Drug Interactions in Primary Healthcare in the George area, South Africa: A Cross-Sectional Study

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Abstract

Background: Drug-drug interactions are a potential cause of morbidity. There is a paucity of research on this topic at primary care level.

The aim was to investigate the prevalence of potential drug-drug interactions in primary healthcare clinics in the George subdistrict; any relationships between patient ages, poly-pharmacy, gender, multiple prescribers, recorded diagnoses, and drug-interactions; to identify and quantify the drugs involved and determine the level of any drug-drug interactions using Hansen and Horn's classification.

Methodology: Following ethics approval a cross-sectional study was performed at four primary healthcare clinics in George from 400 randomly selected patients' files.

Results: The prevalence for moderate interactions was 42%, severe interactions 5.25% and contraindicated combinations was 0.5%. The most common drugs involved in potential drug interactions were: enalapril, aspirin, ibuprofen, furosemide and fluoxetine. The most common drugs involved in potentially severe interactions were: warfarin, aspirin, fluoxetine, tramadol and allopurinol. Two contraindicated combinations were found: verapamil plus simvastatin, and hyoscine butyl bromide with oral potassium chloride. Increasing age and poly-pharmacy were associated with an increased risk for potential drug-drug interactions. Input from the regional hospital specialist departments greatly increased the risk of being prescribed a potential drug-drug interaction. Eighty one per cent of severe interactions were from this group.

Conclusion: Potential drug-drug interactions are 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 designing interventions that reduce the risk.

Introduction

In developed countries, drug-drug interactions (DDIs) are a recognised source of morbidity and mortality.[1] This has led to innovative means of addressing the issue including computerised methods to detect potential interactions.[2] In developing countries like South Africa, little work has been done to determine the extent of the problem and even less to reduce the risk. In a country where a significant percentage of the population is on anti-retrovirals, anti-tuberculous drugs or medications for chronic diseases it would seem prudent to investigate and develop practical methods of reducing this risk.

In the George subdistrict, primary healthcare practitioners saw and treated an average of 3450 patients per day in four primary healthcare clinics during February to April 2010. Many of these patients have complex conditions and are managed by a number of doctors, including specialists from secondary and tertiary hospitals. The resultant discontinuity of multiple doctors and clinical nurse practitioners servicing these patients increases the potential for DDIs. In addition, large numbers of patients are elderly, suffer from chronic diseases and receive a multitude of medications.

It would appear therefore that the likelihood of significant numbers of DDIs occurring in this context should be similar to that of other South African primary healthcare clinics and be at least as high as in countries where the problem has been researched.[1-19,21-41] Adverse clinical effects due to DDIs are often not recognised by health care practitioners and further medications are added to treat these signs and symptoms. Clinically, it may be difficult to decide between drug interactions, adverse reactions, side effects or deterioration of the patient's condition as the cause of the presenting clinical picture.[3] Consider Mr H who presents at an emergency centre with generalised muscle pains after a day's gardening. The medical officer examines him and, finding nothing prescribes diclofenac and discharges him. Two days later he presents in severe pain with apparent haematuria and renal failure and is admitted. Subsequently it is discovered that the haematuria is in fact myoglobinuria secondary to rhabdomyolysis. Mr H has hypertensive heart disease and is on a number of drugs including simvastatin, prescribed by his physician. He developed tinea unguium of the toenails for which he was prescribed itraconazole by his general practitioner (GP) resulting in toxic levels of simvastatin and rhabdomyolysis. The potentially nephrotoxic diclofenac increased the likelihood of Mr H developing renal failure.

This and similar cases led to the question: "What is the prevalence of potential drug-drug interactions as reflected in the prescriptions of patients from primary healthcare clinics in the George subdistrict, which drugs are involved and what are the associated risk factors?"

Literature Review

A Medline search using the terms "prevalence AND drug-drug interactions AND primary healthcare" returned 121 articles of which 37 were relevant. Other databases were searched but were not contributory. Many studies were found dealing with adverse drug reactions (ADRs) in elderly and hospitalised patients[1,4] but few studies addressed ADRs in primary healthcare (PHC).[2] DDIs are a subset of ADRs that are preventable, but hardly any studies dealt with DDIs in PHC. Only two of these studies came from developing countries, viz. Mexico and South Africa.[7,20]

The drugs involved varied from country to country and even from region to region, making it impossible to extrapolate data from other studies to the South African context. However warfarin was commonly implicated in severe interactions.[9,12,15,19] A systematic review of the world-wide literature found that the top four drug classes comprised 51% of interactions.[18]

- Antiplatelets (16%)
- Diuretics (16%)
- NSAIDs* (11%)
- Anticoagulants (8%)

