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Clinical risk management of herb–drug interactions

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The concomitant use of conventional and herbal medicines can lead to clinically relevant herb–drug interactions. Clinical risk management offers a systematic approach to minimize the untoward consequences of these interactions by paying attention to: (i) risk identification and assessment; (ii) development and execution of risk reduction strategies; and (iii) evaluation of risk reduction strategies. This paper reviews which steps should be explored or taken in these domains to improve the clinical risk management of adverse herb–drug interactions.

Introduction

It has become clear that conventional and herbal medicines are often used concomitantly [1–4] and that this can lead to clinically relevant herb–drug interactions [5–7]. A systematic approach is required to minimize the untoward consequences of these interactions. The concept of clinical risk management offers such an approach by aiming at a shift from organizational vulnerability of healthcare processes towards organizational integrity [8, 9]. Most of the work on clinical risk management has been undertaken in secondary care, but in recent years this approach has also emerged as valuable for improving healthcare processes in primary care [10] and for the monitoring of medicinal products [11, 12].

Clinical risk management acknowledges that all healthcare processes, by their very nature, carry risks. It provides a systematic approach to controlling these risks, which mainly consists of: (i) risk identification and assessment; (ii) development and execution of risk

reduction strategies; and (iii) evaluation of risk reduction strategies [8, 9, 12]. This paper reviews which steps should be explored or taken in these domains to improve the risk management of adverse herb–drug interactions.

Risk identification and assessment

This first phase of clinical risk management requires that hazards are identified and stratified in terms of evidence, probability and significance.

Spontaneous reporting

It is important to find out what is not yet known about the nature of herb–drug interactions. Various countries, including the UK [13], have incorporated herbs into their pharmacovigilance systems to improve the identification of new herb-associated risks. It is relatively inexpensive to collect and interpret voluntary reports, and the major strength of this methodology lies in its ability to serve as a warning mechanism [14]. In 2004, the European Community passed a directive, which permits a simplified registration scheme for traditional herbal medicines which do not fulfil conventional requirements for licensing as medicines. Hereby, companies holding licences for herbal medicines will be legally obliged to conduct pharmacovigilance for their products and to report all suspected adverse events to the health authorities [15].

The effectiveness of herbal pharmacovigilance depends, of course, on the perceptivity of everyone involved in prescribing, dispensing and using herbal medicines, and on willingness to come forward with suspected and possible adverse events. Concerns about reporting by doctors and pharmacists are the highly variable quality of current reports (which frequently makes it impossible to draw any conclusion) [16, 17] and the potential for considerable underreporting. In a questionnaire study among community pharmacists in the UK, 70% of the respondents rarely or never asked patients about their use of complementary medicines when receiving reports of suspected adverse reactions to conventional medicines [18]. More education and encouragement are warranted to increase the quality and quantity of herbal case reporting by doctors and pharmacists.

The same applies to herbal medicine practitioners, because it seems unlikely that they are doing better than their conventional counterparts [14]. In a UK study on the safety of Chinese herbal medicine, only 13% of the 549 practitioners invited to participate agreed to ask patients for their cooperation [19]. Hopefully, the recent UK initiative to bring about statutory self-regulation of herbal medicines practitioners [20] will provide a stepping stone for embedding herbal case reporting in their education and professional code of conduct.

Consumers should also become more aware of the importance of herbal case reporting. A telling finding in the UK has been that 69% of herbal medicine users would not consult their general practitioner (GP) in case of a serious adverse event [21]. The least that should be done to remedy this, is the inclusion of a general advice in herbal package inserts to contact a physician or pharmacist in case of an unexpected adverse event.

Experimental studies

Subclinical experimental studies of potential and suspected herb–drug interactions are important to elucidate underlying mechanisms (such as modulation of cytochrome P450 enzymes [22] and P-glycoprotein [23]) and to provide guidance as to which herb–drug interactions deserve priority when planning clinical studies, but they do not obviate the need for well-designed human studies [24, 25]. Fortunately, the number of clinical studies on the nature and magnitude of herb–drug interactions is rapidly growing [5–7].

