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ESCP BEST PRACTICE

Management of drug-disease interactions: a best practice from the Netherlands

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Abstract

Background Drug-disease interactions are situations where pharmacotherapy may have a negative effect on patients' comorbidities. In these cases, it can be necessary to avoid that drug, adjust its dose or monitor therapy. In the Netherlands, pharmacists have developed a best practice how to systematically evaluate drug-disease interactions based on pharmacological considerations and implement recommendations for specific drug-disease interactions. *Aim* To describe the development of recommendations for drug-disease interactions and the implementation in prescribing and dispensing practice in the Netherlands. *Setting* Pharmacies and physicians' practices in primary care and hospitals in the Netherlands. *Development* A multidisciplinary expert panel assessed if diseases had clinically relevant drug-disease interactions and evaluated drug-disease interactions by literature review and expert opinion, and subsequently developed practice recommendations. *Implementation* The recommendations were implemented in all clinical decision support systems in primary care and hospitals throughout the Netherlands. *Evaluation* Recommendations were developed for 57 diseases and conditions. Cardiovascular diseases have the most drug-disease interactions (n = 12, e.g. long QT-syndrome, heart failure), followed by conditions related to the reproductive system (n = 7, e.g. pregnancy). The number of drugs with recommendations differed between 6 for endometriosis and tympanostomy tubes, and up to 1171 in the case of porphyria or even all drugs for pregnancy. *Conclusion* Practice recommendations for drug-disease interactions were developed, and implemented in prescribing and dispensing practice. These recommendations support both pharmacists and physicians by signalling clinically relevant drug-disease interactions at point of care, thereby improving medication safety. This practice may be adopted and contribute to safer medication use in other countries as well.

Keywords Best practice · Clinical decision support · Drug-disease interactions · Medication safety · Pharmacy practice · The Netherlands

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Facilitators of best practice

- A systematic methodology for the evaluation of the literature about drug-disease interactions that includes expert opinions gives a sound and transparent background for practice recommendations, with a good balance between risks for drug-disease interactions versus alert fatigue.
- Implementing practice recommendations for drug-disease interactions at point of care contributes to medication safety, since health care professionals can undertake immediate actions.
- A substantial number of diseases with clinically relevant drug-disease interactions forms a good starting point for

implementation of this knowledge in settings outside the Netherlands.

Barriers to best practice

- It is a substantial effort to set up a multi-disciplinary expert panel and maintain existing drug-disease interactions, since the recommendations need to be revised regularly and new recommendations have to be developed for newly marketed drugs.
- Differences in organisation in health care in other countries, other responsibilities of pharmacists and legal issues may limit implementation of drug-disease interaction signalling in other countries.
- Recommendations have been developed mainly in Dutch, which hampers international dissemination. Publication of methodology and findings for specific drug-disease interactions in international, peer-reviewed journals will contribute to further distribution of this knowledge.

Background

In the Netherlands, pharmacists alter 1.8% of all prescriptions in community pharmacies due to drug related problems (DRPs). A contra-indication for a morbidity or condition is the underlying problem in 2.2% of these prescriptions [1]. These figures show that management of medication safety in patients with multi-morbidity—more than one chronic disease—is an important task for pharmacists [2]. European countries are facing an ageing population with more chronic diseases, so organisation of health care is becoming more demanding [3]. In many countries, the number of patients with multi-morbidity is increasing [3], who subsequently use more medication compared to patients with a single condition [4]. Because both the number of patients and the number of medications per patient is increasing, solutions to assist the pharmacist in managing medication safety are required.

Pharmacists contribute to medication safety by identifying, resolving and preventing DRPs [5]. DRPs are circumstances that involve a patient's medication treatment that actually or potentially interfere with the achievement of an optimal health outcome [1, 5]. Pharmacists most commonly use well-known handbooks such as Stockley's Drug Interactions as resources to resolve DRPs regarding drug-drug interactions. Implementation of alerts for drug-drug interactions in clinical decision support systems (CDSSs) facilitates more advanced support to health care professionals than handbooks do [6]. However, for a wide range of DRPs health care professionals are not supported by solutions in their CDSSs.

One of the DRPs where knowledge or practical solutions are not widely available, are drug-disease interactions (DDSIs). DDSIs are situations where pharmacotherapy intended to treat one disease may cause worsening of another comorbidity or condition. In the perspective of this best practice, this does not have to be a pathological condition. Other conditions such as pregnancy and wearing contact lenses are also included as clinically relevant conditions that can lead to a DDSI.

DDSIs are often described in the Summary of Product Characteristics (SmPC). These statements are not always optimal in practice, as advice concerning DDSIs in SmPCs are sometimes not clearly motivated or give impractical recommendations. Other sources for recommendations than the SmPC, are available for some comorbidities and conditions such as renal impairment, cirrhosis and pregnancy/lactation [7]. As far as we are aware, guidelines or practical recommendations for DDSIs covering a wide range of comorbidities are uncommon.

In the Netherlands, pharmacists have developed a practice over several decades to analyse and evaluate possible DDSIs based on pharmacological considerations, and formulated practice recommendations for specific drugs [7]. This practice has resulted in a set of motivated, clinically relevant DDSIs and practice recommendations. On the other hand, some comorbidities and drugs were assessed as clinically irrelevant DDSIs for which no practice recommendations were developed. The clinically relevant practice recommendations are implemented in CDSSs, which are able to signal DDSIs and give specified recommendations at point of care.

