Drug interactions in primary health care in the George subdistrict, South Africa: a cross-sectional study

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Abstract

Objectives: To investigate the prevalence of potential drug-drug interactions in primary healthcare clinics in the George subdistrict, to determine which drugs were involved, and to identify associated risk factors.

Design: A cross-sectional retrospective folder review was performed.

Setting and subjects: Four hundred randomly selected patient files from four primary care clinics in the George subdistrict.

Outcome measures: The prevalence of potential drug-drug interactions in primary care, drugs involved in potential drug-drug interactions and associated risk factors.

Results: The prevalence of scripts containing at least one moderate potential interaction was 42%; severe potential interaction, 5.25%; and contraindicated combinations, 0.5%. The most common drugs involved were enalapril, aspirin, ibuprofen, furosemide and fluoxetine. The most common implicated drugs in potentially severe interactions were warfarin, aspirin, fluoxetine, tramadol and allopurinol. Two contraindicated combinations were found, namely verapamil plus simvastatin, and hyoscine butyl bromide plus oral potassium chloride. Advancing age and polypharmacy were associated with an increased risk of potential drug-drug interactions. Input from the regional hospital specialist departments greatly increased the risk of a patient being given a prescription that contained a potential drug-drug interaction. Eighty one per cent of severe interactions were from this group.

Conclusion: The potential for drug-drug interactions occurring was common in primary healthcare clinics in the George subdistrict. Drug interactions are predictable and preventable. The risk factors identified in this study may assist in the design of interventions that reduce the risk.

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Introduction

Drug-drug interactions are a recognised cause of morbidity and mortality worldwide.[1] However, a PubMed search found only two studies that dealt with the occurrence of drug-drug interactions in primary health care from developing countries, namely a South African[2] and a Mexican[3] study. Adverse clinical effects due to drug-drug interactions occurring are often not recognised by healthcare practitioners and further medications are prescribed to treat these signs and symptoms. Clinically, it may be difficult to decide between drug interactions, side-effects or deterioration of the patient's condition as the cause of the presenting clinical picture.[4]

The prevalence of potential drug-drug interactions ranges from 0.7-80%.[2-6] Denmark has a highly computerised healthcare system. In a study in that country, 94.3% of prescriptions had one or more inappropriate ratings in terms of the Medication Appropriate Index,[5] while only 0.7% of these were due to potential drug-drug interactions occurring.[5] Earlier studies found that four per cent of hospital admissions were due to drug-drug interactions[6] and a 12% prevalence of potential drug-drug interactions in primary health care.[4] In contrast, a study of prescriptions issued to patients over 50 years of age in family medicine clinics in Mexico City revealed that 80% of scripts contained one or more potential drug-drug interactions and 3.8% had contraindicated drug combinations.[3]

The only South African study listed in PubMed deals with potential drug-drug interactions and human immunodeficiency virus (HIV) drugs in a medical-aid database.[2] Of 43 482 prescriptions analysed, 18 035

potential drug-drug interactions were found. However, this study excluded all anti-tuberculosis medications. No studies were found in PubMed or Medline that dealt specifically with the prevalence of potential drug-drug interactions in primary health care in South Africa as at 23 May 2011.

The responsible drugs vary worldwide, but four drug classes comprise 51% of interactions:[7]

- Antiplatelets: 16%
- Diuretics: 16%
- Nonsteroidal anti-inflammatory drugs (NSAIDs): 11%
- Anticoagulants: 8%.

Risk factors for drug-drug interactions are:

- Polypharmacy[1,8]
- Extremes of age (very young[9] or elderly[10])
- Multiple co-morbidities,[1,8] especially cardiovascular disease[3]
- Increasing numbers of prescribing physicians.[11]

This study aimed to investigate the potential drug-drug interactions that could occur from the prescriptions issued at primary healthcare (PHC) clinics, to determine the prevalence of potential drug-drug interactions, which drugs were implicated, and to determine any other associations, such as specific diseases.

Method

Study design

A cross-sectional descriptive study was conducted of prescriptions from four PHC clinics (Sentrum, Pacaltsdorp, Conville and Thembelethu) in the George subdistrict, in the Eden district of the Western Cape. The study population was the patients who made use of PHC facilities at the above clinics from 1 February 2010-30 April 2010. Single drug scripts were excluded. No other inclusion or exclusion criteria were applied.

Sampling

Simple random sampling was used. The sample size needed to estimate a proportion with a 95% confidence interval (CI) with precision of 5% (Cp = 5%), was determined by the statistician to be 385 scripts. Four hundred scripts were analysed from a cohort of 207 468 patient files.