Risk factors for DDIs from the literature were:

- Polypharmacy[1,4]
- Extremes of age (very young[5] or elderly[9])
- Multiple co-morbidities[1,4] especially cardiovascular disease[7]
- Greater number of prescribing physicians[21]

The prevalence of DDIs in the international literature ranges from 0.7% to 80%. In 2007 in Denmark, with its highly computerised healthcare system, 94.3% of prescriptions had one or more inappropriate ratings in terms of the Medication Appropriate Index.[6] Only 0.7% of these were due to drug-drug-interactions.[6] In an earlier (2003)

* Non-steroidal anti-inflammatory drugs

study in Denmark, Bjerrum found that 4% of hospital admissions were due to drug interactions.[8] While in 1993 Linnarson[3] found a 12% prevalence of Potential-DDIs (P-DDIs) in primary healthcare in Denmark. (The decrease in prevalence over time is possibly due to the increased use of computer-assisted decision making.)

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 had one or more DDIs and 3.8% had level 1 (contraindicated) drug interactions.[7] However, these studies are difficult to compare. They differ in methodology, which DDIs are included, and what denominator is used to calculate prevalence and incidence. The only South African study listed in PubMed deals with DDIs and HIV drugs in a medical-aid database.[20] Of 43482 prescriptions analysed, 18035 P-DDIs were found. This study however excluded all anti-tuberculous medications. No studies were found in PubMed or Medline dealing with the prevalence of DDIs in primary healthcare in South Africa (23 May 2011).

Aim:

To investigate potential drug-drug interactions in the prescriptions issued at primary healthcare clinics in the George subdistrict.

Objectives:

1. To determine the prevalence of potential DDIs in prescriptions issued at four PHC clinics in the George subdistrict.
2. To determine the most common drugs involved.
3. To grade the levels of drug-drug interactions according to the OpeRational Classification of drug interactions (ORCA).[12,13]
4. To establish any association between specific chronic diseases and prescriptions containing P-DDIs.
5. To determine the effect that specialist prescribers from George Hospital have on the prevalence of DDIs in the scripts of patients followed up in PHC clinics.

Methodology

Ethics approval was obtained from the University of Stellenbosch Ethics Committee, reference N09/08/203. The main ethical consideration was protecting patient privacy. This was dealt with by using a de-identified database and password protection of sensitive data. A waiver of informed consent was granted by the ethics committee. Permission for the study was obtained from the Western Cape Department of Health, reference 19/18/RP114/2009. The study sites were four primary health care clinics in the George subdistrict of Western Cape:

- Thembalethu
- Sentrum
- Pacaltsdorp
- Conville

Design:

A cross-sectional study of the drugs prescribed to patients in PHC clinics was used to determine the prevalence of P-DDIs and to evaluate associations. The study population was the patients making use of PHC facilities at the above clinics from 1st February to 30th April 2010. No other inclusion or exclusion criteria were applied. Simple random sampling was used. The sample size needed to estimate a proportion with a 95% Confidence Interval (CI) and a precision of 5% (Cp = 5%) was determined to be 385 scripts. Four hundred scripts were analysed.

Method of Data Collection:

Data was 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 recorded in the files. The data was transferred into a de-identified spread-sheet to protect the privacy of patients and prescribers. The drug lists were analysed using Medscape's drug interaction checker for drug interactions (www.medscape.com) and verified using ePocrates® software as a form of concurrent convergent validity. These are valid and reliable instruments to detect DDIs.[26,32] ePocrates® compares favourably with drug compendia for accuracy.[27] Each interaction was classified according to the ORCA classification.[12,13] Data from each site was collected individually allowing analysis of this data separately and as part of the total. Rigour was ensured by linking a range of validity and reliability checks in the database and spreadsheet. In order to distinguish trivial from significant effects the ORCA classification levels 1 to 3 were identified (Table 1) and recorded as contraindicated, severe, or moderate interactions.

