A mixed methods analysis of clozapine errors reported to the National Reporting and Learning System (NRLS)

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Abstract

Background: Clozapine is the most effective antipsychotic for treatment resistant schizophrenia but is considered a high risk drug due to the risk of side effects. Clozapine incidents are the second most frequently reported by mental health services to the National Reporting and Learning System (NRLS), which uses reports for learning.

Aim: To review and analyse clozapine errors reported to the NRLS.

Methods: Following extraction of one year of clozapine incidents from the NRLS, a qualitative analysis (thematic analysis and re-classification) and quantitative analysis was undertaken.

Results: “Issues with stock/supply/ordering” was the most common theme derived from the qualitative thematic analysis (n=338), followed by wrong dose/strength/frequency (n=221) and medication omissions (n=202). Most errors occurred in the “Administration/supply” medication stage. Over half of reported clozapine incidents involved people 26-55 years old (n=830) and 82% of errors were reported by mental health services (n=1270). Only 1.5% of reports were classed as moderate/severe harm.

Conclusion: Issues with availability, stock and supply was found to be the most common cause. This usually entailed a lack of stock to fulfil a patient’s dose/supply. Such incidents could potentially be reduced by improved management of the supply process, and liaison between pharmacy and clinical staff. The implementation of emergency drug cupboards at the discretion of an on-call pharmacist may prove to a preventative measure for such errors. Despite the potential adverse effects associated with clozapine, very few incidents led to moderate/severe harm. Encouragement of NRLS reporting is recommended, for incidents of all degrees of harm.

Introduction

A medication error is defined as a failure in the medication process that causes, or has the potential to cause, harm[1,2]. Medication related harm accounts for up to 6.5% of unplanned admissions[3], costing the National Health Service (NHS) approximately £774million annually[4]. Consequently, it is imperative to report medication errors so that healthcare providers can learn from incidents.

As part of its patient safety function, the NHS collates and manages a central database of safety incidents, via its NHS Improvement body[5]. The National Reporting and Learning System (NRLS) is the database which records information about incidents which can be submitted electronically through local systems or online[6,7]. Incident data is then analysed with clinical input and reports are published on the NHS Improvement website. Patient safety alerts may be issued if significant trends are identified nationally.[5]

The atypical antipsychotic clozapine[8] was found to be the second most frequently reported medication by mental health services to the NRLS, between 01/01/07 to 31/12/07[2]. Clozapine has been shown to have greater efficacy than other antipsychotics in treatment resistant schizophrenia[8] and it reduces mortality through a reduction of suicide rates[9]. The National Institute for Health and Care Excellence (NICE) guidelines for England/Wales place clozapine as third line therapy in patients who have been unresponsive or intolerant to two other antipsychotics – at least one atypical[10]. In the USA and Europe, clozapine is similarly used in treatment-resistant schizophrenia[11,12,13].

Clozapine has a range of side effects[14]. To reduce the severity and risk of adverse events, patients must adhere to a strict gradual titration (starting at 12.5mg). This however, must be balanced with the delay to therapeutic response which may pose a risk to the patient and/or others. If clozapine is missed for greater than 48 hours, the dose must be re-titrated and monitoring must return to a weekly cycle[15]. This has a negative impact on the patient and can prove to be a preventable burden to NHS resources.

Clozapine's potentially fatal haematological side effects (neutropenia and agranulocytosis) demonstrates the importance of regular blood monitoring of white cell counts, neutrophils and platelets. Blood monitoring is conducted every week, two weeks or month based on treatment duration[14,15,16].

Clozapine is a high risk drug and is therefore usually initiated and prescribed by a consultant psychiatrist in secondary care. Once stable, GPs may prescribe clozapine through a shared-care protocol (although uncommon)[17].

It has been highlighted that antipsychotics account for the majority of harmful medication errors reported in mental health[18]. Despite this, coupled with the concerns around clozapine's safety profile[19] and the high frequency of errors reported[2], clozapine incidents have not been analysed using qualitative methods. Consequently, this study is the first in-depth analysis of clozapine incidents reported to the NRLS. The aim of this study was to analyse clozapine associated NRLS errors in order to identify any significant error types and themes. The objectives were to

collect NRLS clozapine data; analyse the data qualitatively through a thematic analysis and re-categorisation; analyse the data quantitatively; briefly examine reporting quality; and identify possible solutions to common clozapine errors.

