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Laboratory Tests in the Clinical Risk Management of Potential Drug-Drug Interactions

A Cross-Sectional Study Using Drug-Dispensing Data from 100 Dutch Community Pharmacies

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Abstract

Background: Patient safety and the life cycle of a drug are negatively influenced by the still increasing occurrence of potential drug-drug interactions (DDIs). Clinical risk management of potential DDIs is required in patients using drugs to influence the benefit-risk profile positively. Information about laboratory test results, in particular, may be useful in the assessment of potential DDIs for the individual patient.

Objective: The objective of this study was to examine the frequency and nature of laboratory tests required for the assessment of the clinical relevance of potential DDIs in Dutch community pharmacies. In addition, the nature and clinical relevance of these potential DDIs is analysed.

Methods: All patients from 100 Dutch community pharmacies using, according to dispensing information, two or more drugs concomitantly on a specified date (Wednesday, 4 April 2007), were included (n = 223 019). The anonymous dispensing data of the included patients were analysed against a list of DDIs requiring laboratory tests for the assessment of their clinical relevance. The number of patients at risk for these potential DDIs with severe adverse reactions was calculated. The frequency of potential DDIs requiring laboratory tests were stratified by age, sex and degree of polypharmacy.

Results: Of the included patients, 24.4% had one or more potential DDIs (n = 54 427). In 9.0% of the included patients, one or more laboratory tests for the assessment of clinical relevance of the potential DDI were required (n = 19 968). The frequency of DDIs requiring laboratory tests increased with increasing age and number of drugs, but was not related to sex. The most commonly required laboratory tests were for renal function (42.2%), electrolytes (20.1%) and coagulation (13.1%). The percentage of patients at risk for potential DDIs requiring laboratory tests with adverse reaction category F (serious, irrecoverable disablement or death) was 2.5%; category E (increased risk of failure of life-saving therapy) was 0.6%; and category D (inconvenience with residual symptom and failure of therapy concerning serious but non-fatal diseases) was 3.8%.

Conclusions: A large number of patients in Dutch community pharmacies are at risk for potential DDIs requiring laboratory tests for the assessment of the clinical relevance of the interaction. There is a strong relationship between the frequency of DDIs requiring laboratory tests and age and the number of drugs concomitantly used. In the clinical risk management of potential DDIs, information about laboratory test results is of additional value. Future research is necessary in order to obtain more evidence on using laboratory tests in terms of which tests should be linked to pharmacy data, in which patients they should be done, how often and what actions should be taken when an abnormal value is found.

Background

Drug-drug interactions (DDIs) have shown to contribute significantly to the negative consequences of drug treatment.[1-3] The prevalence of DDIs with potential serious adverse reactions in patients taking more than one drug concomitantly has been estimated at 6–14%.[4,5] In a study carried out in an elderly population in the Netherlands, the prevalence of DDIs increased from 10.5% in 1992 to 19.2% in 2005.[6] In another study carried out in Sweden in people aged ≥75 years, the prevalence of type C (potentially clinically relevant) DDIs was 26% and the prevalence of type D (potentially serious) DDIs was 5%.[7] Clinical risk management of potential DDIs aims to protect the patient from drug-induced adverse reactions.[8]

DDIs are not only a threat to patient safety but may also negatively influence the life cycle of a drug. A high potential for DDIs may stop the development of a new drug and may contribute to the ever-growing development costs and decreasing clinical success rates.[9,10] In addition, newly detected and difficult-to-manage DDIs have significantly contributed to the withdrawal of approved drugs in recent years (e.g. cisapride and mibefradil).[11] Currently, guidelines for the management of several DDIs include the use of laboratory tests as a risk modifier in the assessment of the DDI. For healthcare providers, monitoring of drug concentrations as well as clinical chemistry and/or haematological tests could provide important information about the clinical relevance of the DDI for the individual patient.[12-14]

The objective of this study was to examine the frequency and nature of laboratory tests required for the assessment of clinical relevance of potential DDIs in community pharmacies. In addition, the nature and clinical relevance of these potential DDIs is analysed.

