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Facilitating Safe and Accurate Self Medication

Facilitators and Barriers to Safe Medication Administration to Hospital Inpatients: A Mixed Methods Study of Nurses' Medication Administration Processes and Systems (the MAPS Study)

Abstract

Context

Research has documented the problem of medication administration errors and their causes. However, little is known about how nurses administer medications safely or how existing systems facilitate or hinder medication administration; this represents a missed opportunity for implementation of practical, effective, and low-cost strategies to increase safety.

Aim

To identify system factors that facilitate and/or hinder successful medication administration focused on three inter-related areas: nurse practices and workarounds, workflow, and interruptions and distractions.

Methods

We used a mixed-methods ethnographic approach involving observational fieldwork, field notes, participant narratives, photographs, and spaghetti diagrams to identify system factors that facilitate and/or hinder successful medication administration in three inpatient wards, each from a different English NHS trust. We supplemented this with quantitative data on interruptions and distractions among other established medication safety measures.

Findings

Overall, 43 nurses on 56 drug rounds were observed. We identified a median of 5.5 interruptions and 9.6 distractions per hour. We identified three interlinked themes that facilitated

successful medication administration in some situations but which also acted as barriers in others: (1) system configurations and features, (2) behaviour types among nurses, and (3) patient interactions. Some system configurations and features acted as a physical constraint for parts of the drug round, however some system effects were partly dependent on nurses' inherent behaviour; we grouped these behaviours into 'task focused', and 'patient-interaction focused'. The former contributed to a more streamlined workflow with fewer interruptions while the latter seemed to empower patients to act as a defence barrier against medication errors by being: (1) an active resource of information, (2) a passive information resource, and/or (3) a 'double-checker'.

Conclusions

We have identified practical examples of system effects on work optimisation and nurse behaviours that potentially increase medication safety, and conceptualized ways in which patient involvement can increase medication safety in hospitals.

Introduction

Medication administration errors (MAEs) occur in 8.0% to 19.6% of doses in hospitals worldwide [1]. Although these figures should be interpreted with some caution due to important differences among studies [2], it is clear that MAEs are common. Even in countries where MAE rates appear relatively low, such as the United Kingdom (5.6% of non-intravenous doses administered to adult hospital inpatients [2]), it has been estimated that 0.6–21% of MAEs may lead to severe patient harm [3]. Considering the vast number of medication administrations that occur, the actual number of patients that suffer harm is likely to be substantial. However, while many studies have measured the incidence of MAEs [1,2] and identified causes that arise from both individuals and systems [4], few have examined this area from the other perspective: how do nurses work within hospital systems to administer medications safely and successfully?

A system is any set of interdependent elements or processes interacting to achieve a common aim [5]. High-profile public inquiries and reports [5–11] provide a stark reminder that while humans err, systems can fail. In some cases, system failures that contributed to patient suffering were also the result of an organizational culture that disproportionately prioritized achieving financial targets over providing quality patient care [12]. System-based failures in healthcare organizations can occur in any processes and are likely to be important underlying contributory factors for recurring medication errors [5,10,13]. Poorly designed systems and overly complicated processes can increase the risk of an error occurring, while intuitive user-centred designed systems and more streamlined or simpler processes may reduce this risk [13,14].

In the context of hospital drug administration rounds, persistent system-related challenges such as medicines not being available, limited equipment, inefficient workflow and frequent interruptions are known contributors to MAEs [15,16]. However, variation in ward-based systems (such as medication ordering, storage and transport systems) exist within and between countries [3,17,18]; research suggests such variation can affect the frequency of different types of MAEs [19–22]. While it is important that such causes of MAEs are identified, this only provides us with information about which systems and processes do not work well. It does not tell us which *do* work well. For instance, studies of reworks and workarounds associated with medication administration suggest that alternative and sometimes 'deviant' processes (which may

also be procedural failures, violations, shortcuts or improvisations) are relatively common and can create 'more holes in the system', bypassing essential safety defence barriers, and thereby increasing the risk of a medication safety incident occurring [23–26]. However, in some cases, alternative or deviant processes may be deliberate pre-emptive actions taken by an individual to increase efficiency or to overcome known error-prone system-based failures [25]. Thus, alternative processes may act as an indicator of underlying latent conditions for future incidents [13]. It is therefore important to not only identify potential contributory factors for MAEs but also how individuals manage them within the resources available.

We aimed to address this knowledge gap by identifying and describing system factors that facilitate and/or hinder successful medication administration, focused on three interrelated areas: (1) individual nurse practices and workarounds, (2) medication administration workflow, and (3) the frequency and nature of interruptions and distractions during medication administration.

Methods

This was a mixed methods ethnographic study of medication administration by nursing staff in three wards, each in a different English National Health Service (NHS) hospital trust. Study wards were purposively selected to represent a range of inpatient medication systems; the sampling frame was based on findings from our national survey of hospital medication systems [27]. One ward (site A) was selected as a 'typical' English inpatient ward (including paper medication prescription charts, patient bedside medication lockers plus drug trolleys, and the use of patients' own medications where appropriate). One ward (site B) used an established electronic prescribing and medication administration (EPMA) system (since 2008). The final ward (site C) used a relatively new EPMA system (since July 2012) and had two nurses administering medication together to each patient. Other ward characteristics and dates of observation are summarised in Table 1.

Ethics statement

NHS research ethics approval was not required as this study met the criteria for service evaluation and focused on staff as participants [28]. Academic research ethics approval was granted by the School of Pharmacy, University of London, in January 2011. All participants provided written consent.

Data collection

Nurses mainly administered medications during scheduled drug rounds (Table 1); data collection therefore focused around these times. A convenience sample of nurses was observed by one experienced pharmacist researcher (MM) for seven to ten consecutive days on each ward. Prior to starting observations, MM went through a participant information leaflet with the nurse concerned, answered any questions and requested written consent. Observations were divided into 'qualitative' and 'quantitative': each was conducted during separate drug rounds. MM observed nursing staff as they went about their usual routines before, during and after scheduled rounds. The start time, duration, number of patients, and number of steps taken by the nurse (using a pedometer, Yamax Digi-Walker SW-200) during each observed drug round were documented. During the first set of observed drug rounds (qualitative), detailed descriptions of the medication administration processes and systems were documented as field notes, photographs, 'spaghetti diagrams' (maps of the ward annotated by hand to show nurses' walking patterns during drug rounds), and narratives. Field notes ranged from including the greatest level of detail, described by Lofland and Lofland [29] as 'practices' (an activity that the

Table 1. Characteristics of study wards and summary of data collected.

Study wards	Staffing	Medication systems and administration processes	Observations
Site A: 27-bed vascular/ cardiology ward in an acute NHS trust	24 nurses. Observed nurse to patient ratio 1:8 on both day shift and night shift. Nurse participants reported fewer staff than usual during the data collection period	Paper drug prescription and administration chart; four drug trolleys; RFID controlled electronic bedside medication cabinets; nurses administered drugs to patients they were looking after; patient's own drugs from home were permitted to be used during their inpatient stay.	26 March to 3 April 2012; 14 nurses (includes 2 bank/agency)[a] (13 female; 1 male); 18 drug rounds (three at 6am and five each at 12pm, 6pm and 10pm); total 27 hours of observation, of which 15 hours 20 min were during drug rounds; 11 hours 40 min were before and after drug rounds.
Site B: 28-bed adult elective surgical ward in an acute hospital of a foundation NHS trust	16 nurses. Observed nurse to patient ratio 1:6 on both day shift and night shift. Nurse participants reported fewer patients than usual during the data collection period	Trust-wide EPMA system since 2008; EPMA access: two desktop computers, three tablet devices, and one COW; two drug trolleys; RFID controlled bedside medication cabinets; nurses administered drugs to patients they were looking after; patient's own drugs from home were permitted to be used during their inpatient stay.	20–31 August 2012; 13 nurses (includes 2 bank/agency)[a] (12 female; 1 male); 20 drug rounds (four at 6am, five at 12pm, six at 6pm, and five at 10pm); total 29 hours of observation, of which 14 hours 13 min were during drug rounds; 14 hours 47 min were before and after drug rounds.
Site C: 18-bed adult neurological rehabilitation ward in an acute hospital of a foundation NHS trust	15 nurses. Observed nurse to patient ratio 1:9 on both day shift and night shift. Nurse participants reported fewer staff than normal during the data collection period	EPMA system since July 2012, trust-wide roll out in progress at time of data collection; EPMA access: one desktop computer, one laptop attached to the drug trolley, and two COWs; one large drug trolley; conventional metal bedside medication lockers; two nurses administered drugs to all patients together; 'opt-out' patient self-administration policy; patients' own drugs from home were permitted to be used during their inpatient stay; HCAs helped patients to take their medications after the nurse had prepared the doses.	12–19 November 2012; 16 nurses (includes 3 bank/agency)[a] (13 female; 3 male); 18 drug rounds (two at 6am, four at 8am, four at 12pm, five at 6pm, and three at 10pm); total 29 hours of observation, of which 20 hours 35 min were during drug rounds; 8 hours 25 min were before and after drug rounds; no IV doses were prescribed (patients on this ward do not usually require IVs).

Abbreviations: COW, computer on wheels; EPMA, electronic prescribing and medication administration system; HCA, health care assistant; IV, intravenous; NHS, National Health Service; RFID, radio frequency identification.

[a]Bank nurses were employees of the hospital trust who may also be a regular staff member of the study ward. Agency nurses were employees of an external company who were contracted by the hospital trust to provide nursing staff cover to wards for specific work shifts.

participants regard as unremarkable normal feature of on-going life), to the highest level 'life-styles or subcultures' (the global adjustments to life by large numbers of similarly situated persons). The level of detail to be abstracted during observations was not determined *a priori* as we wished to explore interactions at different levels between 'humans' and 'systems'. During the second set of observed drug rounds (quantitative), additional quantitative data plus explanatory field notes were documented: details of the medicines administered, storage locations accessed, and the number and sources of interruptions and distractions. Data collection was not focused on detecting MAEs; however the number of observed opportunities for error (as defined below) was documented so that the MAE rate could also be calculated if any MAEs were observed.

Definitions and categories

To facilitate interpretation of our quantitative findings [2] we used Allan and Barker's [30] MAE definition: a deviation from the prescriber's medication order as written on the patient's chart. Errors prevented by the patient or persons other than the nurse themselves were also

included as MAEs. The following were excluded as MAEs: wrong time, doses omitted for therapeutic reasons or due to the patient not being on the ward, and procedural violations such as not checking the patient's allergy status or leaving a dose at the patient's bedside for the patient to self-administer. All doses where both preparation and administration were observed were included as opportunities for error (OE); the total number of OEs was the denominator for calculating MAE rates. Detailed definitions of these are provided elsewhere [3].

There is no standard operational definition for an interruption or distraction, or standard categories for the source of the interruption or distraction [31]. We therefore adapted previous definitions [16,31,32]: an interruption was defined as a situation in which a nurse ceased the medication preparation, administration and/or documentation task before it was complete [31,32] and a distraction was a stimulus from a source external to the nurse that was not followed by cessation of activity but by the nurse continuing productive efforts while responding in an observable manner [32]. Specific sources of interruptions and distractions were grouped into 16 categories [31,33]; detailed definitions of the sources of interruptions and distractions are reported elsewhere [3].

Data analysis

All data were transcribed within 24 hours of observation to maximize recall, identify further areas to focus subsequent observations, and facilitate concomitant data analysis during data collection. Qualitative data were analysed using a framework approach [34]; an initial high level thematic framework based on the study objectives was produced which comprised: medication systems available, use of medication systems in practice, medication safety, drug round workflow, and interruptions and distractions. MM analysed all data and further developed the framework; BDF independently reviewed several iterations of the expanded thematic framework, verified the coding schemes and indexed two sets of field notes from each study ward (approximately 10% of all field notes). The final coding scheme and thematic framework were produced after further iterative work by MM and BDF. Quantitative data were summarized descriptively. MAE rates were calculated for both non-IV doses and IV doses [2] as a percentage of the total number of OEs observed. Separate and combined interruption and distraction rates per drug round hour were also calculated [31,35].

Authenticity, plausibility, and criticality

We used three interpretative criteria to increase validity of our findings: authenticity, plausibility, and criticality [36]. Authenticity has been described as "immersion in the case through extended fieldwork" [36]; we report in our findings a range of evidence to demonstrate this. Plausibility is "developing explanations of local phenomena which made sense to participants and drawing these together into a coherent overall narrative" [36]; this was achieved through feedback and discussions with participants at the end of the observation period at each site. Criticality is the systematic questioning of assumptions made in describing the explanations of the phenomena under study. Both plausibility and criticality considerations also formed a key component of the data analysis by having two researchers (MM and BDF) analyse the data iteratively until both agreed on the final themes.

Results

Overall, 85 hours and 43 different nurses on 56 drug rounds (26 qualitative and 30 quantitative) were observed across the three study wards (Table 1). One newly qualified nurse who initially declined later agreed to be observed when she was able to give medications unsupervised.

