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# Detecting drug interactions using personal digital assistants in an out-patient clinic

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## Summary

**Background:** The installation of drug databases on personal digital assistants (PDAs) allows for rapid detection of adverse drug interactions at the point of care.
**Aim:** To test the ability of a drug interaction database (ePocrates RX) to correctly identify clinically significant adverse drug interactions in an out-patient setting.
**Design:** Retrospective file review of 1801 drug prescriptions in out-patients consulting a medical walk-in clinic.
**Methods:** Each prescription was assessed independently by a clinical pharmacologist using drug-drug interaction compendia, and by a general internist using the drug interaction database. Discrepant results were systematically reviewed by both, using published literature, and a consensus was then reached. This consensus was used as the criterion against which the PDA drug interaction database was judged.
**Results:** The prevalence of potential adverse drug interactions was 23%. When compared to the opinion of the clinical pharmacologist and drug-drug interaction compedia, the sensitivity of the drug interaction database to correctly identify clinically relevant adverse drug interactions was 81% (95%CI 77%–85%) and the specificity was 88% (95%CI 86–89%). The positive predictive value was poor (67%, 95%CI 62%–71%) but the negative predictive value was excellent (94%, 95%CI 92%–95%).
**Discussion:** The database was an efficient tool for rapidly checking for potentially harmful drug interaction, but also flagged up several clinically non-significant interactions. When used appropriately, this drug interaction database could help physicians decrease prescription error, by ruling out the risk of clinically relevant adverse drug interactions for newly prescribed drugs, and thereby increase patient safety.



## Introduction

Drug prescription is the most common therapeutic act in primary care. Physicians need to be aware of adverse drug events (ADEs), as they are common, under-reported, result in dissatisfaction with care and decreased quality of life, and also account for frequent visits to the Emergency Department (ED).[1,2] Awareness of ADEs is becoming increasingly important because of its medical and economical consequences, especially as a considerable percentage of all ADE-related visits and ADE-related admissions are considered to be avoidable.[3–7] A prospective observational study reported that 28% of ED visits were due to medication-related problems, of which 70% were felt to be preventable.[5] A review of 15 studies conducted worldwide found a median drug-related hospital admission rate of 7%.[8] Among the elderly, this figure can rise to 30%.[9] In in-patient settings, the frequency of ADEs

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has been estimated to vary between 7% and 20%.[10] In out-patient care, despite the large proportion of prescription drugs used, the incidence of ADEs has not been well documented. One prospective cohort study suggested that it may be a common problem involving up to 25% of patients, of which 23% were estimated as preventable.[1] One third of these preventable errors could have been detected by an advanced computerized system.

Adverse drug interactions (ADIs) are a subset of ADEs that is entirely preventable. Potential risk factors for the development of ADIs include polypharmacy, multiple morbidities, and certain drug specificities (for example, pharmacokinetic properties such as important first-pass metabolism, high transporters or enzyme affinity, high potencies, narrow therapeutic range or low therapeutic index). The rates of potential drug interactions for patients receiving two or more drugs can vary from 2%[11] to 42%,[12] with the proportion of visits to the ED or hospital admissions due to ADIs varying from 1 to 4%.[13,14] Among out-patients, the proportion of ADEs caused by ADIs is estimated to be 3%.[15] In a retrospective review of prescription data in a primary health-care centre, the incidence of potential interactions was 12%, rising to 22% for elderly patients.[11]

Systematic screening for drug interactions can be fastidious and time-consuming in the rapidly growing field of therapeutics.[16] Computer databases have been shown to limit prescription errors in both hospitalized patients and dispensing pharmacies, and have been adopted by several hospitals and pharmacies.[17,18] However, the efficacy of this approach in out-patient settings is less well documented. A prospective study with Australian general practitioners (GPs) working with out-patients showed that when a change was proposed by a pharmacist, 54% of GPs followed the advice, and the action taken had a positive outcome in 71% of cases.[19]