Aim

The aim of this best practice paper is to describe the development of recommendations for drug-disease interactions and the implementation in prescribing and dispensing practice in the Netherlands.

Development

DDSIs in prescribing and dispensing practice in the Dutch healthcare system

Around 2000 pharmacies are established in the Netherlands, evenly distributed across the country, serving around 8650 patients each [8]. The geographical access to healthcare services is good, with a mean distance of 1 km between the patient's home and the general practitioner (GP) or pharmacist [9]. Residents of the Netherlands register with a single GP of their choice and also with a single community pharmacy [10]. The patient can choose his or her own pharmacy,

yet switching between community pharmacies is rare: almost 90% of the patients visit only their own community pharmacy [11]. Registering with a pharmacy provides several benefits: dispensing of chronic medication is organized more efficiently and the pharmacist has a full medication history to check medication safety before dispensing a new drug according to the most recent patient and medication characteristics. Nearly all (80–90%) of the GPs use a system to allow for standardized exchange of relevant patient data with community pharmacies (relevant lab results, DDSIs, medication history) [12]. Diseases or conditions of a patient are registered by code, making exchange of this information with other systems possible. Since July 2007, community pharmacists in the Netherlands have been included in the Dutch Medical Treatment Contracts Act (WGBO). The WGBO regulates the contract between health care professional and patient and sets out requirements on professional confidentiality, maintaining adequate medical records and patients' rights [13]. This means pharmaceutical patient care is a shared responsibility between pharmacist and physician, and exchange of information and discussion of appropriate management is an essential part of this process [14].

A referral from a GP is always necessary to see a medical specialist for the first time in the Netherlands, unless in the case of an emergency. If a patient is hospitalized or otherwise sees a specialist other than the GP, the specialist will inform the GP and/or pharmacist with the most recent medical data of the patient [15]. The prescribing of medication is, with a few exceptions, the responsibility of physicians, and the process starts with identification of the problem (diagnosis) and setting a therapeutic goal. Next, the physician chooses the treatment, and determines whether this option is suitable for the individual patients by checking, for instance, potential contra-indications [16]. After prescription, the community pharmacist dispenses medication to ambulatory patients. Before dispensing, the pharmacist is responsible for management of DRPs [5]. Hospital pharmacists are responsible for dispensing medication that is prescribed to patients admitted to the hospital. Medication prescribed to ambulatory patients by consulting physicians in outpatient wards is dispensed by community pharmacies. In many hospitals, outpatient pharmacies that are specialised in transitional aspects of pharmaceutical care are located near the hospital.

In the Netherlands, pharmacies use clinical decision support implemented in their pharmacy information system that generates alerts for DRPs, such as drug hypersensitivity, drug-drug interactions and DDSIs. Alerts are based on information in one of two national drug databases, called Pharmabase and G-standaard, which contain 2063 authorised drugs. The two databases are very similar and share a common methodology for the evaluation of most DDSIs (see also Development) [7]. All pharmacies in the Netherlands have access to the information on DDSIs described in this best practice paper. Hospitals in the Netherlands use different CDSSs but rely on the same databases for their digitalized drug safety information as primary care pharmacists and physicians [17]. On top of the general information from the database, hospital pharmacists have often developed additional clinical rules [18]. Use of these clinical rules is out of the scope of this article. To provide a better overview of the Dutch healthcare setting, the patient journey for getting a prescription drug in primary care, and the role of supporting software is illustrated in Fig. 1.

Besides getting a prescription drug from a pharmacy, it is also possible to buy Over The Counter (OTC) drugs without a prescription in drugstores or supermarkets. These drugs are generally recognised as safe, such as nicotine patches, non-opioid analgesics and some antacids, and are sold in small packages only. A certified person needs to give advice when necessary. Patients are advised to inform their physician and pharmacist of non-prescription drugs bought at other retailers.

The process of developing the recommendations for DDSIs

A national, multi-disciplinary expert panel develops recommendations for DDSIs. This panel consists of 12 health care professionals: community and hospital pharmacists, several physicians (e.g. GPs, internists), and pharmacists experienced in evidence-based medicine and clinical decision support. The panel follows a six-step plan starting with a definition of the scope of the DDSI, describing the relevant effects for the specific disease or condition (step 1), and the drugs to be evaluated (step 2). These steps result in a specific disease or condition for which clinically relevant alerts have to be developed and specific drugs to be evaluated. Next, evidence for the DDSI is collected from literature, the product information, and secondary sources as guidelines and handbooks, which is presented in a report (steps 3 and 4). The panel discusses the reports and concludes about practice recommendations after which they will be implemented (steps 5 and 6). The steps of this standardized methodology are described in more detail in a separate review [7].