Ethical considerations

Permission for the study was obtained from the University of Stellenbosch ethics committee, (N09/08/203) and from the Western Cape Department of Health (19/18/RP114/2009).

Data collection

Data were collected from the prescriptions from patients' files and recorded in a password-protected database. The variables included age, sex, all drugs prescribed concurrently during the period in question and chronic diseases that were recorded in the database. The data were transferred into a de-identified spreadsheet to protect the privacy of patients and prescribers. The drug lists were analysed using Medscape's drug interaction checker for drug interactions[12] and verified using ePocrates® software. Each interaction was classified according to the Online Record of Clinical Activity (ORCA) classification.[13,14] ORCA classification levels 1-3 were identified and recorded as contraindicated, severe or moderate interactions.

Statistical analysis

The data were analysed with support from the Centre for Statistical Consultation, Stellenbosch University, using Statistica® version 10. Summary statistics were presented using frequency tables, histograms, means and standard deviations. Comparisons of different subgroups were carried out using the chi-square test to compare nominal responses, and one-way analysis of variance (ANOVA) to compare continuous responses. Analysis was conducted to determine associations between chronic disease conditions and potential drug-drug interactions. Similarly, the relationship between patients' age and potential drug-drug interactions, and between the numbers of drugs prescribed and drug-drug interactions, was determined. The impact of prescribers from the George hospital specialist departments was also examined. A significance level of 5% was used for all hypotheses tested.

Results

Of the 400 scripts analysed, 2 265 drugs were prescribed, which was an average of 5.66 drugs per script. One hundred and seventy-three scripts (43.25%) were found to have at least one potential drug-drug interaction. The prevalence

Table I: Number of prescriptions containing potential drug-drug interactions at the four primary healthcare clinics

Site	Scripts analysed (n)	Moderate interactions	Severe interactions	Contraindicated combinations
Thembalethu	200	81 (40.5%)	5 (2.5%)	1 (0.5%)
Conville	65	24 (36.9%)	3 (4.6%)	0 (0%)
Sentrum	65	35 (53.9%)	9 (13.9%)	1 (1.5%)
Pacaltsdorp	70	28 (40%)	4 (5.7%)	0 (0%)
Total	400	168 (42%)*	21 (5.3%)**	2 (0.5%)***

The prevalence of prescriptions containing potential drug-drug interactions is given for each (in brackets) and according to the classification of potential drug-drug interactions.
*: chi-square (df = 3) = 4.68, p-value = 0.99660; **: chi-square (df = 3) = 10.63, p-value = 0.01392; chi-square (df = 3) = 2.26, p-value = 0.52055

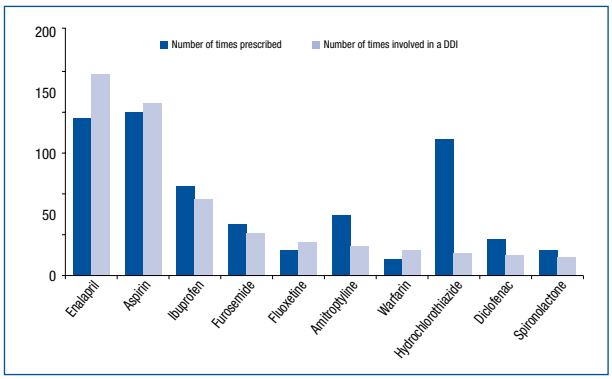
Table II: Top 15 drugs prescribed in descending order of frequency and the percentage of prescriptions containing that drug (n = 400)

Ranking	Drugs	Number of times prescribed	Percentage of prescriptions
1	Paracetamol	162	40.5
2	Aspirin	131	32.8
3	Enalapril	124	31
4	Hydrochlorothiazide	109	27.3
5	Amlodipine	99	24.8
6	Simvastatin	86	21.5
7	Ung methyl salicylate	77	19.3
8	Ibuprofen	71	17.8
9	Amoxicillin	63	15.8
10	Metformin	57	14.3
11	Atenolol	49	12.3
12	Amitriptyline	48	12
13	Vitamin B complex	45	11.3
14	Forosemide	40	10
15	Chlorpheniramine	37	9.3

of prescriptions that contained moderate interactions was 42%, severe interactions 5.3%, and contraindicated combinations 0.5%. However, many prescriptions were found to contain more than one interaction. There were a total of 366 potential drug-drug interactions in the 400 scripts analysed. Of these, 336 were potentially moderate drug-drug interactions, 28 severe, and two contraindicated combinations. Table I presents a breakdown of these findings.