Methods

Setting

At the end of 2006 there were 1825 community pharmacies in the Netherlands. For the present study, anonymous drug-dispensing data from 100 (5.5%) Dutch community pharmacies were received through the Foundation for Pharmaceutical Statistics (SFK), which collects exhaustive drug dispensing data in the Netherlands. The 100 participating pharmacies belonged to the franchise organization 'Kring-apotheek' (n = 330) and included pharmacies from all over the country. The pharmacies within this scheme focus on pharmaceutical care projects with the aim of improving individual patient care and enhancing medication safety. In Dutch community pharmacies, the prescription medicine history of individual patients can be considered as nearly complete because most patients visit only one single pharmacy.[15]

The drug-dispensing data included information about the patient (age, sex, unique anonymous identifier), dispensed drug, dispensing date, number dispensed and prescribed dosage regimen. Dispensed drugs were coded according to the Anatomical Therapeutic Chemical classification system.[16] The use of the drug-dispensing data was performed in compliance with Dutch privacy regulations and approved by the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences.

Study Population

The eligible study population consisted of all patients who had been dispensed at least two prescriptions by one of the 100 included pharmacies from July 2006 to July 2007. Patients were included if they were using two or more different drugs concomitantly on a fixed date (Wednesday, 4 April 2007). In this study, products with more than one pharmacologically active substance are considered as one dispensed drug. To assess whether drugs were used concomitantly on the specified date, the theoretical duration of drug use was needed. For each dispensed drug the theoretical duration of drug use was estimated by dividing the number of dispensed units by the prescribed dosage regimen. If the dosage regimen was unknown (4.5%) or the estimated duration was less than 1 day (4.4%) or more than 1 year (0.2%) [e.g. antithrombotic agents], the duration was estimated by the calculated average of valid durations of that drug.[17] The duration of use was multiplied by 1.1 to correct for irregular drug use and early drug collection from the pharmacy.[18]

Patients of unknown sex (0.1%) or unknown age (0.09%), those over 99 years of age (0.06%), patients missing a unique identifier (0.003%) or those using more than 50 different drugs (0.002%) were excluded because they probably reflect fictitious patients used for administrative purposes, e.g. drugs dispensed directly to a general practitioner. The final study population therefore consisted of 223 019 patients using at least two drugs on 4 April 2007.

Selection of Potential Drug-Drug Interactions

One of the study outcomes was the nature of potential DDIs requiring laboratory tests for the assessment of clinical relevance of the interaction. In the Netherlands, a working group of the Scientific Institute of Dutch Pharmacists developed and now maintain a computerized surveillance guideline for the management of DDIs.[19] In this

Table I. Classification of drug-drug interactions in the Dutch surveillance guideline[4,20]

Category	Description
Quality of evidence	
0	Pharmacodynamic animal studies; *in vitro* studies
1	Incomplete, published case reports
2	Well documented, published case reports
3	Controlled, published interaction studies with surrogate endpoints
4	Controlled, published interaction studies with clinically relevant endpoints
Seriousness of potential adverse reactions	
A	Clinically irrelevant effect
B	Short-lived inconvenience
C	Inconvenience without residual symptoms; failure of therapy concerning non-serious diseases
D	Inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases
E	Increased risk of failure of life-saving therapy
F	Serious, irrecoverable disablement or death

Table II. Number of drug-drug interactions (DDIs) requiring laboratory tests in the Dutch surveillance guideline (June 2007)[19]

Interactions	No. of interactions (%)[a]
Clinically significant DDIs	329 (100)
DDIs not requiring laboratory tests	222 (67)
DDIs requiring one or more laboratory tests	107 (33)

a The total number of laboratory tests (tables III and IV) is higher than the number of DDIs requiring laboratory tests because each interaction can refer to more than one test.

surveillance guideline, clinical relevance is described in more detail.[4,20] In brief, an alphanumerical code indicates the risk of a DDI using a 6-point scale for the seriousness of the potential adverse reaction (A–F) and by using a 5-point quality of evidence scale (0–4) [table I]. Based on this clinical guideline, 329 potential DDIs have been classified as potentially significant because they should generate a direct interaction alert in the computerized DDI surveillance system in community pharmacies; the assessment of these combinations of drugs is considered necessary in daily patient care. For the clinical relevance of the combination, the Dutch alphanumerical code should be combined with the incidence and existence of risk factors that increase the seriousness and/or incidence of an adverse reaction.

