria.

Inclusion criteria were clinical studies which involved patients who clinically deteriorated or required critical care in the diverse clinical settings of hospital wards (that is outside critical care areas such as ICUs and operating theatres), with English full texts

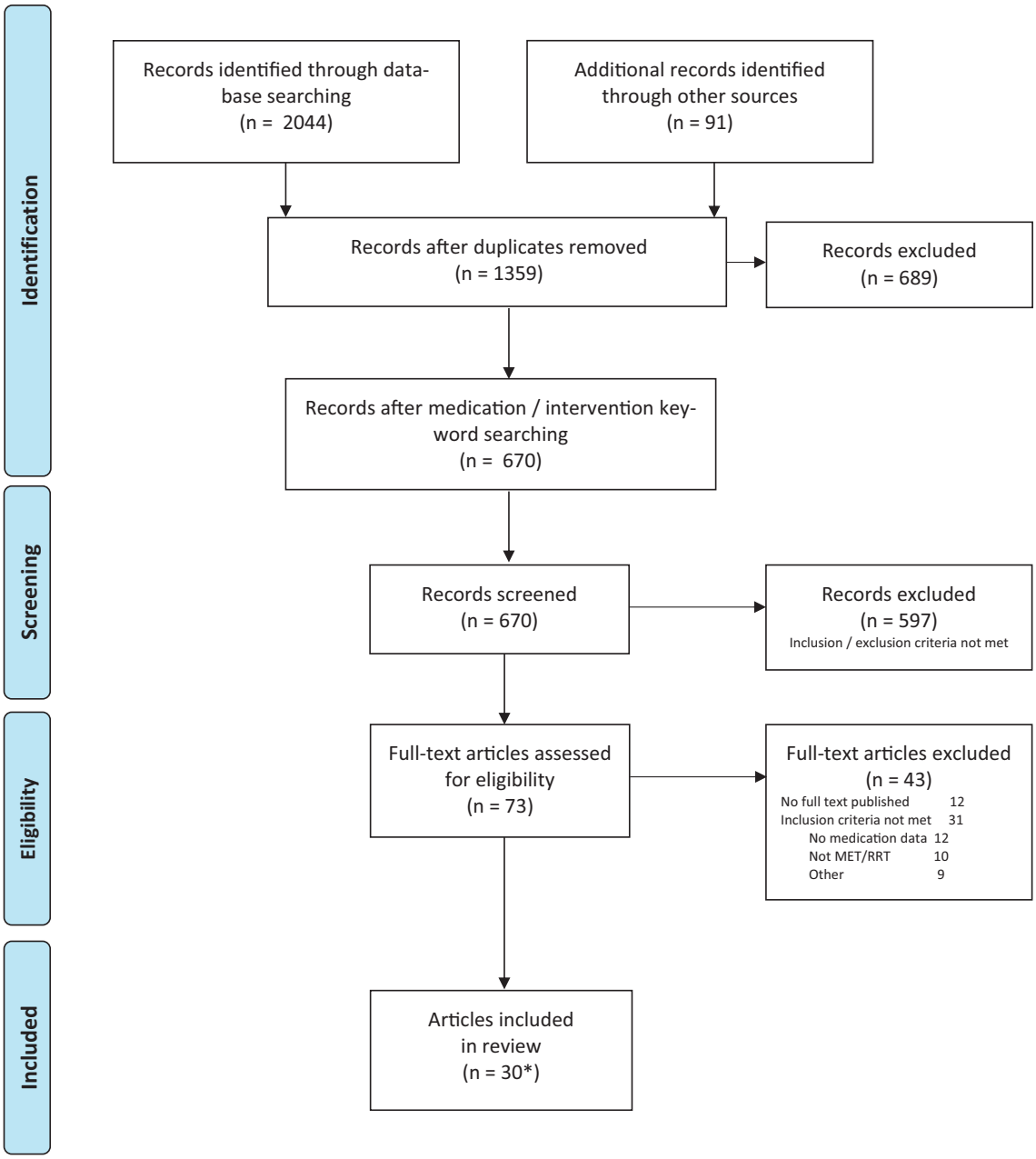

Fig. 1. Structured literature search and study selection results in PRISMA flow diagram format.[70] *includes one study that resulted in 2 articles included in the review. MET = medical emergency team; RRT = rapid response team.

available, a main subject of RRS or MET or RRT and with medications explicitly discussed. Research involving adult, paediatric, or mixed groups of patients were included. Studies conducted in a prehospital or out-of-hospital environment and those including only patients requiring psychiatric care were excluded.

2.3. Data presentation and quality assessment

Data charting was undertaken by two researchers (BJL & DJ) and an independent research assistant. Tabulation facilitated descriptive and thematic analyses. Study quality assessment was performed as an additional step to increase the robustness and relevance to practice and future research of the review findings. The Oxford Centre for Evidence-Based Medicine Levels of Evidence matrix,[24,25] which addresses variety in research question and design,[26] was used. Quality assessment was undertaken independently by two reviewers (BJL & GB) who resolved any disagreement by discussion.

2.4. Data collation and analysis

Data were mapped around the four *a priori* defined major themes to address the aims of the review: (i) medications as a cause of deterioration; (ii) medications as predictors of deterioration; (iii) medications as RRT interventions; and (iv) RRS medication management systems. The primary analyses were descriptive and summative. Statistical analyses included counts, frequencies, and proportions. Distributed data were reported as median, range, and interquartile range.

3. Results

3.1. Studies identified

Thirty articles, resulting from 29 studies, were selected for review (Fig. 1). Sixteen of these articles were published since 2013. Nine articles (30%) investigated an aim explicitly involving medications[27–35] (Table 1). Studies predominantly occurred at larger, tertiary or teaching hospitals in the United States of America (USA) and usually involved physician-led teams of critical care staff responding to activations outside critical care areas, such as ICUs, emergency departments, and operating theatres. Three nursing-led RRTs reported having no medical responder[34,36,37]; treatment decisions were ratified with remote medical staff in two of these studies.[36,37]

Twenty-six studies (90%) involved adult patients (Table 1), predominantly males in their late fifties to early seventies. The Australian, New Zealand, and Belgian studies[31,38–45] had older populations (reported mean ages 66–73 years) and contributed 59% of adult patients. The three paediatric studies[30,32,46] explored the medication causes and predictors of deterioration and did not contribute to other analyses.

The overall quality of the studies was low (Table 1). Most studies were single-centre and observational, often in specific populations, limiting the ability to control for confounders and decreasing generalisability. Comparative studies were predominantly pre and postcohort designs with small sample sizes and low rates of key outcomes, further weakening reliability.

3.2. Medications as a cause of clinical deterioration

Twelve studies identified medications as contributing to acute clinical deterioration (Table 2). These studies varied in patients included, definitions of cases, and methodologies of case identification, review, and event classification. Medications contributed to clinical deterioration in up to one in three cases; however, most reported rates were much lower (Table 2). Medications designated as high risk,[47,48] such as opiates and anticoagulants, were reported to contribute to deterioration events. Medications not generally considered high risk, such as bronchodilators and antihypertensives, were also found to contribute to clinical deterioration. Both medication errors and adverse reactions appeared to contribute to deterioration, but limited data prevented quantification or detailed analysis of this and the associated patient outcomes. When medication management errors, predominantly in prescribing and administration, contributed to deterioration, it was often judged to be preventable.