In recent years, personal digital assistants (PDAs) have become increasingly popular among health-care professionals.[20–22] Sufficient portable storage capacity allows for easy use of even large drug databases, potentially bringing point-of-care technology and prescription safety to out-patient settings. ePocrates RX is a free-of-charge core drug information database that was first introduced in 1999 and can be easily installed on a PDA. It allows for the simultaneous and expeditious checking of ADIs between up to 30 drugs.[20] Comparison of different drug information databases designed for PDAs to detect ADIs have shown that they vary in completeness and ease of use.[23–26] In these studies, the performance of ePocrates RX with respect to other drug databases in detecting drug interactions varied from intermediate to very good. Physicians perceived its use as an improvement in their clinical behaviour (better drug decisions), practice efficiency (time saved) and patient care.[27] A recent study conducted on clerkship students found that they rated drug databases on PDAs (ePocrates RX) as being, along with the Griffiths' five minute Consult, the most useful medical software, and their satisfaction correlated with the documented use of these programs.[22] This is currently the only core drug database available for PDAs that is both free of charge and regularly updated.[26]

We tested the ability of this drug interaction database to correctly identify clinically significant ADIs in prescriptions written out for patients consulting a medical out-patient clinic and to document the prevalence of clinically significant ADIs in this setting.

# Methods

## Data collection

Prescription data for 591 consecutive patients consulting the medical out-patient clinic of the Geneva University Hospitals over a 2 week period were retrieved from the medical file records. Patient drug profiles, including drugs that the patient was currently taking, as well as those prescribed during the visit, were individually entered into a database. Information regarding the symptoms for which the patient consulted (e.g. cough) and the diagnosis made by the physician during the consultation (e.g. sinusitis) were also recorded. Drugs were classified according to the Anatomical Therapeutic Chemical Classification Index. For each consultation, a double assessment was performed. First, a clinical pharmacologist (JD) evaluated whether the different prescribed drugs could result in a clinically significant ADI, basing his decision on drug-drug interaction compendia that are considered as reference textbooks by clinical pharmacologists.[28–30] Second, a board-certified general internist (MFD) entered all the prescribed drugs into the PDA drug interaction database, and noted when a warning message flagged an ADI. When the drug used was not found in ePocrates RX, a drug with a similar pharmacological profile was used instead. Certain drugs (e.g. moclobemide, a monoamine inhibitor anti-depressant drug) could therefore not be entered into the drug interaction program. The assessments were performed on separate databases that were then merged to identify discrepancies. Discrepant results were systematically reviewed by both

assessors using published literature, and a consensus was then reached. This consensus was used as the criterion against which the PDA drug interaction database was judged.

ADIs were classified into two broad categories according to the drug interaction mechanisms that were involved: pharmacokinetic and pharmacodynamic. Pharmacodynamic interactions were further divided into synergistic (e.g. the risk of serotonin syndrome when using tramadol and SSRIs such as sertraline) and antagonistic interactions (e.g. using an antihypertensive treatment along with a vasoconstrictor such as phenylephrine, largely prescribed for a common cold).

### Statistical analysis

The statistical analyses were performed at two different levels. First, we computed descriptive statistics at the patient level to give general information about drug prescriptions and overall ADI prevalence. Then, to determine the ability of the drug interaction database to detect clinically significant ADI, each drug prescription was analysed separately to determine whether it could be involved in a significant ADI. The level of accuracy of the drug interaction database was compared to the consensus, as previously defined. These data were used to compute the sensitivity, specificity, positive and negative predictive values for the PDA drug interaction database. We also computed 95%CIs around these estimates.[31,32]

## Results

The mean age of patients included in this review was 39 years (SD 17; quartiles 26–35–48; min 16, max 94) and 54% ($n$=319) were female. For 59% of the patients (346/591), a pre-existing drug had been documented in the medical file (1.4 pre-existing drug treatments/patient; SD 1.7; quartiles 0–1–2; min 0; max 10). New drugs had been prescribed in 78% (460/591) of consultations (1.6 drugs new drug treatment/patient; SD 1.3; quartiles 1–2–2; min 0; max 8).