Table 1 Hansten and Horn's OpeRational Classification of drug interactions (ORCA). Adapted from references 10,12,16,39

Level	Management	Examples
1 (Contraindicated)	Avoid combination because the risk always outweighs the benefit	nitroglycerin - sildenafil
2 (Severe)	Usually avoid the combination -alternatives are available for one or both drugs -avoid unless the benefit outweighs the risk of the DDI	simvastatin and amiodarone
3 (Moderate)	Minimise risk -consider alternatives that may be less likely to cause DDI -circumvent the interaction by taking precautionary measures -monitor for early detection of the DDI	warfarin and rifampicin
4	No special precautions needed as risk of adverse effect is small	efavirenz and TMX/SMX
5	Ignore as DDI does not occur per existing evidence	paracetamol and codeine

Statistical Analysis

The data was analysed by the researcher with support from the Centre for Statistical Consultation, Stellenbosch University, using STATISTICA version 10.0 www.statsoft.com. Summary statistics were conducted using frequency tables, histograms, means and standard deviations. Comparisons of different sub groups were done using the Chi-square test for comparing nominal responses and one-way ANOVA for comparing continuous responses. Analysis was done to determine associations between chronic disease conditions and DDIs. Similarly, the relationship between patients' age and DDIs and between the numbers of drugs prescribed and DDIs were determined. The effect of prescribers from the George hospital specialist departments was also examined. A significance level of 5% was used for all hypotheses tested.

Results

The following tables and figures that present the results deal firstly with the prevalence of P-DDIs. Thereafter, the drugs that were involved are outlined and the findings as regards severe interactions as well as contra-indicated combinations are presented. Finally, the different associations that were investigated are detailed.

There were 2265 drugs prescribed in the 400 scripts analysed, (5.66 drugs per script). Using Medscape's interaction checker, 173 scripts (43.25%) were found to have at least one potential-drug-to-drug interaction. (Table 2)

Table 2 Number of prescriptions containing P-DDIs at the four PHC clinics. The percentage of the scripts containing a DDI is in brackets.

Site	Scripts analysed	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 (0.0%)
Sentrum	65	35 (53.9%)	9 (13.9%)	1 (1.5%)
Pacaltsdorp	70	28 (40.0%)	4 (5.7%)	0 (0.0%)
Totals	400	168 (42.0%)	21 (5.3%)	2 (0.5%)
Statistica		Chi-square(df=3)=4.68, p=.99660	Chi-square(df=3)=10.63, p=.01392	Chi-square(df=3)=2.26, p=.52055

Overall 366 potential-drug-interactions were present, an average of 0.92 potential-interactions per script.(Table 3). Table 4 presents the fifteen drugs that were most commonly prescribed in descending order of frequency.

Table 3 Breakdown of the total P-DDIs found

Total potential drug interactions	366
No. of moderate interactions	336
No. of severe interactions	28
No. of contraindicated interactions	2

Table 4 Top fifteen drugs prescribed

Ranking	*Drugs*	*Number of times prescribed*
1	Paracetamol	162
2	Aspirin	131
3	Enalapril	124
4	Hydrochlorothiazide	109
5	Amlodipine	99
6	Simvastatin	86
7	Ung methyl salicylate	77
8	Ibuprofen	71
9	Amoxicillin	63
10	Metformin	57
11	Atenolol	49
12	Amitriptyline	48
13	Vit Bco	45
14	Furosemide	40
15	Chlorpheniramine	37