To determine DDIs requiring a laboratory test, the documentation of each interaction in the surveillance guideline of June 2007[19] was screened for the words 'drug monitoring', 'clinical chemistry test' and/or 'haematological test'. All laboratory tests were included and their nature was classified into two categories: 'clinical chemistry and haematological tests' or 'drug monitoring'. The distribution of relevant DDIs requiring laboratory tests in the Dutch DDI surveillance system of June 2007 is presented in tables II, III and IV. We identified 107 potentially significant DDIs (33%) with at least one laboratory test mentioned in the documentation, out of 329 potentially significant DDIs. Because each interaction can refer to more than one laboratory test, the total number of laboratory tests was 125. For example, in the documentation of drug-interaction 'methotrexate and NSAIDs' the advice is to monitor methotrexate concentration and also to check blood cells, renal function and perform biochemical liver tests.

Data Analysis

To determine how many patients were at risk for potential DDIs requiring laboratory tests, the drug-dispensing data were analysed. The number of patients with a potential DDI requiring laboratory tests was used for the nominator. For patients with two or more potential DDIs, the DDI with the highest risk code was selected. The number of patients in the study population was the denominator.

To determine the nature and frequency of laboratory tests, all potential DDIs were included and categorized by laboratory test subcategories, and classified by age, sex and number of dispensed drugs.

Results

According to the dispensing data of the 100 selected pharmacies, 719 022 patients were served. Patients using two or more different drugs concomitantly on the specified date were finally included in the study (n = 223 019) [table V]. The mean age of the patients included in the study was 59.2 years (SD = 18.9; range 0–99) and, on average, patients had been dispensed 3.9 drugs (SD = 2.2; range 2–27).

Of the included patients, 24.4% (n = 54 427) used a combination of drugs with potential DDIs. In 36.7% of these patients, i.e. 9.0% (n = 19 968) of the study population, one or more laboratory tests were required for the assessment of clinical relevance of the potential DDI. The frequencies for categories D, E and F were 3.8%, 0.6% and 2.5%, respectively; the most common of these

Table III. List of drug-drug interactions (DDIs) requiring clinical chemistry and haematological laboratory tests in the Dutch surveillance guideline (June 2007)[19]

Type of Test	No. of tests (%)
Total	63 (100)
Coagulation	31 (49.2)
Renal function	11 (17.5)
Biochemical liver test	7 (11.1)
Electrolytes	5 (7.9)
Blood cell count	4 (6.3)
Blood glucose	3 (4.8)
Thyroid function	1 (1.6)
Creatine phosphokinase	1 (1.6)

Table IV. List of drug-drug interactions (DDIs) requiring drug monitoring in the Dutch surveillance guideline (June 2007)[19]

Therapeutic group	Test	No. of tests (%)
Total		62 (100)
Cardiac glycosides	Digoxin	6 (9.7)
	Quinidine	3 (4.8)
	Disopyramide	1 (1.6)
Immunosuppressants	Ciclosporin (cyclosporine)	8 (12.9)
	Tacrolimus	4 (6.5)
	Everolimus	3 (4.8)
	Sirolimus	3 (4.8)
	Mycophenolic acid	2 (3.2)
Antiepileptics	Phenytoin	9 (14.5)
	Carbamazepine	4 (6.5)
	Valproic acid	3 (4.8)
	Lamotrigine	2 (3.2)
	Phenobarbital (phenobarbitone)	1 (1.6)
	Other antiepileptics	1 (1.6)
Antipsychotics	Lithium	4 (6.5)
	Clozapine	1 (1.6)
	Haloperidol	1 (1.6)
Tricyclic antidepressants	Antidepressants	1 (1.6)
Xanthines	Theophylline	5 (8.1)

potential DDIs are given in table VI. The nature and frequency of the nine different laboratory tests are given in table VII. The frequency of potential DDIs requiring laboratory tests increased with increasing age (figure 1) and a higher number of dispensed drugs (figure 2). For example, the overall mean frequency of potential DDIs requiring laboratory tests was 9.0%, with no difference between men or women, 3.1% in those aged 20–40 years and 13.4% in those aged over 65 years. In patients using 2–5, 6–10 or >10 different drugs, the mean frequency of potential DDIs requiring laboratory tests was 5.9%, 33.2% and 65.6%, respectively. Illustrative of these results is the case of a 76-year-old woman who had been dispensed 15 drugs on the specified date. This patient was at risk for six potential DDIs (categories D, E and F). For the assessment of two potential high-risk combinations (category F), potassium levels were required, and for two category D interactions, the International Normalized Ratio and theophylline monitoring were recommended.