Requests for diseases to be evaluated come from health care professionals based on their needs for guidance in medication safety in clinical practice. Not all requests result in new DDSIs, as for many diseases there is no need or insufficient evidence for practice recommendations. For instance, conditions such as hyperkalemia or hyponatremia require immediate treatment in the hospital, and are therefore no longer a relevant comorbidity at discharge. Dementia is another example for which no practice recommendations were developed. According to the expert panel, this disease was not specific enough and treatment will often occur in specialized nursing homes where safe

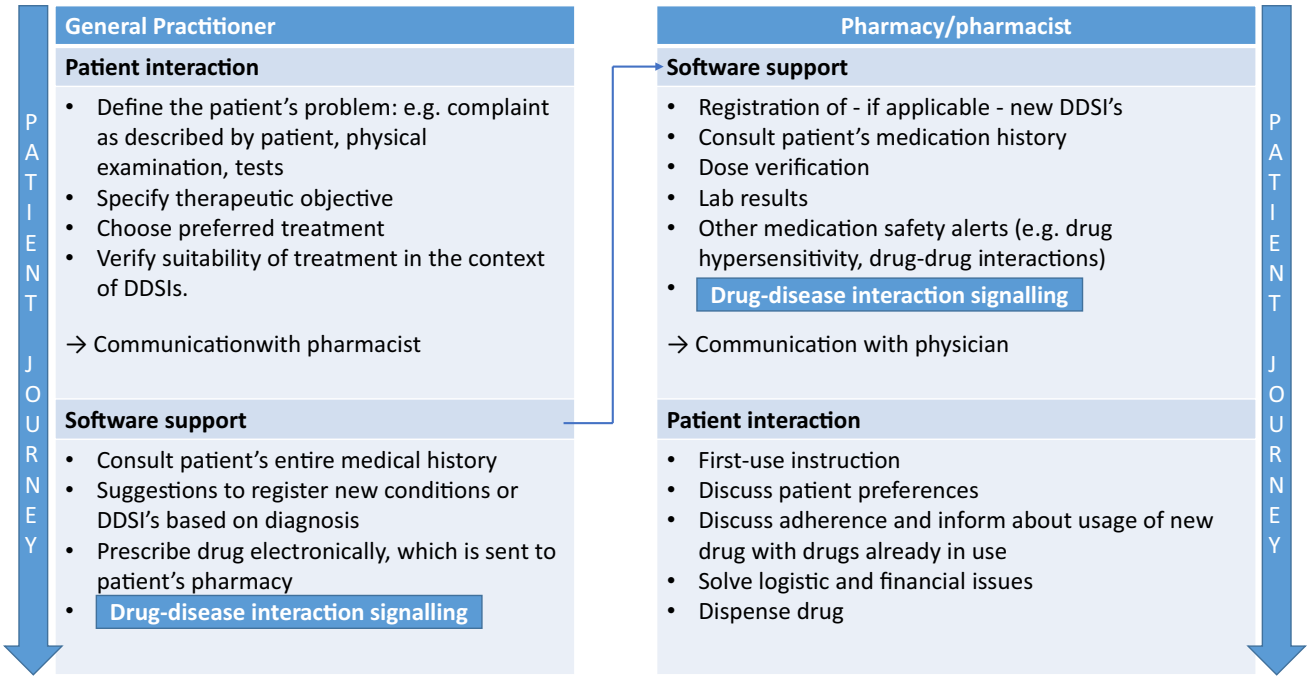

Fig. 1 Example of patient journey from GP office to pharmacy and the way clinical decision support software can help these health care providers with signalling and resolving DDSIs

use of medication is guided by protocols developed for this setting [19].

An important aspect of the development of recommendations is the authority of the expert panel to exclude a specific DDSI because it is deemed to be irrelevant for clinical practice. In this situation, no alert will be generated, even if this is in contrast with information in the official product information or evidence from clinical studies. These conclusions aim to prevent alert fatigue. The motivations of these conclusions are available to all users in the background information, including expert opinions. An example of a clinical irrelevant DDSI is use of the anti-depressant sertraline in diabetic patients. The SmPC of sertraline gives a warning for the use of the drug in diabetic patients. There are studies that describe some effect of sertraline on glucose levels [20]. However, there are also studies that do not see significant effects [21]. Besides these contradictory results, the indication of sertraline—depression—can also affect the patient's diabetes and subsequently treatment of this disease as well. Therefore, it was concluded that evidence and clinical relevance were too little and no practice recommendation was implemented.

Implementation

If the DDSI is assessed as clinically relevant and practice recommendations are developed, these practice recommendations are implemented in the two national drug information databases and uploaded to the CDSSs of Dutch pharmacies (circa 2000), general practices (circa 5000) and hospitals (circa 116) [22]. Integration of these practice recommendations are part of the CDSSs, so there is no need for additional software or subscriptions. Hospital pharmacists use other CDSS software than community pharmacist. Often, a selection of all available DDSI recommendations (e.g. renal impairment) is used, mostly implemented as separate clinical rules. Once a disease or condition that is part of a DDSI is registered in the patient record, the CDSSs will check if a prescription will lead to a DDSI at point of care. If so, an alert will show the practice recommendation for the specific DDSI. To show the routing and possible resolutions of DDSI alerts, several examples are presented in Fig. 2.

