An investigation into the types of drug related problems that can and cannot be identified by commercial medication review software

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Abstract.
A commercially used expert system using multiple-classification ripple-down rules applied to the domain of pharmacist-conducted home medicines review was examined. The system was capable of detecting a wide range of potential drug-related problems. The system identified the same problems as pharmacists in many of the cases. Problems identified by pharmacists but not by the system may be related to missing information or information outside the domain model. Problems identified by the system but not by pharmacists may be associated with system consistency and perhaps human oversight or human selective prioritization. Problems identified by the system were considered relevant even though the system identified a larger number of problems than human counterparts.

Keywords: Clinical decision support system, multiple-classification ripple-down rules, expert system, pharmacy practice

1 Introduction

A drug-related problem (DRP) can be broadly defined as "…an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"[1] DRPs comprise a spectrum of problems including over- or under-dosage, drug-drug or drug-disease interactions, untreated disease and drug toxicity. Patient health education and compliance with therapy may be sub-standard and subsequently also be considered as drug-related problems. DRPs can be dangerous; For instance, a marginally high daily dose of warfarin has the potential to cause fatal bleeding.

Home medicines review (HMR) is a Commonwealth Government funded service conducted by accredited pharmacists to identify and address DRPs among eligible patients [2]. The main aims of the service are to enhance patient knowledge, quality use of medicines, reconcile health professional awareness of actual medication use and, ultimately, improve patient quality of life. The HMR service is a collaborative

activity between health professionals, typically accredited pharmacists, general practitioners (GPs), and patients. Since its inception in 2001 the service has steadily grown with nearly 80,000 HMRs funded in the 2011/2012 period [3].

An HMR is initiated for eligible consenting patients by a GP. Eligible patients are identified if they regularly take 5 or more medications among other criteria [2]. An HMR accredited pharmacist then obtains medical information from the GP, covering medical history, current medications and pathology.

A core component of an HMR is an interview between the pharmacist and the patient, with interview typically conducted in the patient's home. The interview, elicits additional information such as: actual medication use, additional non-prescribed medications, an understanding of the patient's motivation behind actual rather than directed medication use, and the patient's health and medication knowledge [4]. This process allows for a deeper understanding of the patient's situation and gives the pharmacist insight into cultural or language barriers, physical and economic limitations and family support.

The amassed information is reviewed by the pharmacist to identify actual and potential DRPs. The pharmacist writes a report of findings for the patient's GP, which includes recommendations to resolve any actual or potential problems. Consultation between the GP and the patient culminates in an actionable medication management plan designed to trial changes to existing therapy, and ideally, lead to improved medication use and improved patient health outcomes [4].

An important component is the professional skill of the pharmacist to be able to identify clinically relevant DRPs from the available information. This requires a wide scope of knowledge, not only of medications, but of evidence-based guidelines and contemporary management of a variety of medical conditions.

Evidence-based guidelines can be difficult to implement due to their apparent complexity. An example is provided from Basger *et al.'s Prescribing Indicators in Elderly Australians*: "Patient at high risk of a cardiovascular event (b) is taking an HMG-CoA reductase inhibitor (statin)"[5] If a patient did not meet this criterion this would be considered a DRP. It can be reasonably expected that pharmacists would be aware of statin medications currently available in Australia, in October 2012 these were: atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. Note (b) specifies those patients at high risk of cardiovascular event: "age>75 years, symptomatic cardiovascular disease (angina, MI[myocardial infarction], previous coronary revascularization procedure, heart failure, stroke, TIA[transient ischemic attack], PVD[peripheral vascular disease], genetic lipid disorder, diabetes and evidence of renal disease (microalbuminuria and/or proteinuria and/or GFR[glomerular filtration rate]<60ml/min". Determining patients at high risk of cardiovascular events is more problematic and requires sufficient additional information to make such a determination. One obvious problem is the amount of information that needs to be screened, both within the guideline text and the patient data, to identify appropriate patients.

A commercial product developed by Medscope, Medication Review Mentor (MRM)[6], incorporates a clinical decision support (CDSS) tool to assist with the detection of DRPs. MRM utilizes a knowledge-based system to detect DRPs and provide recommendations for their resolution. This knowledge-based system uses the

multiple classification ripple-down rules (MCRDR) method and was based on the work of Bindoff *et al.* who applied this approach to the knowledge domain of medication reviews [7, 8]. The ripple-down rules method was considered appropriate as knowledge could be gradually added to the knowledge base, broadening the scope and refining existing knowledge as the system was being used [7, 9]. Bindoff *et al.* suggested intelligent decision support software developed for this knowledge domain may improve the quality and consistency of medication reviews.

No prior research had been undertaken to determine the clinical decision support capacity of this commercial software, apart from contemporary research by the authors. This contemporary research by the authors assessed opinions from pharmacology experts and had determined that MRM is capable of identifying clinically relevant DRPs [10-12].