Discussion

In our study, many patients were at risk for potential DDIs with potential serious adverse reactions (categories D, E and F), and results from laboratory tests were frequently required according to clinical guidelines for the assessment of their clinical relevance. Some of the most common DDIs in our results are in line with previous research.[4-6,21] Agents acting on the renin-angiotensin system (RAS), (potassium-sparing) diuretics, NSAIDs and aspirin (acetylsalicylic acid) were the most frequently involved drugs. Some less common combinations of drugs were also analysed. For example, 178 patients were at risk due to taking the combination of lamotrigine and valproic acid, and 201 patients due to taking the combination of tricyclic antidepressants and SSRIs. In 9.0% of the patients, nine different laboratory tests were required for the assessment of clinical relevance. Information about renal function and electrolytes

Table V. Characteristics of the study population in 100 Dutch pharmacies, 2007 (n = 223 019)

Characteristics of study population	No. of patients (%)
Age (y)	
0–10	2 856 (1.3)
10–20	5 925 (2.7)
20–30	10 030 (4.5)
30–40	14 752 (6.6)
40–50	26 901 (12.1)
50–60	40 340 (18.1)
60–70	48 947 (21.9)
70–80	43 920 (19.7)
80–90	25 279 (11.3)
≥90	4 069 (1.8)
Sex	
Male	92 599 (41.5)
Female	130 420 (58.5)
No. of drugs concomitantly used	
2–4	159 290 (71.4)
5–7	46 958 (21.1)
8–10	12 900 (5.8)
11–13	3 067 (1.4)
14–16	639 (0.3)
17–19	135 (0.1)
≥20	30 (0.01)

Table VI. Most common potential drug-drug interactions in the study population

Interactions	Quality of evidence[a]	Frequencies/1000 patients
Type F (serious, irrecoverable disablement or death)		
Agents acting on the RAS + potassium-sparing diuretics	2	24
Tricyclic antidepressants + SSRIs/duloxetine	3	1
Potassium salts + potassium-sparing diuretics	3	1
Type E (increased risk of failure of life-saving therapy)		
Methotrexate + NSAIDs/aspirin (acetylsalicylic acid)	3	2
HMG-CoA reductase inhibitors ('statins') + gemfibrozil	3	2
Lamotrigine + valproic acid	3	1
Type D (inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases)		
Diuretics + NSAIDs/aspirin	3	13
Agents acting on the RAS + NSAIDs/aspirin	3	11
Digoxin + verapamil/diltiazem	3	2
Acenocoumarol/phenprocoumon + amiodarone/propafenone	3	2
Acenocoumarol/phenprocoumon + SSRIs	1	2
Acenocoumarol/phenprocoumon + antibacterials	3	1
Acenocoumarol/phenprocoumon + phytomenadione	1	1
Acenocoumarol/phenprocoumon + allopurinol	1	1
Non-selective β-adrenergic receptor antagonists + insulins	3	1
Lamotrigine + other antiepileptics/rifampicin (rifampin)	3	1

a Quality of evidence is assessed using a 5-point quality of evidence scale (0–4) developed by a working group of the Scientific Institute of Dutch Pharmacists.[20] Details can be found in table I.

RAS = renin-angiotensin system; **SSRIs** = selective serotonin reuptake inhibitors.

was needed most frequently. Almost 25% of the patients using two or more drugs concomitantly on the specified date were at risk for potential DDIs.

Other investigators have found different DDI frequencies because of differences in study population, period, setting and definition of DDI. In a Dutch study, the prevalence of DDIs in people aged ≥70 years increased from 10.5% in 1992 to 19.2% in 2005, largely due to the increased use of spironolactone in this patient group. The prevalence of potentially life-threatening DDIs was 2.9% in people aged ≥70 years in 2005, but no prevalence for DDIs requiring laboratory tests for assessment was available.[6] In another study, the frequency of DDI alerts as a percentage of the total number of prescriptions was 6% and the overall frequency of potentially life-threatening DDIs was 0.7%.[4] A study carried out in Sweden in 1999 showed at least one potential drug interaction for 13.6% prescriptions[5] and, in a more recent study in people aged ≥75 years, the prevalence of type C potential DDIs was 26% and the prevalence of type D potential DDIs was 5%.[7] The prevalence of DDIs requiring laboratory tests increased with age and number of drugs concomitantly used, which was similar to other studies investigating the prevalence of potential DDIs.[6,7]