Evaluation

Table 1 describes the diseases and conditions that are considered as clinically relevant DDSIs in the Netherlands, and for which practice recommendations were developed. For every disease or condition, the frequency in the Netherlands is shown to give an idea of the health care burden. The total number of diseases and conditions with DDSI alerts is 57, with cardiovascular diseases (n = 12) and conditions related to the reproductive system (n = 7) as the largest groups. The Table illustrates that there is great variation between the diseases and conditions with respect to the number of

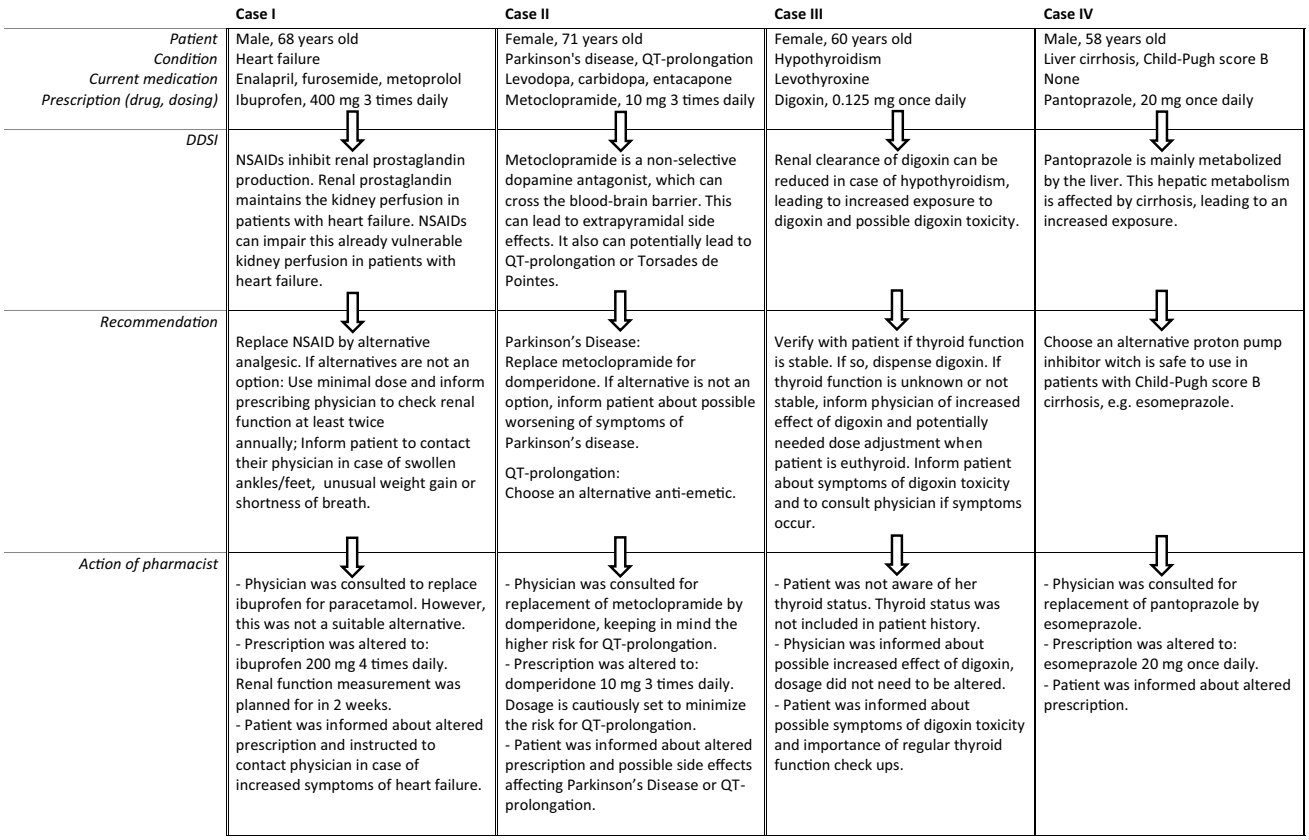

Fig. 2 Routing and possible resolutions of several DDSI alerts in pharmacy practice

individual drugs that were assessed as clinically relevant DDSIs, ranging from 6 to 1171, or even all registered drugs. For all assessed drugs or drug classes a unique practice recommendation is developed, of which the number is also given. This number of unique practice recommendations is smaller than the number of drugs with the specific disease as DDSI, because one practice recommendation is often developed for a drug class (e.g. ACE-inhibitors) instead of for the individual drugs. An example of the most common recommendation per disease or condition is given. Some practice recommendations are a 'safe to use'-signal. For these situations, the outcome of the evaluation is given also when the medication is evaluated as safe. This 'safe-to-use' information can be important for the patient and contribute to improved adherence. The subsequent action for these safe signals is to inform the patient, for example in the case of pregnancy. Finally, the Table also depicts the possible pharmacological mechanisms of the DDSI and an example of individual drugs or drug classes.

This best practice is not a static given, but is updated monthly. Up to 2020, the development of recommendations was a combination of ad-hoc searches for evidence and expert opinion. However, the standardized and therefore more transparent methodology that has been developed, will gradually replace the older evaluations when DDSIs will be periodically re-assessed [7]. The SmPCs of newly marketed drugs will be screened for potential DDSIs and updates of SmPCs will be assessed as well. Lastly, updates of existing recommendations happen after periodical revisions or are initiated by questions from health care professionals.