This evaluation attempts to provide light on the scope of DRPs that can be identified by this software by presenting summary counts and examples of the types of problems that were identified by MRM and by pharmacists. This paper evaluates the similarities and differences between pharmacist findings and MRM findings more in terms of a qualitative comparison by highlighting common findings, extremes of difference and discussing the possible advantages and limitations of the software, as well as discussing areas for potential improvements.

2 How MRM works

The decision support component of MRM is a knowledge-based system which uses MCRDR as its inference engine. MCRDR provides the knowledge engineer a way to incrementally improve the quality of the knowledge base through the addition of either new rules – which are added when the system fails to identify a DRP, or refinements to existing rules – which are added when the system incorrectly identifies an inappropriate DRP. The system's knowledge base is managed by medication review experts, who regularly review cases, examining the findings of the system for that case, and then adding/refining rules until the system produces a wholly correct set of findings for that case [8]. The validity of new rules is always being ensured, as the system identifies any conflicts which may arise from the addition of the new rule, and prompts the pharmacist to refine their rule until no further conflicts arise.

3 Methods

Australia-wide data collected during 2008 for a previous project, examining the economic value of HMRs, was used for this study [13]. The data contained patient demographics, medications, diagnoses and pathology results for 570 community-dwelling patients aged 65 years old and older. The 570 HMRs were obtained from 148 different pharmacists. Supplementing this data were the original reviewing pharmacists' findings, detailing pharmacist-identified DRPs and recommendations.

The HMR data were entered into MRM and DRPs identified by MRM were recorded. MRM utilized a wide range of information including basic patient de-

mographics such as age and gender, medication type including strength, directions and daily dose. MRM could calculate daily dose from strength and directions in many cases. Duration of use of medication could be entered, which included options of less than 3 months and more than 12 months. Medications were assigned Anatomic Therapeutic Chemical classifications (ATC) [14]. ATC is a five-tier hierarchical classification system allowing medications with similar properties to be grouped together in chemical classes which are then grouped into therapeutic categories.

Diagnoses could be entered and were based on the ICPC2 classifications [15]. The ICPC2 classification system was also hierarchical, grouping diagnoses under similar categories. Diagnoses could be assigned temporal context as recent, ongoing or past history. Medication allergies and general observations including height, weight and blood pressure could be entered. A wide range of pathology readings could be entered, including biochemical and hematological data.

At the time of the data entry and collections of results, August 2011, MRM contained approximately 1800 rules [16]. Rule development was undertaken by a pharmacist with expertise in both clinical pharmacology and HMRs [6].

Direct comparison of the DRPs identified by MRM and those identified by the original pharmacists was not possible due to the individual textual nature of each DRP. Each DRP identified by either the pharmacist or MRM was mapped to a concept (defined here as a theme) that described the DRP in sufficient detail to allow comparisons of similarity and difference between pharmacists and MRM. The themes often described the type of drug or disease and other relevant factors involved. The development of a list of themes and the mapping of DRPs to themes was performed manually by the author, a qualified pharmacist.

Examples of the text of two DRPs identified by a pharmacist and by MRM in the same patient are shown in Table 1. These DRPs were assigned the theme *Hyperlipidemia under/untreated*, which captured the basic problem identified within the text of each DRP.

Table 1. Example DRP text

MRM	**Pharmacist**
Patient has elevated triglycerides and is only taking a statin. Additional treatment, such as a fibrate, may be worth considering	Patient's cholesterol and triglycerides remain elevated despite Lipitor [statin]. This may be due to poor compliance or an inadequate dose

These themes provided a common language for comparison of the DRPs found by the original pharmacist reviewer and MRM. The initial themes were created where at least two of three published prescribing guidelines for the elderly [5, 17, 18] were in agreement concerning the same types of DRPs. DRPs from MRM and pharmacists were mapped to this table of themes. Further themes were added if both pharmacist and MRM DRPs could be mapped to any remaining 'non-agreement' prescribing guideline DRPs. New themes were developed for remaining pharmacist and MRM DRPs where concepts were clearly similar but were not contained within prescribing guidelines. These new themes were very broad such as *Vitamin, no indication*, and

may have included the DOCUMENT DRP classification text such as, *Therapeutic dose too high* [19]. The remaining DRPs were unique to either pharmacists or MRM and themes were provided where possible, such as, Skin disease *(un)dertreated* – pharmacist only DRP. Lastly miscellaneous otherwise unclassifiable DRPs were assigned *Other DRP pharmacist* and *Other DRP MRM*.

A list of 129 themes was developed. Many themes described disease states and/or drug classes describing identified DRPs in general terms. A descriptive analysis of the themes was performed.

