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Targeting Outpatient Drug Safety
Recommendations of the Dutch HARM-Wrestling Task Force

Margaretha F. Warlé-van Herwaarden,[1] *Cees Kramers,*[2] *Miriam C. Sturkenboom,*[3] *Patricia M.L.A. van den Bemt*[4,5] and *Peter A.G.M. De Smet*[1]

1 IQ Healthcare, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
2 Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
3 Pharmacoepidemiology Unit, Department of Medical Informatics and Epidemiology and Biostatistics, Erasmus University Medical Center, Rotterdam, the Netherlands
4 Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands
5 Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, the Netherlands

Abstract

Background: Two Dutch observational studies (HARM [Hospital Admissions Related to Medication] and IPCI [Integrated Primary Care Information]) have shown that approximately 5% of all unplanned hospital admissions are associated with adverse drug events (ADEs), of which 40–46% are potentially preventable. These studies prompted the initiation of a Dutch multidisciplinary task force, which was assigned to reduce the number of prescriber-related hospital admissions related to medications (HARMs) in a quick-win way.

Objective: The aim of the study was to identify the most relevant ADEs and to develop a limited number of recommendations for concrete interventions, which should be feasible and relatively easy to convert into computerized drug safety alerts.

Method: To identify the major ADEs, crude data of HARM and IPCI were reanalysed and compared with different international studies, followed by structured literature searches for further characterization of the identified ADEs, their risk factors and potential risk-reduction strategies. Based on this information, the Task Force drew up general and drug-specific recommendations. As the recommendations of the Task Force are a mixture of evidence- and expert-based risk-reducing strategies, they have been graded in accordance with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

Results: Seven pharmacologically predictable ADEs associated with ten drug classes were responsible for more than half of all potentially preventable hospital admissions in the IPCI and HARM studies, which was comparable to the results of international studies. Gastrointestinal and other bleedings were the most frequent ADE, followed by disturbances of diabetes mellitus

control, electrolyte disturbances, fractures, renal insufficiency and heart failure. Nine general and 34 drug-specific recommendations were developed.
Conclusions: As HARMs constitute a significant public health problem, the Task Force underlines the need to implement its recommendations as soon as possible. They do not replace existing guidelines, but reinforce, complement and fine-tune existing Dutch and international guidelines. Further research is still required to assess the cost consequences and cost effectiveness of some recommendations, and to monitor the implementation of the recommendations and their effect on the incidence of potentially preventable HARMs.

Background

After a Dutch literature review in 2002 had shown that hospital admissions due to adverse drug events (ADEs) pose a significant, expensive and partially avoidable public health problem,[1] two Dutch research groups performed studies to establish the nature, volume and preventability of drug-related hospital admissions in the Netherlands.

The first, a retrospective cohort study in the 'Integrated Primary Care Information' database (hereafter designated as the IPCI study) evaluated the extent, characteristics and determinants of ADE-related hospitalizations.[2,3] Hospital admissions associated with deliberate or unintentional overdose or non-adherence were excluded, and preventability of the drug-related reasons for hospital admission was assessed by applying the algorithm of Hallas et al.[4] and the criteria of Schumock and Thornton.[5] The IPCI study identified 3515 hospital admissions, of which 2238 were unplanned; 115 cases of these unplanned admissions were medication related. The study indicated that 5.1% of all unplanned hospital admissions in the Netherlands were definitely or probably associated with ADEs.[2,3]

Subsequently, a larger, prospective, case-control study, the so-called HARM (Hospital Admissions Related to Medication) study, looked at unplanned medication-related hospitalizations and determined their potential preventability and associated risk factors.[6,7] Over a period of 40 days, all unplanned admissions (exclusion criteria were age below 18 years, admission for obstetric indications, psychiatric admissions and admissions for self-poisoning) were evaluated for their potential relation to drug use by using the algorithm of Kramer et al.[8] Preventability of the admissions was assessed by applying a modified version of the criteria of Schumock and Thornton.[5] The HARM study identified 13 000 unplanned hospital admissions, of which 714 were related to medication. The study showed that 5.6% of all unplanned hospitalizations in the Netherlands were drug related, and that 46% of these were potentially preventable.[6,7]

These studies prompted the Dutch Ministry of Health, Welfare and Sport to initiate a multidisciplinary task force, which was assigned to make concrete recommendations on how to reduce the observed, potentially preventable HARMs in a quick-win way ('low-hanging fruit').