Clinical studies are generally rated as more valuable than case reports [26–28], but when a controlled clinical study does not provide significant evidence of a herb–drug interaction, this does not necessarily mean that the herb–drug combination is safe in all users. First, a flaw in the design of the controlled study may have led to an inaccurate conclusion. For example, an early study of St John's wort claimed incorrectly that this herb was unlikely to affect CYP 3A4 activity, because the test subjects had not been exposed long enough to St John's wort to make its enzyme-inducing effect manifest [29]. Second, controlled herb–drug interaction studies are mostly performed in small homogeneous populations of healthy volunteers or relatively healthy patients. As a result, potentially relevant risk modifiers (e.g. infrequent genotypes, frailness, co-morbidities, additional herbal or conventional medicines [30]) may be insufficiently represented. Consequently, a well-documented case report (especially with a positive rechallenge) does not always constitute a lower level of evidence than a negative controlled interaction study [17]. The aspects which a reporter has to take into account when documenting cases of herb–drug interactions are listed in Table 1. Most of these aspects are equally important for case reports about drug–drug interactions, but there are particular issues that deserve special attention when a herbal product is involved, i.e. its phytochemical constituents and its quality. With respect to these points, the recent CONSORT statement concerning the reporting of

Table 1
Aspects to be considered when documenting a case of a herb–drug interaction

Aspect	Specification
Characteristics of user	Age/gender/ethnicity
	(Co-)morbidity/anamnesis
Characteristics of herbal product/conventional drug	Composition/dosage form
	Phytochemical constituents/quality of herbal product
Use of herbal product/conventional drug	Reason for/duration of use
	Route of administration/dose/time and dose/day
Use of other products	Conventional/unconventional products
Characteristics of adverse event	Clinical signs/symptoms
	Laboratory findings
	Conventional drug levels
Evaluation of adverse event	Temporal time sequence
	Dechallenge/rechallenge
	Formal causality assessment
	Stability of patient before/after adverse event
	Coverage of existing literature
	Product-bound/user-bound/circumstances-bound risk modifiers (e.g. frailness/infrequent genotype)
Evaluation of confounding factors	Change in (co-)morbidity
	Change in intake food/alcohol/recreational drugs
	Change in conventional/unconventional products
	Change in patient adherence

randomized controlled trials of herbal interventions is inspirational [31].

Pharmacoepidemiological studies

Pharmacoepidemiological studies help to overcome the limitations of spontaneous case reports and clinical studies [14, 32], but, so far, pharmacoepidemiological evaluations of the nature, volume and risk modifiers of herb–drug interactions have been scarce [3]. A main reason is probably that, in European and North American countries where pharmacoepidemiological research is currently concentrated, most herbal medicines are available without a prescription and do not end up systematically in healthcare records or prescription databases [33, 34]. The most structural way to solve this shortcoming would be, of course, to include all prescription-free herbal medicines (and other unconventional products) in routine collections of patient data for pharmacoepidemiological purposes. It should be carefully weighed, however, whether the expected benefits of such continuous efforts would outweigh the extra time and money that would be required. An alternative way forward would be to collect such data within the context of specific goal-oriented pharmacoepidemiological studies, e.g. on the contribution of herb–drug interactions to the haemorrhagic and thrombotic complications of patients on oral anticoagulants [17].