There was wide variation in the frequency of medication-related deterioration reported (Table 2). The lowest rate (2.5%) was reported when responding clinicians identified an association between medications and deterioration during the RRS activation.[31] Interestingly, retrospective case identification in the same study reported a higher rate (8%).[31] The highest rate of medication-related deterioration was 37% determined retrospectively amongst surgical patients activating the RRS within 24 hours of anaesthesia.[49]

Medications appeared more likely to contribute to RRS activations for respiratory, mental state, and cardiovascular compromise.[40,42–44,50] One study also reported worry and high aggregate early warning system scores as being associated with adverse medication effects.[44] However, the methods of determination, classification, and presentation of this data prevent further analysis and may limit generalisability.

The medications most commonly attributed as causes of clinical deterioration were opiates,[31–33,43,49–51] cardiovascular medications,[31,33,37,50–52] and benzodiazepines.[31,50] Studies did not report medication route or other administration details. Further description and quantification was impaired by the use of convenience classifications of types of medications in almost all studies. The most recent publication from the Belgian adverse event study[33] did use a recognised classification system as recommended for pharmacoepidemiological studies.[53] Studies involving surgical patients, both adult and paediatric, identified opiates as the predominant medication causing deterioration.[32,49–51] There were conflicting data regarding the timing of deterioration in relation to anaesthesia reported for adult postoperative patients.[49–51] One study referred to preoperative opiate use as problematic[51] while the paediatric study explicitly excluded these patients.[32] One study cited treatment decision errors as contributory[50] and another highlighted drug interactions.[51]

A variety of mechanisms were reported for how medications contributed to deterioration (Table 2). While no standard classification system was used between studies which may have contributed to misclassification bias, medication errors and adverse reactions predominated.

Almost all medication-related clinical deterioration was deemed preventable in the two studies which explicitly measured it.[41,52] The Belgian adverse event study found 100% of “drug therapy adverse events,” which described medication errors and drug interactions, examined to be preventable.[41] In the more detailed analysis of these events, predictors of preventable events were reported as the number of medications prescribed before admission, physical wellness defined by American Society of Anesthesiologists score, and age.[33] A similar preventability result was seen in a surgical case series looking specifically for errors leading to deterioration.[52]

The outcomes of medication-related deterioration reported in two studies with limited generalisability and two in more general populations appeared moderately severe (Table 2). It was not possible to compare these outcomes to deterioration from other causes. In-hospital mortality was reported for one of 18 (5.6%) medication-related hypotension events in a recent Australian cohort of RRT and arrest calls.[43] Transfer to a higher level of care was the most commonly reported outcome, although the definition was inconsistent.[32,41,50] While all cases they examined required a higher level of care, Marquet et al reported that 111 MET activations in 50 patients did not result in transfer to the ICU;[41] the breakdown of these as medication-related was not reported. In studies that used the definition of “transfer to high dependency or ICU” the rates were 20%[32] and 80%.[50] These studies, conducted in specialist populations of paediatric and otolaryngology surgery patients, were unlikely to be representative of more general populations of deteriorating patients.

3.3. Medications as predictors of deterioration

In contrast to causing deterioration, some medications have been reported to indicate or predict impending deterioration, usually in conjunction with other physiological abnormalities. Two included studies of paediatric patients found some antibiotics, diuretics, corticosteroids, anti-inflammatories, sedatives, analgesics, and nebulised airway dilators may be useful in augmenting triggers for RRS activation.[30,46]

The smaller study[46] identified potential indicators of future deterioration from interventions and investigations performed in the emergency department (Table 1). Patients who required RRS activation within 24 hours after admission to the ward commonly had been administered, in the emergency department, nebulised hypertonic saline, salbutamol or epinephrine, or intravenous antibiotics.[46] No specific antibiotics were detailed. While the limitation

Table 1
Summary of studies included in review.

Study	Country; hospital type (number of sites)	Population Sample size	Medical staff in efferent RRS limb	Study design	Primary aim	Primary outcomes	Key medication findings	Strengths and limitations Comments	Study quality[a]
Flabouris et al, 2010[38]	Australia; multicentre (23 centres)	Adult Control = 512 calls; MET = 1864 calls	Yes	Cluster, randomised controlled trial	To examine the interventions and timings of emergency team calls in hospitals with or without a MET	Only 5 of 2376 calls were free of critical care interventions. MET hospitals had proportionally fewer critical care type interventions. Emergency teams spent less than 30 min on average at each patient attendance. All calls were consistently distributed across the week.	The proportions of use of some critical care medication interventions (IV sedation, IV antiarrhythmics) were lower at MET hospitals. The use of ward-type medication interventions was similar between control and MET hospitals.	Strongest study design Convenience classification used for medications	2
Benson et al, 2014[36]	USA; teaching	Adult Pre = 133 calls; post = 123 calls	No	Pre and postcohort	To both improve identification of patients who meet SIRS criteria on the medical-surgical floors and increase compliance with the EGDT and surviving sepsis guidelines by the nurse practitioner-led RRT using a SIRS documentation database query	Nurse practitioner-led RRT intervention with an electronic health record increased the detection of SIRS and the number of interdisciplinary conversations about EGDT. Implementation of all key components of EGDT was increased.	Nurse practitioner-led RRT intervention with an electronic health record increased the frequency of prescribing and timeliness of administration of antibiotics as part of EGDT.	Analyses excluded patients in intervention group already on all 4 EGDT components at screening (n = 174)	4
Feih et al, 2017[35]	USA; university	Adult Pre = 234 patients; post = 157 patients	Yes	Pre and postcohort	To characterise rapid response events, identify deficiencies in the medication use system, and determine the impact of pharmacist involvement on a MET	Addition of a pharmacist to the MET reduced time from medication order entry to medication administration	Medications were administered less often after a pharmacist was added to the MET. Treatment for acute atrial fibrillation and reversal agents were the most common medications administered during MET calls.	Low MET activation rate. Convenience classification used for medications. Did not achieve calculated sample size or event rate used to calculate sample size. Multiple participants/ observers self-reported data.	3
Kim et al, 2014[71]	Korea; university	Adult Pre = 103 patients; post = 215 patients	Yes	Pre and postcohort	To compare the incidence of immediate complications of emergency endotracheal intubation before and after MET implementation and demonstrate an association between MET intervention and mortality	Early intervention of a MET with a computerised screening program reduced the incidence of cardiopulmonary arrest as a cause of emergency intubation and complications related to emergency intubation. No differences in mortality observed.	Vasopressor use after intubation was lower in patients in the intervention group. MET interventions, including diuretics and bronchodilators, provided earlier tailored management of unstable patients decreasing morbidity associated with intubation.	High APACHE II scores and proportion of patients with cancer at hospital admission. All emergency endotracheal intubations performed without neuromuscular blockade.	3
Miano et al, 2012[29]	USA; university	Adult Pre = 13 patients; post = 59 patients	Yes	Pre and postcohort	To determine whether use of a locally developed antibiotic algorithm, based on institution-specific bacterial resistance patterns, improved adequacy of empiric antimicrobial therapy administered by the MET.	The use of an institution-specific antibiotic algorithm significantly improved the adequacy of empiric antimicrobial therapy provided by the MET.	Antimicrobial prescribing by the MET was significantly altered following introduction of the algorithm. For a third of patients, the algorithm was not followed strictly. Aminoglycosides and vancomycin were often withheld. Antibiotic recommendations led by MET nurses and pharmacists. Pharmacist MET member.	Convenience sample Low yield from number of patients screened as positive bacterial cultures required. Some differences in patient demographics between pre and postcohorts demographics—surgical and oncology patients, hospital stay pre-MET.	4