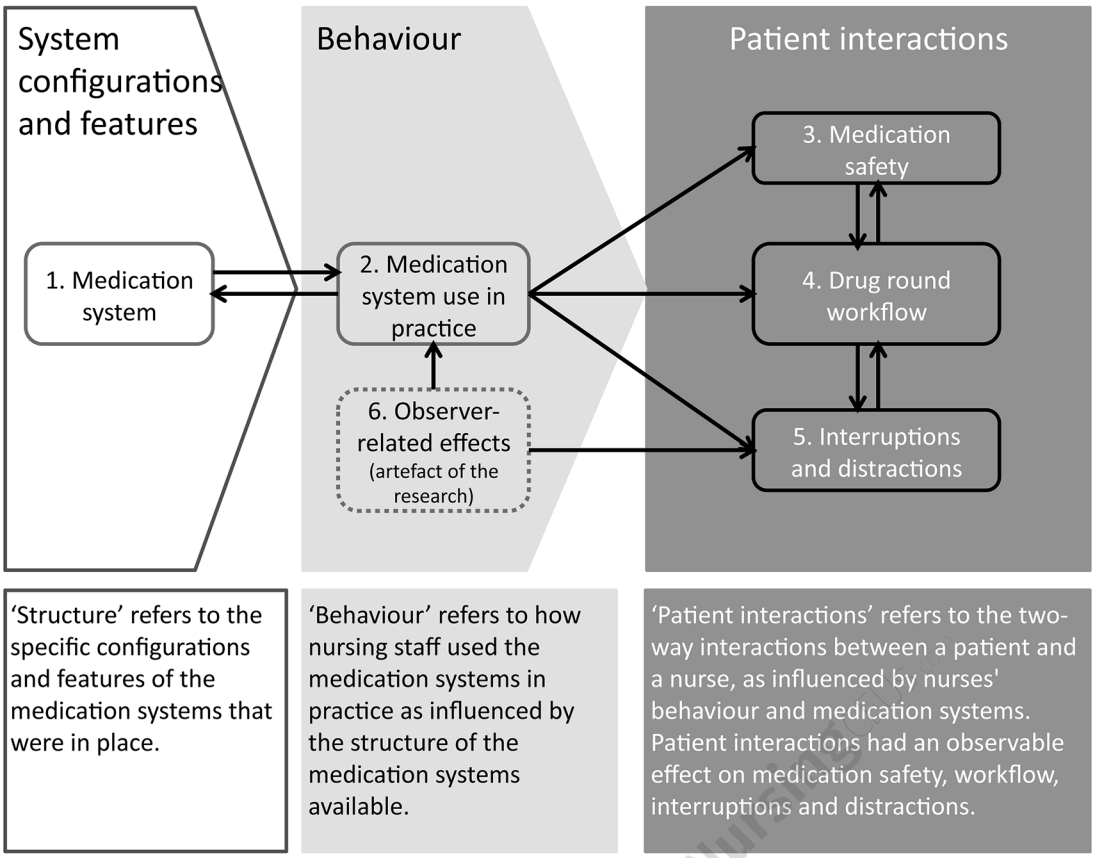

Fig 1. Conceptual overview of thematic factors that influence medication administration errors, workflow, interruptions and distractions associated with the hospital medication administration process. There are three over-arching interlinked themes: structure, behaviour, and patient interactions that encompass the six main areas (numbered). Arrows indicate the direction of influence between areas. Dotted lines indicate the presence of the observer as an artefact of the research directly on nursing staff behaviour, and on interruptions and distractions.

All other nurses consented to participate. Verbal nursing feedback suggested that they did not mind being observed and many expressed interest in the study.

During the quantitative observations, 458 doses were included as OEs (445 non-IV and 13 IV doses). The MAE rates were 2.7% of non-IV OEs (95% confidence interval (CI), 1.2 to 4.2) and 30.8% of IV OEs (95% CI, 26.3 to 35.2).

We identified three inter-related themes that encompassed the five main areas in our initial thematic framework; a sixth, 'observer-related effects', was added to reflect actual and potential effects of having an observer on both nurse and patient behaviour (Fig 1). The three inter-related themes were: (1) structure—related to configurations and features of the medication systems, (2) behaviour—referring to different types of nursing staff behaviour, and (3) patient interactions—referring to the two-way interaction between a nurse and a patient. Structure was the foundational theme that affected different types of nurse behaviour, which in turn, incited different types of patient interactions; each comprised components that exerted a positive and/or negative impact on medication safety, drug round workflow, interruptions and distractions.

'Structure'—system configurations and features

Specific configurations (location and arrangement of human and material resources) and features (characteristics, interpretability, and pre-conditions for use) of structure-related

Table 2. Examples of system configurations and features, and their potential positive and negative effects on medication safety, workflow, interruptions and distractions.

Potential positive aspects of system configurations and features	Potential negative aspects of system configurations and features
Facilitating medication preparation next to drug chart/EPMA system (1) A desktop computer was near the stock cupboard for oral medicines, thus allowing nursing staff to check the EMAR while preparing medicines that may not be available from the drug trolley; (2) The patient bedside medication locker was a removable drawer which could be moved to an alternative area while preparing medicines (for example, if there was limited space at the locker to place the drug chart or mobile EPMA device, or if more than one drug was required from the bedside medication locker).	Practicalities of the drug chart/EPMA system (1)Drug administration codes for 'patient refused' and 'patient did not require' were used interchangeably Reported unreliability of tablet computer devices and font size too small on laptop led to nurses reporting a preference for using the desktop computer on some drug rounds. This meant that the EMAR was sometimes not used at the patient's bedside or at the drug preparation location (e.g. treatment room); (2) Password and training required to use EPMA system, therefore EPMA could not be used by agency staff. Instead, regular nursing staff printed out medication administration records for agency staff and transcribed medication administration documentation on to the EPMA system after each drug round (signature on EPMA system was of the transcribing nurse).
Facilitating medication retrieval during drug round (1) Some patients kept their bedside medications together in a box which seemed to make it easier for nursing staff to find medications not stored in the bedside medication locker, for example, creams and inhalers; (2) Medications in the drug trolley were arranged such that the front (rather than the side) of most packs were facing the nurse to aid identification: (3) Drug trolley was kept in the treatment room and was often replenished immediately prior to and/or after the drug round; (4) Drug trolley was kept in the treatment room which also had a fridge; fridge items were placed in the drug trolley prior to starting the drug round.	Travel (1)Not all the medications or equipment (drug charts, keys, paper/plastic medicine cups) required during the drug rounds were available at the patient's bedside. Some may be temporarily placed elsewhere but others such as infusion pump equipment were located in a separate room some distance away from the patient's bedside and potentially increased travel for nurses; (2) The day room was located some distance away from the patient bed areas which was a particular problem on one ward as some patients were mobile and were often in the day room during drug rounds; thus potentially increased travel and opportunities for interruptions.
Reducing interruptions and distractions (1) Ward staff developed a standard form for documenting medication-related tasks that required follow-up after the drug round; (2) Ward staff placed a 'ward screen' at the entrance of a bay in which patients were being washed, this discouraged interruptions to anyone inside the bay including interruptions to nurses who were carrying out the drug round at the same time; (3) Nurse checked EPMA at the nurse station prior to starting lunchtime drug round for doses that were due. Nurse expected very few doses and did not use drug trolley on the drug round but prepared medications at the nurse station from the stock cupboard.	Medication security and accessibility (1) A few medicines (for example, nebules and pre-filled syringes) were sometimes kept on the shelf at the bottom of the drug trolley in addition to inside the drug trolley which was accessible to passers-by; (2) Some frequently used IV drugs (e.g., paracetamol [acetaminophen] and metronidazole) were stored on high shelves which made them difficult to retrieve; (3) Some patient bedside medication lockers were positioned so that the locker opened towards the bed to facilitate patient self-administration (rather than towards the nurse opening it) which made it more difficult for the nurse to access the contents when the patient was not self-medicating; (4) Nurses had to stoop to open patient bedside medication lockers.

Abbreviations: EMAR, electronic medication administration record; EPMA system, electronic prescribing and medication administration system; HCA, health care assistant; HCP, health care professional; IV, intravenous.

aspects [37] of the medication system acted as a physical constraint on some drug round tasks. Such structure-related aspects increased medication safety in some cases, but contributed to interruptions, distractions, impaired workflow, and medication problems in others (Table 2, Figs 2 to 5).

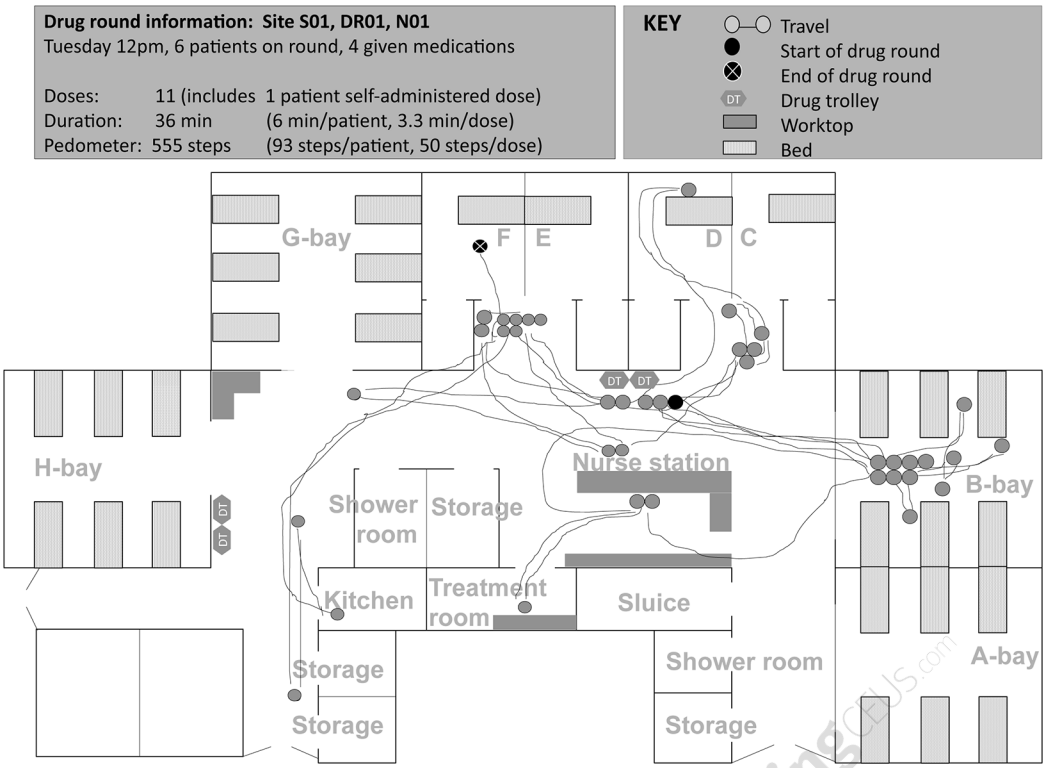

Fig 2. Spaghetti diagram showing non-linear travel by one nurse (qualified 2 years, 1 year experience on study ward) during a noon drug round at site A (map of ward not drawn to scale). Nurse started the drug round by wheeling the drug trolley from opposite the nurse station to side room D. Nurse went to another drug trolley located near G bay (3 times): once each to find medication, a tablet cutter and a plastic medication cup. Nurse also walked and attended to a patient other than the patient she was preparing medications for during the drug round (2 times), to the nurse station to look for a paper drug chart (2), to the kitchen to retrieve nutritional supplement (1), and to help another nurse to exit the ward (1). S01, site code; DR001, drug round code; N01, nurse code. Letters refer to ward bay areas.

Both potentially 'positive' and 'negative' system configurations and features for medication safety were identified on each study ward; these were grouped under broad headings as in Table 2. Nurses rarely commented on the benefits of existing medication systems and processes on medication safety, workflow, interruptions or distractions; however nurses did report perceived negative aspects as areas for improvement. In general, few nurses sought to resolve underlying problems during the periods observed. In a number of cases, individuals seemed to have accepted these and worked around the problem:

Nurse sometimes likes to put two drug trolleys together so she can prepare the medicines more easily [implied medications were not always available from one drug trolley].

(Site A, comment documented during a drug round. Nurse had one year of experience on the ward)

Nurse preferred to use the tablet computer over the computer on wheels (COW) as she found the mouse pad tricky to use on the COW. However, she preferred to sign for medication administrations at the desktop as the tablet computer was too small.

(Site B, comment documented during a drug round. Nurse had over seven years of experience on the ward)

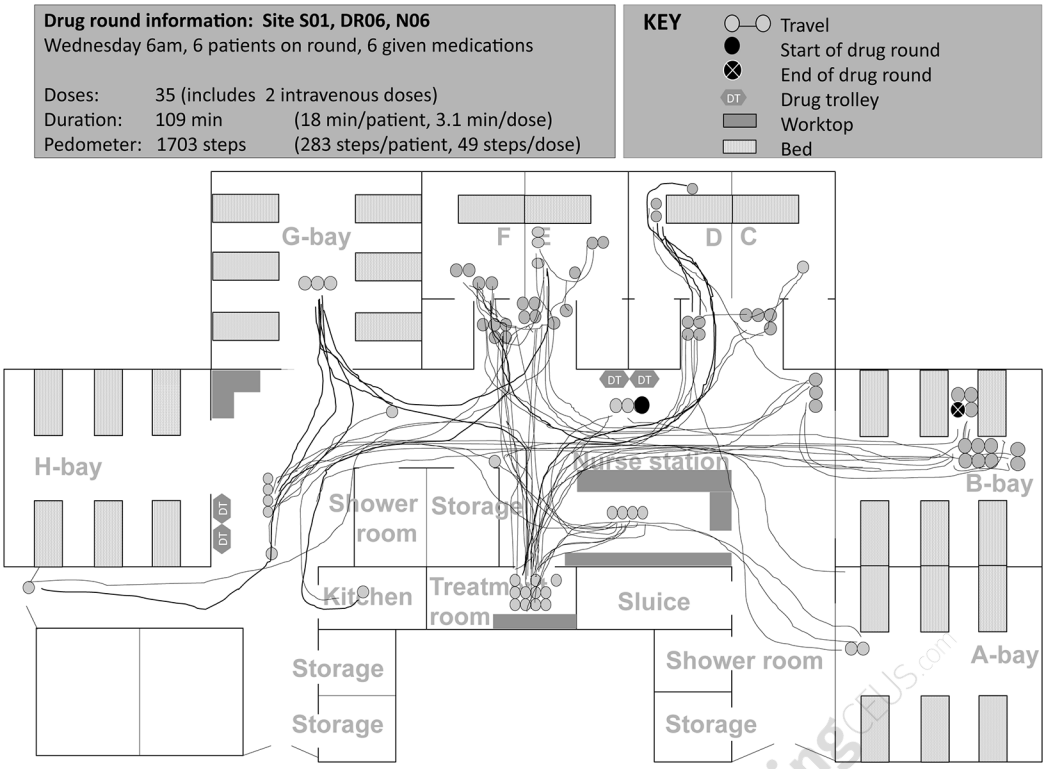

Fig 3. Spaghetti diagram showing non-linear travel by one nurse (bank staff) during a morning drug round at site A (map of ward not drawn to scale). Nurse started the drug round by wheeling the drug trolley from opposite the nurse station to side room D. Nurse went to the treatment room 11 times during the drug round: to look for medicines in the stock cupboard (2 times),to prepare medications for intravenous administration (5), to look for the drug chart (1) and to access the medicines fridge (3). During the drug round, the nurse also travelled to locations other than between the drug trolley and patients' bedside: another drug trolley to look for medicines (4 times), nurse station to look for drug chart (1), nurse station to look for keys (2), kitchen to retrieve nutritional supplement (1), to another nurse to provide handover of patients (2), and to the ward next door to look for medicine (1). S01, site code; DR006, drug round code; N06, nurse code. Letters refer to ward bay areas.

