Drug-drug interactions in repeat prescriptions at village dispensaries (bereġ) in Malta

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ABSTRACT

Background and Objective

Inappropriate treatments and drug-drug interactions (DDIs) are known to occur in settings where repeat prescriptions are issued. In view of this, a study was carried out to document any such problematic drug prescribing and propose changes that would enhance patient safety.

Methods

A random sample of 100 clients who requested a repeat prescription at a group of peripheral village dispensaries (bereġ) in southern Malta was chosen and following anonymisation, the drugs requested for such prescriptions were entered into a database. A freely available online DDI checker was used in the analysis of the results and these were rechecked through the appropriate section of the British National Formulary. The resulting DDIs were then grouped according to type, potential effect or disease for which the drugs were used.

Results

A total of 255 DDIs were detected in the prescriptions of 53 clients. Drug combinations with a potential for increased hypotensive effect were the most common cause of DDIs (49.8%) in this sample, but other categories of DDIs were found. These included DDIs which could affect the management of diabetic patients (27.3%), patients on psychiatric treatment (7%) and anticoagulants (4.8%) as well as DDIs that affected serum potassium levels (2.2%).

Conclusions

The results obtained indicate that DDIs are common at a number of peripheral village dispensaries in Malta, and these could affect disease management in some patients. Other DDIs can be potentially harmful. Awareness, knowledge and vigilance by the prescribers involved remains crucial to address the issues raised by DDIs. Suggestions for addressing these issues on an administrative level are proposed.

KEYWORDS:

Primary Health Care; Drug-drug interactions (DDI); Repeat Prescription Clinic; Malta

INTRODUCTION

Unmonitored repeat prescriptions are known to have adverse, occasional fatal outcomes (Manfredi, Sabbatani, Orcioni, Martinelli and Chiodo, 2006). This is an issue of concern, particularly since it is known that repeat prescribing can occur in settings where patients are not regularly reviewed by their general practitioner, thus exposing patients to serious adverse effects (Zermansky, 1996). Some client categories are also known to be at an increased risk of pharmacological interactions particularly those on polypharmacy, with pluripathology, as well as those in the geriatric age group with a deterioration of cognitive functions (Castillo, García, Barrios, de Pablos, Villar and de la Cuesta, 1995; Shah and Hajjar, 2012). Patients with problems to access care are also at an increased risk (Farmer, 1995). Use of certain drugs, such as warfarin, is another factor which attracts an increase risk. Indeed, in a study by Snaith, Pugh, Simpson and McLay (2008) on a cohort of patients on warfarin it was found that the prescription of interacting medicines was common. The prevalent one-off prescriptions in this study could have arisen from particular clinical scenarios whereby the doctor weighs the benefits and risks of combined treatment. Notwithstanding, the common occurrence of repeat prescriptions for treatments with a potential for drug-drug interactions (DDI) was of concern. The possibility that this arises from the dynamics of the repeat prescription procedure was considered as an important issue in the study by Snaith et al. (2008) and this needs to be considered in Malta.

Regional state health centres, eight in Malta and one in Gozo, serve as hubs for the provision of public primary

health care in the Maltese Islands. General practitioner and nursing services as well as various specialised health services, such as immunisation and speech therapy, are provided here (Ministry of Health, the Elderly and Community Care, 2012). In the villages were no such health centres exist, a further service is provided by peripheral clinics, locally known as bereġ. At these 42 peripheral clinics basic medical and nursing services are provided by appointment (Ministry of Health, the Elderly and Community Care, 2012). Although when originally set up in the first half of the nineteenth century the peripheral clinics were pioneering gateways for access to secondary care (Abela, 2002), these clinics are now mostly used to issue repeat prescriptions or medical certificates (Sciortino, n/d). For repeat prescriptions, the doctor has to rely on the information provided by the patient or his/her representative, with no manual or electronic records held by the doctor or at the clinic. No mechanism is in place such as those used in other countries (Floor-Schreudering, de Smet, Buurma, Amini and Bouvy, 2011) to monitor and reduce adverse effects from DDIs. It was clear that the mechanism for the issuing of repeat prescriptions had to be studied as the potential for harmful DDIs was clear. The criterion was that no harmful DDIs were to be issued in drug prescriptions. The present paper gives an overview of the results of the first part of the audit cycle carried out to document and address DDI issues at these peripheral clinics.