Sebat et al, 2007[56]	USA; regional	Adult Pre = 85 patients; post = 426 patients	Yes	Pre and postcohort	To measure the effect of a RRS for non-traumatic shock on timeliness of key interventions, length of stay, and mortality over time	The RRS for non-traumatic shock greatly reduced time to treatments and led to substantial and continuous improvement in survival. The number needed to treat for an additional survivor was 3 by year 5 of the intervention.	Time to first antibiotic administration was reduced and associated with decreased mortality. Pharmacist MET member.	More than half of patients were recruited prehospital or from the emergency department. Patients were severely unwell: all required ICU admission and severity of illness scores were high.	4
Umscheid et al, 2015[57]	USA; university (3 sites)	Adult Pre = 595 calls; post = 545 calls	Yes	Pre and postcohort	To describe the development, validation, and impact of an electronic sepsis detection and response system to improve patient outcomes	An electronic sepsis detection and response system accurately identified non-ICU patients with sepsis and increased early sepsis care, transfer to ICU, and sepsis documentation. A trend towards decreased mortality and increased discharge to home was observed.	Timely ordering of antibiotics increased significantly following implementation of the sepsis detection and response system.	High false positive rates for electronic alerts. No sample size calculation—likely underpowered to detect mortality difference. Patients were relatively well—low numbers required vasopressor support or transfer to ICU.	4
Huang et al, 2013[30]	USA; tertiary	Paediatric 141 patients	NR	Retrospective case crossover	To identify therapeutic classes of medications associated with clinical deterioration	Nine therapeutic classes of medications were associated with significantly increased risk of clinical deterioration and could be included in multivariable models to detect deterioration.	Four classes were antibiotics; others were corticosteroids and antidotes to hypersensitivity reactions, sedatives, benzodiazepines, opioids, and diuretics.	Adequately powered Almost all patients were medical admissions Excluded patients in hospital for less than 24 h Severely unwell patients	4
Voepel-Lewis et al, 2013[32]	USA; university	Paediatric Controls = 98 patients; cases = 25 patients, including threshold (n = 9) and rescue (n = 16)	NR	Retrospective nested case control	To examine the relationship between patient factors, treatment factors, and opioid outcomes in hospitalised children during the early postoperative period	Early use of adjuvant non-opioids was associated with a lower probability of opioid adverse drug events and need for rescue in children in the early postoperative period. Lower oxygen saturations, higher sedation scores, and use of supplemental oxygen in the early postoperative period were signs of later opioid-related deterioration.	Perioperative and postoperative opioid use were not found to be associated with opioid adverse drug events. Poorer preoperative physical state, a musculoskeletal comorbidity, use of IV continuous infusions, or nurse-controlled analgesia were associated with opiate-related deterioration.	Difficulties in achieving adequate sample size: low number of events over 27 months despite adjustment in case definition. Excluded children taking preoperative opiates. Time period for event identification postoperatively (1 week) longer than clinically relevant.	4
Weingarten et al, 2012[51]	USA; NR (2 sites)	Adult Controls = 318 patients; cases = 181 patients, including MET (n = 168) and arrest calls(n = 13)	Yes	Retrospective case control	To examine factors associated with need for emergency response team activation within the first 48 postoperative hours	Preoperative scheduled use of opioids, history of central neurological disease, and haemodynamic instability during surgery were associated independently with unexpected deterioration within the first 48 postoperative hours.	Preoperative opiate use, and intraoperative cardiac instability requiring phenylephrine infusion were independent predictors of emergency response team activation. After fluid administration, administration of naloxone and opioids were the most common interventions.	No objective criteria for emergency response team activation. Excluded patients in monitored beds, postbronchoscopy and cardiac catheterisation High proportion of patients required transfer to a higher level of care, including ICU, following call	4
Cooper, 2007[55]	USA; teaching	Adult[b] 46 patients	Yes	Prospective observational	To describe the functions of the pharmacist as a participating member of a newly implemented MET	The MET pharmacist assisted in optimising drug therapy in nearly one-third of cases.	Pharmacists attended all MET calls with emergency trolley. Dosing and new treatment recommendations were the most frequent pharmacist interventions and involved cardiovascular agents, diuretics, sedatives, and antidotes.	Study conducted during phased implementation of new MET with very low activation frequency. Standard activation criteria plus temperature and stroke symptoms. No classification used for medications. Multiple participants/ observers self-reported data.	4

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Table 1 (*continued*)

Study	Country; hospital type (number of sites)	Population Sample size	Medical staff in efferent RRS limb	Study design	Primary aim	Primary outcomes	Key medication findings	Strengths and limitations Comments	Study quality[a]
Gokhman et al, 2012[28]	USA; university	Adult 50 calls including MET (condition C) (n = 45) and arrest (condition A) (n = 5)	Yes	Prospective observational	To prospectively assess the rate, type, and severity of medication errors made during MET care at a large, tertiary-care, academic medical centre during medical emergencies	Medication errors were frequent and most reached the patient. Rate of error = 0.5 per dose administered during MET care. 14% of errors had potential for moderately severe harm. MET call mortality of 6% and hospital mortality of 30%.	Median doses per call = 2 (186 doses of 36 different medications during 50 calls) High-risk medications frequently associated with errors. System, knowledge, communication, and training deficits contributed to medication errors during MET care.	Non-consecutive, convenience sample excluding nights and weekends. No classification used for medications. Direct observation by single observer not participating in care.	3
Groth and Acquisto, 2016[34]	USA; university	Adult 32 calls	No	Prospective observational	To investigate the impact a pharmacist could have on the medication use system during a RRT alert	Pharmacists attended 23% of RRT calls during the study period and made 49 pharmacotherapy recommendations including medication access, dose, therapy, adding and discontinuing.	Two thirds of patients required at least one medication during a RRT call. Cardiac medications, sedatives and analgesics, antibiotics and antiepileptic medications were most common. In a small number of cases pharmacists accessed medications from locations remote to the patient ward.	Convenience sample excluding nights and weekends. Convenience classification used for medications. No detail on types of medications requiring intervention. Two participants/observers self-reported data.	4
Lasak-Myell et al, 2012[27]	USA; tertiary	Adult[b] 35 calls	Yes	Prospective observational	To identify opportunities for pharmacy intervention with an existing MET during arrest and patient assessments, define what those interventions were and determine whether there is a role for the pharmacist as a member of MET	The pharmacist MET member had the opportunity to intervene in all emergent situations as well as initial patient assessment. The most common intervention was selecting an appropriate patient-specific antibiotic regimen.	The pharmacist intervened an average of 2.6 times per patient. Interventions included treatment and dosing discussion and recommendations, medication supply and preparation, drug information and education, and medicines reconciliation and handover. Medication therapies involved antibiotics, sedation, analgesia, and ACLS medications; electrolytes, diuresis, seizure, glycemic, and blood pressure control; alcohol withdrawal; and gastrointestinal bleeding management.	Convenience sample excluding nights and weekends (~50% of calls). Convenience classification used for medications. Single participant/observer self-reported data.	4
Mullins and Psirides, 2016[44]	New Zealand; university	Adult 795 calls	Yes	Prospective observational	To describe the type of patients who require MET review, the reasons such reviews are requested, and the subsequent immediate management of these patients by the MET	Older patients on medical wards most commonly required MET activation at the start of the day. Unresponsiveness or seizures and tachycardia were the most common triggers for MET activation while neurological causes and cardiovascular failure were the most common underlying diagnoses. Investigations were more commonly conducted than therapeutic interventions.	Medication administration was the most common therapeutic intervention. Antiarrhythmics, analgesia, beta-blockers, and frusemide were the most commonly used medications. Medications adverse effects were reported as a reason for the activation for all of the 5 most common activation triggers.	Moderately high MET activation rate. Relatively large sample of consecutive calls. Convenience classification used for medications. Limited detail of classification of medication adverse effects.	3