In 23% (135/591) of the consultations, a potentially clinically significant ADI was identified by the consensus. Synergistic pharmacodynamic interactions were found in 84% (114/135), antagonistic pharmacodynamic interactions in 20% (27/135) and pharmacokinetic interactions in 48% (65/135), of which 88% (57/65) were due to inhibition or induction of hepatic cytochromes P-450 by drugs (e.g. inhibition of cyclosporine metabolism by ketoconazole). Concerning the class of medication, anti-inflammatory and anti-rheumatic products were involved in 62% of ADIs (84/135), mainly because of the risk of acute renal insufficiency or of arterial hypertension when administered concomitantly with antihypertensive drugs or nasal preparations containing sympathicomimetic agents. Psychotropes were also frequently involved (19%, 26/135), with the risk of excessive sedation (e.g. prescription of two neuroleptics or concomitant prescription of a neuroleptic with a benzodiazepine or a SSRI). Cardiovascular drugs were involved in 16% (22/135) of the cases.

Among the 1801 drug prescriptions, 418 were identified as having potentially clinically significant ADIs (23%). The PDA drug interaction database identified 339 ADIs correctly (81%), over-detected 170 situations, missed 79 situations, and excluded ADIs in 1213 situations (Tables 1–3). The sensitivity and specificity were 81% (95%CI 77%–85%) and 88% (95%CI 86%–89%), respectively. For this prevalence, the positive predictive value was poor (67%, 95%CI 62%–71%), but the negative predictive value was excellent (94%, 95%CI 92%–95%).

## Discussion

The PDA drug interaction database correctly identified 81% of ADIs and correctly excluded 88%. We are not aware of previous reports using this drug interaction database with real patient profiles in an out-patient setting, but Robinson and Burk found better values for sensitivity and specificity (100% and 88% respectively)[24] using six hypothetical patient profiles, while Perkins *et al*. found sensitivity and specificity to be $\geqslant$90%,[26] also using six simulated patient profiles. Our use of real patient profiles seems more likely to identify the limitations of such drug interaction databases.

The rather low sensitivity of the PDA drug interaction database was partly due to its inability to identify several ADIs, such as concomitant use of different non-steroidal anti-inflammatory drugs or use of NSAIDs and phenylephrine (Table 3). The poor positive predictive value was largely explained by a high prevalence of concomitant prescription of anti-inflammatory agents (NSAIDs) and acetaminophen, a situation considered to be an ADI by the PDA drug interaction database, and which represented over half the cases of over-detection (Table 2). NSAIDs are known for their nephrotoxicity, due largely to decreased prostaglandin production (cyclo-oxygenase-2 inhibition), although other mechanisms such as acute interstitial nephritis, nephrotic syndrome, or papillary necrosis have also been described. The acetaminophen precursor phenacetin has been strongly associated with analgesic

**Table 1** Adverse drug interactions correctly identified (*n*=339) by a personal digital assistant interaction database (ePocrates RX) in 1801 drug prescriptions