The top 15 prescribed drugs are listed in Table II in descending order of frequency.

Figure 1 presents the drugs that were most commonly implicated in potential drug-drug interactions. Some drugs were implicated in more drug-drug interactions than the number of times that they were prescribed. For example, digoxin ranked 14 as a cause of potential drug-drug



DDI: drug-drug interaction

Figure 1: Top 10 causes of potential drug-drug interactions and the number of times they were prescribed

interactions. It was prescribed only four times, but was linked to 10 potential drug-drug interactions with furosemide, spironolactone, simvastatin and metoclopramide. Because these drugs are often prescribed together, it is easy to understand how digoxin had a 250% risk of being involved in a potential drug-drug interaction if it was prescribed. The most common interaction occurred between enalapril and aspirin (moderate interaction), with 86 occurrences. Hydrochlorothiazide was prescribed 109 times, but was only implicated in 18 potential drug-drug interactions.

Note to layout artist: Figure should be Times New Roman 10 pt. Move the two little blocks (legend) beneath the figure and above the title

Table III represents the drugs that were implicated in potential drug-drug interactions more often than they were prescribed. Many of these were introduced by specialist departments from the local level 2 hospital. The final column represents the number of drug-drug interactions divided by the number of times that the drug was prescribed expressed as a percentage to indicate risk.

Table IV contains the top 20 prescribed drugs that were not implicated in a potential drug-drug interaction. The

Table III: Drugs at highest risk of being implicated in an interaction if prescribed

Ranking	Drugs most likely to cause drug-drug interactions	Number of times prescribed	Number of times implicated in a drug-drug interaction	Percentage of times implicated in a drug-drug interaction vs. times prescribed
1	Digoxin	4	10	250
2	Amphotericin-B loz	1	2	200
3	Lamotrigine	1	2	200
4	Venlafaxine	1	2	200
5	Warfarin	12	21	175
6	Propranolol	2	3	150
7	Telmisarten	2	3	150
8	Fluoxetine	19	27	142.1
9	Losartan	3	4	133.3
10	Enalapril	124	161	129.8

Table IV: Drugs least likely to cause drug-drug interactions when prescribed

Amlodipine	Cefixime	Hydralazine
Ung methyl salicylate	Doxazosin Cardura XL	Stavudine
Amoxicillin	Efavirenz	Normal saline nose drops
Vit Bco	Medroxyprogesterone acetate	Promethazine
Chlorpheniramine	Omeprazole	Ipratropium bromide
Codeine	Vidaylin/multivitamins	Orphenadrine
Lamivudine	Sorol citrate powder	

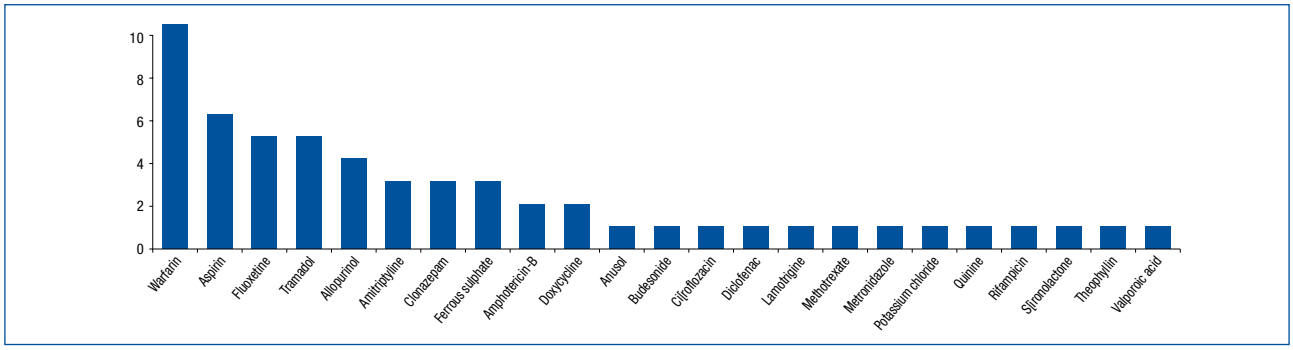


Figure 2: Drugs involved in severe interactions and the number of times they were implicated in a potential drug-drug interaction