Methods

The Task Force successively took the following steps:

1) Identification of the most relevant ADEs.
2) Further analysis of their epidemiology and identification of their risk factors.
3) Identification of HARM-reducing strategies.
4) Structured approach for drawing up concrete recommendations.
5) Identification of prominent general issues.

Identification of the Most Relevant ADEs

Crude data of all potentially preventable HARMs in the IPCI and HARM studies were retrieved in anonymized form from the researchers, combined into one dataset and reanalysed to identify the responsible drug(s), the clinical reason for

hospital admission and any further potentially relevant details. The IPCI and HARM studies both used the algorithm of Schumock and Thornton[5] to classify the preventability. For that reason, their assessments of preventability were not reanalysed.

Our analysis was compared with international studies of drug-related hospital admissions.

Since the Task Force aimed to reduce the number of HARMs with a limited number of concrete interventions, the identification of medications and drug groups as 'risk medications' was more based on absolute numbers than on the relative incidence of potentially preventable hospital admissions. Furthermore, only ADEs related to prescribing errors were included, since user-related complications would require different kinds of interventions.[9]

Further Analysis and Identification of Risk Factors

According to the IPCI and HARM studies, patients at risk for HARMs are characterized by advanced age, polypharmacy, multiple co-morbidity (four or more), impaired cognition, non-adherence to medication, impaired renal function and/or a dependent living situation.[2,3,6,7] To obtain further information about the epidemiology of the identified ADEs and their risk factors, various literature searches were performed. The initial basic search strategy consisted of searching MEDLINE through online consultation of PubMed from 1 January 2000 up to 31 December 2007 for pertinent articles. Further MEDLINE searches on selected topics were performed in October 2008 and October 2009. Searches usually focused on the Medical Subject Heading (MeSH) of a specific drug or drug group with the qualifier 'adverse effects' (e.g. anti-inflammatory agents, non-steroidal/adverse effects) and/or on the MeSH term for a specific adverse effect with the qualifier 'chemically induced' (e.g. haemorrhage/chemically induced) without ticking the MeSH boxes for "Restrict search to major topic headings only" or "Do not explode this term". This basic approach was supplemented with an incremental search strategy that looked at the bibliography of every useful reference retrieved for additional references and that iterated this procedure if necessary. The identification of risks and risk factors was not only based on randomized, double-blind studies, but also on well designed observational studies, since randomized studies are not necessarily designed to compare the safety of different drug treatments. Furthermore, high-risk patients are often excluded in randomized trials.[10,11]

Identification of Hospital Admissions Related to Medication (HARM)-Reducing Strategies

Following the example of many current guidelines, the Task Force decided to look not only for well proven HARM-reducing strategies but to consider potentially relevant strategies as well. Strategies were particularly identified by searching MEDLINE for combinations of the MeSH terms used in the previous step with the MeSH 'intervention studies' or with the publication type 'Clinical Trial'. This basic approach was supplemented with an incremental search strategy that looked at the bibliography of every useful reference retrieved and that iterated this procedure if necessary, and at current Dutch and international guidelines. In addition, the references retrieved in step 2 were screened for information about risk reduction.

Drawing up Concrete Recommendations

The Task Force developed and executed a structured approach for the drawing up of concrete recommendations on the basis of the previous steps. Firstly, it made its assignment to focus on 'low-hanging fruit' operational by stipulating that it should be feasible and relatively easy to convert each recommendation into a computerized drug safety alert and to build in these alerts into the current decision support systems for safe prescribing and dispensing by general practitioners (GPs), community pharmacists and outpatient clinics. For instance, the Task Force decided to advise against the prescribing of glibenclamide to patients ≥70 years (because the risk of potentially serious hypoglycaemia is relatively high), but it did not draw up concrete recommendations on how to improve the self-management of patients with diabetes mellitus.

This stipulation of easy integration into current prescribing and dispensing systems does not only offer the advantage that the recommendations can be integrated relatively smoothly into daily practice, but also facilitates the structural monitoring of adherence to the recommendations by means of quality indicators (for instance, by measuring over time how often glibenclamide is still being prescribed and dispensed to patients ≥70 years).