Figure 1 Top ten causes of P-DDIs and the number of times they were prescribed

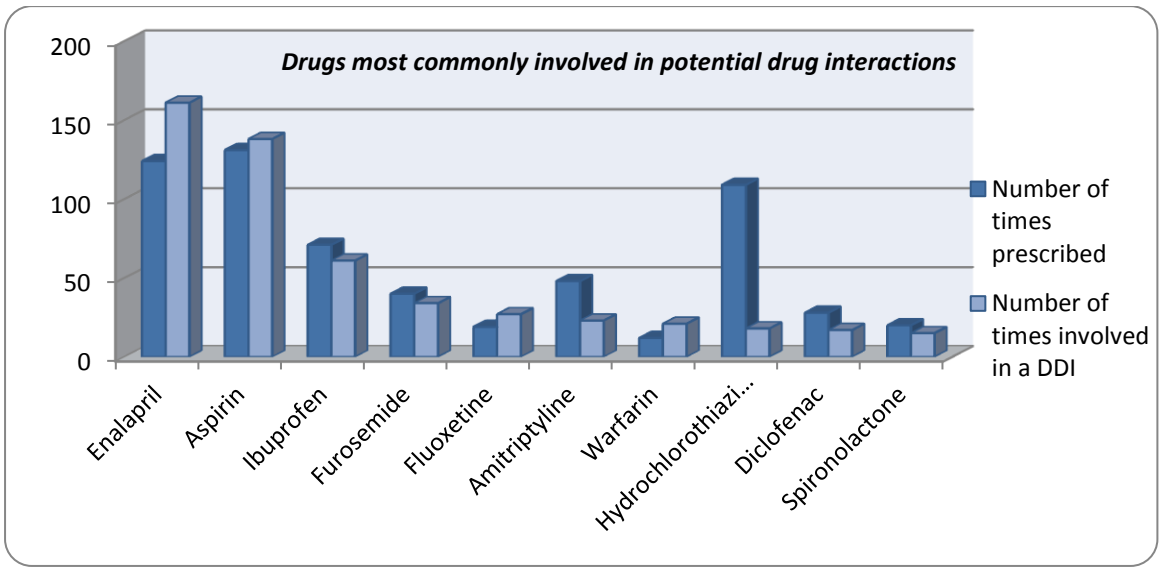


Figure 1 presents the drugs that were most commonly involved in potential-drug-interactions. Some drugs were involved in more DDIs than the number of times that they were prescribed. For example, digoxin ranked 14 as a cause of P-DDIs. It was prescribed only four times but was involved in ten P-DDIs. Furosemide, spironolactone,

simvastatin and metoclopramide were the drugs implicated in moderate interactions with digoxin. Because these drugs are often prescribed together, it is easy to understand how digoxin had a 250% risk of being involved in a P-DDI if it was prescribed. The most common interaction occurred between enalapril and aspirin (Level 3), with 86 occurrences.

Table 5 represents the drugs that were involved in P-DDIs more often than they were prescribed. Many of these were introduced by specialist departments from the local regional hospital. The final column represents the number of DDIs divided by the number of times the drug was prescribed expressed as a percentage to indicate risk.

Table 5 Drugs at highest risk of being involved in an interaction if prescribed.

Ranking	*Drugs Most likely to cause DDIs*	*Number of times prescribed*	*Number of times involved in a DDI*	*Percentage of times involved in a DDI vs. times prescribed*
1	**Digoxin**	4	10	250.0%
2	**Amphotericin B loz**	1	2	200.0%
3	**Lamotrigine**	1	2	200.0%
4	**Venlafaxine**	1	2	200.0%
5	**Warfarin**	12	21	175.0%
6	**Propranolol**	2	3	150.0%
7	**Telmisarten**	2	3	150.0%
8	**Fluoxetine**	19	27	142.1%
9	**Losartan**	3	4	133.3%
10	**Enalapril**	124	161	129.8%

Table 6 contains the top twenty prescribed drugs that were *not* involved in a P-DDI, (except amlodipine which was prescribed 99 times but was only implicated in a single P-DDI with Titralac® (calcium carbonate).

Table 6 Drugs least likely to cause DDIs

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**	

Severe Interactions

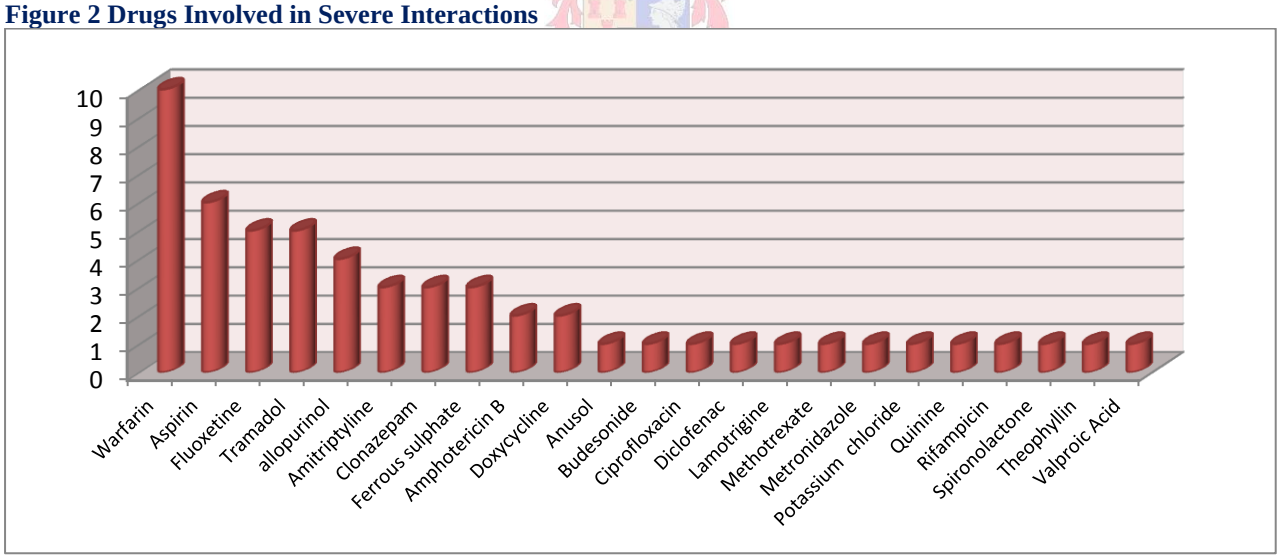
Twenty-one prescriptions contained a total of 28 level 2 (severe) P-DDIs. These were due to 15 different interactions. (Table 7)

Table 7 Severe interactions. The percentages are the percentage of all the potentially severe interactions caused by that combination.