Discussion

A comprehensive way in signalling DDSIs has been developed in the Netherlands. This best practice includes 57 diseases and conditions for which practice recommendations have been implemented in CDSSs and for which—online—background information can be consulted. In primary care, in about half of the patient records at least one disease or condition that could lead to a DDSI was registered by pharmacists [23]. The resolution of these DDSIs is an integrated part of the responsibilities of pharmacists. This practice therefore brings added value to the medication safety of patients in the Netherlands [5, 24, 25].

The largest group of diseases that can lead to a DDSI was the group of cardiovascular diseases. Cardiovascular diseases are the most frequent causes of death and highly

Table 1 Diseases and conditions with relevant drug disease interactions: the number of drugs with the specific DDSI, the most common practice recommendation, the pharmacological mechanism of action and examples of drugs that result in an alert

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Cardiovascular (n = 12)						
Hypertension[b]	167	100	9	Consider alternative or check blood pressure regularly	Effect on smooth muscles of blood vessels, salt and water retention	Corticosteroids, danazol, calcineurin inhibitors
Raynaud syndrome[b]	50	47	3	Consider alternative; inform patient about symptoms	Vasoconstriction of small arteries	Beta-blockers, cytotoxic drugs, triptans
Ischemic heart disease[b]	45	104	27	Consider alternative; inform physician; inform patient about symptoms	Vasoconstriction of coronary arteries, cardiovascular adverse effects (tachycardia)	Tricyclic antidepressants, hormonal contraceptives, NSAIDs
Ischemic stroke and TIA	29 (incl. haemorrhagic stroke)	43	5	Consider alternative	Increased risk for arterial thrombosis	Hormonal contraceptives; NSAIDs
Haemorrhagic stroke	29 (incl. ischemic stroke)	46	5	Consider alternative; inform patient about symptoms	Increased bleeding risk or (intracranial) blood pressure	Anticoagulants, platelet aggregation inhibitors, NSAIDs
Heart failure[a]	14	96	13	Consider alternative; inform patient about symptoms	Negative inotropic or proarrhythmic effects; salt and water retention	Antiarrhythmic agents, NSAIDs, tricyclic antidepressants
Peripheral arterial disease	3	27	5	Consider alternative; inform patient about symptoms	Vasoconstriction, increase risk of cardiovascular disease	Hormonal contraceptives, NSAIDs
Venous thromboembolism[b]	2.5	33	9	Consider alternative; inform patient about symptoms	Effects on coagulation	Hormonal contraceptives, oestrogen receptor antagonists
Wolff-Parkinson-White syndrome	1.2	30	2	Consider alternative	Slowed AV-node conduction	Beta-blockers, cardiac glycosides, Calcium-antagonists
Bleeding disorders (haemophilia, Von Willebrand disease, thrombocyte disorders)	Depending on specific disorder (0.2, 1–10 or rare respectively)	75	8	Consider alternative; inform patient about symptoms	Increased bleeding risk	Anticoagulants, platelet aggregation inhibitors, NSAIDs
Long QT syndrome[c]	0.5	229	1	Consider alternative	Proarrhythmic effects	Antiarrhythmic agents, tricyclic antidepressants, macrolides
Brugada syndrome[c]	0.1–0.5	62	3	Consider alternative; preform ECG; inform patient	Proarrhythmic effects	Antiarrhythmic agents, lithium, tricyclic antidepressants
Reproductive system (n = 7)						
Male fertility	*Not applicable*	153	2	Inform patient about effect on fertility	Reproductive toxicity	Antineoplastics

Table 1 (continued)

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Trying to conceive (female)[c]	*Not applicable*	2063	33	Safe to use or (possible) risk or risk unknown during possible pregnancy; advise to choose an alternative which is safe or safer	Teratogenic effects	All drugs
Pregnancy[c]	*Not applicable*	2063	31	Safe to use or (possible) risk or risk unknown and advise to choose an alternative which is safe or safer	Teratogenic effects	All drugs
Breast feeding[c]	*Not applicable*	2063	11	Safe to use, (possible) risk or risk unknown and advise to choose an alternative which is safe or safer	Excretion of drug in breast milk with possible effects on infant	All drugs
Breast cancer	14 (♀)	46	4	Consider alternative, inform physician about increased risk for breast cancer	Increased risk of (re)developing breast cancer	Hormonal contraceptives, postmenopausal hormone replacement therapy, selective oestrogen receptor modulators
Endometriosis[a]	6 (♀)	6	2	Inform patient about increasing symptoms	Negative effect on ectopic endometrium tissue	Oestrogens, tamoxifen
Endometrium cancer[a]	Incidence 1900 (♀)	8	2	Monitor increased risk for developing endometrium cancer	Endometrium proliferation, increase in oestrogen and progesterone receptors	Oestrogens, tamoxifen
Genetic disorders (n = 6)						
Pseudocholinesterase deficiency	34–40	8	2	Consider alternative muscle relaxant or take extended duration of action into account	Decreased degradation of choline esters	Skeletal or local muscle relaxants
Glucose-6-Phosphate Dehydrogenase deficiency	1	66	3	Consider alternative or, provided that a therapeutic dose is used, inform patient about symptoms	Haemolytic anaemia	Antimalarial drugs, analgesics/anti-pyretics, antibiotics
Familial Hyperlipidaemia	Depending on specific disorder (0.001–1)	30	6	Check lipid spectrum	Increased VLDL, triglycerides, LDL/HDL-cholesterol	Atypical antipsychotics, bile acid sequestrant, oestrogens
Sickle Cell Disease	0.1–0.5	14	4	Consider alternative	Vaso-occlusive crisis	Colony stimulating factors, PDE5 inhibitors
Porphyria[c]	0.01	1171	3	Consider alternative, inform about symptoms	Haemolytic effects	Barbiturates, carbamazepine, erythromycin