As patients may personally attend the clinic or delegate the request of a repeat prescription to third persons, the term 'client' is used to refer to persons attending the clinic while the 'patient' is the person needing the prescription irrespective of whether he personally attended the clinic or not.

METHOD

Anonymised records were kept of clients asking for a repeat prescription from the author at the peripheral clinics for the months of June-July 2012. The age and gender of the clients as well as the pharmacological name and dosage of the medicine requested was recorded. A note was also taken of whether the client personally attended the clinic or not, and the type of forms presented to doctor.

A random sample of 100 clients was chosen from this population according to a sampling method provided by World Health Organisation (1993) for studies of drug use in health facilities. Each client's list of drugs was checked through an online computer programme for DDIs (Drug Interactions Checker, 2012) and the resulting DDI pairs verified against the Interactions Appendix of British National Formulary September issue (2012). The resulting DDIs were then grouped according to type, potential effect or disease for which the drugs were used.

RESULTS

During the two months, a total of 473 clients from eight peripheral clinics (i.e. Birżebbuġa, Għaxaq, Gudja, Mqabba, Qrendi, Tarxien, Żejtun, and Żurrieq) were included in the study. Out of the 100 clients randomly selected for study, it turned out that there were equal numbers of females (50%) and males (50%). Sixty one clients personally attended the clinic, 34 (56%) were females while 27 (44%) males. A slightly lower number of females, 16 (41%), as compared to 23 (59%) males delegated the prescription collection to third persons. This random sample of 100 clients had a mean age of 63 years (median 65 years), the youngest being 14 years and the oldest 90 years. Most clients (78%) were between 50 and 79 years (Table 1).

Table 1: Age range of clients in the random sample of patients included for study (%males= Number of males in the age group expressed as percentage; %att.= Number of patients in the age group who personally attended the clinic expressed as percentage; % m. att.= Number of male patients in the age group who personally attended the clinic expressed as percentage)

AGE GROUP (YEARS)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
Number	0	3	1	4	6	19	33	26	7	1
%males	0	66	0	75	33.3	47.4	61	38	43	1
% att.	0	0	0	25	33.3	63	70	77	29	100
% m. att.	0	0	0	33.3	50	42	50	40	0	100

Table 2: Characterisation of clients according to number of drugs requested (%M att.= Number of males making the request for the particular number of items who actually attended the clinic, expressed as percentage; %F att.= Number of females making the request for the particular number of items who actually attended the clinic, expressed as percentage; % tot. att.= Total number of persons making the request for the particular number of items who actually attended the clinic, expressed as percentage)

NUMBER OF ITEMS PRESCRIBED PER CLIENT	NUMBER OF CLIENTS	MALE	MALES PERSONALLY ATTENDING CLINIC	% M ATT.	FEMALES	FEMALES PERSONALLY ATTENDING CLINIC	% F ATT.	% TOT. ATT.
1	17	12	6	50	5	2	40	47.1
2	22	9	5	55.6	13	9	69.2	63.6
3	13	9	4	44.4	4	4	100	61.5
4	6	1	0	0	5	5	100	83.3
5	14	7	6	85.7	7	4	57.1	71.4
6	10	3	0	0	7	4	57.1	40
7	4	3	3	100	1	1	100	100
8	5	1	0	0	4	4	100	80
9	3	3	2	66	0	0	0	66
10	1	0	0	0	1	0	0	0
11	1	1	1	100	0	0	0	100
12	2	0	0	0	2	0	0	0
13	0	0	0	0	0	0	0	0
14	1	0	0	0	1	1	100	100

A whole array of documentation, averaging around 1.6 per client, was brought to the doctor for a prescription. Eighty five (M=42, F=43) had a yellow Schedule V cards and/or the related extension form (DH 29 and DH 29(ii) respectively). These cards are used by patients to obtain free medicines for chronic diseases. A pink form (DH128), used by clients with low income or diabetics to obtain free medicines was presented by 24 clients (M=13, F=11). In the studied population, 21 (M=6, F=15) asked for a prescription of at least one controlled drug by using a drug control card - DH 680 (i). These cards are used to monitor and control the use of narcotic and psychotropic drugs as stipulated by Maltese law.