Method

Following NRLS approval, one year of reported clozapine incidents were extracted from the database by DG using "SAS Enterprise Guide" [20]. Terms searched were clozapine and its brand names (including misspells).

Reporting to the NRLS

Incidents can be reported to the NRLS via local trust reporting systems or the online form (https://report.nrls.nhs.uk/nrlsreporting/).

When reporting an incident to the NRLS, there are three fields that allow the reporter to transcribe incident details (free text descriptions): 'Description of what happened', 'Actions preventing reoccurrence' and 'Apparent causes'. There are also NRLS fields with drop down menus (as shown in Figure 1), from which a single option can be chosen. These fields include the medication process stage, medication error category, age range, degree of harm and care setting of occurrence.

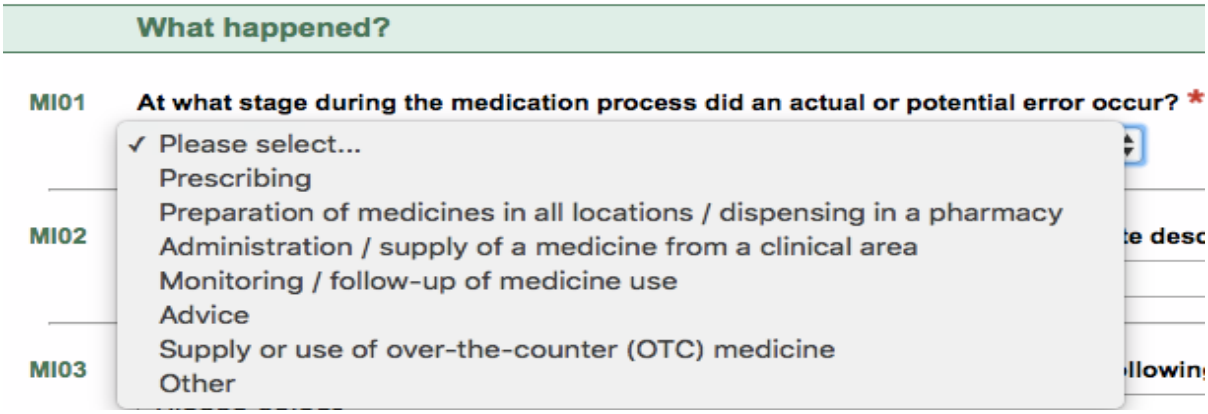

Figure 1: Reporting page for the NRLS (https://report.nrls.nhs.uk/nrlsreporting/)

Qualitative analysis – thematic analysis

From the incidents extracted, the three free text fields were analysed (as one entity) for the thematic analysis (Figure 2). Firstly, descriptions were read and irrelevant reports/ duplicates were discarded. Reports were considered if they met the medication error criteria (i.e. a failure in the medication process). Medication process stages include prescribing, dispensing, preparing, administering, monitoring or advising[2,4]. Incidents were considered irrelevant if the error was not directly associated with clozapine – e.g. clozapine patient missed Kwells dose (for clozapine-induced hypersalivation).

For incidents relevant to clozapine, summaries were produced for each. Each summary was then condensed and broken down further to produce “themes” - in some cases up to four themes were relevant to each incident. After all themes were constructed, grouped and finalised, the occurrence of each theme was counted using a Pivot Table (Microsoft Excel).

Themes were either influenced by existing NRLS categories or were constructed based on the incident summary. For example, the three NRLS categories “Wrong frequency”, “Wrong quantity” and “Wrong/ unclear dose or strength” could overlap – administering 2 tablets instead of 1 could be categorised as “Wrong quantity” or “Wrong/unclear dose or strength”. Consequently, “Wrong dose/strength/frequency” was developed as a theme. It was chosen when the wrong quantity, frequency or strength of tablets led to, or could have potentially led to, the wrong dose. “Wrong quantity” was generated as a separate theme where the patient received 28 tablets instead of 14 for example, but did not take the wrong dose.