| | *n* | % | Interaction type |
|---|---|---|---|
| NSAIDs and 2nd NSAID e.g. aspirin, mefenamic acid) | 51 | 15.0 | PD |
| NSAIDs and anti-hypertensive drugs (e.g. ACE inhibitors and sartans, diuretics, beta-blockers) | 32 | 9.4 | PD |
| NSAIDs and prednisone | 15 | 4.4 | PD |
| NSAIDs and quinolones | 12 | 3.5 | PD |
| NSAIDs and COX-2 inhibitors | 8 | 2.4 | PD |
| NSAIDs and warfarin/heparin | 5 | 1.5 | PD |
| NSAIDs and phenylephrine* | 2 | 0.6 | PD |
| NSAIDs and lithium | 2 | 0.6 | PD |
| NSAIDs and methotrexate | 1 | 0.3 | PD |
| Piroxicam and formoterol* | 1 | 0.3 | PD |
| Benzodiazepines and 2nd benzodiazepines | 32 | 9.4 | PD |
| Benzodiazepines and anti-psychotic | 16 | 4.7 | PD |
| Benzodiazepines and analgesics (e. g. codeine, morphine, tramadol) | 12 | 3.6 | PD |
| Benzodiazepines and anti-histamine (e.g. cetirizine) | 10 | 3.0 | PD |
| Benzodiazepines and anti-depressant (e.g. paroxetine, mirtazapine, amitryptiline) | 6 | 1.8 | PD |
| Flurazepam and clarithromycine | 4 | 1.2 | PK |
| Carbamazepine and buspirone | 2 | 0.6 | PK |
| Anti-psychotic and 2nd anti-psychotic | 8 | 2.4 | PD |
| Anti-psychotic with anti-depressant (e.g. trimipramine, venlafaxine, paroxetine) | 6 | 1.8 | PD |
| Anti-psychotic and anti-histamine | 2 | 0.6 | PD |
| Anti-psychotic and nitrates | 2 | 0.6 | PD |
| Anti-psychotic and methadone | 1 | 0.3 | PD+PK |
| Anti-psychotic and metoclopramide | 1 | 0.3 | PD |
| Anti-psychotic and lithium | 1 | 0.3 | PD |
| Tizanidine and benzodiazepine/ anti-depressant/ anti-psychotic | 11 | 3.3 | PD |
| Tizanidine and enalapril | 1 | 0.3 | PD |
| ACE inhibitors/sartan and loop diuretics | 10 | 3.0 | PD |
| ACE inhibitors and spironolactone | 2 | 0.6 | PD |
| Warfarin and low molecular weight heparin | 9 | 2.7 | PD |
| Warfarin and simvastatin | 2 | 0.6 | PK |
| Metoclopramide and scopolamine | 8 | 2.4 | PD |
| Antihistamine and 2nd antihistamine (e.g. cetirizine and hydroxyzine) | 6 | 1.8 | PD |
| Valproic acid and clarithromycine | 4 | 1.2 | PK |
| Valproic acid and mefloquine | 2 | 0.6 | PK |
| Valproic acid and mirtazapine | 1 | 0.3 | PD+PK |
| Valproic acid and warfarin | 1 | 0.3 | PK |
| Iron and proton-pump inhibitors | 4 | 1.2 | PK |
| Amiodarone and warfarin | 3 | 0.9 | PK |
| Amiodarone and digoxine | 1 | 0.3 | PD+PK |
| Amiodarone and beta-blockers | 1 | 0.3 | PD |
| Amiodarone and sulfonylurea | 1 | 0.3 | PK |
| Amiodarone and simvastatin | 1 | 0.3 | PD |
| Beta-blockers and sulfonylurea | 3 | 0.9 | PD |
| Beta-blockers and simvastatin | 1 | 0.3 | PK |
| Codeine and antihistamine (e.g. clemastine) | 3 | 0.9 | PD |
| Codeine and tramadol | 3 | 0.9 | PD |
| Sulfonylurea and 2nd sulfonylurea | 2 | 0.6 | PD |
| Digoxine and thiazide diuretic | 2 | 0.6 | PD |
| Fluvoxamine and thioridazine | 2 | 0.6 | PD+PK |
| Quinolones and cisapride | 2 | 0.6 | PD |
| Phenylephrine and anti-hypertensive drugs (beta-blockers) | 2 | 0.6 | PD |
| Phenylephrine and 2nd phenylephrine (nasal)* | 2 | 0.6 | PD |
| Phenylephrine and ergotamine | 1 | 0.3 | PD |
| Hydrocholrothiazide and furosemide | 2 | 0.6 | PD |
| Tramadol and venlafaxine | 2 | 0.6 | PD |
| Verapamil and simvastatin | 3 | 0.9 | PK |
| Verapamil and nitrates | 2 | 0.6 | PD |
| Verapamil and danazol* | 1 | 0.3 | PK |
| Verapamil and theophylline | 1 | 0.3 | PK |
| Others | 5 | 1.5 | Varied |

ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; PK, pharmaco-kinetic interaction; PD, pharmaco-dynamic interaction. *Interaction no longer listed in the drug interaction database.

nephropathy.[33] However, the suspected nephrotoxicity of acetaminophen is largely based on a single case-control study of patients with end-stage renal disease, which showed an association between the cumulative intake of acetaminophen and the relative risk of renal failure. The risk associated with acetaminophen use could have been biased; as patients with renal disease are more likely to have

**Table 2** Adverse drug interactions incorrectly detected ($n=170$) by a personal digital assistant drug interaction database (ePocrates RX) in 1801 drug prescriptions

| | *n* | % |
|---|---|---|
| Acetaminophen and NSAIDs | 95 | 55.9 |
| Acetaminophen and warfarin | 2 | 1.2 |
| Tizanidine and tramadol | 9 | 5.3 |
| Tizanidine and codeine | 2 | 1.2 |
| Tizanidine and anti-histamine* | 1 | 0.6 |
| Oral contraception and antibiotics | 9 | 5.3 |
| Oral contraception and tizanidine | 4 | 2.4 |
| Sulfonylurea (e.g. glimepiride) and diuretics | 7 | 4.1 |
| Sulfonylurea and metformin | 2 | 1.2 |
| Sulfonylurea and isoniazid | 2 | 1.2 |
| Glimepiride and aspirin* | 2 | 1.2 |
| Metformin and valacyclovir* | 2 | 1.2 |
| Metformin and insulin | 1 | 0.6 |
| Metformin and beta-blockers | 1 | 0.6 |
| Metoclopramide and benzodiazepines | 5 | 2.9 |
| Prednisone and beta-2 bronchodilators* | 5 | 2.9 |
| Beta-2 bronchodilators and diuretics | 2 | 1.2 |
| Ferrous sulfate and thyroid hormones | 2 | 1.2 |
| Allopurinol and amoxicilline | 2 | 1.2 |
| Proton pump inhibitor and pancrelipase | 2 | 1.2 |
| Prednisone and oestrogen | 1 | 0.6 |
| Trimethoprim/sulfamethoxazole and mycophenolate mofetil | 1 | 0.6 |
| Fixed drug combination (e.g. valsartan and hydrochlorothiazide) | 5 | 3 |

NSAID, non-steroidal anti-inflammatory drug.
*Interaction currently no longer mistakenly listed in the drug interaction database.

symptoms requiring analgesics, they were probably advised to use acetaminophen preferentially over aspirin or NSAIDs.[34] The increased use of acetaminophen could thus be a consequence of end-stage renal disease and not necessarily its cause. Because of the retrospective nature of this study, a definite temporal link could not be made. Furthermore, acetaminophen is not known to inhibit cyclo-oxygenase 2 at therapeutic doses (3–4 g/day) and the renal toxicity of chronic monotherapy with acetaminophen, a primary metabolite of phenacetin, remains unproven. So far there are no clinical trials or case reports of ADIs when using these two drugs together, despite the wide use of NSAIDs and acetaminophen for pain relief. For these reasons, we did not consider concomitant use of NSAIDs and acetaminophen as an ADI.

Drawbacks perceived when using ePocrates Rx were the absence of mechanism of the interaction for some drug combinations, the level of evidence (theoretical, case reports versus clinical trials),