Severe Drug Interactions	*Occurrences*
Warfarin ↔ Aspirin	***6(21.43%)***
Fluoxetine ↔ Clonazepam	***3(10.71%)***
Tramadol ↔ Amitriptyline	***3(10.71%)***
Warfarin ↔ Allopurinol	***3(10.71%)***
Ferrous sulphate ↔ Doxycycline	***2(7.14%)***
Tramadol ↔ Fluoxetine	***2(7.14%)***
Allopurinol ↔ Theophyllin	***1(3.57%)***
Amphotericin B ↔ Anusol	***1(3.57%)***
Amphotericin B ↔ Budesonide	***1(3.57%)***
Ferrous sulphate ↔ Ciprofloxacin	***1(3.57%)***
Lamotrigine ↔ Valproic Acid	***1(3.57%)***
Methotrexate ↔ Diclofenac	***1(3.57%)***
Quinine ↔ Rifampicin	***1(3.57%)***
Spironolactone ↔ Potassium chloride	***1(3.57%)***
Warfarin ↔ Metronidazole	***1(3.57%)***

Warfarin was involved in ten and aspirin in six severe P-DDIs. (Figure 2)

Figure 2 Drugs Involved in Severe Interactions



Contraindicated Combinations

Two instances of contraindicated combinations were found. Hyoscine butyl bromide and oral potassium chloride were prescribed together at Thembalethu while simvastatin with verapamil were prescribed at Sentrum clinic.

The Associations Investigated

1. Diseases associated with DDIs

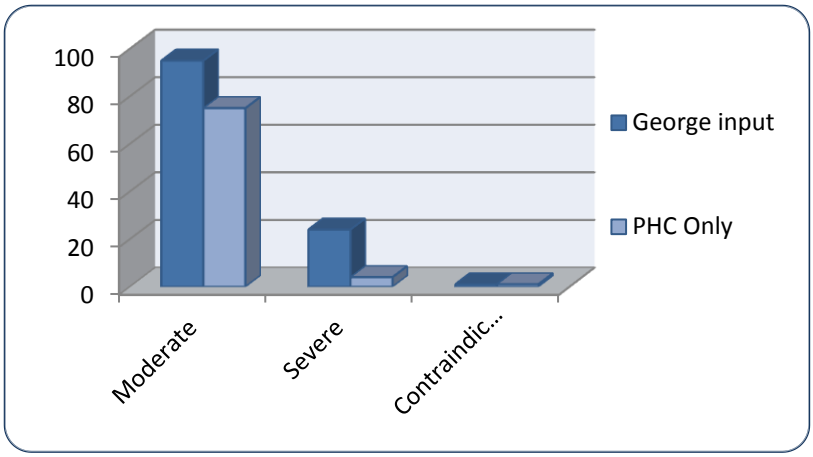
The top four diagnoses recorded in the files were hypertension, type-2-diabetes, Human Immunodeficiency Virus infection (HIV) and osteoarthritis. These were examined to determine the percentage of scripts with a P-DDI. The percentage of scripts containing a severe P-DDI was also determined. (Table 8)

Table 8 Chronic diseases and P-DDIs (Total number of scripts = 400)

Disease	Number of patients diagnosed with	Percentage of scripts containing a potential DDI	Percentage of scripts with a potentially severe DDI	Average number of drugs per script
Hypertension	150 (37.5%)	72.7%	6.7%	7.2
Type 2 Diabetes	58 (14.5%)	81.0%	12.1%	8.3
HIV	39 (9.8%)	38.5%	2.6%	7.7
Osteoarthritis	32 (8.0%)	81.3%	6.3%	8.9

2. The effect of prescribers from George hospital

Figure 3 P-DDIs with input from George hospital compared to P-DDIs with input from PHC staff only (Chi-squared(df=2)=16.18, p=0.00031)



A total of 109 (27%) of the prescriptions had evidence of input from the George provincial regional hospital (GH) specialist departments. Of the 173 prescriptions that contained at least one DDI, 41% had input from GH.

Significantly more level 2 interactions were found in the group of scripts that were influenced by GH. Most (81%; 17/21) of the severe interactions came from this group of patients compared to 19% (4/21) that only had input from the PHC staff.

In the group where the drugs originated from George hospital, 63.3% (69/109) of the scripts had at least one moderate interaction with a corresponding figure of 34% (99/291) for the group where all the drugs originated from the PHC clinics only. (Chi-square (df=1) =27.77, p<0.001).