Based on individual feedback and observations, the type of action taken to manage perceived medication system related problems or inefficiencies seemed to partly depend on individual behaviour types, which are next described.

'Behaviour'—types of behaviour among nursing staff

As illustrated in Figs 2 to 5, medication administration was not a linear process; nurses encountered a number of tasks which took them to locations other than the patient's bedside. Observed variation between individual approaches to drug round tasks, even on the same ward, suggests that workflow was not only influenced by structure-related configurations and features, but also by behaviours that partly depended on the individual ('inherent behaviour') and on the immediate environment in which medications were given ('situational behaviour').

Broadly, nurses appeared to have an inherent tendency to be either primarily 'task focused' (main goal of drug round appeared to be administer drugs as efficiently as possible), or 'patient-interaction focused' (drug round appeared to be an opportunity for the nurse to interact with their patients in addition to administering medications). Excluding urgent tasks, task-focused individuals generally used a streamlined workflow and carried out few non-medication administration related tasks during the drug round; when the need for such tasks was identified during the round, the nurse either deferred the task to the end of the round, or carried out the

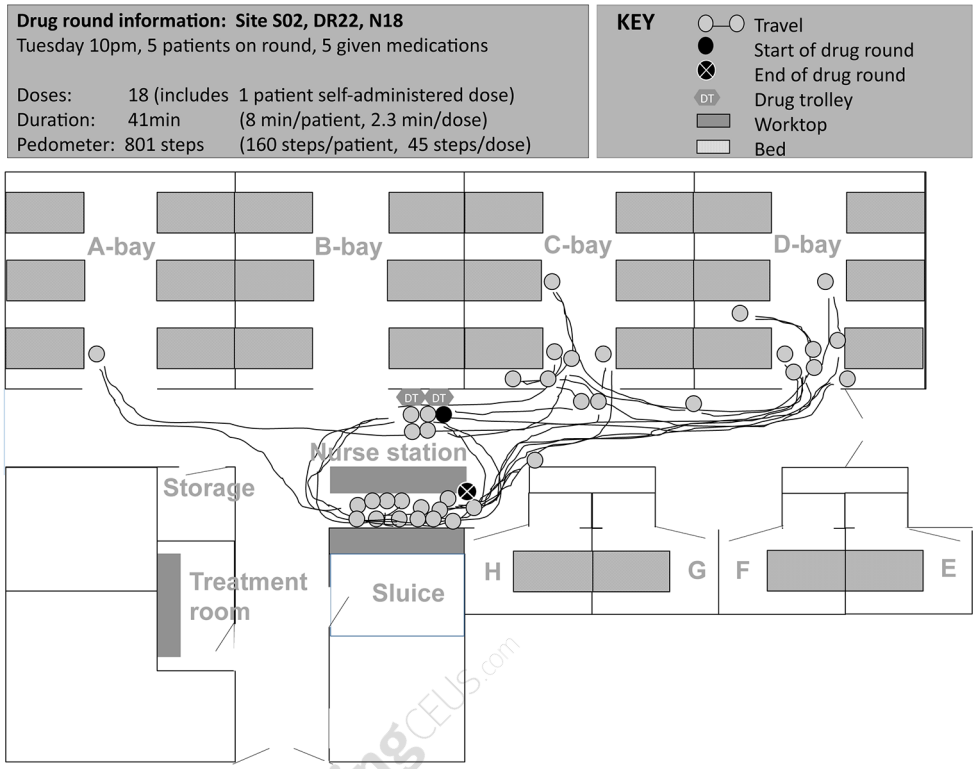

Fig 4. Spaghetti diagram showing non-linear travel by one nurse during night-time drug round at site B (map of ward not drawn to scale). Nurse started the drug round by logging on to the tablet computer next to the drug trolleys at 21:05, placed tablet computer on drug trolley and wheeled it to each patient starting in C-bay. Nurse went to the nurse base station area 13 times during the drug round: to look for master key to patient's bedside medication locker (2 times), to look for medicines in stock cupboard (4), to access desktop computer to view and/or sign patient medication orders (5), to take a telephone call (1), and to prepare from the controlled drugs cupboard (2). Nurse ended the drug round at the nurse base station double checking on the electronic prescribing and medication administration system that all the relevant doses had been signed. S02, site code; DR022, drug round code; N18, nurse code. Letters refer to ward bay areas.

task when another task took the nurse to a convenient location to carry out multiple tasks together (Fig 6). By contrast, patient-interaction focused individuals adopted a relatively less streamlined workflow, and appeared to encourage communication with patients and/or other staff during the round; the patient-interaction focused individuals either multi-tasked, carried out the non-medication administration related task shortly after they completed the primary task, or stopped the primary task to carry out the non-medication administration related task.

Additionally, a number of self-reported intentional 'alternative' practices ('non-conforming behaviour') from ward routines and trust policies were identified: some examples are presented in Fig 7. We identified three main overlapping reasons for non-conformance: perceived inefficient process or system, clinical risk, and personal preference. The resulting action may or may not violate policy.

Overall, all behaviour types had the potential to either increase or decrease medication safety. Sometimes the alternative practice observed was part of an established tried-and-tested routine for the individual; at other times it was more spontaneous. In general, the behaviour types exhibited were not fixed; individuals appeared to shift from one to another, depending on the needs of the patient, the medication system being used at the time, the task being carried out, and other situational circumstances.

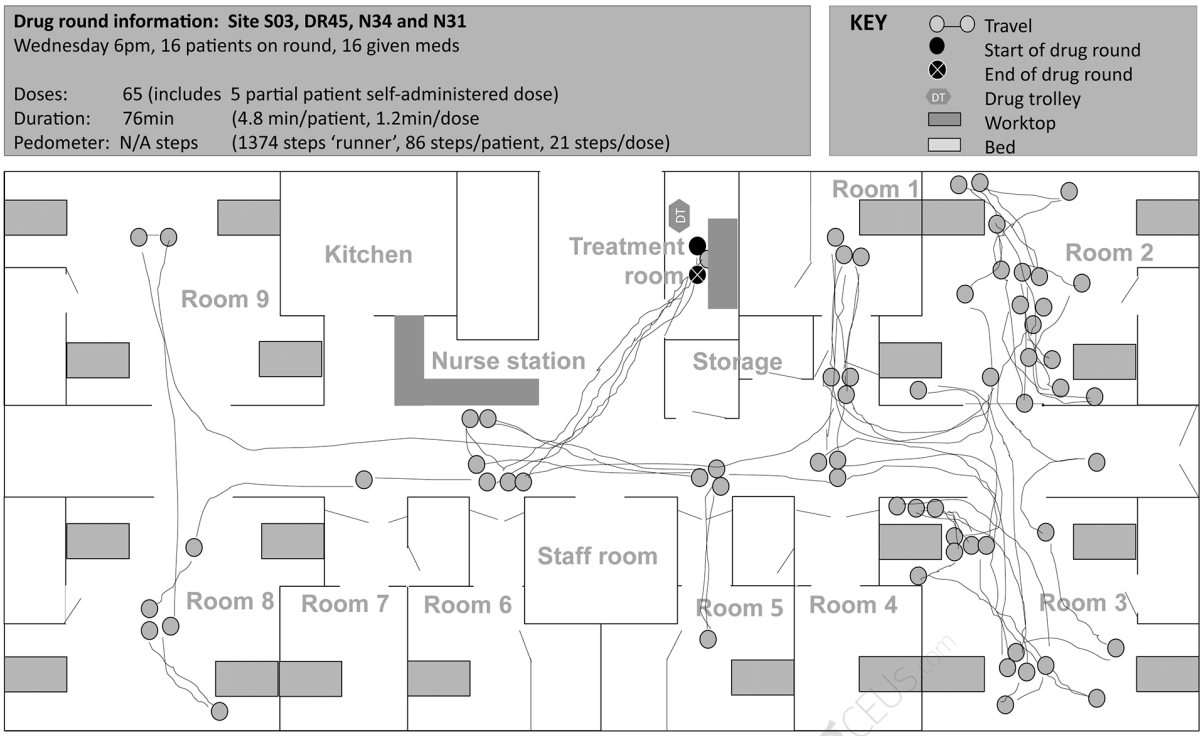

Fig 5. Spaghetti diagram showing changes in travel pattern of one nurse during a 'two-nurse' evening drug round at site C (map of ward not drawn to scale). At site C, two nurses typically worked together on the drug round to administer medications to all patients; one nurse 'caller' and one nurse 'runner'. The diagram shows the path of travel by the nurse 'caller' who initially stayed with the drug trolley: she used the laptop attached to the drug trolley to access the patient's electronic medication administration record, called out doses to the 'runner' to retrieve medications from the bedside medication locker and prepared some doses from the drug trolley. After preparing medicines for the patient in room 6, the nurse caller went 'ahead' while the nurse runner remained to administer the doses; this process was repeated whenever a patient required assistance to take the medicines and led to a 'single-nurse' drug round for parts of the remaining round. During the drug round, the nurse caller went to the nurse base station twice (to retrieve a patient's folder to check oxygen saturation and to retrieve another patient's folder for paper warfarin medication order) and treatment room once (to retrieve medication from the fridge). S03, site code; DR045, drug round code; N34 and N31, nurse codes.

Given that the nurse him/herself was the third most common source of interruptions and distractions (Fig 8), it is likely that individuals' inherent tendencies may influence the potential for MAEs. However, the 'direction' of influence (positive or negative) on drug round workflow and MAEs depended on the medication systems being used and the task being carried out at the time. By contrast, 'other nurses' were the most common source of interruptions and distractions to the nurse on the drug round. Observations suggest that these interruptions and distractions were frequently made by those who themselves were also involved in medication administration around the same time; multiple nurses administered medications simultaneously to their own individual patients on two study wards and therefore the same medication system problems were potentially affecting the nurses at the same time. The percentages of other sources of interruptions and distractions are summarized in Fig 8; the presence of the observer had a measurable effect on the number of interruptions and distractions experienced by the nurse. However, the overall percentage of observer-related interruptions and distractions was considerably less than those from patients despite the observer's continued presence.

Patient interactions

As depicted in Fig 1, interactions between patients and nursing staff resulted in an observable effect on medication safety and drug round workflow. Patients were the second most common

Task focused

- Nurse deferred a task for later. As the nurse was at patient C3's bedside about to move on with the drug round, patient C4 interrupted and asked the nurse to remove her intravenous cannula. A brief discussion followed, nurse explained that she still had medications to give and will come back to see patient C4 later (site B)
- Nurse grouped some tasks to do together rather than stop what they were doing. Whilst the nurse was preparing ketamine in the treatment room, she also picked up a box of tinzaparin and then some plastic cups (these were needed in the drug round earlier) from the other drug trolley outside a patient bay before going back to patient G1 to administer the ketamine, then prepared the oral morphine sulphate solution, gave to the patient, then paracetamol [acetaminophen], and then administered the tinzaparin to the patient (site A)
- Nurse re-ordered some tasks to increase efficiency. Patient was fast asleep and was due medication, nurse N28 told nurse N36 that she'll "sign for it now so all the paperwork is done", wrote a reminder to administer medications on a pre-printed job list form and said she will give the medications to the patient when he is awake (site C)

Patient-interaction focused

- Nurse prioritised a non-drug round related activity over the drug round. Nurse N12 talked to the patient as she was administering slow IV bolus of co-amoxiclav. Later saw another nurse helping patient G1 with his vacuum-assisted closure dressing, N12 went to help, took about 20 min for N12 to go to TR, draw up saline flush, go back to G1 to try to unblock tube, got interrupted by another nurse several times, decided to change a vacuum-assisted closure dressing, prepared dressing trolley and changed dressing before returning to the drug round (site A)
- Nurse dealt with a patient's query straight away. Patient asked the nurse about her aspirin, said she hasn't taken it today. Nurse stopped what she was doing to talk to the patient. Patient said nurse last night gave her an injection to replace the aspirin, nurse confirmed that she will also give the injection (site B)

Fig 6. Examples of inherent behavioural tendencies and associated influences on how systems were utilized, and how medication administration related problems, interruptions, distractions, and workflow were managed.

source of interruptions and distractions during drug rounds (Fig 8) and therefore potentially contributed to reduced medication safety. However, some nurse-patient interactions potentially increased safety. Specifically, we found three manifestations of the patient being a defence against medication errors: (1) patients as an active resource of information (volunteering information about their medicines without prompting), (2) patients as a passive resource of information (providing information about their medicines when asked or prompted), and (3) patients acting as a 'double-checker' with the intention to check the medication being prepared or administered (Table 3).