**Table 3** Adverse drug interactions missed ($n=79$) by a personal digital assistant drug interaction database (ePocrates RX) in 1801 drug prescriptions

| | *n* | % | Interaction type |
|---|---|---|---|
| NSAID and a 2nd NSAID (e.g. ibuprofen with diclofenac) | 10 | 12.7 | PD+PK |
| NSAIDs and phenylephrine | 8 | 10.1 | PD |
| NSAIDs and salbutamol | 2 | 2.5 | PD |
| NSAIDs and venlafaxine | 2 | 2.5 | PD |
| Aspirin and ibuprofen* | 2 | 2.5 | PD |
| Aspirin and prednisone | 1 | 1.3 | PD |
| Oral and nasal phenylephrine | 8 | 10.1 | PD |
| Hypotensive drugs (e.g. nifedipine) and NSAIDs | 3 | 3.8 | PD |
| Hypotensive drugs (e.g. enalapril) and phenylephrine | 1 | 1.3 | PD |
| Hypotensive drugs (e.g. enalapril, nifedipine) and prednisone | 3 | 3.8 | PD |
| Hypotensive drugs (e.g. sartans, beta-blockers) and tizanidine | 3 | 4.8 | PD |
| Enalapril/captopirl and losartan | 2 | 2.5 | PD |
| Moclobemide (MAO inhibitor) and tryptan | 1 | 1.3 | PD |
| Moclobemide (MAO inhibitor) and ethylephrine | 2 | 2.5 | PD |
| Isradipine (calcium channel blocker) and tacrolimus | 2 | 2.5 | PK |
| Beta-blocker and codeine | 1 | 1.3 | PK |
| Beta-blocker and simvastatin | 3 | 3.8 | PK |
| Simvastatin and SSRI | 3 | 3.8 | PK |
| Simvastatin and cyclosporine* | 1 | 1.3 | PK |
| Anti-histamine and 2nd anti-histamine (e.g. fexofenadine, loratidine) | 1 | 1.3 | PD |
| Anti-histamine (e.g. fexofenadine, loratadine) and codeine | 4 | 5.1 | PK |
| Loperamide and codeine | 2 | 2.5 | PD |
| Loperamide and ciprofloxacine | 1 | 1.3 | PK |
| Benzodiazepines and SSRI | 3 | 3.8 | PD |
| Codeine and flunarizine | 2 | 2.5 | PD |
| Ciprofloxacine and benzodiazepines | 1 | 1.3 | PK |
| Mefloquine and nifedipine | 1 | 1.3 | PK |
| Paroxetine and anti-psychotics (e.g. olanzapine) | 1 | 1.3 | PD + PK |
| Tramadol and efavirenz | 1 | 1.3 | PK |
| Warfarin and chlordiazepoxide | 1 | 1.3 | PK |
| Others | 2 | 2.5 | Varied |

MAO inhibitors, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitor; NSAID, non-steroidal anti-inflammatory drug; PK, pharmaco-kinetic interaction; PD, pharmaco-dynamic interaction.
*Interaction now added to the drug interaction database.

and alternative therapeutic options. Also, some drugs commonly used outside the US cannot be found in the drug database. However, improvements are being continually made, and drug information is regularly updated. Thus some ADIs that were under-detected at the time of the study are now correctly identified (e.g. aspirin and ibuprofen), and concomitant use of certain drugs is no longer considered an ADI (e.g. glimepiride and aspirin). These situations have been marked with an asterisk in the Tables.

We found an incidence of potential clinical adverse drug interactions of 23% in our setting. This high estimate is probably because data were collected during the winter season, when a large number of prescriptions contained a combination of NSAIDs with systemic and/or topical vasoconstrictors. Among other limitations, the use of a single pharmacologist could be perceived as a major weakness. However we did not base our 'gold standard' only on his single opinion, as all discrepant results were systematically reviewed. We believe that this process limited the risk of bias of having a single expert opinion.

## Conclusions

Adverse drug interactions are a preventable subset of adverse drug events. Identifying them has become a challenge for general practitioners, as the speedy retrieval of pertinent drug information is often difficult, as is also the memorizing of all possible interactions. With the advent of PDAs, and their growing popularity among healthcare professionals, point-of-care technology can be extended to an outpatient setting. Use of drug databases allows for expeditious retrieval of relevant information, and may thereby limit potential prescription errors. The PDA drug interaction database we used had an excellent negative predictive value, allowing for a safer prescription of drugs when no ADIs were detected.

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