Table V: Severe interactions

Severe drug interactions	Occurrences
Warafin plus aspirin	6 (21.43%)
Fluoxetine plus clonazepam	3 (10.71%)
Tramadol plus amitriptyline	3 (10.71%)
Warfarin plus allopurinol	3 (10.71%)
Ferrous sulphate plus doxycycline	2 (7.14%)
Tramadol plus fluoxetine	2 (7.14%)
Allopurinol plus theophyllin	1 (3.57%)
Amphotericin-B plus anusol	1 (3.57%)
Amphotericin-B plus budesonide	1 (3.57%)
Ferrous sulphate plus ciprofloxacin	1 (3.57%)
Lamotrigine plus valproic acid	1 (3.57%)
Methotrexate plus diclofenac	1 (3.57%)
Quinine plus rifampicin	1 (3.57%)
Spironolactone plus potassium choloride	1 (3.57%)
Warfarin plus metronidazole	1 (3.57%)

The percentages are the percentage of all the potentially severe interactions caused by that combination.

exception was amlodipine which was prescribed 99 times, but was only implicated in a single potential drug-drug interaction with Titralac® (calcium carbonate).

Severe interactions

Twenty-one prescriptions contained a total of 28 potentially severe drug-drug interactions. These were due to 15 different interactions (Table V).

Warfarin and aspirin were implicated in 10 and six potentially severe drug-drug interactions, respectively (Figure 2).

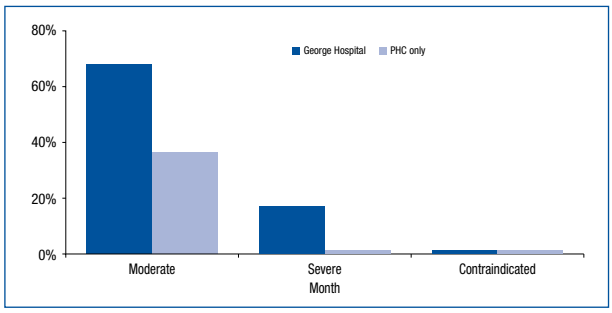
Note to layout artist: Figure should be in Times New Roman 10 pt. Change allopurinol to Allopurinol. Change Amphotericin B to Amphotericin-B, close up the extra space between Potassium and choloride, change Valproic Acid to Valproic acid

Contraindicated combinations

Two instances of contraindicated combinations were found. Hyoscine butyl bromide plus oral potassium chloride were prescribed together, and simvastatin was prescribed with verapamil.

Table VI: Chronic diseases and potential drug-drug interactions (total number of scripts n = 400)

Disease	Number of patients diagnosed with	Percentage of scripts containing a potential drug-drug interaction	Percentage of scripts with a potentially severe drug-drug interaction	Average number of drugs per script
Hypertension	150 (37.5%)	72.7	6.7	7.2
Type 3 diabetes mellitus	58 (14.5%)	81	12.1	8.3
Human immunodeficiency virus	39 (9.8%)	38.5	2.6	7.7
Osteoarthritis	32 (8%)	81.3	6.3	8.9



PHC: primary health care

Figure 3: Prevalence of potential drug-drug interactions with input from George Hospital compared to potential drug-drug interactions with input from primary health care staff only (p-value < 0.001)

The investigated associations

Diseases associated with drug-drug interactions

The top four diagnoses recorded in the files were hypertension, type 2 diabetes, HIV and osteoarthritis. These were examined to determine the percentage of scripts containing a potential drug-drug interaction. The percentage of scripts containing a potentially severe drug-drug interaction was also determined (Table VI).

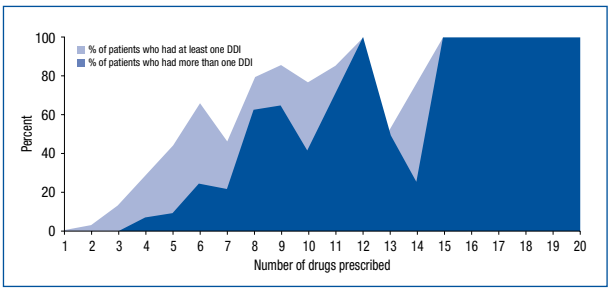
The impact of prescribers at the George level 2 hospital

A total of 109 (27%) of the prescriptions had evidence of input from the George provincial hospital specialist departments. Of the 173 prescriptions that contained at least one drug-drug interaction, 41% were adjusted at the George provincial hospital specialist department. Significantly more level 2 interactions were found in the group of scripts that were influenced by George provincial hospital. Most (81%; 17/21) of the severe interactions related to this group of patients compared to 19% (4/21) that only had input from the PHC staff. This may be due to the effect of multiple prescribers and because these patients may have had more complex pathologies.