While patient interactions primarily related to relationships between nursing staff and the patient, a number of system-related influences on these relationships were also observed. For example, nurses typically did not take the computer on wheels (sites B and C) or drug trolley (all sites) into patient side rooms (single-bed), and often relied on their memory and/or brought medications out of the room to prepare doses, thus potentially reducing patient

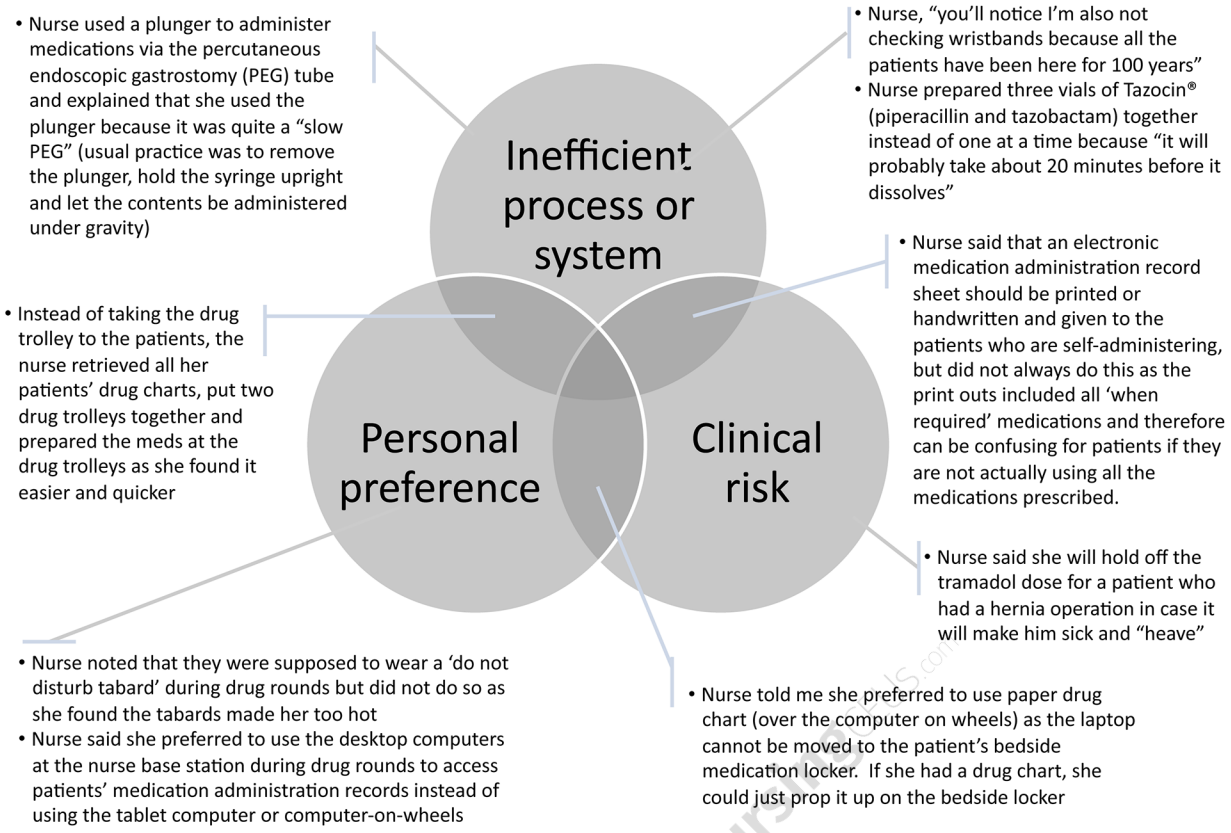

Fig 7. Three main overlapping reasons for intentional 'alternative' practices identified from nurses' feedback.

involvement. Patient involvement was important not only as a potential defence barrier for MAEs but also to optimize their treatment. The dose omission rate due for clinical reasons, such as a patient declining to take tramadol as it made them feel sick and they were not in any pain, was 11.4% of 458 OEs, many of which were the result of direct nurse-patient interaction during the drug round.

Discussion

This is the first study to combine qualitative and quantitative methods to explore how nurses administer medications safely to hospital inpatients despite various challenges of the ward environment. Variations in hospital ward medication systems in English NHS hospitals exist [18,27] but we identified much more subtle variations than previously reported. Overall, medication administration is not a linear process, and we identified three inter-related themes that acted as both facilitators and barriers to safe medication administration. The first relates to specific configurations and features of the ward-based medication system (theme 1). This in turn can influence nursing staff behaviour (theme 2) in terms of workflow, how nurses manage interruptions and distractions, and how they interact with patients (theme 3). Based on our findings, a number of system-related nurse behaviour types were identified. Importantly, nurses appeared to have a general inherent tendency to be either primarily 'task focused' (main goal of drug round was to administer medications as efficiently as possible), or 'patient-interaction focused' (drug round was an opportunity for the nurse to interact with their patients in addition to administering medications) during the drug round. Both types of behaviour had

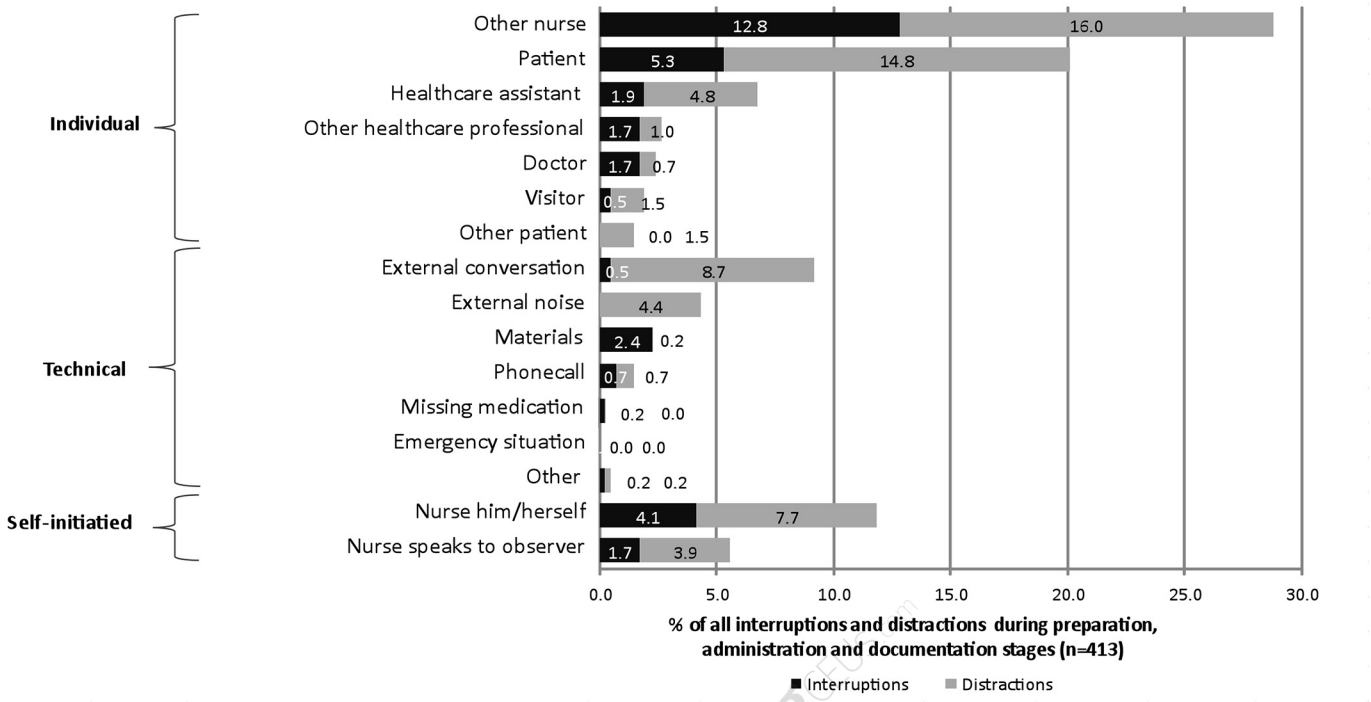

Fig 8. Sources of interruptions and distractions during drug rounds percentage of a total of 413 interruptions and distractions observed at the preparation, administration, and documentation stages of drug rounds). Median 5.5 interruptions per drug round hour, range 0 to 24; median 9.6 distractions per drug round hour, range 0 to 30; median 15.5 interruptions and distractions combined per drug round hour.

the potential to increase medication safety in different ways: task focused behaviour may lead to a more streamlined and efficient workflow thereby minimizing interruptions and distractions that potentially contribute to MAEs [16], while patient-interaction focused behaviour may lead to increased patient involvement with their medication thereby better enabling the patient to act as a defence against errors. A focus on alternative practices also led to the identification of three overlapping causes for intentional non-conformance. Analysis of alternative practice behaviour was based on nurses' feedback during the observations and was therefore primarily associated with structure-based inefficiencies. Other unreported reasons for alternative practices were not explored. Nonetheless, our findings support previous research which identified that "workarounds can [both] subvert and augment patient safety" [25]. Furthermore, by studying nurse behaviour types, our research suggests that potential latent conditions for MAEs, analogous to the 'resident pathogens' described by Reason [13], can be identified by examining non-conformance with typical local practices.

Consistent with the literature, patients sometimes acted as a defence barrier to medication error [38]. We identified and conceptualized three ways in which patients acted as a defence, emphasizing the importance of patient involvement in their medicines even in hospital. The challenge is identifying how this can best be facilitated, while recognizing how this is likely to change during different stages of the inpatient stay.

Implications for practice

In the UK, the high-profile Francis Report [6–8] highlighted inadequate nurse staffing (numbers, skill mix, knowledge and experience) as a major patient safety concern in one NHS trust.

Table 3. Three observed manifestations of the patient as a defence against medication errors.

Description	Examples
Patients as an active resource of information (volunteered information) about their medicines	• Patient highlighted discrepancy in pregabalin dose, told the nurse it should be 250mg twice a day, but it was prescribed as 100mg twice a day, nurse documented this and talked to patient about changes in medications. Later it was confirmed that the wrong dose had been prescribed (site C).
	• Patient told the nurse that she (the patient) could not break up the cocodamol [contains paracetamol and codeine] and therefore did not take the dose that was given to her in the previous drug round. The dose had been signed as administered but was not actually taken. Nurse was aware, helped patient crush tablets by using two spoons (could not find tablet crusher on the ward) (site B).
Patients as a passive resource of information (provided information when asked or prompted) about their medicines	• Nurse noticed on the drug chart that the patient had not received tinzaparin recently (there were two doses crossed off and one blank administration box), she asked the patient "do you know of any reason why you haven't been given the tinzaparin?" "I get it on dialysis" replied the patient. Tinzaparin had been prescribed for once daily administration and there was no documentation on the drug chart to indicate that the patient was to receive this on dialysis days only (site A).
	• Nurse told the patient what she was giving (included naproxen and omeprazole); patient explained he takes both at night: “only take it at night” “not morning?” “only take it at night” “ah they prescribed it for this morning. . ...I don’t know why [they] prescribed it for morning” explained to patient that she did not give these last night and so patient took the medications at the morning drug round (site B).
	• Medication order did not specify which eye(s) to which the eye drops were to be applied. Nurse asked the patient, "your eye drops, do we do it for you or you do it?" "You do it" "Is it both of the eyes?" Patient confirmed it was for the right eye, nurse administered it to the patient’s right eye (site A).
Patient acted as a double-checker during drug rounds	• Metformin dose prescribed was 500mg- 1g three times a day on the drug chart and the prescriber had written “1g OM” (meaning once daily in the morning) in additional section of chart for metformin. Nurse had prepared 500mg and given to patient during a morning drug round but later corrected it when prompted by the patient and gave 1g in total (site A).
	• Nurse went straight to the patient’s bedside medication locker to retrieve the patient’s own gliclazide, omeprazole, metronidazole and pioglitazone. During this time, the patient asked “is it metformin?” Patient told the nurse that the metformin was in the same packet as the gliclazide (site B).

However, our study highlights additional complex issues; it provides a timely insight into specific challenges of the work environment in three different wards and how nurses worked within them to administer medications safely.

First, we have identified practical examples of resource optimization to increase medication safety which may be used as a platform for further discussion within individual healthcare

organizations. Intuitive adoption of safe medication practice behaviours may be facilitated by optimizing system configurations and features [39]. Optimizing ward-based medication systems to streamline workflow may therefore be an effective and cost-neutral way to increase medication safety; this could include simple steps to ensure that all relevant medication, documentation and equipment is available in one place when needed during medication administration (Table 2). However, how can potentially suboptimal processes and systems be identified? Our research suggests that some nurses express their identification of known system-based problems by developing routine alternative practices or workarounds. It is therefore important that healthcare organizations engage effectively with ward staff to 'tap into' their tacit knowledge of system problems. Direct observation is an important research method that allows some of this tacit knowledge to be identified; however this approach is likely to be too time-consuming to be of practical use on a regular basis. Instead, the use of 'soft intelligence', for instance information gathered from conversations, observations and experiences, incorporated into regular routine multi-professional walkarounds may be more practical [40]. As highlighted by Berwick [9] in his report on the Francis Inquiry, "most healthcare organizations have very little capacity to analyse, monitor, or learn from safety and quality information", and therefore more inventive methods are needed. Hard information, such as objective and quantitative data has long been used in the NHS and other healthcare institutions as an indicator of performance. However research suggests the use of such information in isolation can be misleading [41]. Evidence suggests that a combination of hard and soft information can be complementary and allow better triangulation of findings on which to base decisions; the risk of using soft information only is that decisions may be based on out of date anecdotes rather the current experience [40,41].

Second, nurses are highly adaptable healthcare professionals who need to balance conflicting priorities and demands during drug rounds. While medication administration is one of many nursing tasks, research suggests that senior clinical nursing staff are concerned that their staff are becoming overly task-focused in general and providing less patient-centred care [42]. In our study, we found both task focused and patient-interaction focused behaviour to have different potential benefits. Our conceptual analysis of the two types of inherent nurse behaviour may therefore offer a way to facilitate behaviour change in nursing staff, for example, by helping task focused nurses to better see the importance and benefits of a patient-interaction focused approach, and vice versa for primarily patient-interaction focused nurses. This could be based on a supportive peer-review process in which staff periodically observe each other's medication administration practices and consider the advantages and disadvantages of different approaches. To further support the development of beneficial nurse-patient interactions, we suggest efforts should also be focused on supporting nurses to manage interruptions and distractions, some of which are potentially important and beneficial [43], rather than avoiding them completely, as advocated elsewhere [16,31]. Further work should focus on characterising and differentiating positive and negative interruptions, identifying strategies to prevent avoidable and non-urgent 'delayable' interruptions, and supporting nursing staff in addressing important beneficial interruptions in an appropriate manner. In advocating an increase in patient involvement with their medications (beyond self-administration) to enhance medication safety, it is also important to consider potential unintended consequences of actual or perceived shifting of responsibility to the patient.

Finally, our research exemplified the potential benefits of the observational approach to 'looking' and 'seeing' practices in natural settings to identify safe practices that are not always recognized or reported by staff. Thus, there is a need to use observational methods strategically and share the findings across healthcare organisations to maximize their utility and increase patient safety.

Comparison of quantitative findings with previous research

The MAE rate for non-IV OEs identified in the present study (2.7%; 95% CI 1.2–4.2%) was lower than previously reported in a systematic literature review of UK studies using similar observational methods (5.6%; 95% CI 4.6–6.7%) [2]. The lower MAE rate may be partly due to the relatively restricted range of medications used on the study wards; a large proportion of patients were either admitted electively, transferred from another ward or undergoing rehabilitation. The present study identified a median rate of 5.5 interruptions per drug round hour and 9.6 distractions per drug round hour. The former is similar to the 6.7 interruptions per hour reported in the literature review of Biron et al [31], based on a total of 2,622 interruptions observed in 14 studies across a range of acute care settings. However, the definition of an interruption varied between studies and it was unclear whether or not the interruption rates reported by Biron et al [31] included 'distractions', which we defined and reported separately.