Table 1 (continued)

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Angio-Oedema	0.01	24	2	Consider alternative	Increased bradykinin levels or decreased C1 esterase inhibitor activity	ACE-inhibitors, hormonal contraceptives
Gastro-intestinal (n = 5)						
Gastro-oesophageal reflux disease[b]	14	33	2	Consider alternative; inform patient about symptoms	Relaxation of lower oesophageal sphincter	Calcium antagonists, theophylline
Oesophageal stenosis	14	39	3	Consider alternative	Ulceration or irritation of oesophagus	Bisphosphonates, NSAIDs, Tetracyclines
Dyspepsia[b]	9	124	9	Prescribe Proton Pump Inhibitor; inform patient about symptoms	Increased bleeding risk, ulcerogenic effects	Anticoagulants, corticosteroids, NSAIDs
Peptic Ulcer[b]	2.4	85	9	Prescribe Proton Pump Inhibitor; inform patient about symptoms	Increased bleeding risk, ulcerogenic effects	Anticoagulants, corticosteroids, NSAIDs
Inflammatory Bowel Diseases[b]	0.1	69	2	Depends on remission of patient: consider alternative or inform patient about symptoms	Negative influence on pathological intestinal mucosa	NSAIDs
Kinetic interactions (n = 5)						
Renal impairment[c]	20.8	641	327	Consider alternative or adjust dose	Decreased elimination of drug	Antibiotics, anti-epileptics, RAS-inhibitors
Renal Replacement Therapies[c] *Haemodialysis* *Peritoneal dialysis*	Depending on type of therapy (respectively 0.3 and 0.05)	862	177	Consider alternative or adjust dose	Decreased elimination of drug	Antibiotics, anti-epileptics, RAS-inhibitors
Liver cirrhosis[a]	9.5	767	133	Consider alternative or adjust dose, depending on Child–Pugh score	Decreased elimination of drug, altered pharmacodynamics	Benzodiazepines, proton pump inhibitors, statins
Morbid Obesity[c]	10–15	20	16	Consider alternative or increase dose depending on body weight	Increased volume of distribution	Direct Oral Anticoagulants, heparins, penicillins,
Bariatric surgery[c]	0.7	156	10	Prescribe Proton pump inhibitor, consider alternative or prescribe preparation without sugar	Altered absorption or metabolic state, increased risk of gastro-intestinal side effects	Corticosteroids, antidiabetics, NSAIDs
Neurological (n = 5)						

Table 1 (continued)

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Sleep Apnoea[a]	22–29	78	6	Not contra-indicated if treated with CPAP, otherwise consider alternative, inform patient about worsening of symptoms	Respiratory depression	Anaesthetics, benzodiazepines, opioids
Epilepsy	3	171	21	Consider alternative with lower seizure risk; inform patient about symptoms; do not exceed maximum dose	Interference with GABA(-receptors)	Several antibiotics, antidepressants, antipsychotics
Parkinson's Disease	3	70	12	Consider alternative with less dopamine interference, inform patient about symptoms	Interference with Dopamine(-receptors)	Antipsychotics, anti-emetics
Myasthenia[b] *Myasthenia Gravis* *Lambert-Eaton Syndrome*	Depending on specific disorder (respectively 0.2 and 0.003–0.004)	217	4	Consider alternative, inform patient about temporary increase in symptoms	Interference with postsynaptic acetylcholine receptors, or presynaptic calcium channels	Antibiotics, anti-epileptics, corticosteroids
Tardive Dyskinesia	*Unknown*	80	5	Consider alternative with other side effect profile, inform patient about symptoms	Interference with dopamine and/or acetylcholine	Anticholinergic drugs, antipsychotics, anti-emetics
Respiratory (n = 3)						
Asthma[a]	33	101	7	Consider alternative, inform patient about symptoms	Induction of bronchospasms, bronchoconstriction or bronchial obstruction	Beta-blockers, NSAIDs
Chronic Obstructive Pulmonary Disease[a]	33	86	6	Inform patient about symptoms	Induction of bronchospasms or bronchoconstriction, respiratory insufficiency	Benzodiazepines, beta-blockers
Endocrine system (n = 3)						
Diabetes mellitus[b]	67	166	18	Advise patient to monitor glucose if possible, inform about symptoms of hyper/hypoglycaemia	Effect on glucose homeostasis, insulin sensitivity or insulin secretion	Atypical antipsychotics, corticosteroids, thiazide diuretics
Hypothyroidism	24	105	5	Depending on stable thyroid function: inform patient and physician about extra thyroid function tests and symptoms	Effect on pharmacokinetics or pharmacodynamics, effect on thyroid function	Amiodarone, digoxin, iodine containing products