Risk stratification

It is important to distinguish the following parameters when stratifying the clinical risks of herb–drug interactions: (i) quality of the evidence for the interaction; (ii) seriousness of the resulting adverse reaction; (iii) incidence of the adverse reaction; and (iv) existence of risk factors resulting in increased seriousness and/or increased incidence of the adverse reaction [27]. While a structural assessment of the quality of the evidence for herb–drug interactions is sometimes presented in the literature [35], a comprehensive classification of herb–drug interaction risks has not yet materialized. A good starting point would be the classification system for the transparent and reproducible incorporation of drug–drug interactions in computerized interaction surveillance programmes which was developed in the Netherlands [27] following an earlier Swedish example [26]. In the Dutch system, the quality of the evidence is indicated by the numbers 0–4 (Table 2) and the seriousness of the potential adverse reaction by the letters A–F (Table 3). Together, the number and letter form an alphanumeric code which provides insight into the risk of the combi-

Table 2
Structured assessment of drug–drug interactions: categories for the quality of evidence [27, 36]

Category	Description
0	Pharmacodynamic animal studies; *in vitro* studies with a limited predictive value for the human *in vivo* situation; data on file
1	Incomplete, published case reports (no re- or dechallenge, presence of other explanatory factors for the adverse reaction)
2	Well-documented, published case reports; retrospective analyses of case series
3	Controlled, published interaction studies in patients or healthy volunteers with surrogate end-points
4	Controlled, published interaction studies in patients or healthy volunteers with clinically relevant end-points
–	Posters and abstracts from scientific meetings: 0 or 1, depending on the information provided. When the information of the poster or abstract is not published in a peer-reviewed journal within 3 years after the scientific meeting, this information is recategorized as 0
–	Information from the Summary of Product Characteristics/European Public Assessment Report (EPAR): 0, 1 or 2, depending on the information provided
–	Retrospective case series: 2 or 3, depending on the information provided

nation [27]. These drug–drug interaction codes can be applied seemlessly to stratify herb–drug interactions in a consistent way. However, several caveats should be taken into account.

Caveats of the Dutch coding system

First, codes should not be considered in isolation but in combination with an assessment of the incidence and the existence of risk factors increasing the seriousness and/or incidence of the adverse reaction [27]. The former is important, because the clinical impact of an interaction at the population level depends not only on the seriousness of the adverse drug–drug interaction, but also on the chance that the adverse drug–drug interaction actually occurs [37]. An understanding of risk factors is important also, especially since the codes give priority to controlled interaction studies over case reports or case series, no matter how well the latter are documented (Table 2). As outlined above, this may lead to a false sense of security, which should be reduced by allowing more than one alphanumeric code per herb–drug interaction.

A second caveat is that the Dutch coding system provides drug–drug interactions with the lowest possible ranking when there are no or only unpublished data (Table 2). A potentially untoward consequence is that herb–drug interactions which are fairly predictable on the basis of pharmacological principles have to wait for an actual case report or study before their level of evidence rises above the lowest possible ranking. Again, this may lead to a false sense of security when the system is applied indiscriminately. A practical solution would be to provide theoretical but predictable herb–drug interactions with a special code, particularly when the predicted adverse reaction would be potentially serious in nature. This would help to prevent (or at least monitor) such potentially hazardous herb–drug combinations. For example, there is ample evidence that St John's wort is a potent inducer of CYP 3A4 [5, 38, 39]. One should therefore take into consideration that this herb may diminish the clinical effectiveness and increase the dosage requirements of any well-established CYP 3A4 substrate, even when there are no clinical publications yet to underpin such an interaction (Table 4).

A third caveat is that any system for the transparent and reproducible assessment of the risks of herb–drug interactions can only function properly when it is complemented with an adequate system for collecting and assessing new emerging evidence without unnecessary delays. It is remarkable, for example, that current interaction surveillance systems in Dutch pharmacies and GP practices do not include the interaction between garlic and saquinavir [43, 44], even though a clinical study in which garlic reduced the AUC of saquinavir by 51% was published in 2002 [45].

Development and execution of risk reduction strategies

This phase of clinical risk management aims at the definition of operational strategies needed to reduce health risks, at the identification of resources, and at the execution of selected strategies.