Peebles et al, 2011[58]	UK; district general	Adult[b] 17 calls	NR	Prospective observational	To identify causes for delay in recognition and treatment of critically ill patients with a focus on factors that have potential for modification by system design in future studies	Modifiable delays were common, quantifiable, and observed in almost every MET episode. Delays in calling for help and team performance and logistical problems were identified as contributors to potentially harmful delays in care. No association of delays with disease severity as measured by triggering Modified Early Warning Scores.	Delays in medication administration were observed due to problems with team performance—failure of medical staff to relay information to nursing staff, sequential performance of actions that could be performed concurrently by different team members (drug prescription and preparation). Logistical delays: first line antibiotics were not always available on the ward.	Very small pilot study Prospective mixed methods study design. Non-consecutive convenience sample. Direct observation by two observers not participating in care.	4
Smith et al, 2017[43]	Australia; university	Adult 937 calls including MET (n = 902) and arrest calls (n = 35)	Yes	Prospective observational	To describe the frequency and hospital mortality of the diagnoses that the MET encounters	A large number of diagnoses were identified. Neurological and consciousness problems and circulatory and breathing problems were the most common groups of diagnoses. Atrial fibrillation and oversedation or narcosis were the most common diagnoses. A small number of diagnoses accounted for the majority of in-hospital mortality.	The most common medications used at MET calls were electrolytes, frusemide and antiarrhythmic agents. Medication-related diagnoses leading to MET calls were identified in 11.6% of calls. Cardiac, circulatory, adverse reaction, and neurological/ consciousness diagnoses groups included medication-related diagnoses. Only one medication-related event (hypotension) had an outcome of in-hospital death.	Large sample of consecutive calls. Convenience classification used for medications. Independent verification of diagnoses by single clinician and independent case review of all cases at end of study.	3
Taguti et al, 2013[54]	Brazil; university	Adult 150 calls	Yes	Prospective observational	To describe the epidemiological data of clinical instability events in adult in-patients at a university hospital attended by the MET and to identify prognostic factors	Activation of the MET was frequent and involved patients at high risk of death. These patients, most commonly with respiratory or haemodynamic insufficiency, required specialised interventions and had high mortality.	Most common therapies were vasoactive medications, antimicrobials, fluids, analgesia, oxygen, sedatives, and bronchodilators.	Severely unwell patient group with high incidence of sepsis and malignancy. Convenience classification used for medications	4
Topple et al, 2016[45]	Australia; university	Adult 309 calls	Yes	Prospective observational	To prospectively audit the tasks undertaken by nurses from the MET during a routine call	Non-technical skills were performed more frequently by MET nurses than technical skills. The majority of MET nurses felt confident and competent during calls.	Preparation and administration of medications as single doses or infusions were commonly conducted. At calls for airway triggers administering medications for intubation was reported. At calls for respiratory criteria nebulised medications were administered.	Non-consecutive sample with patient demographics correlating with all calls. Missing data for calls requiring ICU admission. Limited medication detail reported. Multiple participants/ observers self-reported data.	4
White et al, 2016[42]	Australia; university	Adult 1151 calls	Yes	Prospective observational	To detail patient characteristics, processes, and outcomes of an established RRS in a large tertiary adult hospital	Call rate of 69.1 per 1000 admissions. MET calls were more likely to involve older, surgical emergency patients who were unlikely to have a resuscitation plan documented.	Adverse drug reactions contributed to a small number of calls. Calls for medication-related decreased level of consciousness were also reported. Antiarrhythmics,	Large sample of consecutive calls. Included outpatient RRS calls. Causes of activation were retrospectively assigned following medical record review.	3

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Table 1 (*continued*)