Strengths and limitations

Strengths of our research were (1) inclusion of multiple wards that used distinctly different medication systems to reflect some of the diversity of practices within the English NHS, (2) using an ethnographic approach, rather than self-report, to identify 'real-world' practices, (3) using a mixed-methods approach to triangulate our findings, and (4) reporting quantitative data based on established methods and definitions to facilitate comparison with previous studies. Furthermore, informal feedback from nursing staff about the observation experience was generally positive and the presence of the observer was not perceived to be a problem. Staff seemed generally quite open about their opinions of the systems relating to medication administration and provided invaluable additional insights into their rationale for approaches taken during drug rounds.

Sociotechnical interactions are complex; there are multiple interconnecting systems and processes that are not always apparent. Limitations of our research were that (1) we did not explore the wider impact of system optimization on the work processes of other health care professionals, (2) we did not explore other individual nurse or environmental factors, such as age and qualifications, or noise and lighting, that may be associated with nursing errors and efficiency [44], (3) our study was not powered to detect quantitative differences between wards, such as the effect of paper versus electronic systems on medication safety, or the relationship between structural factors and errors, distractions or interruptions—our findings may be used to design quantitative studies to explore these issues, (4) despite efforts made to maintain a balance between objectivity and subjectivity (e.g. encouraging feedback from nursing staff and collection of objective data to support our interpretation), data were collected by one researcher to facilitate the formative nature of ethnographic research and therefore may be limited to some degree by the beliefs and experience of the researcher. Furthermore, findings from the interruptions and distractions recorded in the current study indicate the presence of the observer had a measurable influence on nurse behaviour during drug rounds. Thus, the observer may have influenced MAE rates in a positive way through the Hawthorne effect. However, it is also possible that the observer increased the risk of an MAE by being a distraction to the nurse. While previous studies suggest that there is no effect of observation on MAE rates provided the observer is discreet, non-judgmental, and tactful [45,46], our study was not designed to quantify this further. We suggest future observational studies of MAEs consider documenting the frequency of participant-observer interactions.

Conclusion

Overall, a number of subtle structural variations in available resources appear to influence individual nurse behaviour and patient interactions, with some notable positive and negative unintentional consequences on medication safety. Our findings suggests that efforts to reduce MAEs be focused on three main areas (1) optimization of ward-based medication systems, (2) supporting nurses to manage interruptions and distractions, and (3) actively encouraging inpa-tient involvement with their medications where appropriate.

Medication adherence, medical record accuracy, and medication exposure in real-world patients using comprehensive medication monitoring

Abstract

Background

Poor adherence to medication regimens and medical record inconsistencies result in incomplete knowledge of medication therapy in polypharmacy patients. By quantitatively identifying medications in the blood of patients and reconciling detected medications with the medical record, we have defined the severity of this knowledge gap and created a path toward optimizing medication therapy.

Methods and findings

We validated a liquid chromatography-tandem mass spectrometry assay to detect and/or quantify 38 medications across a broad range of chronic diseases to obtain a comprehensive survey of patient adherence, medical record accuracy, and exposure variability in two patient populations. In a retrospectively tested 821-patient cohort representing U.S. adults, we found that 46% of medications assessed were detected in patients as prescribed in the medical record. Of the remaining medications, 23% were detected, but not listed in the medical record while 30% were prescribed to patients, but not detected in blood. To determine how often each detected medication fell within literature-derived reference ranges when taken as prescribed, we prospectively enrolled a cohort of 151 treatment-regimen adherent patients. In this cohort, we found that 53% of medications that were taken as prescribed, as determined using patient self-reporting, were not within the blood reference range. Of the medications not in range, 83% were below and 17% above the lower and upper range limits,

respectively. Only 32% of out-of-range medications could be attributed to short oral half-lives, leaving extensive exposure variability to result from patient behavior, undefined drug interactions, genetics, and other characteristics that can affect medication exposure.

Conclusions

This is the first study to assess compliance, medical record accuracy, and exposure as determinants of real-world treatment and response. Variation in medication detection and exposure is greater than previously demonstrated, illustrating the scope of current therapy issues and opening avenues that warrant further investigation to optimize medication therapy.

Introduction

The United States spends more on healthcare and prescribes more medications per patient than any other country [1, 2]. Despite this, health outcomes in the United States are poor compared to other industrialized countries. The greatest portion of expenditure is for chronic conditions; for example, in 2013 diabetes ranked first in overall healthcare spending at over $100 Billion, and of that cost, more than 57% was driven by pharmaceuticals [3]. Although diabetes medications have proven to be efficacious in clinical studies, the effectiveness of these and other medications must be improved, as there is a disconnect between drug efficacy in controlled clinical trials and effectiveness in real-world patient settings [4]. Lack of medication effectiveness may result from poor patient behavior, healthcare delivery flaws, inter-individual variability in medication response, or a combination of these factors [5, 6]. To better understand medication effectiveness, it is vital to know if patients are compliant with prescribed medication regimens, if the medical record used by the healthcare provider is accurate, and if medication concentrations are within target blood ranges. Knowing the medication concentration in blood is particularly relevant to medication effectiveness and has demonstrated treatment utility, particularly in the field of psychiatry [7]. Levels below the therapeutic reference range may not provide therapeutic benefit, while levels above the therapeutic reference range may increase the risk of adverse events without offering additional benefit.

While adherence to test medications in clinical trials is typically high, the post-FDA-approval reality is that real-world patient adherence is variable and difficult to measure [8, 9]. Adherence to medication treatment regimens is driven by economic, health literacy, side effect profiles, or a host of other factors [10, 11]. Approximately 25% of patients do not pick up their medications after the initial prescription, and 40% do not refill prescriptions for medications prescribed for chronic conditions. The cost to the healthcare system of nonadherence is staggering, estimated to be greater than $200 billion, largely driven by avoidable hospitalizations [12]. A recent study by Kymes et. al., demonstrated the benefit of addressing patient adherence, showing cost savings in the thousands of dollars annually for co-morbid patients when adherence was improved. Moreover, this study and others have demonstrated that persistence—keeping adherent patients adherent—was largely responsible for the savings incurred [13–16].

The electronic monitoring of medication container usage may represent the gold standard for assessing medication adherence, surpassed only by direct observation of medication intake [17]. Objective direct methods, such as unscheduled blood monitoring, may be attractive, but these methods have been mostly limited to testing for drugs of abuse. Furthermore, there are

documented studies of improved adherence shortly before physician appointments, demonstrating the need to measure adherence in real-world workflows to determine the impact on hospitalizations, ED visits, and other outcomes. Indeed, improving how current medicines are taken could have far reaching implications on outcomes; maybe more so than newly developed treatments [18].

Each patient's accounting of medications is located within their electronic health record (EHR). Complex patients often have multiple healthcare professionals using separate EHR systems, each of which provide an incomplete view of the patient's care. Using patient pharmacy records, the EHR, and patient interviews, discrepancies were observed in over 33% of patients when assessed at hospital admission [19]. When reconciliation was led by a trained pharmacist, post-hospitalization healthcare utilization was improved, including hospital revisits, emergency department visits and hospital readmissions [20, 21]. When delivered as an integrated solution, adherence intervention and medical record reconciliation represent opportunities for innovation that can un-blind the healthcare provider to the patient's true treatment regimen.

Therapeutic drug monitoring has been an effective means to improve therapy for select medications, typically those with narrow therapeutic margins. When coupled with genetics, therapeutic drug monitoring can identify causes as to why medications do not fall within therapeutic reference ranges, and can be used to guide medication selection or dosage changes [22–25]. A properly attained circulating exposure measurement offers a surrogate biomarker of drug action and can minimize the guess-work often associated with dose selection [26]. The measurement of medication concentrations takes into consideration all sources that impact exposure, as these measurements are the manifestation of variability in patient treatment and response. Historically, therapeutic drug monitoring has been impractical for polypharmacy patients due to cost, pharmacokinetic considerations, and sample volume necessary to cover the wide spectrum of medicines. In addition, current approaches to therapeutic drug monitoring are limited in their scope and can be criticized as "looking under the streetlight", missing medications that are unknown to the physician. Improvements in medication monitoring technology using sensitive, high-throughput approaches [27, 28] have now made it possible to comprehensively assess multiple medications simultaneously and assess total medication burden in the polypharmacy patient.

Herein we utilized a liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay capable of quantifying 38 medications from multiple medication classes in a single blood sample. We assessed medication exposure at the time of sample collection, and subsequently matched the detected medications with the primary medical record. We quantified medications in two distinct patient cohorts, each to answer a different question. First, by performing the comprehensive medication test during visits to healthcare facilities where medication testing was not anticipated, we explored the use of medication detection as an unambiguous measure of real-world adherence to ascertain the fidelity of the medical record. In a second cohort, we measured medication concentrations in prospectively enrolled, adherent patients with reconciled medical records, comparing the measured concentration of each detected medication to established reference ranges. By enrolling adherent patients and reconciling records prior to testing, we were able to explore exposure variability for the 38 drugs queried. The present investigation is the first to empirically assess compliance, medical record accuracy, and exposure as determinants of real-world treatment and response in complex patients, providing insight to the scope of current therapy issues and potential avenues to optimize medication therapy.

Materials and methods

Clinical samples

The two studies included in this report were conducted at the Cleveland Clinic, Cleveland OH. Trials were conducted by Cleveland Clinic personnel and approved by the Cleveland Clinic Institutional Review Board. All patients provided written informed consent, and for patients below the age of 18, informed consent was obtained by parent or legal guardian. Patient enrollment began in April 2015 and last patient visit was in September 2015. All samples were collected from both cohorts within this timeframe. Sample analysis was performed by Sano Informed Prescribing Inc., Franklin, TN.

A patient cohort representative of U.S. hospital patients (Residuals Cohort) was obtained by randomly selecting residual samples from patients receiving a Vitamin D test. Vitamin D testing was chosen because it is a high-volume test that is routinely ordered in otherwise generally healthy outpatients. The Cleveland Clinic central electronic health record database was utilized to match medication lists with residual serum samples from 1000 subjects. Samples with non-unique identifiers or origin numbers that did not match extraction criteria were excluded from the analysis. The resulting cohort consisted of 821 patients with available serum and a matching medication list. A second patient cohort (Reconciled Cohort) with improved adherence and demonstrated polypharmacy was obtained by prescreening medication lists from patients prescribed at least five overall medications, including at least two medicines represented in the test panel and one medicine of the psychotropic drug class. These enrollment criteria, coupled with an interview-based reconciliation of the medical record prior to admission, blood draw, and analysis created a biased cohort with improved medication adherence and demonstrated polypharmacy. Adherence improvement was likely a result of: 1) removing medications within the EHR no longer taken by the patient based on interview and 2) consent bias toward more adherent patients. Approximately 500 patients were approached based on pre-enrollment criteria resulting in a final cohort of 151 patients.

For both study cohorts, serum samples were transferred into microsample tubes bearing study-specific identifiers. The key linking study-specific identifiers to EHR information was maintained by study personnel at the Cleveland Clinic and not shared externally. Serum samples were stored at -70˚C, until shipping to Sano Informed Prescribing Laboratories for LC/MS/MS analysis. The medications measured in the assay were prescribed for the treatment of psychiatric disorders, idiopathic or anatomical pain, cardiovascular disease, diabetes, and gastrointestinal complications. Sano Informed Prescribing, Inc. is accredited through the College of American Pathology (CAP# 9265097) and CLIA registered (44D2096427). Sample analysis was executed under the guidelines set forth by the CAP and standard operating procedures commensurate with CLIA-registered operations.

Sano laboratory personnel were blinded to study participants' records and reported medications during the measurement phase of the studies. After measurement, deidentified medication lists from the EHRs were compared to LC/MS/MS measured results and classified into one of the following three categories: 1) detected and prescribed (DAP); 2) prescribed, but not detected (PND); or 3) detected, but not prescribed (DNP). Additional analyses included the comparison of quantitative measurements for each detected medication to serum reference ranges available in the literature (S1 Table).

Reagents and standards

Optimal grade methanol and acetonitrile were obtained from Fisher Scientific (Waltham, MA). Formic acid, ammonium acetate, ammonium formate, and water were all LC/MS grade

and obtained from Sigma-Aldrich (St. Louis, MO). Dimethylsulfoxide was obtained from Sigma-Aldrich. Ammonium hydroxide was obtained from Thermo Fisher Scientific. Drug naïve human serum used in validation studies was obtained from Bioreclamation IVT (Westbury, NY). All analytical standards were obtained at the highest purity available. Stock solutions were prepared individually in DMSO, water, methanol, or acetonitrile, then combined. Standard Curve and Quality Control samples were prepared in drug naïve human serum.

Sample extraction

Serum samples were collected in red top gel barrier-free microsample tubes, frozen, and shipped on dry ice to Sano Informed Prescribing for processing. Samples were thawed, mixed, and transferred to 96-well plates for processing. Internal standard working solution was added and protein precipitation was performed using Phenomenex Impact Protein Precipitation Plates. Eluate was transferred to a new plate and dried under Nitrogen. Sample was reconstituted for LC/MS/MS analysis.

LC/MS/MS analysis

Reconstituted samples were processed using a Shimadzu Nexera X2 liquid chromatography system (Columbia, MD)) fitted with a 2.1 x 50 mm, 1.7um C18 column (Phenomenex, Torrence, CA)). Sample analysis was performed on a Sciex 5500 QTrap Mass Spectrometer (Framingham, MA) with TurboV ion source and polarity switching. Data collection was performed with Sciex Analyst software, version 1.6.2, and data analysis was performed using Indigo BioAutomation Ascent software (Indianapolis, IN).

Assay linearity, precision, accuracy, and detection were validated by adding various amounts of each test drug to human serum. Each of the 38 drugs assayed passed strict analytical validation criteria. Three medications originally intended to be included in the multi-plex assay exhibited poor analytical performance and were excluded from analysis. Bupropion exhibited plasma instability, and lovastatin and phenytoin exhibited poor performance near the lower levels of the therapeutic reference range necessary for data interpretation. The final number of medications tested and included in all analyses was 38 (S1 Table).