As the Task Force recommends a mixture of evidence-based and expert-based risk-reducing strategies, all its recommendations were graded in accordance with the method of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[12-14] The grading was performed independently by three experts (PDS, MW, PvdB). In case of discrepancies, the grading was set in consensus meetings. Each recommendation is provided here with a code that is composed of:

- a number to indicate the power of the recommendation: 1 = strong; 2 = weak;
- a letter for the methodological quality of the underlying evidence: A = high-quality evidence from randomized clinical trials (RCTs) without important limitations or exceptionally strong evidence from observational studies; B = moderate-quality evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence from observational studies; C = low-quality evidence from observational studies with at least one critical outcome, case series or from RCTs with serious flaws or indirect evidence.

For each type of ADE the Task Force analysed, it looked at the literature to find out which risk factors were known to play a significant role so that these factors could be taken into consideration when drawing up recommendations. In each case, the results of the analyses are presented under the separate header of 'Risk factors' in the full report, which is publicly available through our website.[15]

To further enhance acceptance and implementation, the Task Force geared its recommendations as much as possible to existing national and international guidelines.

The Task Force also presented a preliminary draft of its report to various medical and pharmaceutical professional societies in the Netherlands with a request to pass on any constructive criticism. Finally, the Task Force made an effort to minimize unnecessary discrepancies between its separate recommendations (for instance, by preferring the same general age limit of 70 years wherever possible).

Identification of Prominent General Issues

In the course of its work, the Task Force identified several general issues that needed to be addressed in addition to its specific recommendations:

Reduction of Unintentional Rechallenges

Studies have shown that a drug that has been stopped during a hospital stay because of an ADE, is sometimes re-prescribed to the patient after his or her hospital discharge.[16-18] Yet a previous ADE can be an important risk factor for the recurrence of an ADE, if the patient is exposed again to the same medication.[19-22] It is therefore important that the hospital-based specialist does not only pass on to the GP in a clear way *that* the drug has been discontinued in the hospital but also *why* this has happened.

Informing Patients about Alarm Signs and Symptoms

Besides its recommendations to improve computerized prescribing and dispensing, the Task Force would like to demand special attention to the recognition of alarm signs and symptoms by the drug users themselves. The direct reason was that, according to some of the discharge letters that were analysed in the IPCI study, melaena had already been present in the days preceding hospitalization because of gastrointestinal bleeding. Information about alarm signs and symptoms should be presented, of course, very carefully (preferably in the form of oral communication supported by written material)[23] so that patients are not frightened by this information in such a way that they decide on their own not to take the prescribed medication.

Economic Analyses

Although the performance of economic analyses was beyond its assigned scope, the Task Force recognized that some of its recommendations needed to be submitted to formal cost-consequence and cost-effectiveness analyses because they require additional medication (e.g. for gastric protection) or laboratory testing (e.g. creatinine and potassium), which will therefore generate extra costs.

Results

Pooling the IPCI and HARM study results yielded a total of 829 medication-related hospital admissions, of which 367 (44%) had been rated as potentially preventable. When only the prescriber-related problems were taken into consideration, seven types of ADE associated with ten different drug classes accounted for more than half of all these potentially preventable admissions (table I). These results were in line with the results of international studies.[25-27] Gastrointestinal and other bleedings were the most frequent ADE, followed by disturbances of diabetes mellitus control, electrolyte disturbances, fractures, renal insufficiency and heart failure, constipation and bradycardia. These seven ADEs were further analysed, followed by identification of HARM-reducing strategies. This resulted in 9 general and 34 drug-specific recommendations.

General recommendations are summarized in table II and the drug-specific recommendations can be found in table III. To understand how the Task Force reached its drug-specific recommendations and graded these, it is essential to see the underlying analysis of each ADE and potential HARM-reducing strategy in the full report, publicly available on our website.[15]

Table I shows how many recommendations for each ADE were developed, and in which section of the full report they can be found.