Detecting potential DDIs with a computerized surveillance system based on drug-dispensing data has some limitations. Interactions will only take place when the patient is actually using both drugs according to the prescribed dosage regimen. In addition, many potential DDIs never lead to an actual clinical adverse reaction in a patient. Since we were looking for potential DDIs, the prevalence of actual interactions will be much lower. In the risk estimation of potential DDIs, several factors have to be considered to determine the total risk of a DDI. These factors are clinical evidence, seriousness of the adverse reactions, incidence of the DDI, risk factors (other DDIs, mechanism of interaction) and patient characteristics (genotype, weight, age, race and co-morbidity). For example, the interaction between RAS inhibitors + NSAIDs (category D)

is only relevant when the indication is heart failure. Since the reason for use is unknown in community pharmacies, the frequency for this interaction is overestimated.

For effective clinical risk management, the Dutch surveillance guideline for computerized DDI surveillance systems should enhance the specification of laboratory tests and patient characteristics that are relevant for the clinical relevance assessment of DDIs and drug-disease interactions.

Laboratory tests are not always necessary in reducing the risk of potential DDIs. For example, in DDIs with digoxin, dose adjustment based on clinical symptoms is also recommended in the Dutch surveillance guideline as an alternative for laboratory monitoring, and therefore overestimates the frequencies of these kinds of interactions. Another limitation is calculation of the theoretical duration of use, based upon the number of dose units and the prescribed daily dose. If the prescribed daily dose was incomplete or missing we estimated the duration of use and could have included drugs not used concomitantly. We only used data from 5.5% of the Dutch pharmacies because these pharmacies provided the drug-dispensing data. The prevalence of DDIs requiring laboratory tests could be underestimated for different reasons. The included pharmacies focus on pharmaceutical care projects with the aim of enhancing medication safety and to improve individual patient care, which may have led to selection bias. In addition, over-the-counter drugs and herbal drugs are not registered systematically, so the number of potential DDIs requiring laboratory tests for assessment could be underestimated. In the Netherlands, pharmacy shopping behaviour is limited and dispensing registers are relatively complete.[15] Prevalences may be even higher because the healthcare provider could have rejected prescriptions before dispensing as a result of adequate intervention of DDI alerts. Besides DDIs, other laboratory-pharmacy interactions are advised in the summary of product characteristics, i.e. drug-disease interactions, dose adjustment and monitoring toxicity. These interactions may require different biomarkers, e.g. pharmacogenetic testing, and they were not an objective of this study. Finally, modified or newly included DDIs were not reviewed, but the DDI surveillance system is updated once every month; in the last year, 26 new DDIs have been added, thereby increasing the prevalence of DDIs.[22]

Therefore, a laboratory test could be a good marker for potential serious adverse reactions of

Table VII. Laboratory tests required for the assessment of clinical relevance of potential drug-drug interactions in the study population

Category	Test	No. of tests (%)
Clinical chemistry + haematological tests		
Renal function	Serum creatinine; estimated glomerular filtration rate	13 902 (42.2)
Electrolytes	Serum potassium	6 602 (20.1)
Coagulation	International Normalized Ratio	4 315 (13.1)
Blood glucose	Glucose	3 143 (9.5)
Biochemical liver test	AST, ALT, γ-glutamyltransferase	1 103 (3.4)
Blood cell count	Leukocytes, neutrophils, granulocytes, thrombocytes, haemoglobin	596 (1.8)
Creatine phosphokinase	Creatine phosphokinase	507 (1.5)
Thyroid function	Thyroid-stimulating hormone	13 (0.04)
Subtotal		**30 181 (91.7)**
Drug monitoring	Digoxin	776 (2.4)
	Immunosuppressants	57 (0.2)
	Antiepileptics	1 283 (3.9)
	Antipsychotics	333 (1.0)
	Tricyclic antidepressants	209 (0.6)
	Theophylline	83 (0.3)
Subtotal		**2 741 (8.3)**
Total no. of laboratory tests		**32 922 (100.0)**