Quantitative medication reporting

Reference ranges for each of the 38 parent drugs were obtained using triaged data sources as indicated in S1 Table. The primary information source was obtained from the AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry, which is a comprehensive, evidence-based summary of therapeutic reference ranges for 128 marketed medications. If the medication was not listed in this primary source, secondary sources derived from primary literature were utilized. Finally, if no literature values could be obtained, drug label information was utilized [29–35]. Medications were mapped to drug classes according to the NHANES resource (https://wwwn.cdc.gov/nchs/nhanes/1999-2000/RXQ_DRUG.htm; accessed 3/9/2017.

Results

We developed a multiplex assay for the quantitative assessment of serum concentrations for medications used clinically in the management of chronic disease. The 38-medication panel was biased toward medications that target the central nervous system, with the balance prescribed for cardiovascular, metabolic, or gastrointestinal indications. Over-the-counter and non-centrally acting medications were selected that are known to be co-prescribed at high

rates with psychotropic medications [36], known perpetrators of drug interactions, or metabolized through pathways with documented genetic influence. Both acute-acting and chronic-acting medications were included in the test panel. The average coefficient of variation (CV) established for quality control was less than 20% for the lower (17.3%) and upper range (16.8%) of quality control samples. The therapeutic reference range, as defined in Hiemke et.al. [26], was determined for each medication from literature. Measures of inter-assay precision and accuracy for each analyte and corresponding range parameters are presented in S1 Table. Nearly all medications in the assay were detected in at least one patient, except for gemfibrozil, which was prescribed three times but never detected, and clozapine/phenytoin that were not prescribed or detected in either patient cohort.

Two patient cohorts were selected to answer separate questions pertaining to medication treatment and pharmacokinetic response. The first cohort consisted of 821 patients randomly selected from routine clinical testing for serum Vitamin D levels (Residuals Cohort). Patients ranged in age from 5 to 103 years, with an average age of 54. In 39% of patients, zero panel medications were detected and 4% of patients had five or more panel medications detected. A second cohort consisting of 151 patients with documented polypharmacy, including at least one psychotropic medication, was prospectively enrolled based upon prescreening criteria (Reconciled Cohort). Owing to the selection criteria, 19% of patients had five or more detected panel medications. Enrollment criteria for this cohort created a strong bias of 78% female patients with an average age of 57. Patient characteristics and summary medication results are listed in Table 1.

The distribution of total number of detected medications differed significantly across the cohorts ($p = 1e\text{-}14$, Mann-Whitney U-test; Fig 1), with more medications detected per patient in the prospectively enrolled Reconciled Cohort. Across individual patients, the number of detected drugs was correlated with the number of prescribed drugs (Spearman $\rho = 0.61$ and 0.69 in Residuals and Reconciled cohorts, respectively; S1 Dataset). The rate of detection for individual drugs was correlated in the two cohorts (Spearman $\rho = 0.81$), although the median rate of detection in the Reconciled Cohort was 2.4 times greater (Fig 2). Psychotropic medicines were detected at an even greater rate in the Reconciled Cohort, which required at least one psychotropic medication for enrollment.

Table 1. Characteristics of patient cohorts.

	Residuals Cohort	Reconciled Cohort
Demographics		
Total Subjects	821	151
Male Subjects	34%	22%
Female Subjects	66%	78%
Average Subject Age	54	57
Youngest Subject	5	24
Oldest Subject	103	75
Prescriptions and detections		
Average prescribed medications in assay	1.5	3.4
Fewest prescribed medications in assay	0	1
Most prescribed medications in assay	7	7
Average detected medications in assay	1.3	3.2
Fewest detected medications in assay	0	0
Most detected medications in assay	8	8

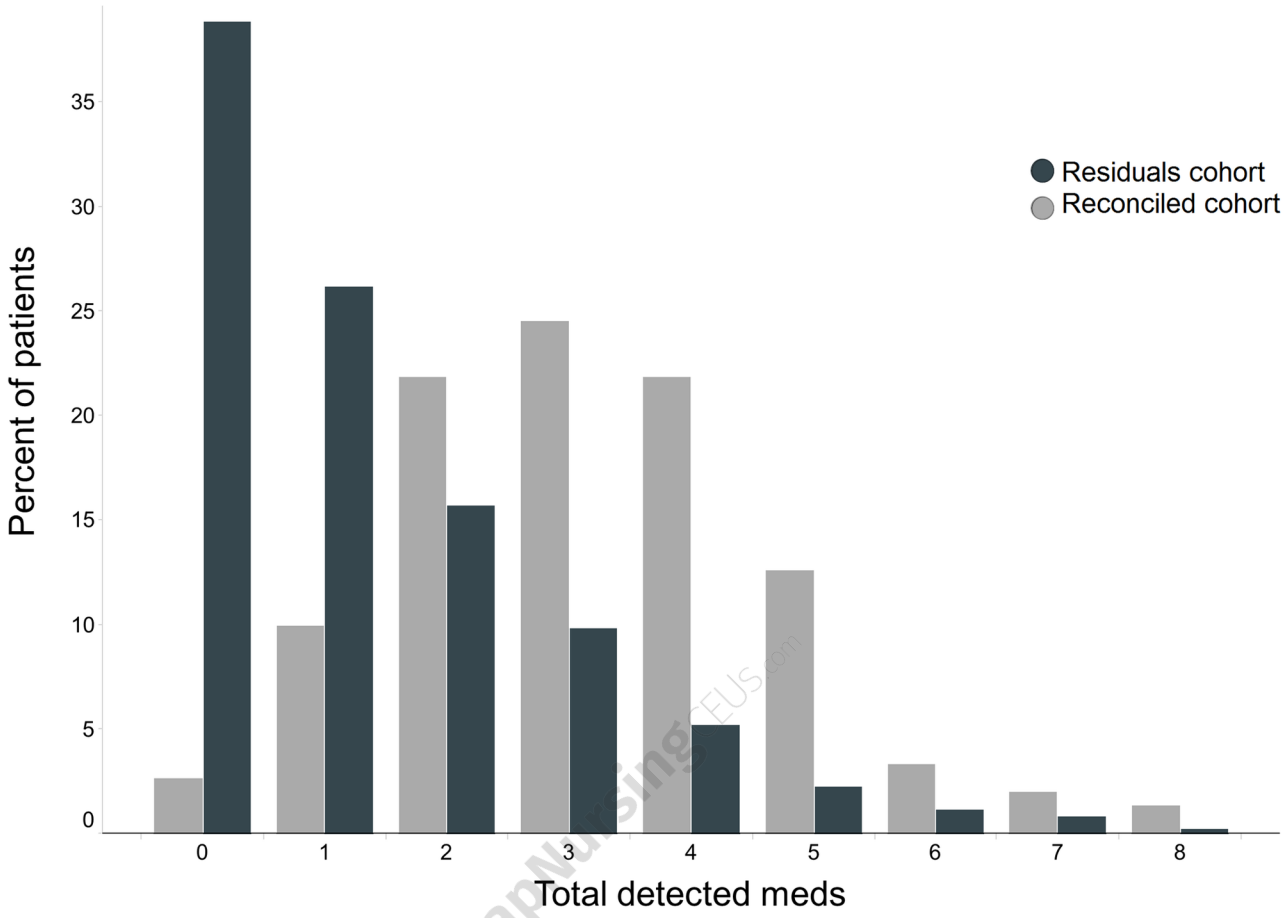

Fig 1. Distribution of total detected medications for two cohorts. Percent of patients having between 0 and 8 detected medications in the Residuals vs. Reconciled cohorts.

We tabulated drugs across categories denoting whether each detected medication was consistent with the medication list in the patient's EHR (Table 2). There were three potential scenarios. A medication could be detected and prescribed (DAP), prescribed but not detected (PND), or detected but not prescribed (DNP). For drugs that were prescribed but not detected, we identified and removed the subset that were prescribed on an 'as needed' basis (PND prn), because failure to detect such medications could not be used as a surrogate measure of non-adherence. We noted that the proportion of prescribed medications that were detected was significantly higher (Fig 3A, p = 3e-13, two-sided χ^2-test), and the proportion of detected medications not in the medical record was significantly lower (Fig 3B, p = 7e-14, two-sided χ^2-test) in the Reconciled Cohort relative to the Residuals Cohort. These trends further illustrate bias from the Reconciled Cohort enrollment criteria. Within this Cohort the number of medications prescribed not detected was similar for males vs. females (93% vs. 86%, p = 0.06, two-sided χ^2-test).

We examined frequency trends for drugs that were detected in both cohorts. A higher proportion of prescribed metabolic agents, such as statin medications, were detected in the Residuals Cohort, while a larger proportion of prescribed antidepressants, including paroxetine and trazodone, were detected in the Reconciled Cohort (Fig 4A). Conversely, the proportion of detected medications not in the medical record was higher for over-the-counter analgesics

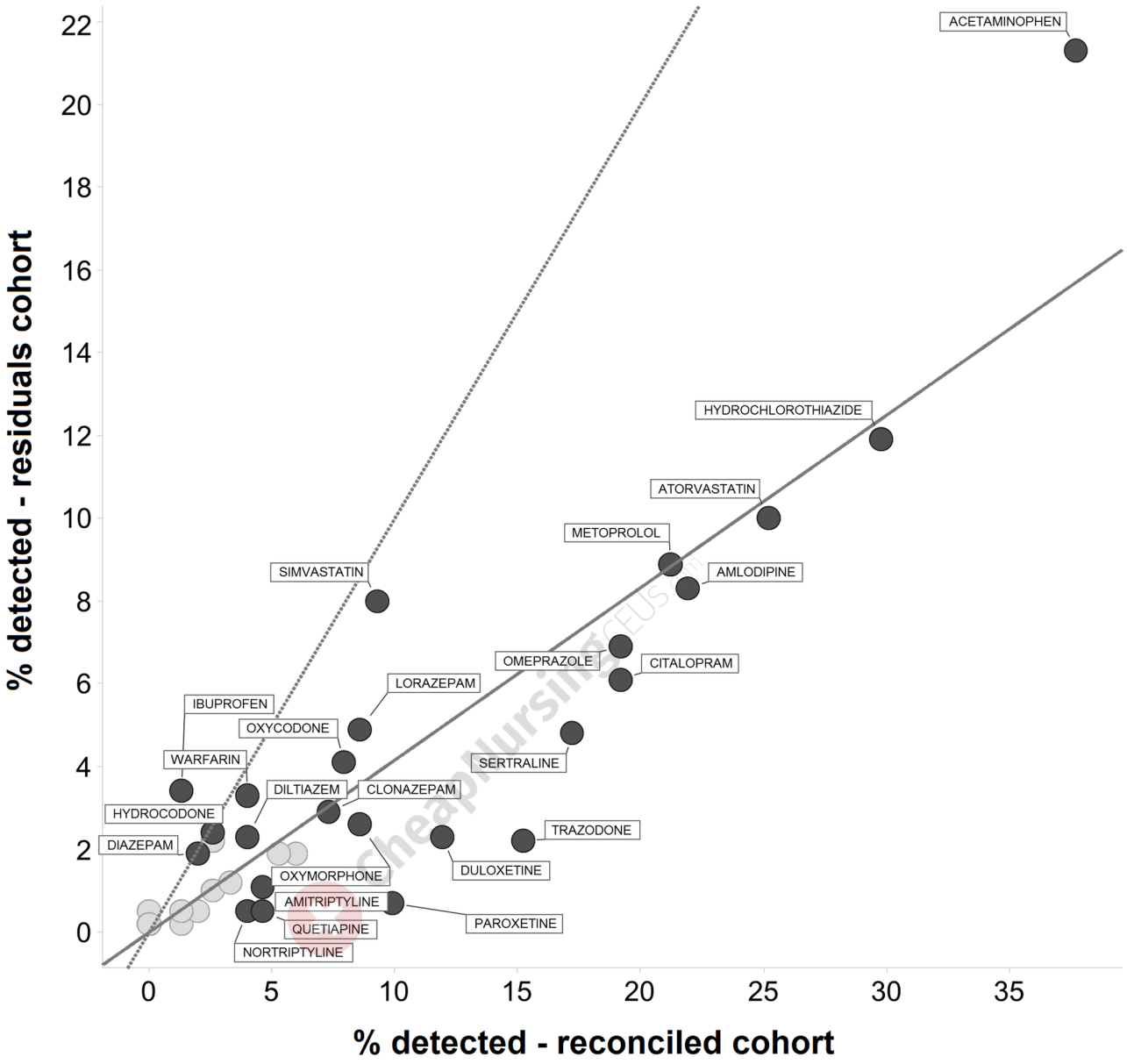

Fig 2. Detection rate for panel medications in two cohorts. Percent of patients for whom a given medication is detected in Residuals vs. Reconciled Cohorts. The dotted line indicates equal detection rates in both cohorts, while the solid line indicates the ratio of overall detection rate in both cohorts: 1.3 detected drugs per patient in Residuals Cohort vs. 3.2 detected drugs per patient in Reconciled Cohort.

such as ibuprofen and acetaminophen, and drugs of abuse, including benzodiazepines, in the Residuals Cohort than in Reconciled Cohort (Fig 4B).

Several drugs with lower levels of detection relative to prescribing rates have short oral half-lives, making them theoretically difficult to detect upon q.d. dosing. Therefore, we examined the proportion of detected medications as a function of drug half-life in the Reconciled Cohort, where we gathered self-reported time of dosing and where patients exhibited overall higher medication adherence (Fig 5). The percentage detected was generally lower for simvastatin, pravastatin and omeprazole, but not for acetaminophen and metoprolol. All these medications have average literature half-lives less than three hours (Table 2). Comparing simvastatin

Table 2. Medication panel characteristics and detection relative to prescription record for two patient cohorts.