The number of unique themes found in each patient was considered more important than the raw number of themes found in each patient. That is where two DRPs matched the same theme in the same patient, that theme was counted once. The reason behind this decision was to compare the number of different types of conceptual problems that could be identified across patients rather than raw numbers across patients.

Each theme identified in each patient was allocated into one of three categories: 1. Identified by pharmacists only, 2. Identified by MRM only or 3. Identified by both.

4 Results

The patient cohort was predominantly female, with an average age of 80 and an average of 12 medications and 9 diagnoses, as described in Table 2.

Table 2. Patient Demographics

Patient (N = 570)	**Demographics**
Age (years)	79.6 ± 6.7
Gender	Male 234 : Female 336
Number of medications	12.0 ± 4.4
Number of diagnoses	9.1 ± 5.2

Pharmacists identified a total of 2020 DRPs, an average of 3.5±1.8 per patient, with a range of 0 to 13 DRPs. MRM identified 3209 DRPs, of which 256 were excluded due to duplicated findings, leaving 2953 MRM DRPs, and an average of 5.2±2.8 per patient, ranging from 0 to 16 DRPs.

The 2953 MRM DRPs were able to be assigned to 100 different themes that described in general terms the central issue of each of the DRPs. Similarly, the 2020 pharmacist DRPs were able to be assigned to 119 different themes. Ninety of these themes which were identified by pharmacists were also able to be identified by MRM. Within these 90 themes, the software was able to identify the same issues as the pharmacists in one or more of the same patients for 68 particular themes.

The number of different themes identified by MRM or by pharmacists per patient was considered more important than the raw totals. The 2953 MRM DRPs were aggregated into 2854 themes. Pharmacist DRPs which were clearly identifiable as compliance or non-classifiable cost-related problems and outside the scope of MRM's

ability to identify were excluded, leaving 1726 pharmacist DRPs which were aggregated into 1680 themes.

MRM was able to identify the same themes as identified by pharmacists in the same patients 389 times, a 23% (389/1680) overlap of pharmacist findings by theme and patient. This then left 1291 themes identified by pharmacists only and 2465 themes identified by MRM only. For each patient a Jaccard coefficient was calculated as the number of themes in common divided by the number of different themes found by either MRM or pharmacists. For the 570 patients Jaccard coefficients ranged from a minimum of 0 to a maximum of 1, with a mean of 0.092 ± 0.117.

The top five themes by number of patients in common are shown in Table 3. Not surprisingly several of the most common themes found align with common health conditions in this cohort, namely hyperlipidemia and osteoporosis.

Some of the problems that can be identified by the software are shown in Tables 3 and 4. Table 3 shows there is some overlap of the ability of MRM to find the same kind of problems as pharmacists in the same patients. However, both pharmacists and MRM find many instances of the same problem in different patients. Table 4 shows examples of some of the themes at the extremes of overlap. The two example themes *calcium-channel blocker and reflux* and *anti-lipidemic drug, no indication* were identified in many patients by MRM but only once each by pharmacists. Similarly, the two example themes *vitamin, no indication* and *combine medications into combination product* illustrate that pharmacists identified many patients with particular problems that MRM could not identify.

Table 3. Top five themes by patients in common

Top five themes by cases in common	**Patients MRM found**	**Patients pharmacist found**	**Patients in common**	**Total Patients: pharmacists + MRM**
Osteoporosis (or risk) may require calcium and or vitamin D	137	117	49	205
Renal impairment and using (or check dose for) renally excreted drugs	122	48	24	146
Hyperlipidemia under/untreated	83	31	20	94
Sedatives long-acting or sedative long term	55	31	18	68
NSAID not recommended (heart disease/risk of bleed/other)	59	28	17	70

Table 4. Themes skewed in favour of MRM or pharmacists

Skewed themes with cases in common	Patients MRM found	Patients pharma-cist found	Patients in common	Total Patients: pharmacists + MRM
Calcium channel blocker and reflux	120	1	1	120
Anti-lipidemic drug, no indi-cation	56	1	1	56
Vitamin, no indication	1	6	1	6
Combine medications into combination product	3	10	1	12

5 Discussion

The majority of the unique pharmacist themes involved non-classifiable, mostly drug cost and compliance, problems. These pharmacist-only themes were not captured in the knowledge domain model. Although the majority of unique MRM themes could have been identified by pharmacists they were not. This was not due to lack of information on the part of pharmacists but more likely to be due to pharmacists having additional knowledge that rendered these issues moot. It is also possible that pharmacists were not aware of or simply missed these particular issues. Alternatively, the software may have produced erroneous findings.

The wide variety of variables including temporal context encapsulated in the model were manifested in the broad scope of problems that could be identified by the software. For 68 themes (out of 100 themes identified by MRM) the software showed the ability to identify the same issues that pharmacists could find in the same patients. In some circumstances half to all instances of a theme identified by pharmacists was also identified by MRM; most of the themes shown in Table 3 are examples of this.