Study	Country; hospital type (number of sites)	Population Sample size	Medical staff in efferent RRS limb	Study design	Primary aim	Primary outcomes	Key medication findings	Strengths and limitations Comments	Study quality[a]
						Only 10% of calls involved lifesaving interventions. One in seven calls resulted in transfer to a higher level of care. One in eight patients died in hospital, and 20% died within 28 days. Multiple activations increased mortality risk.	vasopressors, and seizure medications were used by the MET. The MET accessed crash trolleys transferred to the bedside by emergency department nurses.	Convenience classification system used for level of interventions and medications.	
Wong and Levy, 2005[39]	Australia; tertiary	Adult 22 patients including MET calls (n = 13) and direct ICU consults (n = 9)	Yes	Prospective observational	To review the experience with a MET response on surgical team involvement in the care of critically unwell surgical patients, with particular emphasis on the contribution by members of the surgical team to decision-making and the impact of the MET on surgical training	Early consultation with surgical team members during MET call had an impact on decision-making and performance of tasks relevant to patient resuscitation and management. Routine in-person attendance by a surgical registrar as part of the MET does not seem justified as urgent surgical decision-making often is not required.	IV pharmacotherapy was initiated more often for ICU consults than MET-managed patients; however, the MET was more likely to initiate this than the surgical team. One decision regarding anticoagulation was made by a surgical team member in a MET-managed patient.	Very low MET activation frequency No details of statistical analyses reported Convenience classification used for medications MET managed patients potentially were less unwell than ICU consult patients.	4
Husband et al, 2014[40]	Australia; tertiary	Adult 82 respiratory arrests including 17 MET calls	Yes	Retrospective[c] observational	To characterise antecedent causes and outcomes of respiratory arrests occurring within a metropolitan tertiary teaching hospital in Melbourne, Australia.	Respiratory arrests were rare and associated with significantly lower mortality than cardiac arrests. Respiratory arrests involved predominantly medical patients with significant comorbidities, most commonly respiratory, cardiac, or neurological.	Medication side effects were identified by attending clinicians as the cause of 14.6% of respiratory arrests.	Events identified from screening of emergency call database and independently verified by two clinicians. Heterogeneous sample including arrest and MET calls.	3
Kaplan et al, 2009[52]	USA; university	Adult 98 calls	Yes	Retrospective observational	To examine the proximate causes and preventability of surgical MET activation	MET calls principally resulted from team-based errors of omission, more often overnight and between 24 and 72 hours postoperatively, which were often preventable or potentially preventable. Almost all patients required transfer to a higher level of care post MET activation.	Medication-related causes of MET call include injudicious fluid administration, not restarting preadmission medications and inadequate prophylaxis for alcohol withdrawal. MET medication therapies included: diuretics, antiarrhythmics, bronchodilators, fluid, and antibiotics.	Low MET activation rate Multidisciplinary committee assigned error and preventability without use of validated tools or scales. No details of types of surgical population.	3
Krmpotic and Lobos,2013[46]	Canada; university	Paediatric 39 calls	Yes	Retrospective observational	To determine the frequency at which unplanned admission to the PICU occurs within the first 24 h of hospitalisation from the ED and to describe the clinical characteristics and outcomes for hospitalised children who required early unplanned admission to PICU	A tenth of all MET calls occurred within 24 hours of hospitalisation from the ED and resulted in an unplanned admission to PICU. Males, infants aged <1 year, and children with respiratory complaints accounted for a large proportion of these children.	Nebulised medications (hypertonic saline, salbutamol, and adrenaline) were the most common intervention in ED for patients requiring PICU admission within 24 hours of hospital admission. A third of patients required antibiotics in ED with median time from triage to antibiotic of 3 h 20 min.	Two trained reviewers completed case reviews. Severely unwell population No classification used for medications.	4
Marquet et al[d], 2015[41]	Belgium; multicentre (6 centres)	Adult 830 patients including MET calls (n = 111) and unplanned	NR	Retrospective observational	To determine the prevalence, the preventability, the type, and the level of harm of adverse events that require unplanned transfer to a higher level of care and to	Adverse events leading to transfer to a higher level of care were common. A quarter of unplanned transfers to a higher level of	Drug therapy adverse events were most common accounting for a quarter of reported events. All were deemed highly	Recognised, published methodology, with validated scales, using an independent multidisciplinary panel for	3

		admissions to ICU (n = 719)			describe, more specifically, the incidence and preventability of in-hospital adverse drug events requiring a transfer to a higher level of care, the type of drugs involved, the risk factors associated, and the patient outcomes at hospital discharge.	care were due to highly preventable adverse events, principally involving drug therapy or surgery.	preventable. Antibiotics and antithrombotics were most commonly involved. Adverse reactions to medications and anaesthesia-related adverse events (excluded from above definition) were less common and not as preventable.	identifying and assessing adverse events. Adequately powered. Convenience classification used for medications. Large proportion of severely unwell patients.	
Marquet et al, 2017[33]	As above	As above	As above	As above	To describe the incidence and preventability of in-hospital adverse drug events requiring a transfer to a higher level of care, the type of drugs involved, the risk factors associated, and the patient outcomes at hospital discharge.	A third of adverse events leading to a higher level of care were medication-related. The incidence of patients requiring a higher level of care due to an adverse drug event was 40.5 per 100 000 patient days. The majority (83.8%) of these adverse drug events were preventable.	Adverse drug reactions were most frequently caused by antineoplastic agents. "Physical wellness", the number of medications prescribed before admission, and age were associated with preventable adverse drug events. All-cause mortality was 28.1%. A third of adverse drug events resulted in temporary or permanent harm or need for permanent care.	As above Recognised classification systems for medications and adverse drug events used.	3
Oliver et al, 2009[50]	USA; university	Adult 67 calls including MET (n = 64) and arrest calls (n = 3)	Yes	Retrospective observational	To investigate the utilisation of the MET on a specialised otolaryngology care unit in a university teaching hospital	The RRS activation criteria identifies otolaryngology patients at increased risk for in-hospital mortality. About half of MET calls were due to respiratory events and 70% of patients required immediate transfer to higher level of care. System errors and educational deficits contributed to events requiring MET activation.	Five calls were medication-related. Respiratory and mental state calls were due to opiates and/or benzodiazepines and required ICU admission. A cardiac call was due to omission of regular rate control medication due to enteral access issues and was resolved on the ward. MET interventions included medication administration.	Relatively unwell specialist surgical population. Limited detail regarding MET medication interventions.	4
Rayan et al, 2011[37]	USA; tertiary	Adult 115 patients	No	Retrospective observational	To descriptively evaluate the experience over a 4-year period with a RRT intervention for selected patients with severe hyperkalaemia and to perform an in-depth exploration of the RRT intervention process.	Hyperkalaemia occurs frequently in inpatient settings and a specific RRT intervention facilitated timely corrections of critical laboratory test results and consistent treatment through use of a standardised protocol.	Medication interventions were common during RRT interventions for severe hyperkalaemia. Cessation of medications as an intervention by the RRT indicates some severe hyperkalaemia is medication-related.	Relatively well and heterogeneous patient group No classification used for medications.	4
Sarani et al, 2011[49]	USA; university	Adult 1082 calls including surgical (n = 286) and medical (n = 796)	Yes	Retrospective observational	To evaluate the impact of a RRS on out of ICU cardiac arrests & hospital mortality in hospitalised patients on the medical and surgical services and to identify differences in triggers for RRS activation, interventions performed and outcomes for medical and surgical patients.	Implementation of a RRS had a greater impact on reduction of out of ICU cardiac arrest and mortality in medical in-patients. While triggers were similar to medical patients, surgical patients demonstrated substantial risk for decompensation within the first 24 hours after operation.	A third of events within 24 hours of surgery were attributed to complications of excessive opiate administration. Medications, including antiarrhythmics, antibiotics, antidotes, and vasoactives, were among the common interventions performed by the MET for both groups. Pharmacist MET member.	Excluded cardiac surgical patients Convenience classification used for medications Moderate severity of illness with no difference between medical and surgical patients.	4

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Table 1 (*continued*)

Study	Country; hospital type (number of sites)	Population Sample size	Medical staff in efferent RRS limb	Study design	Primary aim	Primary outcomes	Key medication findings	Strengths and limitations Comments	Study quality[a]
Van de Vreede and Leong, 2007[31]	Australia; university	Adult baseline = 108 calls; validation[b] = 470 calls	Yes	Retrospective[c] observational	To introduce a process to ensure medication errors identified via MET calls are notified and included in the medication safety continuous quality improvement program	The inclusion of the "adverse medication effect" category established an ongoing link between the MET and the medication error reporting framework and provided valuable information about medication errors and near-misses not identified through other reporting mechanisms.	MET calls associated with medications errors and adverse reactions were identified by MET clinicians during calls. Medications involved varied between baseline and validation arms and included opiates, sedatives, electrolytes, antiepileptics, and cardiovascular medications. Medication omission contributed to MET calls.	Few clinical or activation trigger data reported. No classification used for medications. Convenience classification used for adverse drug events.	4

Calls = activations; RRS = rapid response system; MET = medical emergency team (medical lead); IV = intravenous; RRT = rapid response team (nursing lead); NR = not reported; USA = United States of America; UK = United Kingdom; SIRS = systemic inflammatory response syndrome; EGDT = early goal directed therapy; PICU = paediatric intensive care unit; ED = emergency department; ICU = intensive care unit; ACLS = advanced cardiac life support.