Description of what happened	Actions preventing reoccurrence	Apparent causes	Relevant to clozapine? (Y/N)	Summary of event	Theme 1	Theme 2	Medication stage re-classified	Medication category re-classified
Clozapine order not placed and thus insufficient stock. Patient missed night time dose	Staff to check stock levels each morning	Staff member forgot to order patient clozapine	Yes	Issue with ordering = patient missed dose	Omission	Issues with stock / supply / ordering	Administration / supply of a medicine from a clinical area	Omitted medicine / ingredient

Figure 2: Steps taken for the qualitative analysis

Qualitative analysis – re-classification

It was agreed amongst the authors that the medication process stage and medication error category fields were likely to be most subjective. Therefore, for all incidents, both of these fields were re-classified using the NRLS website for guidance(https://www.eforms.nrls.nhs.uk/staffreport/help/AC/Dataset_Question_References/Medicine_incident_details/MD02.htm).

The purpose of re-classification was to have an accurate and consistent representation of what happened in reported incidents.

The medication process stage was classified based on which stage of the medication process the error took place, not which stage it was found. If none were suitable, such as self-administration errors, then “Other” was the option chosen.

Validation

The primary author (pharmacist), was responsible for theming and re-classifying all incidents for consistency; 10% of these incidents were validated by a chief pharmacist. Other authors from NHS Improvement were consulted on occasions where there was a lack of clarity.

Quantitative analysis of incidents

For all incidents, the following fields were extracted and quantified using a Pivot Table: age range, degree of harm, care setting of occurrence, medication process stage and medication error category. The outcomes from the thematic analysis and re-classification were also quantified using the same method.

Results

A total of 1,667 reports were yielded from the NRLS search. From these, 1,548 reports were found to be true clozapine errors following the exclusion of duplicates and irrelevant reports.

Thematic analysis

In total, 1,904 themes were produced for 1,548 incidents. The ten most common themes identified in this analysis are listed in Table 1 and accounted for over two thirds of incidents reported. The most common themes discovered were “Issues with medication stock/supply/ordering”, “Wrong dose/strength/frequency” and “Omission…”, collectively themed for almost half of all reports (n=761). Examples of these themes are listed in Table 2.

Table 1: 10 most common themes derived from the free text

Theme	Incidents coded	Percentage
Issues with medication supply/stock/ordering	338	17.75%
Wrong dose/strength/frequency	221	11.61%
Omission - medication not administered/dispensed/supplied/prescribed	202	10.61%
Communication issues	133	6.99%
Medication chart or prescription incorrectly filled/missing information/unclear	78	4.10%
Patient compliance/adherence issues	73	3.83%
Medication/prescription/medication chart lost or disposed of	69	3.62%
Lack of clarity what/whether dose administered	65	3.41%
Wrong quantity	57	2.99%
Wrong day/time	52	2.73%
Total	**1288**	**67.65%**

Table 1: The 10 most common themes derived from the free text

Table 2: Free text report examples by theme *Reports are mostly unedited except where irrelevant information, dates & names have been removed*	
Theme coded	**Incident free text examples**
"Issues with stock/supply/ordering"	*Delivery of clozapine medication was overlooked on Friday [date]. Member of staff realised on sunday night, unable to get access to [name] centre to enable delivery of medication.*
	Clozapine evening dose omitted due to lack of his medication on the ward.
"Wrong dose/strength/frequency"	*Patient was mistakenly given 12.5 mg of Clozapine at 16:00. She was on titrating regime of Clozapine. She had 150mg Clozapine in the morning and was due to have 150mg at night. Dr was informed and reduced evening dose to 137.5mg.*
	A service user was inadvertently given 300mg of clozapine instead of 225mg as a 100mg strip was in the 25mg box and an extra 100mg tablet ended up being dispensed into the meds pot instead of a 25mg tablet.
	On [date], the pre - admission dose of clozapine (50mg OM and 100mg ON) was prescribed by a junior doctor under the Gastro consultant advice when its use has been discontinued for more than 48 hours... Clozapine is normally re-titrated from lower doses, when the omitted duration is longer than 48 hours...
Omission – medicine not administered/ dispensed / supplied / prescribed	*Staff Nurse failed to administer clozapine to patient.*
	I was administering night medication from his blister pack when I noticed that it was short of the prescribed medication. Missing from the blister pack were clozapine, simvastatin and propranolol.
	Patient had been admitted to hospital on 26th [date]. A pharmacist saw the patient on the ward on the 27th [date] and noted that the patient was on clozapine (200mg, mane and 400mg nocte). The pharmacist asked the care home to bring in the clozapine as it is not something we keep and documented in the notes that it needed prescribing. The medication was bought in but was not prescribed. The patient therefore missed 8 doses of clozapine by the time I saw him on 3rd [date].