As most herbal medicines are available without prescription, it is the consumer who decides for or against combining these products with convenventional medicines. It is therefore of paramount importance to inform consumers about the risks of combining these types of products. Regulatory authorities, manufacturers, prescribers and retail sellers of herbal preparations as well as manufacturers, prescribers and dispensers of conventional medicines should all contribute to this goal without shifting their responsibility to other parties involved [46].

Table 3
Structured assessment of drug–drug interactions: categories of clinical relevance [27, 36]

Category	Description	Examples
A	No or insignificant clinical effect	Increased drug level without clinical symptoms Failure of therapy with digoxin Atrial ectopics INR increase up to 4
B	Transient inconvenience (<2 days) without residual symptoms	Fatigue, headache, nausea, amnesia Adverse reactions from increased bioavailability of dihydropyridine calcium channel blockers
C	Prolonged inconvenience (2–7 days) without residual symptoms	Adverse reactions resulting from increased biovailability of antiepileptics or ciclosporin
	Failure of therapy for nonserious diseases	Decreased effects of methadone or thyroxine
D	Prolonged (>7 days) or permanent residual symptoms or invalidity	Toxic effects of aminoglycosides, lithium, methotrexate, digoxin INR increase >6
	Failure of therapy for serious but nonfatal diseases	Failure of therapy with loop diuretics (leading to hospitalization because of heart failure)
E	Increased risk of dying	Gastric haemorrhage Prolongation of QT interval Rhabdomyolysis
	Failure of life-saving therapy	Failure of therapy with antiretroviral drugs, quinidine, ciclosporin
	Increased risk of pregnancy without risk factors for mother or child	Failure of contraceptives due to enzyme induction
F	Death	Fatally ending insult
	Potentially fatal adverse effects	Torsades de points Serotonin syndrome
	Increased risk of pregnancy with risk factors for the child	

INR, International Normalized Ratio.

Package inserts

All commercially available herbal preparations should have a package insert with appropriate warnings concerning herb–drug interactions. These warnings should also be included in the package inserts of conventional medicines. Package inserts of conventional CYP 3A4 substrates should no longer warn of interactions with CYP 3A4 inducers in general without specifying that St John's wort is a potent CYP 3A4 inducer. The new European legislation for traditional herbal medicines [15] provides a welcome occasion to verify and improve herbal package inserts (including the general advice to contact a physician or pharmacist in case of an unexpected adverse event). When the risk of a herb–drug interaction is pronounced, it should be considered to print a conspicuous warning or to place a special cautionary sticker on the herbal package [47].

Professional contributions

Prescribers and retailers of herbal products should ask their customers about the use of conventional medicines when they recommend or sell herbal products with a well-established risk of herb–drug interactions. They should also make them aware of the possibility that an adverse event may occur which is not yet described in the package insert. They should be adequately trained in these topics and discuss them with their customers, especially when a herbal medicine is compounded to meet the needs of an individual patient following a one-to-one consultation. In such cases, the herbal medicine is

Table 4
Examples of well-established CYP 3A4 substrates for which there are not yet case reports or clinical studies which show a clinically significant herb–drug interaction with the potent CYP 3A4 inducer St John's wort [40, 41]

Drug class	Drug(s)
Anti-arhythmics	Quinidine
Antimalarials	Mefloquine
	Quinine
Calcium channel blockers	Nifedipine
	Verapamil
HIV protease inhibitors	Nelfinavir*
	Ritonavir*
	Saquinavir*
HMG CoA reductase inhibitors	Atorvastatin
	Fluvastatin
	Lovastatin

**While these drugs are listed in the Appendix on Interactions of the British National Formulary as drugs that can interact with St John's wort [42], the other drugs in this Table are not.*

exempt from normal licensing requirements [48], which means that the herbal product will be provided without an independently verified package insert.