For contraindicated combinations, each group had one; GH = 1/109 = 0.9% and PHC = 1/191=0.5%.

3. Age

The mean patient age of 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), for severe interactions, 52.5 years (95% CI,43.8-61.2), and contraindicated combinations, 67 years (95% CI,38.7-95.3). The mean ages do not differ significantly as tested with ANOVA where F(2,170)=0.869 with p=0.42>0.05.

4. Gender

Although 65.5% of the patients in the sample were female, gender was not associated with an increased risk for P-DDIs; 43.13% of female and 43.48% of male scripts contained at least one P-DDI.

5. Effect of poly-pharmacy on the number of DDIs

Using the number of occurrences one can determine the average number of DDIs per script. By plotting this against the number of concurrent drugs prescribed, the tendency is for the number of DDIs to increase as the number of drugs used concurrently increases. (Figures 4 and 5).

Figure 4: The effect of poly-pharmacy on the prevalence of DDIs: The red and blue line represents the average P-DDIs per script. The relationship is greater than linear as shown by the blue line.

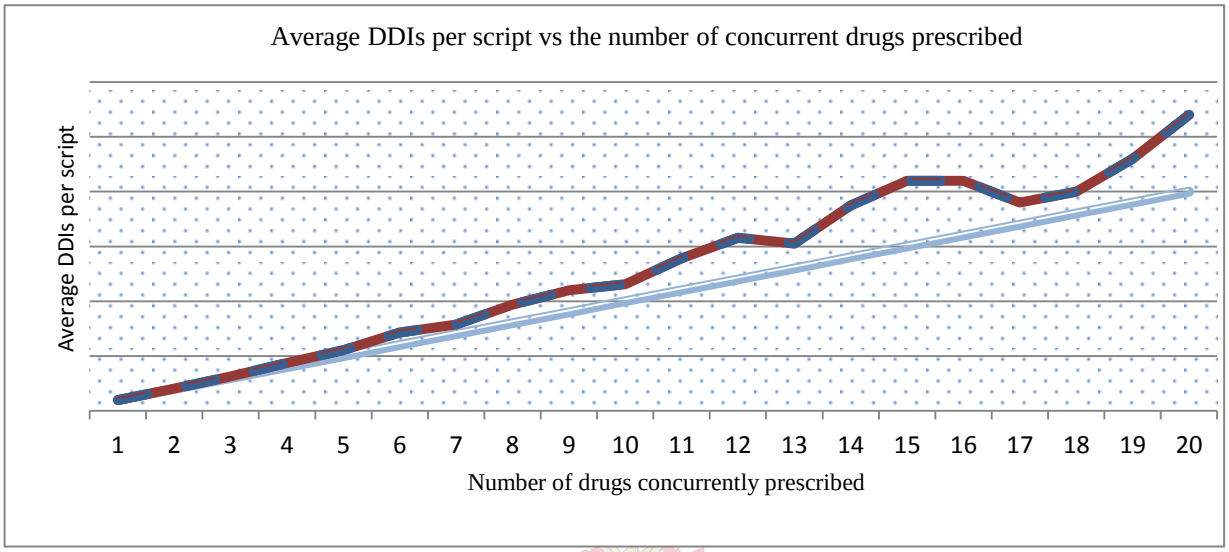
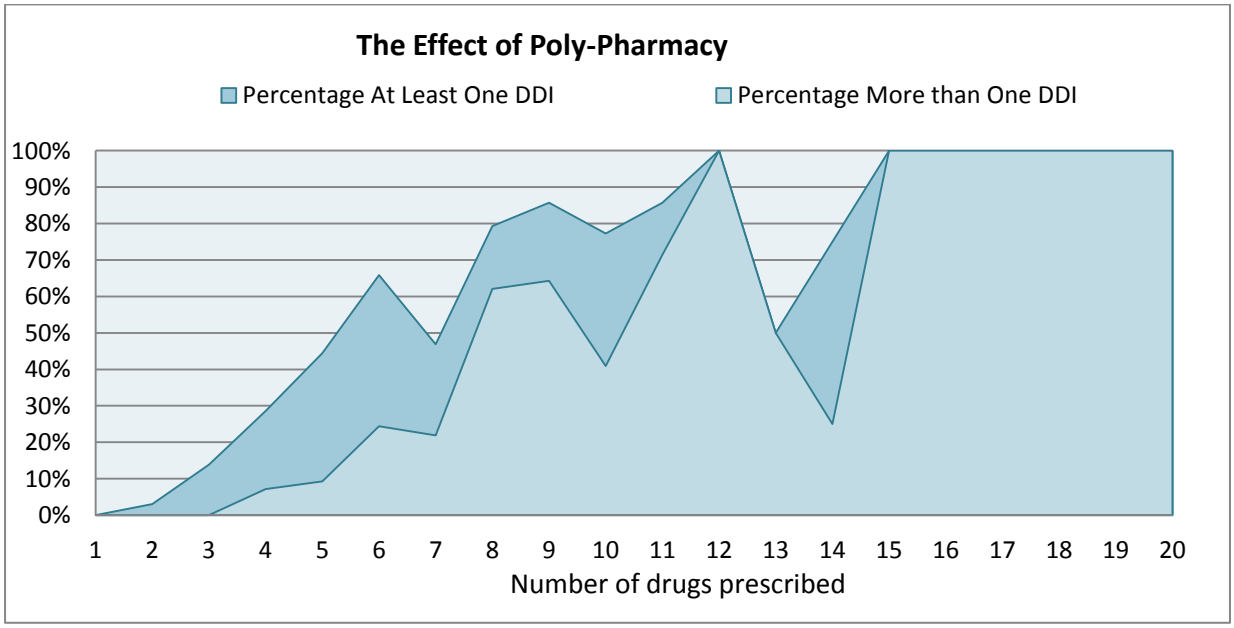