Table 2: Free text report examples by theme

Medication process stage (re-classified)

the re-classification found that most errors occurred during the “Administration / supply of a medicine…” (59.8%, n=926) and “Preparation… / dispensing…” (16.5%, n=255) medication stages, followed by “Prescribing” (13.2%, n=255).

Medication Process Stage	Incidents re-classified	Percentage
Administration/supply of a medicine from a clinical area	926	59.8%
Preparation of medicines in all locations/dispensing in a pharmacy	255	16.5%
Prescribing	204	13.2%
Other	114	7.4%
Monitoring / follow-up of medicine use	44	2.8%
Advice	4	0.3%
Supply or use of over-the-counter (OTC) medicine	1	0.1%
Total	**1548**	**100%**

Table 3: Medication Process Stages (Re-classified)

Medication error category (re-classified)

The three most common re-classified categories, as displayed in Table 4, were “Other” (30.8%, n=477), “Omitted medicine/ingredient” (27.9%, n=432) and “Wrong/unclear dose or strength” (18.6%, n=288). A significant proportion of incidents categorised as “Other” (149 out of 477 reports; 31%) involved problems with medicines supply/stock/ordering, for which no NRLS option is available.

Medication Error Category	Incidents re-classified	Percentage
Other	477	30.8%
Omitted medicine / ingredient	432	27.9%
Wrong / unclear dose or strength	288	18.6%
Wrong quantity	94	6.1%
Mismatching between patient and medicine	46	3.0%
Wrong drug / medicine	45	2.90%
Wrong frequency	36	2.30%
Wrong / transposed / omitted medicine label	28	1.80%
Wrong method of preparation / supply	28	1.80%
Unknown	17	1.10%
Contra-indication to the use of the medicine in relation to drugs or conditions	15	1.00%
Wrong storage	10	0.60%
Wrong / omitted / passed expiry date	9	0.60%
Wrong formulation	7	0.50%
Wrong / omitted verbal patient directions	4	0.30%
Wrong / omitted patient information leaflet	2	0.10%
Wrong route	0	0.00%
Total	**1548**	**100%**

Table 4: Medication Error Category (Re-classified)

Degree of harm

The quantitative analysis for the degree of harm, Table 5, found that no or low harm was reported for 1,526 incidents (from a total of 1,548). No reports led to death and 1.5% of incidents were reported as resulting in moderate or severe harm (n=22).

The incident reported as severe harm (n=1) was found to be misclassified, based on the free text provided. Table 6 below highlights the moderate harm incident types by care setting.

Degree of harm	Incidents Reported	Percentage
No harm	1347	87.0%
Low harm	179	11.6%
Moderate harm	21	1.4%
Severe harm	1	0.1%
Death	0	0.0%
Total	**1548**	**100.0%**

Table 5: Degree of Harm

Table 6: MODERATE harm medication error categories by care setting	
Acute / general hospital	**2**
Omitted medicine / ingredient	2
Community nursing, medical and therapy service	**2**
Omitted medicine / ingredient	1
Wrong / unclear dose or strength	1
Learning disabilities service	**1**
Omitted medicine / ingredient	1
Mental Health Service	**16**
Adverse drug reaction (when used as intended)	1
Contra-indication to medicine's use in relation to drugs or conditions	1
Mismatching between patient and medicine	6
Omitted medicine / ingredient	8
Total	**21**

Table 6: Moderate harm medication error categories by care setting

Age range

As displayed in Table 7, the majority of incidents involved people between the age of 18-65 (69%; n=1063), with 26-35 years (20%; n=314) being the most common age bracket reported. Six incidents were reported as involving children between the age of 0-1 years. However, the free text for these incidents indicated that none of these actually involved children and were therefore data entry errors by reporters. A quarter of incidents did not have an age range reported (n=386).

Age Range (Years)	Incidents Reported	Percentage
0 to 1	6	0.40%
1 to 11	0	0.00%
12 to 17	14	0.90%
18 to 25	116	7.50%
25 to 36	314	20.30%
36 to 45	262	16.90%
46 to 55	254	16.40%
55 to 65	117	7.60%
65 to 76	63	4.10%
76 to 85	12	0.80%
Over 85	4	0.30%
Not reported	6	0.40%
Total	**1548**	**100.0%**

Table 7: Age Range

Care setting

Table 8 illustrates that the majority of reports (82%; n=1270) are from mental health services, with very few (approx. 3%; n=47) being reported by primary care and community settings.