Prescribers and dispensers of conventional medicines should inquire more systematically with their patients about the use of herbal products, and they should urge them to have their herbal products registered in the same records in which their prescription medicines are registered. The latter opens the door to on-line detection of adverse herb–drug interactions, which is a more efficient and reliable strategy than relying solely on the knowledge and perceptivity of an individual physician or pharmacist [49, 50]. To benefit optimally from computerized screening for herb–drug interactions, physicians and pharmacists should know exactly what their programs can and cannot do. For instance, they should realize that current programs do not cover certain risk moments. When patients present themselves for the first time, it is important to ask in that first contact whether they are already on any herbal products, and patients combining a herbal CYP inhibitor or inducer with a conventional CYP substrate should learn that the resulting interaction has a major risk moment not only when the inducer or inhibitor is added, but also when it is withdrawn [51]. For example, patients stabilized on an oral anticoagulant plus St John's wort should be cautioned not to discontinue this herb injudiciously, as this could lead to serious overcoagulation [52].

In the risk assessment of a specific herb–drug interaction, it is important to consider not only the general published evidence, but also the characteristics of the individual patient, because the latter may act as significant risk modifiers [17, 30]. To illustrate this point, some proven and possible risk modifiers of herb–drug interactions and grapefruit–drug interactions are listed in Table 5.

Pharmacy-only status

Regulatory authorities may reclassify general sales medicines as pharmacy-only medicines if information emerges that it is not safe to supply these products without a pharmacist checking that they are suitable for the individual patient [56]. It would be in the spirit of this option to bring herbal medicines with a high risk of serious herb–drug interactions under a pharmacy-only medicine regimen. This would facilitate the incorporation of these herbal medicines into pharmacy records and thereby the computerized screening for interactions between these herbs and conventional drugs. Obvious candidates for such a regulatory move are St John's wort preparations providing a pharmacological dose level of hyperforin [57, 58].

Risk communication

A major difference between the resolution of drug–drug interactions and herb–drug interactions is that the therapeutic value of most herbal products has not yet been satisfactorily proven [59]. From a medical perspective, this makes such products non-essential and thereby avoidable. This is reflected in current Dutch recommendations on how to deal with herb–drug interactions [43, 44]. However, patients may have different ideas about the appropriateness of a treatment to their healthcare providers [60, 61] and many take a sincere interest in complementary medicines [62, 63]. These patient perceptions are built up over time, informed by personal experiences and social networks, and shaped by behavioural norms and media reporting. Fear of the development or progress of a disease, mistrust in conventional pharmaceuticals, and the desire to take responsibility for one's health may all contribute to such patients' views and decisions [64]. Patients may also find it difficult to deal with uncertainties that arise from the lack of good-quality information. For many herbal medicines, the uncertainties about potential benefit and harm leave a wide opening for the values of the individual user to

Table 5
Examples of established and possible risk modifiers of herb-drug and grapefruit–drug interactions

Risk modifier	Botanical CYP inducer/inhibitor	Conventional drug substrate	CYP system involved	Observed or suggested effect
Age	St John's wort (SJW)	Midazolam	CYP 3A4	Elderly subjects are susceptible to SJW-mediated changes in CYP activity. Comparison with earlier studies that employed young subjects suggests that age-related changes in CYP responsivity to botanical supplementation may exist [53]
Liver cirrhosis (LC)	Grapefruit juice (GJ)	Midazolam	CYP 3A4	Interaction between GJ and oral midazolam was more marked in patients with LC than in earlier study in healthy subjects [54]
Pharmacogenetic status	Ginkgo	Omeprazole	CYP 2C19	Ginkgo significantly induced CYP2C19-mediated hydroxylation of omeprazole and this effect was more pronounced in poor metabolizers than in extensive metabolizers [55]

come into play. For example, how is a patient supposed to deal with the warning that garlic *might* interact with his oral anticoagulants?