Together with these documents, 8 (M=4, F=4) presented a diabetic permit (SLH 145) necessary for the free dispensing of anti-diabetic medicines. Sixteen (M=6, F=9) permits necessary to obtain free medicines not listed on government formulary were presented, a client bringing two permits on behalf of one male patient. Although the Maltese Primary Health Care Department has issued a memo encouraging the use of a prescription green card (PHCD REC/16) to have on record all the patient's medication, only 4 (M=3, F=1) presented this card. No patients presented an equivalent form issued by Zammit Clapp Hospital, a geriatric rehabilitation hospital. Although all the discharge letters from Mater Dei Hospital (Malta's main public hospital) contain the list of prescribed drugs for discharged patients, no clients brought this document as a reference. On the other hand 4 (M=3, F=1) used an informal method for making their drug request known and this varied from the use of a handwritten or typewritten paper containing the list of drugs needed, or bringing the medicine boxes to the clinic (Table 2).

Polypharmacy was common with an average of 4 items per client, varying from one item for 17 clients and one client having fourteen items. Clustering tends to occur towards a lower number of drugs, with the sample having a median of 3 items per person, and 72% of clients having 5 items or less.

The drugs or class of drugs with a potential to cause DDIs recorded through the study are presented in Tables 3 to 9. The heading to each table groups the DDIs according to type, potential effect or disease for

Table 3: DDIs which may cause enhanced hypotensive effect

ENHANCED HYPOTENSIVE EFFECT (TOTAL DDIs=113; 49.8%)
Enhanced hypotensive effect when diuretics given with angiotensin-converting-enzyme inhibitors (ACE-inhibitors) (n=20)
Enhanced hypotensive effect when diuretics given with beta-adrenergic-antagonists (beta-blockers) (n=17)
Enhanced hypotensive effect when calcium channel blockers (CCB) given with ACE-inhibitors (n=10)
Enhanced hypotensive effect when anxiolytics given with ACE-inhibitors (n=9)
Enhanced hypotensive effect when CCBs given with beta-blockers (n=8)
Enhanced hypotensive effect when CCBs given with diuretics (n=8)
Enhanced hypotensive effect when anxiolytics given with diuretics (n=8)
Enhanced hypotensive effect when ACE inhibitors given with nitrates (n=7)
Enhanced hypotensive effect when beta-blockers given with ACE-inhibitors (n=5)
Enhances hypotensive effect when anxiolytics given with beta-blockers (n=5)
Enhanced hypotensive effect when beta-blockers given with angiotensin II receptor antagonists (ARB) (n=4)
Enhanced hypotensive effect when anxiolytics given with nitrates (n=3)
Enhances hypotensive effect when anxiolytics given with ARBs (n=2)
Enhanced hypotensive effect when diuretics given with ARBs (n=1)
Enhanced hypotensive effect when ACE-inhibitors given with levodopa (n=1)
Enhanced hypotensive effect when anxiolytics given with hydralazine (n=1)
Enhanced hypotensive effect when alpha-blockers given with diuretics (n=1)
Enhanced hypotensive effect when alpha-blockers given with CCBs (n=1)
Enhanced hypotensive effect when alpha-blockers given with beta-blockers(n=1)
Enhanced hypotensive effect when alpha-blockers given with ACE-inhibitors (n=1)

Table 4: DDIs which may interfere with the management of Diabetes Mellitus

DRUGS USED IN DIABETIC PATIENTS (TOTAL OF POTENTIAL DDIs = 62; 27.3%)
Hypoglycaemic effect of metformin possibly enhanced by ACE-inhibitors (n=15)
Warning signs of hypoglycaemia masked by beta-blockers (n=15)
Hypoglycaemic effect of antidiabetics antagonised by thiazides (n=12)
Loop diuretics antagonise hypoglycaemic effect of antidiabetics (n=7)
Hypoglycaemic effect of sulphonylureas possibly enhanced by ACE-inhibitors (n=6)
ACE-inhibitors possibly enhance hypoglycaemic effect of insulin (n=4)
Maybe improved glucose tolerance and an additive effect when insulin or sulphonylureas given with fibrates (n=3)

which the drugs were used. The total number of relevant DDIs is given as 'total DDIs' and this is expressed as a percentage of all the DDIs found during the study. The rest of the table gives a more detailed breakdown of the DDIs included under the heading of table, with 'n' representing the number of relevant DDIs.