Discussion

The HARM-Wrestling Task Force established that seven types of pharmacologically predictable

Table I. Important, potentially preventable ADEs, their corresponding drug classes and their corresponding recommendations[15,24]

Potentially preventable ADEs	No. of cases (%)[a]	Related drug class(es)	Related recommendations in table III	Corresponding section in full report[b]
Gastrointestinal and other bleedings	84 (22.9)	Vitamin K antagonists	1, 2, 3, 4, 5, 6	3
		Platelet aggregation inhibitors	1, 9, 10, 11, 12	3
		NSAIDs	7, 8, 10, 11, 13, 14, 15	3
Disturbances of diabetic control	32 (8.7)	Blood glucose-lowering drugs (mainly hypoglycaemia)	29, 30	5
		Corticosteroids (hyperglycaemia)	31, 32	5
Electrolyte disturbances	30 (8.2)	Diuretics	16, 17, 18	4
		RASI (hyperkalaemia)	16, 19, 20	4
Fractures	26 (7.1)	CNS medications (through falls)	24, 25, 26, 27	5
		Cardiovascular drugs (through falls)	25, 26	5
		Corticosteroids (through osteoporosis)	28	5
Renal failure/heart failure	13 (3.5)	RASI (renal failure)	16, 21, 22	4
		NSAIDs (renal failure and heart failure)	16, 21, 23	4
Constipation	11 (3.0)	Opioids	34	5
Bradycardia	10 (2.7)	Cardiac drugs (sotalol/digoxin)	33	5
Total (out of 367 potentially preventable admissions)	**206 (56.1)**			

a Percentages of all 367 potentially preventable ADEs.

b This column refers to the sections of the full report.[15]

ADEs = adverse drug events; **RASI** = renin angiotensin system inhibitor.

Table II. Summary of general recommendations (reproduced with permission from the Dutch Ministry of Health, Welfare and Sport, and the Royal Dutch Pharmaceutical Association)[15,24]

No.	Recommendation
1	Discussions on the improvement of drug safety in outpatients should not only focus on short-term quick wins, but also on longer-term risk-reducing strategies. Among the subjects, the following are to be considered:[9]
	a) the reduction of potentially preventable HARMs that occur less frequently
	b) the reduction of potentially preventable adverse effects that do not lead to hospital admission
	c) the prevention, screening and reduction of non-adherence to therapy and other user-related problems affecting drug safety
	d) to extend the attention that this review already pays to risk factors and to improve current computerized medication surveillance systems by taking such risk factors (and their mutual interactions) more systematically into consideration. In complex cases, it may be desirable to estimate the patient's individual risk of an adverse drug effect by means of an especially developed risk model[9]
	e) the furthering of adhering to the principles of 'clinical risk management' by healthcare professionals.[28,29] Examples of questions that should be answered in this context are: • Which risk situations and processes need additional attention? • Can high-risk healthcare professionals be identified in addition to high-risk medications, high-risk patients and high-risk processes? • Do healthcare professionals have an adequate culture with respect to drug safety?[30,31] • Is it possible to improve the current prioritization of computerized medication surveillance signals? • What is the optimal way to surveil each individual risk?
	f) The use of new ICT options, such as consultation and application of electronic patient records through connections between the different computer systems of healthcare professionals and institutions in primary and secondary care
	g) Implementation of a centre for the nationwide collection and evaluation of medication errors in outpatients
2	Healthcare professionals should be aware of the fact that a substantial part of the potentially preventable HARMs are associated with a limited number of well known, pharmacologically predictable ADEs associated with a limited number of well established drug classes. They implement risk-reducing strategies in the short term that are specifically aimed at these drug-related problems
3	When an elderly patient uses at least five or more chronic medications, prescribed by different physicians, these prescribers should reach agreement on which physician is the overall director of drug therapy (which is not necessarily the same as assuming all responsibility in the legal sense). They record this overall director in their patient records and also communicate this to the dispensing pharmacist(s) of that particular patient
4	When a risk medication is initiated that is not intended, by definition, for prolonged use (e.g. a vitamin K antagonist, NSAID, opioid, benzodiazepine), the prescriber informs, if possible, any other relevant physician and the dispensing pharmacist about the expected length of this drug therapy, which should then be recorded in the computerized file of that patient. If the expected length of drug therapy cannot yet be established, because it should first become clear whether a drug will have the desired effect (e.g. in the case of an antidepressant), a date is selected on which the effectiveness of the drug therapy is evaluated and on which the expected length of the therapy can be determined
5	When a medical specialist initiates a drug treatment, which is subsequently continued by a GP, both healthcare professionals agree and document who is responsible for periodic controls, re-evaluation, repeat prescriptions and the length of therapy. GPs who take over repeat prescribing from a medical specialist are responsible for these repeat prescriptions unless there is a well documented agreement with the specialist (e.g. in the form of a discharge letter) that the latter remains responsible[32]
6	In elderly patients receiving polypharmacy, physicians and pharmacists periodically evaluate which drugs could or should be continued by means of a medication review. Since elderly patients receiving polypharmacy are not only at risk of overtreatment, but also of undertreatment,[33,34] it should also be assessed whether any essential drug is unjustly missing
	Healthcare professionals are aware that medication reviews are only appropriate for identifying problems that gradually emerge, but that they are less effective for the prevention of HARMs that primarily become manifest within 1–2 weeks after the start or adjustment of a drug treatment
7	The computer systems of the prescribing physicians and dispensing pharmacists should support the implementation of the recommendations in this report as well as possible. If the systems cannot provide adequate support for this implementation, they should be made more suitable for this task. The Task Force particularly has in mind the following: • recording which physician is the overall director of drug therapy, and who is responsible for the indication and expected length of therapy of each risk medication • the recording of laboratory values (such as creatinine, sodium, potassium) in such a way that it allows automatic use in the computerized medication surveillance of patients taking risk medications