With regard to the group of scripts from George Hospital, 63.3% (69/109) contained at least one moderate interaction. The group of scripts where all the drugs originated from the PHC clinics only contained a corresponding figure of 34% (99/291) for t (chi-square (degree of fredom = 1) = 27.77, p-value < 0.001). The prevalence of severe interactions in the regional hospital group was 16% (17/109), while the PHC only group was 1% (4/291). Each group had one contraindicated combination; George Hospital = 1/109 = 0.9%, and PHC = 1/191 = 0.5% (Figure 3).

The impact of age

The mean age of the patients in the sample was 41 years (95% CI, 39.3-43.3). The mean age for moderate interactions was 52.6 years (95% CI, 49.8-55.3); 52.5 years for severe interactions (95% CI, 43.8-61.2), and 67 years for contraindicated combinations (95% CI, 38.7-95.3). The mean ages did not differ significantly when tested with ANOVA where F (2.170) = 0.869 with p-value = 0.42 > 0.05.



DDI: drug-drug interaction

The light blue area represents the percentage of prescriptions containing at least one potential drug-drug interaction for the number of drugs prescribed. The dark blue area is the percentage with more than one potential drug-drug interaction.

Figure 4: The effect of polypharmacy

The impact of gender

Although 65.5% of the patients in the sample were female, gender was not associated with an increased risk of potential drug-drug interactions. For example, 43.13% of female and 43.48% of male scripts contained at least one potential drug-drug interaction.

The impact of polypharmacy on the number of drug-drug interactions

The risk of being prescribed drugs that could have at least one potential drug-drug interaction increased with the number of drugs prescribed. The risk of being prescribed drugs that could have more than one potential drug-drug interaction was also increased. See Figure 4.

Note to layout artist: Figure should be Times New Roman 10 pt. Change Percentage At Least One DDI to % of patients who had at least one DDI. Change Percentage More than One DDI to % of patients who had more than one DDI. Remove The effect of polypharmacy from the figure as this is repeated in the title. Move the blocks (the legend) beneath the figure and above the title.

Discussion

Drug-drug interactions occur when the precipitant drug alters the effect of the object drug.[6] Over 9 000 drug-drug interactions are recognised.[15] Most are trivial. Only a few are clinically significant.[10] The outcome may be harmful or fatal if the interaction increases toxicity or reduces the intended effect of the object drug.[16] Some interactions are tolerated, e.g. enalapril plus low-dose aspirin. This is a moderate interaction which was responsible for 86 potential drug-drug interactions in this study. Aspirin antagonises the antihypertensive effect of angiotensin-converting enzyme inhibitors, increasing mean blood pressure.[17-19]

The prevalence of potential drug-drug interactions found in the prescriptions in the George subdistrict was half that found in family medicine clinics in Mexico City where 80% of the scripts of elderly patients contained potential drug-drug interactions.[6] The prevalence of severe interactions in this study compares with a recent Spanish study which found the prevalence of potentially severe interactions to

be 5.8% in a family medicine clinic.[20] The most common drugs that were implicated were omeprazole, diazepam, warfarin, ibuprofen and calcium.[20] In the present study, warfarin plus NSAIDs (aspirin, ibuprofen and diclofenac) featured prominently, as did benzodiazepines. By contrast, omeprazole was found to be safer. It was prescribed 13 times and had no interactions (Table IV).

The increasing risk of potential drug-drug interactions with increasing age and polypharmacy is well documented.[3,10,21-24] It was confirmed in this study. The relatively low risk of potential drug-drug interactions in patients who had been diagnosed with HIV was unexpected (Table VI). The average number of drugs per script (7.7) was higher than the number of drugs per script (5.7) of the sample. While only 38.5% of scripts had potentially moderate drug-drug interactions, only 2.6% of the scripts included a potentially severe drug-drug interaction. Most patients were on regimen 1 of the South African national HIV guidelines[25] which excludes protease inhibitors. In medical aid patients in South Africa, 960 potential drug-drug interactions were found in 47 085 prescriptions (2%).[2] However, large numbers of patients were taking only one or two drugs which may explain the low prevalence of potential drug-drug interactions in that study. The scripts from files in which type 2 diabetes was diagnosed recorded the highest prevalence of potentially severe interactions (12.1%). The risk is amplified by altered pharmacokinetics as a result of disease factors, such as impaired renal function. Therefore, potential drug-drug interactions are more likely to manifest as clinical effects in these patients.