DISCUSSION

Drug-drug interactions

Nearly half of the DDIs (49.8%) had the potential of causing an enhanced hypotensive effect. Taking into account the fact that thiazide-like diuretics have not replaced thiazides in the national formulary, 39 DDIs

Table 5: DDIs which may interfere with the management of patients on psychiatric treatment

DRUGS USED IN PATIENTS ON PSYCHIATRIC TREATMENT (TOTAL OF POTENTIAL DDIs = 16; 7%)
Increased sedative effect when tricyclic-related antidepressents (TCA) given with anxioytics (n=7)
Increased sedative effect when anxiolytics and hypnotics given with antipsychotics (n=2)
Increased sedative effect when selective serotonin re-uptake inhibitors antidepressents (SSRIs) given with anxioytics (n=1)
Antipsychotics increase plasma concentration of TCAs – possibly increased risk of ventricular arrhythmia (n=1)
Increased risk of bleeding when aspirin given with SSRIs (n=1)
Anticonvulsant effect of anti-epileptics antagonised by TCAs (n=1)
Increased risk of side-effects when clonazepam given with valproate (n=1)
Plasma concentration of quetiapine possibly increased by valproate (n=1)
SSRIs antagonise anticonvulsant effect of antiepileptics (n=1)

Table 6: DDIs which may interfere with coagulation or the management of patients on anticoagulation

EFFECT ON (ANTI)COAGULATION (TOTAL OF POTENTIAL DDIs = 11; 4.8%)
Allopurinol possibly enhances anticoagulant effect of coumarins (n=2)
Anticoagulant effect of coumarins possibly enhanced by omeprazole (n=2)
Anticoagulant effect of warfarin enhanced by simvastatin (n=2)
Omeprazole reduces antiplatelet action of clopidogrel (n=1)
Increased risk of bleeding when Aspirin given with clopidogrel (n=1)
Anticoagulant effect of coumarins enhanced due to antiplatelet action of clopidogrel; avoidance of coumarins advised by manufacturer of clopidogrel (n=1)
Anticoagulant effect of coumarins possibly enhanced by SSRIs (n=1)

Table 7: DDIs which may increase risk of myopthy

MYOPATHY (TOTAL OF POTENTIAL DDIs = 9; 4.0%)
Increased risk of myopathy when simvastatin given with amlodipine (n=8)
Increased risk of myopathy when statins given with fibrates (n=1)

Table 8: DDIs which may interfere with potassium balance and relevant consequences

EFFECT ON POTASSIUM BALANCE (TOTAL OF POTENTIAL DDIS = 5; 2.2%)
Increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with loop diuretics (n=2)
Increased risk of severe hyperkalaemia when ACE-inhibitors given with potassium sparing diuretics (n=2)
Increased risk of hyperkalaemia when ARBs given with aldosterone antagonists (n=1)

Table 9: A miscellaneous group of DDIs not classifiable under headings of Table 3 to 8

MISCELLANEOUS (TOTAL OF POTENTIAL DDIs = 11; 4.8%)
Excretion of aspirin increased by alkaline urine due to some antacids (n=3)
Omeprazole possibly inhibits metabolism of diazepam (increased plasma concentration) (n=2)
Aspirin antagonises diuretic effect of spirinolactone (n=2)
Thiazides increases cardiac toxicity with amiodarone (n=1)
Plasma concentration of digoxin possibly increased slightly by proton pump inhibitors (n=1)
Increased risk of AV block and bradycardia when cardiac glycosides given with beta-blockers (n=1)
Increased risk of leucopenia and hypersensitivity reactions when allopurinol given with ACE-inhibitors especially with renal impairment (n=1)

involved drugs which correspond to the first three steps proposed by the guidelines of the National Institute of Clinical Excellence (NICE) for the management of hypertension. Their combination may be interpreted as part of an effort to control blood pressure through use of multiple drugs (NICE, 2011).