Incidents reported by acute / general hospitals (13%; n=203) have been categorised by theme in Table 9.

Care Setting	Incidents Reported	Percentage
Mental health service	1270	82.0%
Acute / general hospital	203	13.1%
Community nursing, medical and therapy service	40	2.6%
Learning disability service	28	1.8%
Community pharmacy	5	0.3%
General practice	2	0.1%
Total	**1548**	**100.0%**

Table 8: Incidents by Care Setting

Theme derived from the free text reported by Acute / General Hospital settings	Incidents Coded
Issues with medication supply/stock/ordering	58
Omission - medication not administered/dispensed/supplied/prescribed	45
Wrong dose/strength/frequency	26
Communication issues	26
Delayed or incomplete medicines reconciliation	12
Incorrect or omitted label	12
Total	**179**

Table 9: Most common themes derived from the free text reported by Acute / General Hospital settings

Discussion

This analysis identified common error types and themes, through a combination of quantitative and qualitative methods. Those results of particular interest have been discussed below under the relevant sub-headings.

Thematic analysis

Issues with medication supply/stock/ordering was identified as the most common cause and theme of incidents; a similar finding to thematic analyses based on other medications[2,4,21,22].

This theme may have been the most common as there are additional steps, such as regular blood tests, required to permit the supply of clozapine, compared to other medications. Therefore, overall, the increased need to dispense clozapine, and the impact of this on its supply, could explain the relatively high prevalence of errors associated with supply[15,23].

Another factor for the high occurrence of this theme is that clozapine is only available on a patient named basis[24] and so its availability as stock is limited. In multiple incidents, low or no clozapine stock levels, led to patients not getting their (full) clozapine dose. Some cases involved borrowing another patient's clozapine and replenishing it later; however, most trust policies advise against this[25,26,27].

Medication should be ordered on time to reduce clozapine errors related to its supply, stock and ordering. Expanding limits on clozapine supplies in emergency drug cupboards, with some type of national guidance, may reduce such errors; this could be at the discretion of the on-call pharmacist to provide some control mechanism. Further work is required to verify the feasibility of this recommendation.

Wrong dose/strength/frequency was the second most common theme. This included when clozapine was given at its original dose instead of being re-titrated (after being missed for >48 hours). In many cases where a higher dose was taken, blood tests and physical observations were required; this is associated with staff and laboratory costs[28].

The third most common theme was missed doses. If patients miss clozapine for more than 48 hours, the dose should be re-titrated from 12.5mg from an original dose as high as 900mg[14,16]. Therefore, an omission error puts the patient at risk of two additional errors. The first is that a substantial dose reduction could put the patient at a risk of relapse, and thus refractory psychosis, if they have not already relapsed during the no clozapine period[29]. Second, there is a possibility for the clozapine to be administered at the full dose instead of the re-titration dose, increasing the risk of adverse events[15].

In an attempt to reduce missed doses, primary and secondary care must work together more effectively. For example, mental health services should notify GPs if a patient has been initiated on clozapine and give regular updates regarding dose

changes. This should then be documented on the patient's GP records. As a result, for any subsequent acute hospital admission or mental health admission in a different trust, medication details would be available on the Summary Care Record (SCR). This allows access to the patient's updated medication information, improving the safety and quality of care provided[30]. This would also reduce errors due to communication issues (n=133) between primary and secondary care. A recommendation to reduce errors in acute settings is for clozapine guidance to be issued to acute/general hospitals[31].

Medication process stage

Similar to "Safety in Doses" [2,4], the "Administration/supply…" stage was found to be the most commonly reported medication stage. Using the Swiss Cheese Model, there may be fewer layers of defence when progressing from "Prescribing" (n=204) to "Preparation…/ dispensing…" (n=255) to "Administration/supply…" (n=926), and subsequently more scope for errors[32]. Also, administration is a more frequent process[2] and the supply of clozapine is more frequent than most other medications, especially in the initial stages.

Many incidents with "Other" selected were associated with self-administration. This coincides with the NRLS "Safety in Doses" paper which acknowledges that the selection of the "Other" category could be minimised by the introduction of a self-administration field[2]. More work is needed to identify the causes of these self-administration errors.

Medication error category

The most common medication error option selected to describe the incidents, by reporters and KD, was "Other". The addition of the option "issues with supply/stock/ordering" would have reduced "Other" reports significantly, as discovered in other analyses too[2,4,21,22].