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Table II. Contd

No.	Recommendation
	• recording of earlier ADEs, impaired cognition and other risk factors in such a way that it allows automatic use in computerized medication surveillance of patients taking risk medications
	• the identification of complex risk patients and the proposal of potential actions that are desirable in these particular patients
	Computer systems should be designed in such a way that quality control of the execution of specific recommendations can be realized relatively easily[a]
8	When medication is discontinued in hospital because of a significant adverse effect, the physician quickly and adequately informs the patient himself, other physicians and pharmacists who are directly involved in the treatment of the patient. This is preferably communicated through a special note documenting the discontinuation of the drug (e.g. a pharmaceutical discharge letter). The physician should not only communicate which drug is discontinued, but should also provide the motivation and (if relevant) which alternative medication has been selected. Each physician and pharmacist involved documents this information in his computer system in such a way that it allows automatic surveillance to prevent the drug in question, or a closely related one, being accidentally restarted
	When a drug has caused a serious adverse effect but has to be continued in spite of this (e.g. in the case of an antithrombotic drug), the prescriber rapidly and accurately informs the patient himself and other physicians and pharmacists who are directly involved in the drug treatment of that patient
9	If a drug is added to improve safety of a risk medication, the former should be discontinued when the latter is stopped. Software systems should produce an alert when this does not happen

a For instance, an intervention trial has shown that the combination of brief physician education and the generation of computer alerts improves the prescribing of gastroprotection to high-risk NSAID users.[35]

ADEs = adverse drug events; **GPs** = general practitioners; **HARM** = Hospital Admission Related to Medication; **ICT** = information and communications technology.

adverse effects (haemorrhages, disturbances of diabetes mellitus control, electrolyte disturbances, fractures, renal insufficiency and heart failure, constipation and bradycardia) with ten long-existing drug classes (Vitamin K antagonists [VKAs]; platelet aggregation inhibitors [PAIs]; NSAIDs, diuretics, renin angiotensin system inhibitors [RASIs], CNS medications, corticosteroids, blood glucose-lowering drugs, opioids and cardiac drugs [sotalol/digoxin]) were responsible for more than half of all the potentially preventable hospital admissions. As a consequence, clinical drug risk management should focus not only on pharmacovigilance to detect new risks associated with new drugs but also on intervention measures to reduce specific old risks of specific old drugs.

The Task Force drew up 34 specific recommendations to reduce potentially preventable HARMs in a quick-win way. Many of these recommendations were already present in prevailing clinical practice treatment guidelines, so pursuing a rapid reduction of the observed HARMs is more about implementing and reinforcing existing guidelines than about replacing them.[40] The recommendations do not only focus on risk medications, but also on risk patients and risk situations. More often than not, recommendations could not be based on definitive randomized trials but had to be derived from well designed and well performed observational studies and general pharmacological common sense.

Besides specific recommendations, the Task Force identified nine general issues, such as the need to assign one main physician to each complex risk patient, the need to provide timely feedback about actual HARMs from the hospital to general practice (to avoid that patients are injudiciously re-exposed after discharge) and the need to inform patients about first alarm symptoms and signs without frightening them.

Roughly speaking, half of the recommendations of the Task Force are about appropriate prescribing (e.g. giving drugs only on strict indication or adding a protective drug), one-quarter about careful follow-up (e.g. laboratory monitoring and appropriate duration of therapy) and another quarter about adequate communication (with the patient and/or with other healthcare providers). Many of the recommended actions should not be delayed until the next medication review, but should be carried out as soon as a treatment is started or changed.