The number of DDIs with an enhanced hypotensive effect increases by a further 34 drug pairs when one considers the combination of beta-blockers with these drugs. In five clients, it seems that beta-blockers were added to diuretics, ACE-inhibitors, angiotensin II receptor antagonists (ARBs) and calcium channel blockers (CCBs) to achieve a better control of hypertension, with a further client also using an alpha-adrenergic-antagonist (alpha-blockers). For the other DDIs in this category (see Table 3), a case by case review indicates that their use is mostly not in line with the recommendations provided by the NICE guidelines. Indeed, while these guidelines suggest that beta-blockers should be considered for younger people if ACE-inhibitors and ARBs are contraindicated or not tolerated, the youngest person to be on beta-blockers in the study was aged 52 years (NICE 2011, p.12). Furthermore, a beta-blocker was added in 8 clients without evidence of use of a CCB and in another client without the use of an ACE-inhibitors or ARB as suggested by NICE (2011, p.13). Contra-indications or intolerance to a drug could be behind these cases. One, however, has to consider that in Malta, while beta-blockers can be added by a general practitioner once the patient is entitled to free anti-hypertensive drugs through a Schedule V yellow form, a special permit is required to have a CCB added on this form. This raises the possibility that doctors may be opting for a beta-blocker rather that a CCB to avoid lengthier procedures for drug prescriptions. The fact that one client only out of the eight using beta-blockers rather than CCBs had a permit certainly needs further research to be undertaken in this area.

Thirty-six DDIs which could potentially result in an enhanced hypotensive effect occurred as part of the management of hypertension and another co-morbidity. Contrary to the DDIs described above these were probably unintentional. DDIs involving use of antihypertensives with anxiolytics proved to be the most common (n=25), but an enhanced hypotensive effect resulted when antihypertensives were used with nitrates (n=10) and levodopa (n=1). While short term use of benzodiazepines as an anxiolytic is recommended (BNF 2012, p.218), a "repeat prescription syndrome" by which patients continue taking these drugs long-term is known (Bjerrum and Andersen 1996; Neutel, Walop and Patten, 2003). The present documentation of enhanced hypotensive effect in a country where such long-term use of benzodiazepines is known necessitates a review of the prescription of anxiolytics and the need to monitor blood pressure at least in the patients likely to be effected.

One client had an atenolol and co-amilozide combination considered to increase risk of diabetes (NICE 2011, p.12); the repeat prescription of this once commonly used drug combination needs to be addressed.

A quarter of the DDIs were found to potentially affect diabetic control (Table 4). ACE-inhibitors are often used in diabetic patients (n=25) and together with fibrates (n=3) contribute for the attainment of good glycaemic control. Nonetheless, DDIs which adversely influence control of blood sugar have also been recorded (n=19). Certainly of concern are the number of DDIs which can mask warning signs of hypoglycaemia (n=15). These cases reveal that in patients on anti-diabetic treatment, particularly those with relevant DDIs, patients should be educated and glucose monitoring carried out more intensely (Hendrychová and Vlček, 2012).

Likewise in patients on psychiatric treatment (Table 5), the occurrence of unwanted sedation which arises from unwanted DDIs (n=9) should be monitored, particularly

in elderly patients taking multiple drugs (Heppner, Christ, Gosch, Mühlberg, Bahrmann, Bertsch, Sieber and Singler, 2012). Increased risk of bleeding (n=1), decreased anticonvulsant effects of drugs (n=2) as well as increased risk of ventricular arrhythmia (n=1) confirms that special care needs to be adopted to prevent DDIs in patients on psychiatric treatment (Hahn and Braus, 2012).

Patients on anticoagulants are another well-known risk category for DDIs (Table 6). Allopurinol, omeprazole, simvastatin and SSRIs were responsible for a number of DDIs with warfarin and coumarins (n=7). Omeprazole is well known to reduce the antiplatelet action of clopidogrel (n=1) but some studies suggest that this is not important (Douglas, Evans, Hingorani, Grosso, Timmis, Hemingway and Smeeth, 2012). Likewise even though an increased risk of bleeding occurs when low dose aspirin is given with clopidogrel (n=1), combination of the two drugs is a well known treatment as part of the management of a number of cardiac conditions (BNF 2012, p.153).

Nine DDIs exposed patients to an increased risk of myopathy (Table 7). Indeed, the prescription of amlodipine with simvastatin should be approached with caution as this may lead to muscle injury. The United States Food and Drug Administration (FDA) recommends that the dose of simvastatin should not exceed 20mg when combined with a number of drugs, which include amiodarone and amlodipine (FDA, 2011). Eight patients were on an amlodipine/simvastatin combination in the present study but with the dosage of simvastatin being 20mg or less, these were not of significance.