[a] According to The Oxford 2011 Levels of Evidence.[24]
[b] population was not reported but deduced from use of adult activation criteria.
[c] Medication causation was recorded by attending clinicians.
[d] Single study resulting in two publications, both included in review.

that some of these children were probably incorrectly triaged from the emergency department is acknowledged, the finding of intravenous antibiotics indicating future deterioration is replicated in the larger study which explicitly excluded patients admitted to the ward for less the 24 hours.[30] This more robust study found strong associations between administration of some intravenous antibiotics and deterioration within the next 72 hours (Table 1). Vancomycin and anaerobic antibiotics led to a greater than five-fold increased risk of clinical deterioration, while third and fourth generation cephalosporins and aminoglycosides increased the risk well over two-fold.[30] Associations were also established with corticosteroids and other anti-inflammatory medications, some psychotropic agents, full opioid analgesics, loop diuretics, and diphenhydramine.[30]

These medications were administered as treatments for conditions that may progress, such as infection, airway restriction or oedema, before detection of the patients' deterioration through the established physiological triggers. Hence, some medications, such as vancomycin and other intravenous antibiotics, may be useful in helping to predict impending deterioration in specific clinical scenarios for paediatric medical patients. No studies were identified in adult patients. No reviewed studies incorporated medications into RRS activation criteria in clinical practice.

3.4. *Medications as a RRT intervention*

The overall rate of medication use as a RRT intervention varied from about 40% of calls in recent studies of consecutive calls[35,44] to 100% in more selected samples of calls[28] (Table 3). Both life-saving intravenous and less acute medication interventions often were used by RRTs; however, specific types of medications and frequency of use varied (Table 3). The heterogeneous nature of the RRS activations sampled and the diversity in medication classification limited quantitative analysis of the incidence of specific medication interventions. This heterogeneity was useful in providing some perspective of the clinical circumstances of specific medication use because without this there was very limited data reported about the specific indications for medication use.

Cardiovascular medications, including electrolytes and diuretics, were used in most studies reporting RRT medication interventions (Table 3). Diuretic use in surgical activations had the highest frequency of medication use reported (88%). In this case series, injudicious fluid administration was reported as the most common physician error leading to RRS activation.[52] In general populations, medications to manage blood pressure, particularly vasoactive agents, along with antiarrhythmics were more commonly used than diuretics. Despite the high frequency of antiarrhythmic use reported, reporting of electrolyte administration was low. One study reported medication use by activation trigger: at 64% of calls for tachycardia, 29% of calls for hypotension, and 35% of calls for bradycardia.[44] Although not specifically linked, the authors also reported antiarrhythmic agent use at 13%, beta-blocker and frusemide use both at 9.5%, and electrolyte replacement at 8.5% of all calls.

The use of sedatives, analgesics, and neuromuscular blockers varied widely and was absent in eight studies (Table 3). In early postoperative patients, analgesia tended to be more commonly used than sedatives.[51,54] Use of neuromuscular blocking agents was reported only from observation of an established USA MET that included some arrest calls.[28]

Other commonly reported types of medications, including bronchodilators and antimicrobials, were distributed widely across all types of populations (Table 3). Studies that included small numbers of arrest calls tended to report similar rates of reversal agent and antidote use.[28,49,51,55] The nurse-led RRT specifically for

Table 2
Studies reporting medications as a cause of clinical deterioration and rapid response system activation.

Study	Population[a]	Number of events	Type of events	Frequency of medications as cause (%)		Mechanism of medication causes of deterioration (%)	Types of medication identified as causes	Preventability of events with medication causes	Outcome of events caused by medication
Husband et al, 2014[40]	Ward patients	82	Respiratory arrests	Identified by MET during the call	14.6	NR	NR	NR	NR
Kaplan et al, 2009[52]	Surgical ward patients	82	MET calls	NR		Omission 22% Treatment decision 11% Administration error 2%	Beta-blockers Diuretics Antiarrythmics Alcohol withdrawal treatments	~90% preventable	NR
Lasak-Myell et al, 2012[27]	Ward patients	34	Arrest & MET calls	Pharmacist recommendation to discontinue therapy	6	NR	NR	NR	NR
Marquet et al, 2015[41] Marquet et al, 2017[33]	Ward patients	830	UIA or MET calls	Drug therapy adverse event	25.6 (n = 134)	Incorrect dose 47% Omission 34% Inappropriate drug 8% Contraindication 6% Other (timing, interactions, known side-effect) 4.5%	Antibiotics (J01)[b] 25.4% Antithrombotic agents (B01) 23.1% Blood substitutes & perfusion solutions (B05) 9% Diuretics (C03) 8.2% Analgesics (N02) 3.7% Cardiac therapy (C01) 3.7% Drugs used in diabetes (A10) 3.7% Beta-blocking agents (C07) 3%	100% highly preventable	All required higher level care (MET call included as higher level of care) Temporary harm 53.8% Permanent harm/ care 18.1% All-cause mortality 28.1%
				Medication or fluid adverse reaction	5.0 (n = 26)	Side-effect (NR) Allergic reaction (NR) Anaphylaxis (NR)	Antineoplastic agents (L01)[b] 23.1% Antithrombotic agents (B01) 15.4% Contrast media (V08) 15.4% Antibiotics (J01) 7.7% Diuretics (C03) 7.7% Blood substitutes & perfusion solutions (B05) 7.7% Beta-blocking agents (C07) 7.7%)	None highly preventable	
				Anaesthesia adverse event	2.7 (n = 14)	NR	Anaesthetic agents	28% highly preventable	All required higher level care (MET call included as higher level of care)
Mullins and Psirides,2016[44]	Ward patients	795	MET calls	Diagnosis identified by MET during the call	5.9	Adverse medication effect 5.9%	NR	NR	NR
Oliver et al, 2009[50]	Otolaryngeal surgical ward patients	67	MET calls	Respiratory trigger Mental state trigger Cardiovascular trigger	6 18 6	Treatment decisions (NR) Omission (NR)	Opiates Benzodiazepines Cardiovascular	NR NR	80% required ICU admission Remained on ward
Rayan et al, 2011[37]	Ward patients	115	Hyperkalaemia RRT calls	Hyperkalaemia	NR	Adverse effect (NR)	ARB/ACE inhibitor Spironolactone	NR	NR
Sarani et al, 2011[49]	Ward patients	1082	MET calls	Within 24 h after anaesthesia	37	NR	Opiates	NR	NR
Smith et al, 2017[43]	Ward patients	937	Arrest & MET calls	Diagnosis from retrospective review	11.6	Adverse drug reaction 0.9%	Spinal anaesthesia/ epidural 2.7% Sedation or opiates 4.8%	NR	One diagnosis of medication-related hypotension resulted in in-

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Table 2 (*continued*)