Both the specific and the general issues can only be implemented if different healthcare parties

Table III. Summary of drug-specific recommendations (reproduced with permission from the Dutch Ministry of Health, Welfare and Sport, and the Royal Dutch Pharmaceutical Association)[15,24]

No.	Recommendation and grade of recommendation[a]
Gastrointestinal and other bleedings (section 3)[b]	
1	Antithrombotic agents are prescribed only on strict indication (Grade 1C). The prescribing physician records this indication and passes it on, together with the intended duration of therapy, to all healthcare professionals who are directly involved in the treatment of the patient. This general recommendation applies particularly when patients are at increased risk of bleeding, e.g. (Grade 1B):
	a) because they have a history of bleeding during antithrombotic therapy
	b) because they will be treated with a VKA plus PAI, or with two PAIs
2	Before starting VKA therapy, the treating physician assesses the risk of irregular use (e.g. due to impaired cognition or alcohol abuse) [Grade 1B]
3	VKA users with a history of bleeding or with an unstable INR with supratherapeutic peaks ≥6 require meticulous monitoring (Grade 1B)
	The physician, who diagnoses a major bleeding in a VKA user, passes this information on to all healthcare professionals who are directly involved in the treatment of the patient (Grade 2C)
	The physician who observes a change in the co-morbidity of a VKA user that requires intensified INR monitoring (e.g. decreased diabetic control or worsening heart failure) passes this information on to the clinic or service that is monitoring the anticoagulation intensity of that patient (Grade 1C). Reversely, the latter informs the healthcare professionals who are directly involved in the treatment of the patient when INR values are unstable with supratherapeutic peaks ≥6 (Grade 1C)
4	When a VKA user starts another medication that is known to give a pharmacokinetic interaction with VKAs, the physician or pharmacist reports this directly to the clinic or service that is monitoring anticoagulation intensity without leaving this to the patient (Grade 1C)
	As the simultaneous use of a VKA with cotrimoxazole produces a considerable increase in INR, and as substitution of cotrimoxazole with another antibacterial agent is almost always feasible, the combination of cotrimoxazole with a VKA should be avoided as much as possible, especially when it would be used for more than 1 day (Grade 1B). An exception may be necessary for VKA users with HIV infection (Grade 2C)
	When a medication that gives a strong pharmacokinetic interaction with VKAs is discontinued in a VKA user, the physician reports this by means of a discontinuation note to the dispensing pharmacist who in turn informs the monitoring clinic or service (Grade 1C)
	Computerized medication surveillance systems should produce an alert when antibiotic treatment is started in a VKA user. Pharmacists should pass this information on directly to the monitoring clinic or service without leaving this to the patient (Grade 1C)
5	Genotyping of *VKORC1* (and cytochrome P450 2C9 in the case of acenocoumarol) should be considered as a diagnostic tool, when the INR response to normal VKA doses is unusually high or when VKA dosage is unusually low in an individual user (Grade 2B)
6	VKA users should be well informed about the risks and management of intercurrent diseases and changes in lifestyle or diet (Grade 1B)
	VKA users at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C)
	Patient self-management is recommended for those VKA users who can perform this adequately after being suitably selected, educated and trained (Grade 2B)
7	If possible NSAIDs are avoided if:
	a) patients are older than 70 years (Grade 1C)
	b) patients have a history of one or more UGIEs (Grade 1B)
	c) patients have a history of diverticular disease or lower gastrointestinal bleeding (Grade 1B)
	d) the addition of the NSAID will result in a high-dose level of the NSAID or in the combination of two different NSAIDs (Grade 1B)
	e) patients will be treated concurrently with a VKA, selective COX-2 inhibitor, systemic corticosteroid, low-dose aspirin, clopidogrel, prasugrel (Grade 1B); heparin/LMWH (Grade 1C); SSRI or spironolactone (Grade 2B)
	f) patients have heart failure, diabetes mellitus (Grade 1B) or severe rheumatoid arthritis (Grade 1C)
	NSAID users who are at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C)
8	Adequate gastric protection by means of a PPI is needed when NSAID users:[c]
	a) have a history of one or more UGIEs (Grade 1B)
	b) are older than 70 years (Grade 1C)
	c) have two or more of the following risk factors (Grade 1C):
	• are 60–70 years of age
	• need long-term treatment with a high-dose level of the NSAID