Vigilance should be exerted for DDIs which effect serum potassium levels (Table 8), particularly in a primary care setting were biochemical assessment of serum potassium is notoriously problematic (Muscat and Buhagiar, 2011). The 5 DDIs which effect potassium levels are likely to be significant. Thus, particular attention should be given for prescribing drug pairs that increase serum potassium levels (Eschmann, Beeler, Kaplan, Schneemann, Zünd and Blaser, 2012).

A further 11 DDIs could not be listed under the categories described above (Table 9). Four of these may lead to AV block, cardiac toxicity, leucopenia or effect digoxin levels which may have adverse outcomes. Such combinations need to be avoided.

Addressing DDIs in Maltese Primary Health Care

This study was undertaken by the author as part of a 'Quality Assurance Initiative' within the Primary Health Care Department of Malta (Department of Health, 2012). In view of the fact that the data was collected by a single person, arguments may be made that this represents a limitation as the methodology may have sampled only a number of dispensaries from southern Malta and could have introduced researcher bias. While these limitations may affect the generalisability of the results to other village dispensaries in Malta, the results undoubtedly reveal that DDIs need to be addressed in repeat prescriptions in Maltese public primary health care.

The results presented above are in line with those carried in Primary Health Care settings, such as that carried out by Teixeira, Crozatti, Dos Santos and Romano-Lieber (2012) in Brazil, were the estimated prevalence of DDIs was relatively high. In this study by Teixeira et al. (2012), clinically significant DDIs occurred in a smaller proportion of patients. While this aspect was not studied locally, prevention of unwanted or potentially harmful DDIs remains a desirable goal for patients both locally and abroad.

The method used in the present study is useful to highlight the DDIs prevalent in repeat prescriptions at the peripheral clinics, yet it remains too laborious to be implemented to address all the DDIs of the clients. Computerization of the clinic records and specialised programmes to address DDIs have been successfully used abroad (Rommers, Teepe-Twiss and Guchelaar, 2011) and these can be implemented locally. Nonetheless this will not automatically provide a solution for it is known that despite the availability and daily use of computerized surveillance systems, exposure to potentially relevant DDIs persists. Besides being user friendly and simple to manage, such programmes also need to be applicable to everyday practice (Floor-Schreudering et al., 2011). There will also be the need for the prescribing doctors to adopt the tools made available to them (Malone and Saverno, 2012).

Community pharmacists are known to have been successfully involved in preventing harmful DDIs (Bond, Matheson, Williams, Williams and Donnan, 2000). The implementation of the Pharmacy Of Your Choice (POYC) scheme, places the community pharmacists in a key position to deal with problematic issues with DDIs. The computerization of patient records adopted in this scheme can provide a useful database through which unwanted DDIs can be reduced. Abroad, medication review reports submitted by pharmacists to the patients' general practitioners is known to have had positive outcomes in this regard (Stafford, Stafford, Hughes, Angley, Bereznicki and Peterson, 2011).

The dynamics of issuing cards, such as the Schedule V, to allow patients with chronic disease to obtain free medicines may also be contributing to problems in a local scenario. Hospital consultants in different specialties may be issuing such cards with little or incomplete knowledge of the patient's medication, exposing patients to DDIs.

Reducing the number of such cards may address this situation, but access to a national patient medication database during the application process for such cards remains desirable. Such database will also be useful for any doctors in the management of patients.

Certainly until then, and probably also in such situation, it is clear that the role of the general practitioner issuing repeat prescriptions in the peripheral clinics remains crucial in reducing unwanted DDIs. Any issuing of repeat prescriptions should also be documented and accompanied by the necessary examinations.

CONCLUSIONS

DDIs are common at a number of peripheral village dispensaries in Malta. Some are potentially harmful while others may have unwanted outcomes during management of chronic diseases. Awareness, knowledge and vigilance on behalf of the doctors concerned remains crucial to avoid such circumstances. Community pharmacists attached to the POYC scheme may also contribute. A national database recording patient medication may also be implemented and used to further decrease unwanted DDIs.

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