Table 1 (continued)

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Hyperthyroidism	8	81	8	Depending on stable thyroid function: alternative or inform patient about symptoms and advise thyroid function test	Effect on pharmacokinetics or pharmacodynamics, effect on thyroid function	Amiodarone, digoxin, iodine containing products
Psychiatric (n = 2)						
Depression[b]	31	58	17	Inform patient about increasing/developing depressive symptoms	Development of depressive symptoms, whether or not a causal relation	5-alpha-reductase inhibitors, anti-epileptics, corticosteroids
Schizophrenia/psychosis[a]	3	32	5	Discuss possible alternative or treatment options with physician or psychiatrist	Increased risk for developing psychoses	Amphetamines, anti-epileptics, dopamine agonists
Other (n = 9)						
Glaucoma	19	22	3	Inform patient about symptoms	Increased intraocular pressure	Corticosteroids
Gout	29.8	42	5	Inform patient about symptoms	Increased uric acid levels	Salicylic acid, ciclosporin, isotretinoin
Psoriasis	8	93	8	Inform patient about symptoms and give advice for alternative when symptoms increase/worsen	*Unknown*	Beta-blockers, ACE-inhibitors, lithium
Urinary retention	2–110	120	3	Consider alternative or check urinary retention at start of treatment, inform patient	Decreased contraction of bladder detrusor muscle, increased contraction of sphincter	Parasympatholytic agents, opioids, loop diuretics
Tuberculosis	0.05	12	3	Consider alternative, treat tuberculosis, inform patient about symptoms	Increased risk of developing tuberculosis	Corticosteroids, BCG-vaccine
Sjögren Syndrome	0.1–0.5	142	9	Dependent of dosing frequency (eye drops) or preservatives: consider alternative or inform patient about symptoms	Decreased lacrimal and salivary moisture production	Anticholinergics, beta-blockers
Tympanostomy tubes	*Unknown*	6	2	Advise patient about maximum use for 2 weeks or consider alternative	Risk for ototoxicity	Ear drops containing: aminoglycosides, acetic acid, propylene glycol
Prohibited substances in sports[c]	*Not applicable*	213	6	Included on The Prohibited List of World Anti-Doping Agency, check regulations	Drug can give an advantage in sports and is therefore prohibited	Corticosteroids, beta-2-agonists, erythropoietin -analogues, diuretics

Table 1 (continued)

Disease or condition (n = 57)	Frequency measure (x:1000)[d]	Drugs with proven DDSI	Number of unique practice recommendations	Most common practice recommendation	Pharmacological mechanism of DDSI	Example of drugs that result in an alert
Drugs affecting driving ability[c]	*Not applicable*	352	43	Inform patient about prohibition to drive or restrictions towards driving (time interval of drug and driving)	Decreased reaction speed, drowsiness	Opioids, benzodiazepines, triptans, anti-histamines
Contact lenses	*Not applicable*	115	8	Do not wear contact lenses or wait before wearing them after use of eye drops	Adherence of preservative or drug to contact lenses with possible irritation of the eye	All eye drops (with and without preservatives), systemically used rifamycins

[a]Since 2020, the methodology how to develop DDSIs has been standardized [7]. This DDSI has been fully assessed according to the standardized protocol. [b]Some drugs in this DDSI have been assessed according to the standardized method. DDSIs without footnote are not assessed following this standardized method as of yet. [c]For this disease, an (inter)national guideline is available that is used to select the medication included in this DDSI. [d]Frequency measures are depicted as prevalence, except endometrium cancer which is given as an incidence. Values are generally based on data from National Institute for Public Health and the Environment (RIVM), the annual prevalence numbers of the Netherlands Institute for Health Services Research (NIVEL) or European/global data available on Orphanet

prevalent worldwide [26]. Furthermore, consequences of worsening a cardiovascular disease could be severe: reduced life expectancy or even death. The high prevalence and severe outcomes may be reflected in the number of DDSIs with cardiovascular diseases, since these diseases are probably more widely studied leading to a vast knowledge in—negative—effects of drugs on these diseases.

In the near future, fewer health care professionals will be responsible for more patients, who use more drugs per patient due to multi-morbidity [3, 4]. At the same time, more patient data will become available at point of care, due to innovations (wearables, increasing amount of pharmacokinetic, pharmacodynamics and pharmacogenomic parameters), and data exchange [27]. When these innovative data will be combined with the pharmacological knowledge about DDSIs, more personalised and time saving alerts can be developed for signalling and monitoring DDSIs.

The possibilities of this best practice to contribute to medication safety of OTC drugs depends on the countries' health care system setting. In the Netherlands, OTC drugs are also sold in drugstores and supermarkets. These OTC drugs can still potentially lead to DDSIs (e.g. NSAIDs and heart failure). However, these DDSIs are not signalled in the Dutch setting, since these stores do not have some form of CDSS. Patients are therefore advised to consult their physician or pharmacists if they are using OTC drugs and have comorbidities and/or take other medications. This system, however, is not waterproof [28]. In other countries, where OTC drugs are only sold in pharmacies, signalling of DDSIs for these kind of drugs is far more reliable than in the Dutch situation. The opportunities of this best practice to contribute to medication safety for OTC drugs in other countries is therefore significant.