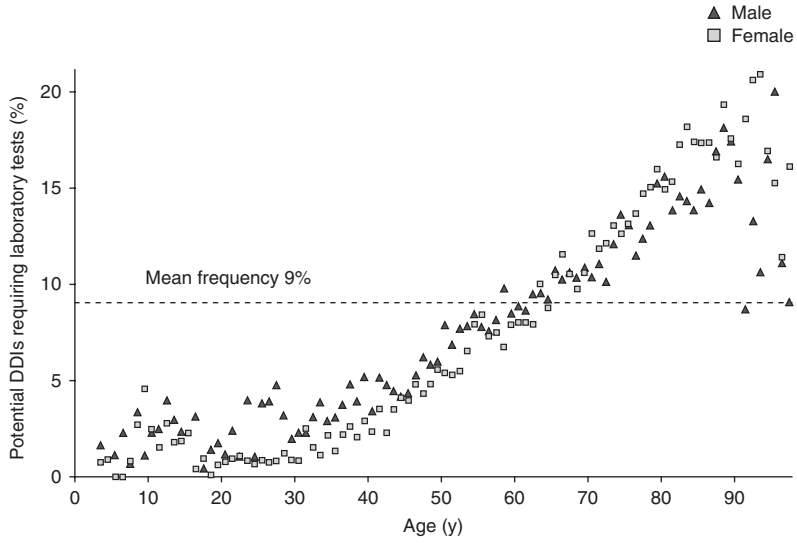

Fig. 1. Frequencies of potential drug-drug interactions (DDIs) requiring laboratory tests by age and sex.

DDIs, but in most countries laboratory testing is not routine. Incorporating evidence in clinical rules could facilitate evidence-based decision-making by the healthcare professional. For a start, healthcare providers could carry out laboratory tests to actively monitor renal function and electrolytes in order to prevent patient harm. For effective clinical risk management, the exchange of more patient characteristics between physicians and pharmacists might prevent more DDIs.

Just as in hospital pharmacies, automated laboratory linkage to medication data is a major new tool for healthcare providers in the risk

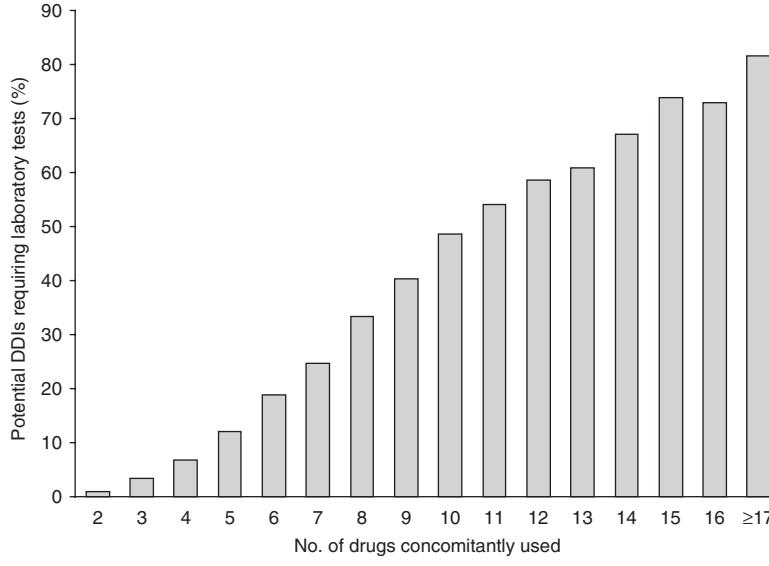

Fig. 2. Frequencies of potential drug-drug interactions (DDIs) requiring laboratory tests by number of drugs concomitantly used.

management of avoidable DDIs and in the improvement of patient safety.[23,24]

Conclusions

A large number of patients are at risk for potential DDIs that require laboratory tests for the assessment of their clinical relevance in community pharmacies. There is a strong relationship between the frequency of DDIs requiring laboratory tests and age and the number of drugs concomitantly used. In the clinical risk management of potential DDIs, information about laboratory test results is of additional value. Future research is necessary in order to obtain more evidence in using laboratory tests in terms of which tests should be linked to pharmacy data, in which patients laboratory tests should be carried out, how often they are needed and what actions should be taken when an abnormal value is found.

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