Medication	t1/2 (hr)	Residuals Cohort			Reconciled Cohort		
		DAP[a]	DNP[b]	PND[c]	DAP[a]	DNP[b]	PND[c]
		Analgesics					
acetaminophen	2	48	127	15	28	29	0
dihydrocodeine	3.5	0	2	0	0	0	0
hydrocodone	4	10	10	5	4	0	0
hydromorphone	2.4	3	1	0	0	2	0
ibuprofen	2	8	20	7	1	1	0
oxycodone	3.5	22	12	1	10	2	3
oxymorphone	NA	0	21	1	0	13	1
		Antidepressants					
amitriptyline	19	9	0	7	7	0	1
citalopram	33	41	9	8	24	5	2
duloxetine	14	18	1	9	17	1	4
fluoxetine	120	13	3	2	8	1	0
nortriptyline	30	3	1	2	5	1	1
paroxetine	28	6	0	6	13	2	2
sertraline	23	33	6	8	25	1	2
trazodone	7.5	12	6	10	23	0	1
		Antipsychotics					
clozapine	14	0	0	0	0	0	0
olanzapine	45	1	3	0	3	0	0
quetiapine	7	4	0	3	7	0	2
		Benzodiazepines					
clonazepam	40	15	9	3	11	0	0
diazepam	36	9	7	1	2	1	0
lorazepam	14	15	25	4	11	2	0
alprazolam	13.5	10	6	5	8	0	0
oxazepam	9.5	0	2	0	0	0	0
temazepam	9	1	1	1	1	1	0
		Cardiovascular/Metabolic					
amiodarone	75	2	2	1	0	0	0
amlodipine	42	63	5	21	31	2	2
atorvastatin	19.5	69	13	28	37	1	3
clopidogrel	2.5	7	3	11	5	0	1
diltiazem	4	14	5	1	5	1	0
gemfibrozil	1.1	0	0	2	0	0	1
hydrochlorothiazide	11	90	8	27	45	0	2
metoprolol	5	61	12	15	31	1	1
pravastatin	2.9	15	3	16	4	0	6
simvastatin	2.5	40	26	27	12	2	10
verapamil	4	5	3	2	4	0	1
warfarin	43.5	26	1	4	5	1	1
		Other					
omeprazole	1	45	12	50	25	4	11
phenytoin	40	0	0	0	0	0	0

Abbreviations used

[a] detected and prescribed (DAP),

[b] detected not prescribed (DNP),

[c] prescribed not detected (PND)

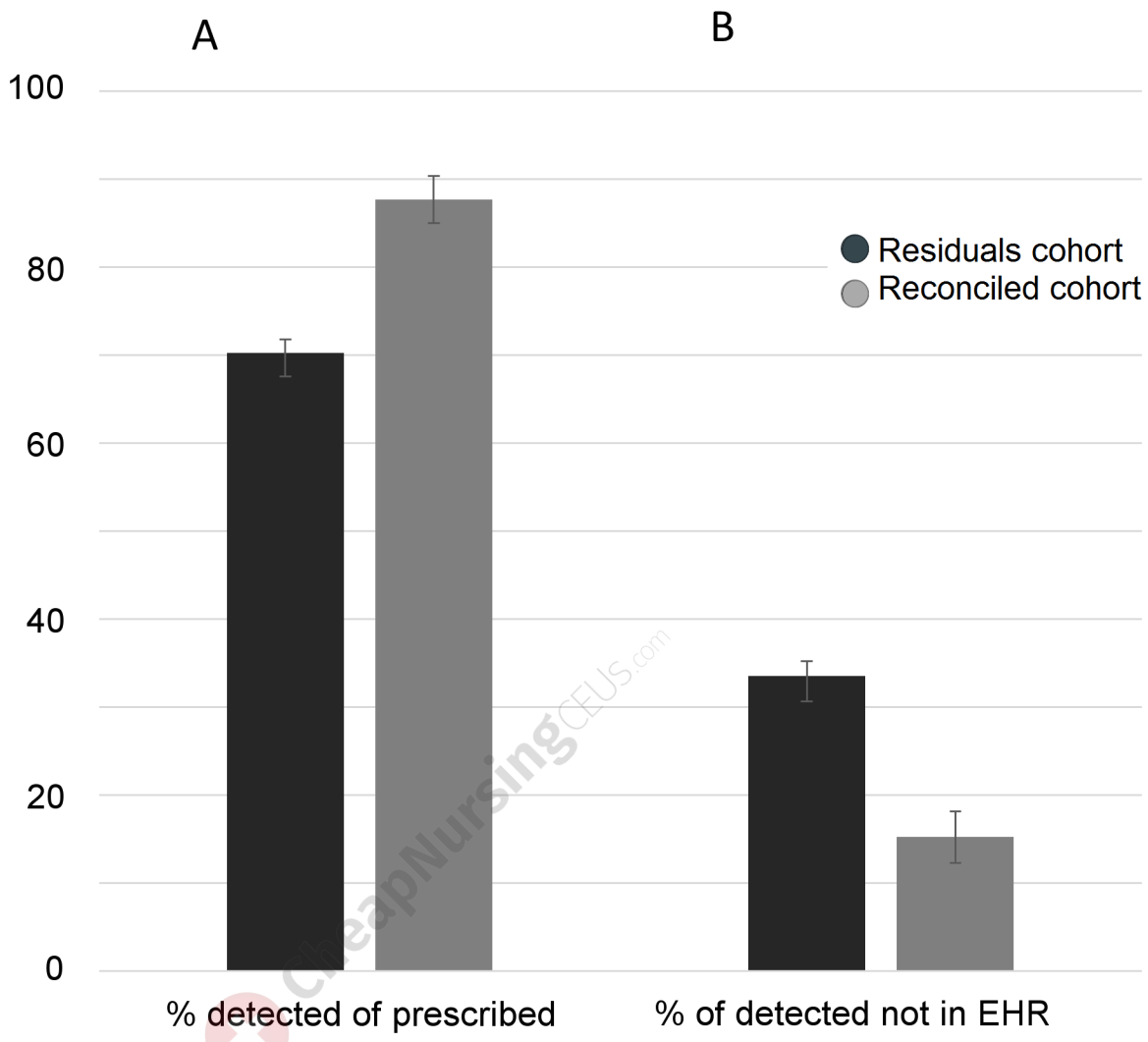

Fig 3. Medication prescriptions according to EHR vs. medication detection in two cohorts. A) Percent of prescribed medications that are detected and B) percent of detected medication that are non-prescribed (i.e. not in the EHR). Error bars were calculated from Bernoulli trials.

(t1/2 = 2.5 hours) and pravastatin (t1/2 = 2.9 hours) to atorvastatin (t1/2 = 20 hours) was instructive, as atorvastatin would be predicted to reach steady state blood concentrations upon q.d. dosing, whereas simvastatin and pravastatin would not based on oral half-life. The detection rate for atorvastatin (93%) exceeded the detection rates of the short-lived statins (55% simvastatin and 40% pravastatin). For drugs with half-lives less than four hours, we evaluated the percentage detected vs. time since last dose (S1 Fig). A decreasing trend of single point exposure vs. time since last dose for simvastatin was observed, but no such trend was observed with other short half-life medications, such as oxycodone. These empirical data show that many such drugs can be detected 12 hours or more after dosing.

A central tenet in pharmacology is to optimize drug concentrations at the target to elicit the intended effect. In practice, measuring drug concentrations in blood is a useful surrogate for most medications, and the optimal blood levels have been established for many drugs. We compared the concentration of each medication detected to the published therapeutic

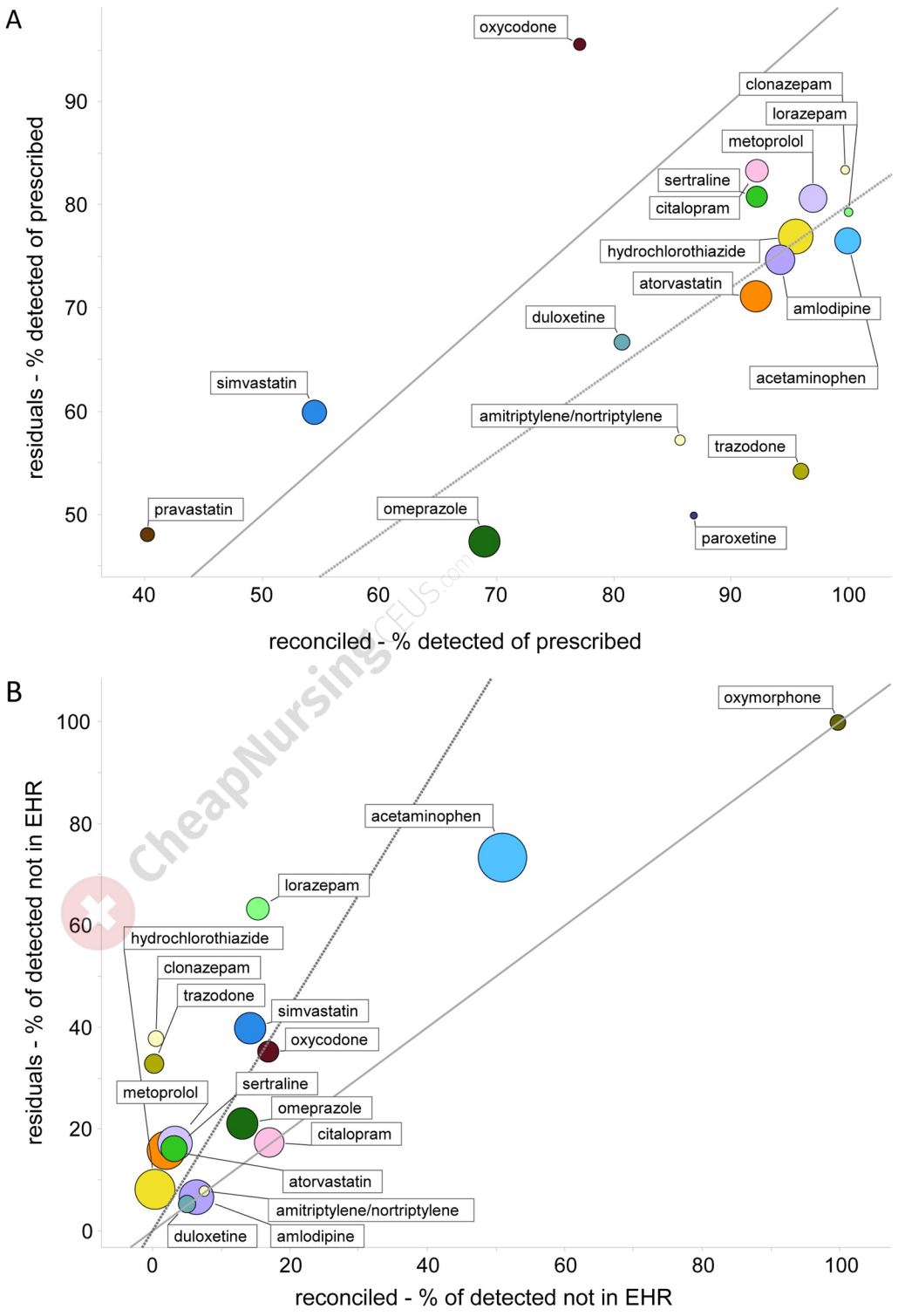

Fig 4. Adherence and non-prescribed medication use in two cohorts. A) Percent of prescribed medications that are detected (adherence), for medications having 10 or more prescriptions in each cohort. B) Percent of detected medications not in the EHR (non-prescribed), for medications having 10 or more detections in each cohort. The solid diagonal line indicates equality in both cohorts, and the dashed line indicates the overall ratio of adherence or non-prescribed use between cohorts, calculated across all medications. Markers are sized proportionally to log10 of prescriptions or detections.

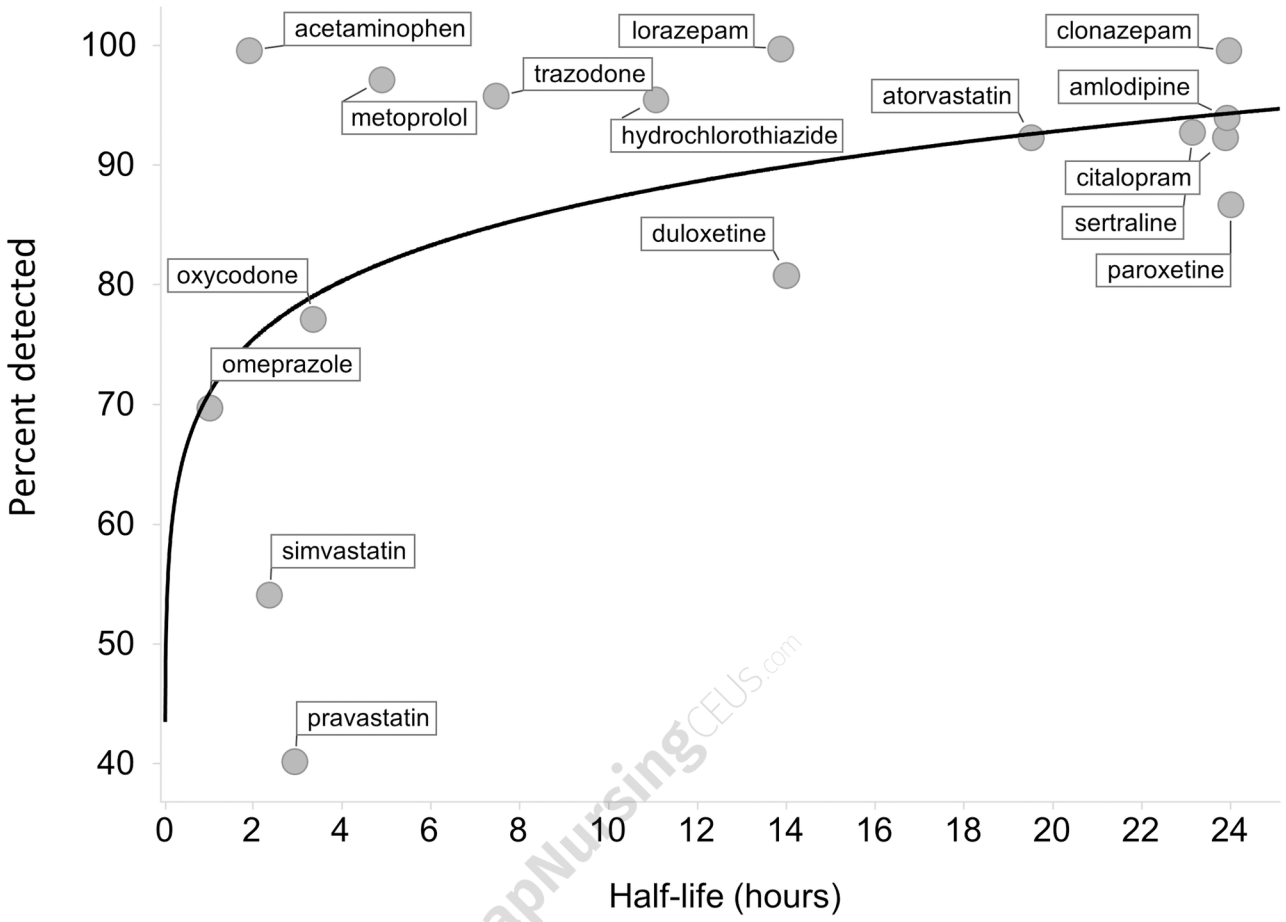

Fig 5. Percent of prescribed medications that are detected vs. medication half-life for Reconciled Cohort. Medications with half-life > 24 hours are shown at 24 hours on the abscissa. The fit denotes the least-squares power curve; the functional form was selected due to expected exponential decay of medication concentration with time.

reference range (Table 3; S2 Fig), focusing on the Reconciled Cohort, where patients took prescribed medications at a high rate. In this cohort 53% of detected drugs were observed to lie outside these ranges (Fig 6). Medications were more frequently detected at concentrations below the therapeutic reference range than at concentrations above the therapeutic reference range, and the percentage of drugs within, above, or below the therapeutic reference range was remarkably consistent between patient cohorts (Table 3). We explored the impact of dose and time since dose, and found modest predictive utility in explaining variation in drug levels (S2 Table)

Discussion

We developed a 38-medication LC/MS/MS assay that crosses therapeutic indications for the detection and quantitation of medications in serum. We used the assay as a surrogate of medication adherence, a tool to improve medical record accuracy, and as a comprehensive method to measure exposure in patients. When reconciled with patient's EHRs, medication measurement in serum offers an empirical measure of adherence and insight into EHR fidelity. Further, quantitative measurement in serum allowed for comparison of each detected medication

Table 3. Prescribed and detected drug rates and levels vs. therapeutic drug range.