Drug-drug interactions are predictable and preventable. While the effects of moderate interactions should be noted, these seldom cause life-threatening complications. However, severe interactions require action to prevent harm. Contraindicated combinations should never be prescribed. It would seem prudent to provide some form of intervention to decrease the prevalence of severe and contra-indicated interactions. While sophisticated technological advances have reduced the risk in first-world countries significantly,[13,26,27] it is unlikely that the South African public healthcare service will embrace these technologies in the immediate future. Furthermore, electronic alerts are inconsistent, vary between products and are often ignored by prescribers and pharmacists.[26-28]

However, simple interventions, such as drug reviews and quality improvement cycles that focus on reducing potential drug-drug interactions, are effective and practical solutions.[22] Improved communication between specialist departments and PHC clinics is also likely to have a positive effect.[11] Regular medication reviews have been shown to substantially reduce the risk of drug-drug interactions and rationalise prescribing in patients with polypharmacy, reducing the number of prescribed medications by 20%.[22] The family physician may discover that dosages were modified and medications prescribed by other healthcare providers of which he or she was unaware. These reviews also enable identification of over-the-counter medications that the patient may be taking. Regular medication reviews would create awareness among prescribers and patients of the risks of polypharmacy, including drug-drug interactions. The identified risk factors in this study could be used to identify patients in PHC who should have a medication review.

This includes prescribing:

- Drugs that are implicated in potential drug-drug interactions more often than they are prescribed (Table III).
- Drugs that commonly cause drug-drug interactions (Figure 1).
- Drugs that cause potentially severe interactions (Figure 2).
- More than five drugs per prescription (Figure 4).
- To patients who are older than 50 years.
- In the case of chronic diseases, such as type 2 diabetes, hypertension or osteoarthritis (Table VI).
- By specialist departments from the regional hospital (Figure 3).

It is likely that identifying these patients and exposing them to regular medication reviews by a team, including a family physician, pharmacist and clinical nurse practitioner, would be beneficial and cost-effective. Relying on memory, drug compendia or software alone is not effective.[20]

Limitations of this study

This study only detected potential interactions and relied on the accuracy of data that were recorded in the patients' files.

Drug-interaction checkers vary in their sensitivity and specificity.[15] In instances in which different results were obtained from Medscape and ePocrates®, Medscape's results were recorded. This was because the evidence that was provided was more detailed. New drug-drug interactions are continually being discovered. The results were correct as per Medscape's interaction checker as at 31 January 2011.

Although a number of comparisons were made from the study, the sample size was not calculated to give adequate power to all of these associations. For example, testing for associations was impossible because of the small number of contraindicated combinations.

Only four PHC sites were evaluated, although these probably reflect the broader population at risk of drug-drug interactions in PHC clinics in the Western Cape.

Conclusion

Polypharmacy is rife. Patients receive up to 20 drugs per script. Potential drug-drug interactions are common. In this study, the overall prevalence of potential drug-drug interactions was 91.5%, while 43.25% of scripts contained at least one potential drug-drug interaction. More than five per cent of prescriptions contained a potentially severe interaction, and one in 200 scripts had a contraindicated combination. Simultaneous prescribing from a regional hospital increased the risk of script containing a potential drug-drug interaction. Common diseases such as hypertension, diabetes and osteoarthritis are the diagnoses that are most likely to be associated with potential drug-drug interactions. Polypharmacy was common in patients with HIV, but there were fewer potential drug-drug interactions. Warfarin and aspirin were the most common drugs that were implicated in potentially severe drug-drug interactions. The elderly are more likely to be given prescriptions that contain potential drug-drug interactions.

Recommendations

The prevalence of clinically significant events is presumed to be much lower than that illustrated by the figures in this study. However, these events are still likely to have significant consequences. By recognising this and implementing simple cost-effective mechanisms that aim to reduce potential drug-drug interactions, medical practitioners are likely to reduce the risk of drug-drug interactions in patients. Electronic media are expensive and drug compendia, clumsy. Identification of high-risk patients and evaluating their scripts as part of a regular medicine review, as well as improving communication between prescribing physicians, nurses and pharmacists, are measures that are likely to improve clinical governance and result in a decrease in the number of potential drug-drug interactions. The identified risk factors in this study included polypharmacy, elderly patients, multiple prescribers, the prescription of specific drugs and type 2 diabetes, hypertension and osteoarthritis. Scheduling these patients to have an annual medicine review may prove to be beneficial to them, while reducing the cost of drugs.

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