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Table III. Contd

No.	Recommendation and grade of recommendation[a]
	• are treated simultaneously with another medicine that increases the risk of gastrointestinal complications (VKA, aspirin, clopidogrel, prasugrel, systemic corticosteroid, SSRI, spironolactone, high doses of heparin/LMWH)
	• have serious co-morbidity (such as severe rheumatoid arthritis, heart failure or diabetes)
9	Adequate gastric protection with a PPI is necessary when users of low-dose aspirin:[c]
	a) have a history of one or more UGIEs (Grade 1B)
	b) are at least 60 years of age and treated simultaneously with two or more other medications that increase the risk of gastrointestinal complications (VKA, NSAID, selective COX-2 inhibitor, clopidogrel, prasugrel, high doses of heparin/LMWH, oral corticosteroid, SSRI and/or spironolactone) [Grade 1C]
	c) are at least 70 years of age and are treated simultaneously with one other medication that increases the risk of gastrointestinal complications (VKA, NSAID, selective COX-2 inhibitor, clopidogrel, high doses of heparin/LMWH, oral corticosteroid, SSRI and/or spironolactone) [Grade 1C]
	d) are at least 80 years of age (Grade 1C)
	To err on the safe side of caution, this recommendation also applies to clopidogrel and prasugrel (Grade 1C)
	Users of PAIs who are at increased risk of gastrointestinal bleeding receive oral and written information about its alarm symptoms (Grade 2C)
10	When a gastric protective agent is added to NSAID or low-dose aspirin treatment to reduce the risk of upper gastrointestinal complications, the prescriber and pharmacist inform the patient about the importance of good adherence to this protective therapy (Grade 1C)
	When the NSAID or low-dose aspirin is discontinued, the gastric protective agent should also be discontinued (Grade 1B)
11	When an NSAID or low-dose aspirin is started in a patient with a history of UGIEs (together with a PPI for gastric protection), the patient is tested for the presence of *Helicobacter pylori* as soon as possible and, if necessary, treated with eradication therapy, if the patient has not been tested and treated before (Grade 1B)
12	When a *Helicobacter* negative aspirin user has a history of healed aspirin-associated upper gastrointestinal bleeding, the combination of low-dose aspirin plus a PPI is preferable to clopidogrel without a PPI (Grade 1B)
13	When a selective COX-2 inhibitor is combined with low-dose aspirin, this compromises the relative gastrointestinal safety of the selective COX-2 inhibitor. Consequently, the recommendations for the simultaneous use of aspirin and a non-selective NSAID also apply to the combination of low-dose aspirin and a selective COX-2 inhibitor (Grade 1B)
14	In view of the potential health risks of NSAIDs and aspirin, it is advisable to reclassify current OTC products with an NSAID or aspirin as 'pharmacy only' products. This makes it possible to dispense these products to named users and to enter them into the personal pharmacy record of their users so that they can be systematically taken into account in the medication surveillance programme of the pharmacy computer system (Grade 2B)
15	Selective COX-2 inhibitors are contraindicated for patients with established ischaemic heart disease or stroke and their application in patients with peripheral arterial disease or risk factors for heart disease (such as hypertension, hyperlipidaemia, diabetes and smoking, or peripheral arterial disease) should be kept as low and as short as possible (Grade 1B)
	Non-selective NSAIDs should also be avoided as much as possible in patients with established ischaemic heart disease or stroke. When a non-selective NSAID cannot be avoided, its use should be as low and short as possible. This also applies to the use of non-selective NSAIDs in patients with peripheral arterial disease or risk factors for heart disease (Grade 1B)
Electrolyte disturbances, renal dysfunction and heart failure (section 4)[b]	
16	Patients at increased risk of an electrolyte disturbance (hyponatraemia, hypokalaemia, hyperkalaemia) receive oral and written information about this risk. The information should not only outline the first symptoms of the electrolyte disturbance but also the risk situations that can lead to increased fluid and salt loss (such as infection, vomiting, diarrhoea, physical exertion, high environmental temperature) [Grade 2C]. Vulnerable elderly are monitored more closely, when they are temporarily at increased risk of fluid and salt loss (Grade 2C)
17	When a thiazide diuretic is started, or when its dose level is increased, the sodium level should be checked in the first 5–9 days if (Grade 1C):
	a) the patient is at least 80 years of age
	b) the patient is at least 70 years of age and also uses an SSRI, venlafaxine or a related drug, NSAID, carbamazepine or loop diuretic
	When a thiazide user is at least 70 years of age and starts to use an interacting drug (SSRI, venlafaxine or related drug, NSAID, carbamazepine or loop diuretic), the sodium level should be checked in the first 5–9 days (Grade 1C)
	A thiazide user who is at least 70 years of age requires careful observation (and if necessary supplemented with a check of the sodium level), when an intercurrent disease (such as diarrhoea or vomiting) increases the risk of an electrolyte disturbance (Grade 1C)