	Detected drugs per patient[a]		Percent of drugs by category[b]	
	Residuals Cohort	**Reconciled Cohort**	**Residuals Cohort**	**Reconciled Cohort**
DAP[c]	0.9	2.7	46	71
PND[c]	0.4	0.4	19	10
PND-prn[c]	0.2	0.2	11	6
DNP[c]	0.4	0.5	23	13
drugs below-range (all)[d]	0.4	1.1	48	44
drugs below-range (T1/2 < 4) [d]	0.2	0.4	21	14
drugs in range[d]	0.4	1.2	45	47
drugs above range[d]	0.06	0.2	7	9

[a] Number of drugs per patient in each category, and

[b] percentage of drugs in each category.

[c] Each prescribed and/or detected drug was assigned to one of 4 categories: detected and prescribed (DAP), prescribed not detected (PND), PND drugs taken as needed (PND-prn), and detected but not prescribed (DNP) drugs.

[d] For detected and prescribed drugs that were measured quantitatively, tabulation by drug level compared to therapeutic drug ranges

concentration relative to the therapeutic reference range, elucidating the extent of patient exposure variability patients.

We queried the systemic circulation in two patient cohorts. The first, 821-patient cohort (Residuals Cohort) was designed to obtain samples from de-identified outpatients blinded to the medication testing paradigm. As such, comparisons between medications detected

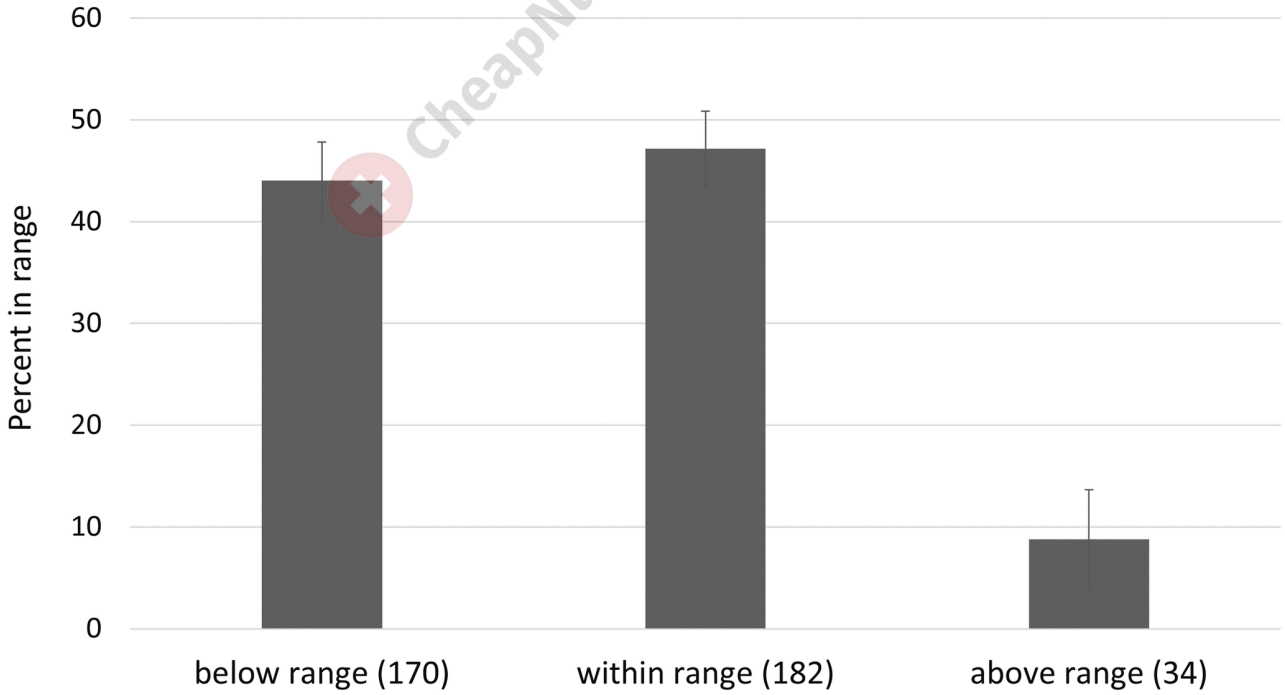

Fig 6. Medication detections vs. therapeutic monitoring ranges in Reconciled Cohort. Percent of medications detected quantitatively below, within or above ranges established in the therapeutic drug monitoring literature, for drugs that were listed in the patients EHR. Error bars were calculating from Bernoulli trials.

empirically and those in the prescription record would not be biased by patient behaviors associated with knowledge of drug testing. The second cohort of 151 patients (Reconciled Cohort) was prospectively enrolled, had medical records reconciled in a self-reporting interview, and consented to have blood tested for the presence of medications. In this cohort, we queried patients with reconciled records and a propensity to adhere to complex medication paradigms on how often medications would fall within the desired therapeutic reference range. Overall medication usage and detection rates were higher in this cohort and fewer medications were detected that were not listed in the medical record (Figs 1–3), producing the desired cohort to investigate quantitative aspects of medication exposure in complex patients that take medications as indicated.

In the residuals cohort, we found that 71% of prescribed drugs were detected in patients, a result slightly higher than estimates of compliance using pill counting and other methods of adherence measurement [37, 38]. Blood concentrations from most medications remain at detectable levels for several days post-ingestion, therefore slightly higher 'adherence' rates using medication monitoring relative to indirect methods likely results from patients that are partially adherent. The most frequently detected medications were drugs prescribed for metabolic and cardiovascular disease. The most disproportionately detected medications were of the psychotropic class, as enrollment criteria for the Reconciled Cohort required one psychotropic medication in the patient record prior to enrollment (Fig 2). Acetaminophen was the most often detected medication in circulation (Table 2). The frequency of detection and cumulative dose of this drug can become unintentionally high in patients, as this medication is found in at least 650 over-the-counter products, many of which are over-the-counter combination products taken simultaneously.

The rate of detection for medications that were not in the prescription record, the converse of the adherence measure discussed above, is novel information for the healthcare provider. Overall, 33% of detected medications in the Residuals Cohort were not in the medical record, with higher rates for over-the-counter medications, such as ibuprofen, and abused medications, such as benzodiazepines (Fig 4). This proportion decreased to 15% in the Reconciled Cohort, demonstrating that adherence and medical record omissions go hand in hand for the polypharmacy patient. Detected medications not in the EHR also create treatment issues, as drug-drug interactions with current treatment or future prescribing cannot be addressed when the medications are unbeknownst to the physician. This offers the opportunity for improving the medication reconciliation process and patient literacy [39–42].

The Reconciled Cohort was used to assess the impact of polypharmacy and biological factors on medication blood levels by testing in patients adherent to complex pharmacy regimens. Reference ranges were derived from published values for each medication in the assay panel, some of which had more supporting literature than others. Serum concentrations below the therapeutic reference range lower limit are unlikely to elicit a therapeutic response and concentrations above the upper limit exhibit tolerability decreases or no evidence that therapeutic improvement will be enhanced. This range is meant to be an orienting value, and is not necessarily applicable to all patients for each individual medication (26). More than half of the medications detected in this cohort were not within the therapeutic range (Fig 6). This finding deserves further study, including investigation into caveats associated with this type of measurement. Therapeutic drug monitoring has been performed with antipsychotic medications as single-medication studies in a variety of healthcare settings, and it has been consistently observed that medications are often out of range [26, 43, 44]. We now extend these findings to non-psychotropic medications, including medications more frequently prescribed to US patients alone or in combination [36]. Typically, therapeutic drug monitoring studies are conducted with patient medications at steady state and samples taken at trough levels. Although we did

not replicate true trough sample collection with the present study design, given the multiplicity of medications tested at one time, our data demonstrate that almost 50% of medications are below the intended therapeutic reference range. This suggests that a significant number of patients have sub-therapeutic levels of medication when multiple medications prescribed.

We collected self-reported time of dosing in Reconciled Cohort patients. Although individual medication half-lives are expected to be important criteria when monitoring medication levels, the correlation of medication exposure with time of dosing varied widely (S1 Fig). The percentage of prescribed medications detected in patients was generally lower for simvastatin, pravastatin and omeprazole, but not for acetaminophen and oxycodone (Fig 5); these drugs have average literature oral half-lives less than 3 hours (Table 2). Reasons patients may be below the reference range are multifactorial and include; 1) patients may be partially adherent, with medication persistence lacking, 2) the therapeutic range, which is often developed in clinical trial patients lacking real-world diversity, may be inaccurate, or 3) pharmacokinetic drug-drug or drug-gene interactions may be manifesting in these polypharmacy patients. There are countless other reasons, including patient health and biological makeup, but the finding of extensive variability in medication exposure is important for optimizing medication therapy. As data accumulate with each medication measured, we will begin to address these issues by comparing measured data to patient outcomes, and de-convolute behavioral vs. biological factors underlying variability in drug treatment and response.

The current study included 38 medications, offering a comprehensive survey of the most frequently prescribed psychotropic medications and select over-the-counter and non-psychotropic medications used to treat other chronic diseases. In theory, the approach applied herein could be scaled to detect several hundred cross-therapeutic medications simultaneously, detecting a very high percentage of written prescriptions. Measuring the majority of frequently taken medications provides the healthcare professional a comprehensive view of therapy for the complex patient that cannot be obtained without empirical measurement, although one must consider the pharmacokinetic limitations that may hamper the detection or quantitation of a particular drug, such as topical administration or short half-life.

There are several limitations in the current study. First, the use of exposure as a surrogate of medication adherence, medical record accuracy, and therapeutic range has caveats given the current state of real-world medication exposure knowledge. Except for medications that are frequently monitored, such as digoxin or phenytoin, published information is lacking information on medication exposure relative to outcomes. For some medications, there have yet to be published studies linking blood levels to outcomes, and in a few, no association was shown to exist when assessed. The measurement of medications using the LC/MS/MS methodology deployed herein is highly precise and accurate, but there are a multitude of reasons a medication prescribed may not be detected. Finally, medication persistence, drug interactions, genetics, disease state, and many other factors contribute to whether a medication detected falls within published therapeutic reference ranges, and with errors in self-reported medication ingestion and therapeutic range derivation issues, it would be premature to use this information quantitatively as stand-alone decision criteria in medication management as it stands today. The best way to circumvent these issues is to collect real-world exposure information on more medications relative to patient outcomes, and build empirical measurement data into largely theoretical clinical decision support on medication exposure relative to response.

Conclusions

These studies demonstrate using a novel and empirical surrogate approach that patients do not take all their prescribed medications, that the medication lists in EHRs are often

erroneous, and that medication exposure is more variable than previously demonstrated. In these studies, only 37% of prescribed or ingested medications were fully in line with the medical record that the healthcare provider was working from. Ours is the first study to empirically measure cross therapy medication levels regardless of prescription record, and illustrates the scope of multifactorial problem underlying medication therapy management. We have shown with 38 medications that the issue of adherence and medical record accuracy is substantial, and expanding these studies to more complex patients, measuring more simultaneous medications, and gathering requisite genetic, wellness, and outcome data will prove valuable in explaining sources of medication exposure and its relevance to treating disease. The quantitative aspect of blood-based medication measurement deserves further study, and with increased sample size driving model building, can ultimately extend this approach beyond simple adherence and record reconciliation into exposure-based prescribing.

Supporting information

S1 Fig. Percent of prescribed medications that are detected vs. time since ingestion. Percent of prescribed medications that are detected for a given range of hours since taking (x-axis), using patient-reported medication ingestion times from Reconciled Cohort. Values on bars denote number of observations in the given time range. The absence of a count label indicates that there are no observations in that time range.
(TIF)

S2 Fig. Distribution of log10 (concentration) aggregated across both cohorts. Vertical reference lines denote the low/high therapeutic drug range according to the literature. Value below the drug name denote its half-life in hours. Only drugs with 10 or more detections are shown.
(TIF)

S1 Table. Reference ranges and assay performance for the medication panel.
(DOCX)

S2 Table. Relationship between drug concentration and patient-reported dose and time since taking medication in cohort 2. [a] Only drugs detected and prescribed 10 or more times; [b] patient-reported doses for detected drugs; [c] Spearman rho correlation between concentration vs. dose or time since dosing; [d] hydrochorothiazide.
(DOCX)

S1 Dataset. De-identified patients, gender, age and summary of prescribed and detected drugs.
(XLSX)

S2 Dataset. Prescribed and/or detected drugs for two patient cohorts.
(XLSX)