Study	Population[a]	Number of events	Type of events	Frequency of medications as cause (%)		Mechanism of medication causes of deterioration (%)	Types of medication identified as causes	Preventability of events with medication causes	Outcome of events caused by medication
									hospital patient death
Van de Vreede and Leong,2007[31]	Ward patients	108	MET calls	Retrospective case review	8	Omission (NR)	Antiepileptics Cardiovascular Opiates Salbutamol	NR	NR
		470		Identified by MET during the call	2.5	NR	Opiates Ketamine Potassium Antipsychotic Benzodiazepines Metoclopramide	NR	NR
Voepel-Lewis et al, 2013[32]	Paediatric ward patients	25	Postoperative opiate-related adverse events	Opiate-related	NR	NR	Opiates	Non-opiate adjuvant use reduced probability	20% high dependency or ICU admission
Weingarten et al, 2012[51]	Surgical ward patients	181	Arrest & MET calls	Post-anaesthesia	7	Drug interactions 7%	Opiates (preoperative) Cardiovascular (intraoperative)	NR	NR
White et al, 2016[42]	Ward patients & outpatients	1151	MET calls	Clinical syndrome from retrospective review	4.4	Adverse drug reaction 3.4%	NR	NR	NR

MET = medical emergency team (medical lead); RRT = rapid response team (nursing lead); NR = not reported; UIA = unplanned intensive care admission; ICU = intensive care unit; ARB = angiotensin receptor blocker; ACE = angiotensin converting enzyme.

[a] Adult patients unless otherwise specified.

[b] Classified using World Health Organisation Anatomical Therapeutic Chemical Category.

hyperkalaemia[37] demonstrated a different profile of medication use to other studies.

Four studies demonstrated a positive impact of RRTs on intervention timeliness and appropriate antibiotic selection for patients with sepsis.[29,36,56,57] One study published the antibiotic algorithm tested; based on the local hospital antibiogram, it included cefepime, levofloxacin, aztreonam, meroperem, amikacin, vancomycin, metronidazole, and caspofungin.[29] The frequency of use of the individual agents was not reported. The types or appropriateness of antibiotics administered to patients in the remaining studies were not reported.[36,56,57] Protocoled care appeared to be the common factor in the benefits observed. In two cohort studies, automated abnormal vital sign alerts through electronic medical record systems combined with treatment algorithms significantly reduced the time to antibiotic and other sepsis treatment administration.[36,57] In settings without the use of an automated afferent limb for detection of deterioration, protocoled treatment improved the selection of appropriate antibiotics[29] and decreased mortality for septic patients who triggered RRS activations.[56]

3.5. RRS medication management systems

Eight studies reported data covering the aspects of medication supply,[27,34,35,42,55,58] prescription,[27,28,55] preparation, and administration.[28,45,58] No single study provided a comprehensive evaluation of medication management systems. While nursing staff appeared predominantly responsible for medication management, pharmacists supported them in several USA studies. Team dynamics were observed as important contributors to delays in medication access and administration in RRS.[58]

In two USA studies, pharmacists were responsible for transfer of the emergency trolley with specialist medications to the bedside[27,55]; in an Australian study, this was the responsibility of emergency department nurses.[42] Two USA studies reported the improved timeliness of medication access when pharmacists worked with RRT nurses to source medications from automated dispensing cabinets and other locations.[34,35] Medication preparation and administration, predominantly intravenous infusions, represented the majority of technical work completed by RRT nurses.[45] While nurses felt confident and competent, there was a wide diversity of tasks and competing demands they needed to complete. The frequency and high implementation rate of pharmacist interventions to optimise medication selection and dosing suggested prescribing during RRT activations required further refinement.[27,34,35,55] These findings were supported by the delays and medication errors with potential for patient harm reported throughout medication supply, prescribing, preparation, and administration.[28,58]

4. Discussion

4.1. Summary of major findings

This review of 30 publications examined how medications contribute to clinical deterioration and are used in RRSs. The review findings were limited by inconsistent reporting and weakness of the studies. Medications contributed to, on average, about a tenth, but up to one-third, of clinical deteriorations. This appeared to vary with types of medications: opiates, benzodiazepines, and cardiovascular agents predominated. While few links were made between how specific medications contributed to deterioration, adverse drug reactions, drug interactions, and medications errors, involving treatment decisions, omission, and administration, were reported. Only errors were judged as preventable. Despite the outcomes of deterioration with medication contributions being

Table 3
Studies that report the frequency of medications as interventions at rapid response system activations.

Study	Call sample	Overall rate of medication use (% of calls)	Medication interventions (reported frequency of use at rapid response team calls %)														
			Cardiovascular					Sedative			Other						
			Anti-arrhythmic	Anti-hypertensive	Vaso-active	Diuretic	Electro-lyte	Sedation	Analgesia	NMB	Anti-microbial	Reversal agent	Anti-epileptic	Broncho-dilator	Sodium Bicarb	Insulin/ Glucose	Other
Flabouris 2010[38]	all calls at MET hospitals	–	11.2	–	6.1	–	–	7	–	–	–	–	27	2.7	–	–	–
Taguti 2013[54]	all MET calls	–	3.3	1.3	19.2	4.7	–	6.6	8.6	–	17.9	–	4	6	–	3.3	–
Mullins 2016[44]	all MET calls	42.5	13.1	9.5	–	9.5	8.5	–	10.3	–	–	–	–	–	–	–	–
White 2016[42]	all MET calls	–	6.1	–	3.4	–	–	–	–	–	–	–	1.8	–	–	–	–
Feih 2017[35]	all MET calls	Pre = 45 Post = 37	12.5	X	–	–	–	X	7.7	–	8.1	7.4	8.1	–	–	–	–
Smith 2017[43]	all MET calls~	–	9.1	–	10.8	9.3	11.2	–	–	–	7.0	–	–	–	–	–	4.3
Sarani 2011[49]	medical patient MET calls	–	6	–	6	–	–	–	–	–	7	8	–	–	–	–	–
	surgical patient MET calls	–	7	–	7	–	–	–	–	–	10	5	–	–	–	–	–
Wong 2005[39]	surgical patient MET calls	61.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kaplan 2009[52]	surgical patient MET calls	–	58	–	–	88	–	–	–	–	17	–	–	44	–	–	–
Weingarten 2012[51]	surgical patient MET calls	–	2	1	3	1	–	2	7	–	–	10	–	3	–	1	–
Oliver 2009[50]	otolaryngeal surgical patient MET calls	–	X	X	X	X	X	–	–	–	–	X	–	–	–	–	–
Rayan 2011[37]	RRT calls for hyperkalaemia	–	–	–	–	19	44	–	–	–	–	–	–	5	24	57	54
Kim 2014[71]	MET calls requiring intubation	–	–	–	36.7	X	–	–	–	–	–	–	–	X	–	–	–
Gokhman 2012[28]	weekday daytime MET calls	100	8.6	3.8	28	1.1	5.9	16.1	5.8	8	–	5.9	1.1	–	9.1	1.6	3.2
Groth 2016[34]	Pharmacist-attended weekday daytime RRT calls	65.6	31.1					20		–	17.8	–	13.3	4.4	–	–	13.3
Topple 2016[45]	Nursing tasks at all MET calls	Prepare = 19.7 Administer = 22	–	–	–	–	–	–	–	–	–	–	–	6.8	–	–	1
Cooper 2007[55]	Pharmacist interventions at all MET calls	–	4.3	11	4.3	6.5	–	2.2	–	–	–	6.5	–	–	–	–	–
Lasak-Myell 2012[27]	Pharmacist interventions at weekday daytime MET calls	–	–	–	15	7	7	21	7	–	21	–	11	–	–	7	–

- not reported; X medication use reported but frequency not reported; ~ data excludes arrest calls.
Calls: activations; NMB – neuromuscular blocker; Sodium Bicarb – sodium bicarbonate.

sparsely and inconsistently reported, the limited data suggested moderately severe outcomes, including rare fatalities. No actions to prospectively identify or address medication-related causes of deterioration were found.