Figure 5 The effect of polypharmacy: The dark blue area represents the percentage of patients who have at least one P-DDI for the number of drugs prescribed and the light blue is the percentage with more than one P-DDI.



Discussion

Drug-to-drug-interactions occur when the precipitant drug alters the effect of the object drug.[8] Over 9000 DDIs are recognised.[41] Most are trivial with only a few being clinically significant.[9] The outcome may be harmful, even fatal, if the interaction increases toxicity or reduces the intended effect of the object drug. Other effects include gastrointestinal bleeding, renal dysfunction, electrolyte imbalances, hypertension/hypotension, and arrhythmias.[10] Many interactions are acceptable, for example enalapril and low dose aspirin, a moderate (level three) interaction, responsible for 86 interactions in this study. Aspirin antagonises the antihypertensive effect of ACE-inhibitors, increasing mean blood-pressure. There may be other negative effects.[35-37]

The prevalence of DDIs in the George subdistrict is half of that found in family medicine clinics in Mexico City, where 80.0% of the scripts of elderly patients contained P-DDIs.[8] However the studies are not directly comparable as they only looked at patients older than 50 years. The prevalence of *severe* interactions compares with a recent Spanish study which found the prevalence of potentially severe interactions to be 5.8% in family medicine clinics in Murcia.[32] The most common drugs involved were omeprazole, diazepam, warfarin, ibuprofen and calcium. In the present study warfarin and NSAIDs (aspirin, ibuprofen and diclofenac) featured prominently as did benzodiazepines. Omeprazole was found to be one of the safer drugs in this study, being prescribed thirteen times with no interactions (Table 5). The use of different interaction checkers complicates comparisons.

The increasing risk of P-DDIs with age and poly-pharmacy is well documented.[7,9,15,22,23,30] However, the relatively low risk of P-DDIs in patients diagnosed with HIV was unexpected (Table 7). At 7.7 drugs per script, the average drugs-per-script was higher than the 5.7 drugs-per-script of the sample. Yet only 38.5% of scripts had moderate interactions and 2.6% of the scripts included a potentially severe-interaction. Snyder found that 77% of scripts of hospitalised HIV patients in tertiary care in Florida had medical errors of which 12% were due to DDIs.[34] Our study involved only ambulatory clinic patients; therefore the studies are not directly comparable. Furthermore, most were on regimen 1 of the SA national HIV guidelines, which excludes protease-inhibitors. In medical-aid patients in South Africa, Katende-Kyenda found 960 P-DDIs in 47085 prescriptions (2%) in private practice.[20] However, large numbers of patients were on only one or two drugs, which may explain the low prevalence of DDIs in this study.

The scripts from files where type 2 diabetes was diagnosed recorded the highest prevalence of potentially *severe* interactions (12.1%). This risk may be amplified by altered pharmacokinetics as a result of disease factors such as impaired renal function. It is probable that P-DDIs are more likely to manifest as clinical effects in these patients.