Age range

Clozapine is primarily used in a young to middle aged population[33] and most incidents involved people who were reported as 26-55 years (Table 7).

The lack of reports in the upper age ranges (66+) may be due to the reduced life expectancy in people with schizophrenia, in whom mortality rates are 2-3 times higher compared to the general population; this corresponds to a 10-25 year lower life expectancy[34]. There is an increased risk of clozapine-related adverse events in the elderly, particularly anticholinergic[2] and haematological side effects; the risk of agranulocytosis increases four to five fold[35]. This side-effect burden could explain

the limited use of clozapine in older people[36] and therefore the lower levels of reporting seen.

Six incidents were reported for children under the age of 1, however upon reviewing, all six were data entry errors. Schizophrenia is rarely diagnosed in childhood due to the lack of diagnostic clarity at young ages[37].

Degree of harm

Clozapine has potentially fatal adverse effects such as myocarditis, constipation and agranulocytosis[38,39,40,41]. Yet, no reports in this analysis were reported as severe or leading to death. Overall, only 0.8% of all incidents were reported as an Adverse Drug Reaction (ADR), possibly due to most ADRs being reported directly to medication manufacturers, license holders, and through the Yellow Card Scheme[22].

Limitations

The results of this analysis cannot be used to imply the strict prevalence of any one category of error. Instead, it suggests that such errors exist, have been reported and that certain incidents have been reported more frequently than others.

However, under-reporting is common, with just one in five NHS incidents being reported[6,42,43]. Generally, primary care settings report significantly less than secondary care[2,4], although in this instance, secondary care tends to support clozapine management.

The NRLS has been criticised for collecting insignificant “wide and shallow” data as opposed to “narrow and deep”. “Narrow and deep” data collection would result in detailed incidents which are less common and more serious in harm[44]. To the contrary, only 1.5% of reports led to moderate or serious harm. This, however, is dependent on what trusts and individuals decide to report. Increased awareness of the NRLS could improve this.

A drawback of NRLS data is that it does not record gender nor ethnicity, thus providing limited information on patient demographics. Also, the NRLS only allows a single option to be chosen per field. However, on numerous occasions, multiple options were suitable. This led to subjectivity, as to which option was most representative of the incident. The addition of a functionality that allows multiple selections would improve the accuracy of reporting.

The subjectivity of coding and re-classification demonstrates the limitation of the qualitative methodology used[45].

Quality of reporting

The quality of reporting was studied by comparing how similarly categories were selected by reporters vs during re-classification. Supplementary Table 10 illustrates this comparison for the medication stage process; e.g. “Administration / supply…” was selected by reporters 715 times compared to 926 times during re-classification (agreed on 608 incidents). This comparison is similarly displayed in Supplementary Table 11 for the medication error category field.

Another limitation of the reports received was the poor clinical detail and lack of root causation. For the “Actions preventing reoccurrence” field, 43% of the column was filled out (n=662); with a median of 19 words per report (Range: 0 – 494 words). The “Apparent Causes” field was only completed for a third of reports, with a median of 14 words per entry (Range: 0 – 391 words). Apparent causes, however, were commonly seen under the “Description of what happened” field. As a result, all three free text descriptions were analysed as one entity.

Age ranges were poorly reported with missing age data for 25% of incidents (n=386). Although a qualitative analysis was not comprehensively performed for the age range, incidents involving children <1 year were reviewed and found to be categorised incorrectly.

Conclusion

This paper reports the first analysis of clozapine incidents reported to the NRLS. It has identified the most commonly reported categories for a range of fields, with the key cause of errors identified as issues with supply, stock and ordering. By having the availability of more clozapine in the emergency drug cupboard and better ordering procedures, it is possible for incidents to be reduced. Emergency drug cupboards could be implemented and tested in practice to see if errors decrease on a local level.

Many errors related to wrong/unclear doses and omissions (second and third most common themes), particularly in acute and general hospital settings, could potentially be reduced by regularly updating the patient’s SCR. This is achievable through improved communication and updates between mental health services and primary care.

Reporting medication errors provides invaluable information for learning and service improvement. It is therefore recommended that further research into the quality of NRLS data reported is explored in more depth; with possible solutions to improve reporting accuracy and reduce subjectivity/inconsistencies. Reporting incidents of all severities of harm should be encouraged so that analyses are comprehensive.

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