The broad scope of themes and similarity of identification of themes in the same patients as pharmacists is encouraging; however, there were many patients who had particular problems identified by either MRM or pharmacists but not by both. Further, twenty-two themes were identified by MRM and by pharmacists without any patients in common. Several explanations are posited to account for these differences.

The first and main point is knowledge not captured and subsequently not able to be utilized by the software. Extending this point, knowledge may have been available but not entered into the software because it was not recorded anywhere by either the patient's GP or the reviewing pharmacist. Several themes stated some drugs had no indication for use because no suitable diagnosis was assigned to those patients. An example in Table 4, *anti-lipidemic drug, no indication*, shows MRM found many instances of this potential problem but pharmacists did not identify this as an issue. Does this mean pharmacists were aware of the indication for the drug? Or does it suggest pharmacists missed the opportunity to identify unnecessary medication?

Overall MRM found more problems than pharmacists. It is not unreasonable to suggest pharmacists may lack consistency in identifying DRPs. Correspondingly, it is not unreasonable to suggest MRM exemplifies consistency, as it is after all computer software. Several studies examining clinical decision support, including two prototypes on which MRM was based, have identified that humans lack consistency or lack the capacity to identify all relevant problems in contrast with the software [7, 8, 20]. Additionally, pharmacists may have focused on more important DRPs through prioritizing more pertinent DRP findings and ignoring lesser issues.

MRM did find substantially more problems than pharmacists, which raises some concerns about potential alert fatigue, a known limitation of many clinical decision support systems, wherein the system identifies so many irrelevant problems that the user simply ignores it entirely. It should be noted a portion of MRMs findings were duplications, 256 of 3209 DRPs. The central requirement and unfortunately concomitant problem of clinical decision support is the need to have sufficient information to present findings in context of the patient's current clinical situation. The application of MCRDR attempts to address the problem of context through incorporation of an extensive array of variables integrated with a knowledge base of many patient cases and inference rules.

However, it appears that MRM may not suffer from alert fatigue, as separate research that we have conducted, concerning the clinical relevance of the DRP findings of MRM and of pharmacists, was recently completed [11]. In that study experts in the field were of the opinion that both MRM and pharmacists identified clinically relevant DRPs [11]. That study supports the position that MRM may be more consistent than pharmacists by identifying a greater number of issues that pharmacists did not identify. Secondly, and importantly, despite the larger number of issues identified by MRM, lack of clinical relevance did not appear to be a factor.

A specific advantage of this implementation of MCRDR was the use of case-based reasoning, allowing the knowledge domain expert to readily add new rules and refine existing rules. This method incrementally increases the precision of rules in context of the uniquely varied situations encountered through amassing knowledge of individual patients. This is an important point, as the development of new medications, or new applications of existing medications, and ever expanding medical knowledge needs to be to be incorporated into such software on an ongoing basis to maintain the relevance of the knowledge base.

Due to the ability to easily add and refine the rules and knowledge-base a follow-up study may produce different, likely improved results. A subsequent investigation applying the same patient cases to the software and comparing the differences may be performed to determine whether DRP identification can be further enhanced over time.

MRM appears to work well in the HMR domain, but improvements may include a greater extent of variables such as compliance or cost-related concepts to widen problem detection scope as well as increasing accuracy of problem identification. Rule refinement to reduce the occurrence of duplicated DRPs is warranted. Another potential issue involves medication classification which was based on the ATC classification system. The ATC classification system included codes for combination products.

There may be limitations when attempting to create rules based on individual ingredients within combination products as each individual ingredient is not uniquely identified. Additionally, with the impending implementation of national electronic health record standards, data entry limitations such as transcription errors or missed data entry may be minimized by implementing these standards.

6 Conclusion

The use of ripple-down rules in this software did perform well in the complex and detailed HMR knowledge domain. It showed a reasonable degree of similarity with the human experts in the both the range of problem types that could be identified within its scope of knowledge, and in the frequency of problems found. MRM cannot find some of the problems that pharmacists could find, some things will always be missed because of incomplete data.

The truly interesting aspect is the software's capacity to identify more problems than pharmacists. This capacity to identify more problems did not appear to involve lack of relevance, but it is likely to be a strong indication of the consistent methodical ability of the machine to identify problems. This finding alone justifies the use of such a tool. MRM cannot replace pharmacists but may help pharmacists make good decisions and avoid missing important problems.

7 Competing interests

The author Gregory Peterson is an investor in Medscope Pty Ltd which developed MRM. The MRM software was based on the work of author Ivan Bindoff. Gregory Peterson was involved with the work of Ivan Bindoff as researcher and supervisor. Peter Tenni, a researcher previously involved with Ivan Bindoff's work, is currently the manager of the clinical division of Medscope Pty Ltd.

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