DDIs are predictable and preventable. While we need to take note of the effects of moderate interactions, these seldom cause life-threatening complications. Severe (level two) interactions however require action to prevent harm. Level one interactions should never be prescribed. It would seem prudent to provide some form of intervention to decrease the prevalence of level one and level two interactions. While sophisticated technological advances have reduced the risk in first world countries significantly,[12,26,27] it is unlikely that the South African public health 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.[26,27,31,40]

However, simple interventions such as drug reviews and quality improvement cycles focusing on reducing P-DDIs are effective and practical solutions.[22] Improved communication between specialist departments and PHC clinics are also likely to have a positive effect.[21]

Regular medication reviews have been shown to substantially reduce the risk of DDIs and rationalise prescribing in patients with poly-pharmacy, reducing the number of medications prescribed by 20%.[22] Dosages modified and medications prescribed by other healthcare providers may be discovered that the family physician was unaware of. Identifying over the counter (OTC) medications is also possible by asking the patient what other medicines (s)he uses. Regular medication reviews would create awareness amongst prescribers and patients concerning the risks of poly-pharmacy, including DDIs.

This study may help to target interventions aimed specifically at clinically important interactions by identifying the severe as well as common interactions found in typical PHC settings in South Africa. This study identified the following risk factors:

1. Drugs that are involved in P-DDIs more often than they are prescribed: Digoxin, amphotericin B, lamotrigine, venlafaxine, warfarin, propranolol and telmisarten (Table 5)

Figure 6 The most important findings

The most important findings of this study are:

1. *Poly-pharmacy is rife, with patients receiving up to twenty drugs per script.*
2. *Potential drug-drug interactions are common; 40.2% of scripts contained at least one P-DDI.*
3. *More than 5% of prescriptions contained a potentially severe-interaction and 1 in 200 scripts have a level-one drug interaction.*
4. *Multiple prescribers, viz. specialist departments from a regional hospital, increased the risk of a script containing a P-DDI from PHC clinics.*
5. *Common diseases such as hypertension and diabetes are the diagnoses most likely to be associated with P-DDIs. Poly-pharmacy is common in HIV patients but there are fewer interactions compared to diabetes, hypertension and osteoarthritis.*
6. *Warfarin and aspirin are the most common cause of severe P-DDIs.*
7. *The elderly are more likely to be prescribed P-DDIs*

2. Drugs that commonly cause P-DDIs: Enalapril, aspirin, ibuprofen, furosemide, fluoxetine, amitriptyline and warfarin (Figure 1)
3. Drugs that cause potentially severe interactions: Warfarin, aspirin, fluoxetine, tramadol, allopurinol, amitriptyline and clonazepam (Figure 2)
4. Poly-pharmacy (more than five drugs per prescription)
5. Patients older than fifty years
6. Chronic diseases: Type 2 diabetes, hypertension or osteoarthritis
7. Involvement of specialist departments from the regional hospital.

Identifying these patients and exposing them to regular medication reviews by a family physician is likely to be beneficial and cost-effective. However, relying on memory, drug compendia or software alone is unlikely to be effective.[32]

Limitations of this study

This study only detected *potential* interactions. Only a few people experience the effects of interactions. Therefore the clinical effects are considerably less than the figures presented here.

This study was also completely reliant on the data as recorded in the patients' files. No attempt was made to interpret or correct possible diagnostic inaccuracies.

Drug-interaction checkers vary in their sensitivity and specificity.[41] Where Medscape and ePocrates® had different results the results from Medscape were recorded. New drug-interactions are continually being discovered. The results were correct as per Medscape's interaction checker on 31 January 2011.

The sample size in this study is small, making the identification of associations for contraindicated combinations (level 1 interactions) statistically insignificant. Only four PHC sites were evaluated, although these probably reflect the broader population at risk in PHC clinics in the Western Cape.

This was a cross-sectional study, thus seasonal variations, changing prescribers or changing illness profiles were not taken into account.

Conclusion/recommendations

As in PHC clinics in other developing countries, P-DDIs are common yet unrecognised by prescribers in PHC clinics in the George subdistrict of South Africa. Although the prevalence of clinically significant events is presumed to be much lower than the figures for P-DDIs found in this study, they are still likely to be significant. By recognising this and implementing simple cost-effective mechanisms aimed at reducing DDIs, medical practitioners are likely to reduce the risk of DDIs to the 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, is likely to improve clinical governance and result in a decrease the number of P-DDIs prescribed. The risk factors identified in this study include poly-pharmacy, elderly patients, multiple prescribers, prescription of specific drugs and type 2 diabetes, hypertension and osteoarthritis. Scheduling these patients to have a medicine review performed by a family physician and then annual follow-up reviews may be prove beneficial to the patients whilst reducing the cost of drugs.

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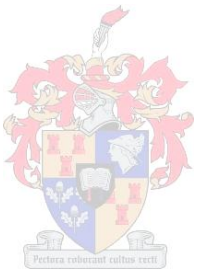

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