Alerts for DDSIs need to be resolved by combining pharmacological knowledge about the influence of medication on the disease with clinical knowledge about the disease in the context of the individual patient. In the Netherlands, it is common practice that pharmacists and physicians resolve such issues in medication safety by interprofessional communication [29]. Lack of interprofessional communications may limit exchange of knowledge between professionals, and lead to suboptimal health outcomes. Resolution of DDSIs is more difficult if interprofessional communication is hampered by for example lack of contact due to different views on the pharmacist's responsibility to safe prescribing or practical issues such as difficulties to contact colleagues at the point of care [30]. There are substantial differences in interprofessional communication between countries, but between settings as well—e.g. primary care versus hospital setting.

A strength of the practice concerning DDSIs in the Netherlands is the wide body of pharmacological knowledge and recommendations that have been developed over a

long period of time, and the experience of pharmacists with implementation in clinical decision support in daily practice. DDSI signalling has been a part of clinical decision support since the eighties [31] and this practice evolved from expert opinions to a transparent, standardized methodology that combines systematic literature review with a multi-disciplinary expert panel [7]. Another advantage is the fact that these DDSI alerts occur at the point of care during prescribing (physician) or dispensing (pharmacist) in all systems and practices. If action is required, both health care professionals can intervene immediately. In the Netherlands, pharmacists and physicians have accepted DDSIs as one of the topics in good prescribing and inter-professional communication for medication safety [29]. This practice stimulates this inter-professional communication: alerts may have consequences for physicians active in another discipline. A pharmacist is the ideal intermediary to signal these situations and conduct proper communication and actions since he/she has a more complete overview of a patient's medication history.

Three barriers for wider implementation and adoption in other countries of our best practice need to be discussed. First, alert fatigue may occur. This is a situation in which a health care professional is exposed to too many alerts by a CDSS, which can lead to—accidentally—overriding some potentially important signals. Alerts without acute risk for the patient or that do not require action of the pharmacist contribute to alert fatigue and overriding of signals. A lack of specificity or sensitivity of alerts could contribute to alert fatigue as well. This could be solved by implementing more patient characteristics into the alerts, yet this requires multidisciplinary agreements on exchange of essential data followed by major adjustment in CDSS software that facilitates complex decision rules and interdisciplinary data exchange [23, 32]. To minimize the risk of alert fatigue, the balance between completeness and feasibility in clinical practice is kept in mind during the entire assessment of a DDSI. Secondly, a significant number of DDSIs requires substantial efforts concerning maintenance [33]. The implemented recommendations are subject to changing clinical insights and newly marketed drugs. Approximately five pharmacists are responsible for general maintenance and organisation of two annual meetings with the multi-disciplinary expert panel. Finally, this practice is embedded in the Dutch health care system and regulation. Practice organisation or legislation in other countries can be different, and may limit the possibilities of direct implementation of this practice. In Germany for example, electronic patient records were introduced only recently in community pharmacies [34], contributing to a more complete medical overview and possibilities to detect DRPs. A legal prerequisite to perform this best practice is to have the professional freedom to deviate from documents such as the SmPC. This best practice sometimes allows prescribing a drug to a patient with a condition contraindicated by the SmPC. Although off-label prescribing is allowed in most European countries to some degree, legal restrictions need to be followed [35]. Another legal restriction may be the new Medical Device Regulation (MDR). This new European regulation states certain software—such as CDSSs—as a medical device, which has to comply with this regulation mandatorily. It is not yet clear if the MDR will affect the pharmacological knowledge or other aspects that have been developed in this best practice and implemented in CDSSs.

Although complete implementation of this best practice can be prone to some legal, technical and practical hurdles, implementation is possible. As implementation costs in a CDSS can be substantial, gradual implementation in clinical rules or via protocols can be organised easier with lower costs. A technical requisite is that the data are coded to guarantee compatibility and exchange between systems and health care providers. This paper could be a start for implementing a practice for DDSI signalling. The pharmacological background will be similar in all countries, but assessment of clinical relevance might differ per medical speciality and country. Therefore, the authors would recommend to 'start low, and go slow' by implementing DDSI signalling one by one, and expand the amount of signals over time. Implementing the practice internationally will contribute to a wider perspective and will generate input for discussion and improvement of the recommendations in the Netherlands. Future research should also be conducted to study the clinical impact of the best practice described in this paper, by evaluating the amount of generated alerts and the actions taken by health care professionals.

Conclusion

In the Netherlands, practice recommendations for drug-disease interactions based on pharmacological considerations and expert opinion have been developed for 57 diseases and conditions. These recommendations have been implemented in clinical decision support systems, supporting both pharmacists and physicians by signalling drug-disease interactions at point of care, thereby improving medication safety. This practice may be adopted and contribute to safer medication use in other countries as well.

Conflicts of interest Maaike M. E. Diesveld, Suzanne de Klerk and Sander D. Borgsteede are employed at Health Base Foundation (HBF), an independent, non-commercial foundation that maintains a drug information database (Pharmabase) and supports health care professional with a clinical decision support system. The drug-disease interactions studied in this manuscript are subject to medical information provided by HBF.

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