Incorporation of medications into the activation criteria of RRSs has not occurred in clinical practice but paediatric studies have identified viable candidates in vancomycin and potentially other intravenous antibiotics. Identification of nebulised bronchodilators administered in the emergency department and diuretics, sedatives, and anti-inflammatory agents administered in the ward setting as other potential indicators highlighted the association between clinical setting and timing of medication administration and clinical deterioration. Considerable crossover with medications which contribute to deterioration was identified. Along with the complexities of triage failure and unrecognised deterioration, careful examination of these relationships is required before medications can be added to trigger tools.

Medications were frequently used as RRT interventions. Considerable diversity in the acuity of medication types used was observed. Cardiovascular agents, principally antiarrhythmics and vasoactive agents, were most common, with sedatives and analgesics and antimicrobials also widely used. Studies in specific populations and selected samples may have over-represented use of diuretics, antimicrobials, and potassium-lowering agents. Specific detail on clinical scenarios and indications for use along with appropriateness and outcome data was very limited.

While medication errors and delays in access and administration during RRS activations had reported potential for patient harm, systems for medication management in RRSs have not been fully evaluated. Possible solutions, including protocoled care for common clinical deterioration syndromes and delegation of medication roles for RRT members, demonstrated improvement in medication use for the deteriorating patient.

4.2. Comparison with other literature

Medications have been consistently reported as a leading cause of harm in hospitals.[13,59,60] Clinical deterioration and RRS activations have been recognised as markers of error and adverse events.[61,62] However, the link between medications and clinical deterioration or RRSs previously had not been reviewed.

The contribution of medications in up to a third of clinical deterioration events was higher than other current estimates of medication-related harm in hospitals which sit at 10–15% of adverse events.[13,59,60] This discrepancy may be due in part to the difficulties in capturing and reporting medication errors and other adverse drug events and establishing the relationship to patient harm.[13] RRS patients also may represent an at-risk group. Clinical deterioration and RRS activation imply harm has occurred and have been used as measures of such for other causes of clinical deterioration.[62] Medication-related RRS activation could be used in a similar way, as a quantifiable measure of harm due to medications in clinical practice and research.

A recent review of RRT interventions around end of life care also reported diversity in the acuity of medications used.[12] This supports our finding that RRTs use a broad range of medications, not only life-saving critical care medications. While the medications frequently reported appeared to correspond to common RRS triggers and syndromes,[1,63] there has been no investigation of this association nor evaluation of appropriateness or efficacy. The success observed with algorithms for sepsis care by RRTs favours standardisation of medication interventions for common deterioration syndromes. This could achieve similar patient safety and outcome improvements to those seen in cardiac arrest resuscitation through protocols of care and associated training of providers.[64] Extrapolation of electronic health record decision support to RRT treatment pathways must be cautious. As in RRT sepsis care, benefit has been demonstrated in acute trauma and anaesthesia when implemented as part of a larger improvement initiative;[65,66] the same was not found for acute stroke.[67]

Standardised protocols for advanced cardiac life support and anaesthesia also translated into medication management systems to increase patient safety and provider efficiency.[66,68] These benefits seem logical and were highlighted early in RRS development.[62] Better matching of medication management systems to treatment needs may prevent patient harm associated with errors and delays by pre-empting requirements and providing clinicians with rapid and reliable access to medications commonly used by the RRT. Given the heterogeneity of RRTs and their patients, especially across institutions, any algorithms, systems, or training for medication use by RRTs should incorporate a local perspective[1] through optimisation and utilisation of the data collected in the RRS. Routinely collected data should identify the most common deterioration scenarios[2] and could be extended to include medications used. Increasingly, this data may be linked or extracted from electronic health records, although reliable use in these emergency situations and data integrity first need to be established.

4.3. Implications for practice and opportunities for research

Clinicians and researchers should consider medications in deterioration and its management to improve RRSs and patient outcomes. While all clinicians have a role in the prevention, detection, and care of deteriorating patients, currently critical care clinicians staff RRTs in most institutions. As such, critical care clinicians need to include medications as a part of differential diagnoses when assessing a deteriorating patient. This increased awareness alone may increase detection and improve management of medication-related deterioration. Critical care clinicians working in RRTs, trained in advanced life support and crisis team management and familiar with the efficiency of advanced cardiac life support protocols, are also well placed to drive improvement in standardisation and medication management systems to better meet their needs and the needs of their patients.

The most urgent research priority is high quality, generalisable studies to understand which medications in what clinical context contribute to deterioration. The results would facilitate development and assessment of prevention strategies for medication-related clinical deterioration which could eventually reduce RRS activation and the not insignificant burden of RRT staffing, generally carried by ICUs. However, the low rates of medication-related deterioration identified by clinicians during RRS activations suggest detection is the first step. Robust definitions of medication-related deterioration with clinical meaning and relevance must be introduced, along with the use of recommended classification systems for medications, as demonstrated by Marquet et al.[33] This will allow accurate capture, quantification, description, and synthesis in clinical practice and research.

Given the high degree of preventability observed for some medication-related deterioration events, earlier recognition and a coordinated management system may improve outcomes as observed with acute stroke.[69] These require a better global understanding of which medications are used by RRTs and why, along with local data from the quality improvement arm of the RRS. Again this data must be captured and described using recognised classifications to optimise its use.[53] Clinical deterioration and activation of the RRS may prove useful markers of medication-related harm in the hospital setting for future research.

4.4. Limitations

While the structured search strategy strengthens this review by providing a comprehensive view of the available literature, the weak evidence available limited the insights made. Furthermore, keyword searching was used to overcome the challenge of limited indexing of medications; however, this may still have decreased the yield of studies. Studies published only as conference abstracts without peer-reviewed full texts were excluded introducing potential for publication bias. Case identification methods, settings, populations and end points were heterogeneous. Medication findings were usually secondary or incidental and not uniformly classified further limiting comparisons. Gaps in understanding were identified by the multidisciplinary team of authors without the optional scoping review step of consultation.[20] Given these limitations, the findings of this review should be interpreted as cautious suggestions of how medications contribute to and are used in RRSs.

5. Conclusion

Medications contribute to potentially preventable clinical deterioration and are common interventions for its management. While these emerging data lack detail, there is potential for critical care clinicians at this clinical convergence of RRSs and medication safety to improve practice, systems, and patient outcomes. Despite limited evidence, medications appear important in clinical deterioration and RRSs, and clinical studies with well-defined and reproducible medication-related, patient-centred outcomes are a priority.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.aucc.2018.05.006.

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