Further research in this domain is needed to guide writers of herbal product information and professionals counselling consumers of herbal medicines. In the meanwhile, conventional healthcare providers should aim for a middle ground between paternalism and consumerism by looking at ways to reconcile their professional powers with the ethics of informed choice [65].

Evaluation of risk reduction strategies

The third phase in clinical risk management is the evaluation of risk minimization strategies, i.e. have these strategies actually worked effectively and efficiently. This final phase is crucial in the clinical risk management of drug–drug interactions [26, 66–68] and should therefore not be overlooked in the risk management of herb–drug interactions either.

Herbal package inserts

As the package insert of herbal medicines is the main tool for informing consumers about the risks of herb–drug interactions, its use by consumers and its usefulness to these consumers should be carefully evaluated. Which herbal medicines do not yet offer adequate package inserts, which consumers actually read such inserts, how well informed does this make them, and how does this affect their actual consumption behaviour?

Professional performance

A second area of evaluation is professional performance. If two-thirds of the community pharmacists in the UK rarely or never ask about complementary medicines when dealing with suspected adverse reactions to conventional medicines [18], how often will they inquire into the use of herbal medicines when dispensing a conventional medicine with well-established herb–drug interactions? To what extent do patients asking for herbal products in pharmacies and health food stores receive appropriate and up-to-date counselling about herb–drug interactions? And if patients order herbal products through the internet, how often will the e-seller ask for relevant consumer details and provide advice accordingly? An Australian research group made up a case of a 35-year-old female who had been on fluoxetine because of depression for the past months and ordered St John's wort on her behalf from e-pharmacies in various countries. Only 19% of the e-pharmacies that delivered asked for details that would have enabled them to detect the fluoxetine use (which entails the risk of a serious serotonergic drug interaction with St John's wort) [69].

If the registration of herbal medicines in healthcare records can be raised to such a level that on-line screening for hazardous herb–drug interactions becomes a reality, it can be monitored how often healthcare professionals allow such interactions to pass despite their computerized medication surveillance. In a recent Dutch study, nine potentially hazardous drug–drug combinations, that

should be generally absent in the dispensing patterns of community pharmacies and dispensing general practices, were still encountered. The differences between individual pharmacies were remarkable: the total number of times that a pharmacy had dispensed the investigated drug–drug combinations varied from 0 to 99 [66]. An example of a herb–drug combination that should not be allowed to pass is the combination of St John's wort with a conventional selective serotonin reuptake inhibitor. There is no evidence that this combination offers any therapeutic advantage, but it does entail the risk of a potentially life-threatening serotonin syndrome [5, 59]. Another Dutch study on drug–drug interactions assessed how community pharmacists deal with computerized alerts in daily practice [68]. The study made clear that pharmacists particularly like to take action when they observe a drug–drug interaction in a patient for the first time. Yet it is well known that certain interactions need prolonged attention. For example, when a nonsteroidal anti-inflammatory drug is combined with an ACE inhibitor or angiotensin II antagonist, it is important to monitor closely over time whether this combination increases blood pressure [43]. Another finding was that there is still room for improving patient counselling on drug–drug interactions [68]. It is likely that this also applies to counselling on herb–drug interactions.

Conclusions

Clinical pharmacologists can further the clinical risk management of herb–drug interactions by contributing to all of the above-mentioned domains: the collection and interpretation of spontaneous reports; the design and interpretation of prospective clinical studies; the development of pharmacoepidemiological investigations; the synthesis and weighing of the available evidence; the expert counselling of regulatory authorities and manufacturers on relevant issues; and the evaluation of existing and emerging risk reduction strategies. Clinical pharmacologists should also educate other healthcare professionals in these matters and, if necessary, bring serious herb–drug-related concerns into the societal arena [30, 46].

Peter De Smet works for the Scientific Institute Dutch Pharmacists, which is financially dependent on the Royal Dutch Society for the Advancement of Pharmacy (the professional pharmaceutical association in the Netherlands). He has no further sources of funding or conflicts of interest to declare.

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