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Table III. Contd

No.	Recommendation and grade of recommendation[a]
18	If a potassium-losing diuretic is started, potassium and creatinine levels are checked beforehand if (Grade 1C): a) the patient is at least 70 years of age b) one of the following situations applies: • the potassium-losing diuretic is combined with a potassium-sparing diuretic • there is an increased risk of hypokalaemia or an increased risk from hypokalaemia (e.g. pre-existent hypokalaemia, cardiac arrhythmia or coronary heart disease) • the potassium-losing diuretic is combined with digoxin in the absence of a potassium-sparing agent (RASI, renin inhibitor or potassium-sparing diuretic) Potassium and creatinine levels are checked again within 1–2 weeks after the start of a potassium-losing diuretic and then every year and following every dose increase in any of the following situations (Grade 1C): a) if the patient is ≥80 years of age b) if the patient is ≥70 years of age and uses a combination of a potassium-losing diuretic and a potassium-sparing diuretic c) if the patient is ≥70 years of age and simultaneously uses a potassium-losing diuretic and digoxin in the absence of a potassium-sparing agent (RASI, renin inhibitor or potassium-sparing diuretic) d) if the patient is ≥70 years of age and there is an increased risk of hypokalaemia or an increased risk from hypokalaemia (e.g. pre-existent hypokalaemia, cardiac arrhythmia, coronary heart disease or age ≥70 years)
19	If a RASI or renin inhibitor is started, potassium and creatinine levels are checked beforehand if: a) the patient is at least 70 years of age (Grade 1C) b) there is an increased risk of hyperkalaemia or an increased risk from hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes, renal insufficiency, simultaneous use of a potassium-sparing diuretic [Grade 1B]; simultaneous use of a thiazide diuretic and loop diuretic [Grade 1C]) Potassium and creatinine levels are checked again within 1–2 weeks after the start of the RASI or renin inhibitor and then at least every 6 months and following every dose increase in any of the following situations: a) There is an increased risk of hyperkalaemia or an increased risk from hyperkalaemia (e.g. heart failure, cardiac conduction disorder, diabetes, renal insufficiency, simultaneous use of a potassium-sparing diuretic [Grade 1B]; simultaneous use of a thiazide diuretic and loop diuretic [Grade 1C], age ≥70 years [Grade 1C]) b) Within 1–2 weeks after the addition of a potassium-sparing diuretic to a RASI or renin inhibitor, and after every dose increase of such a potassium-sparing diuretic (Grade 1B)
20	When the user of a RASI is at increased risk of hyperkalaemia,[d] the prescribing of NSAIDs (including COX-2 selective inhibitors) should be avoided if this is in any way possible (Grade 1B)
21	When prescribing a RASI, one should carefully weigh the expected benefits against the increased risk of renal insufficiency, and monitor creatinine level in any of the following situations: • pre-existing renal insufficiency or renal artery stenosis (cave: generalized atherosclerosis) [Grade 1B] • reduced effective circulating volume (cave: heart failure, intercurrent diseases, inadequate fluid intake or aggressive diuresis with a loop diuretic) [Grade 1C] • sepsis (Grade 1C) • simultaneous use of an NSAID (including COX-2 selective inhibitor) or calcineurin inhibitor (ciclosporin, tacrolimus) [Grade 1C]
22	In patients with existing renal insufficiency, one should take into consideration that most ACE inhibitors may further compromise renal function through accumulation of an active metabolite. Dose adjustment is not necessary for fosinopril and for most AT_1 antagonists (with the exception of olmesartan) [Grade 1B]
23	If it is in any way possible, the prescribing of NSAIDs (including selective COX-2 inhibitors) should not only be avoided in cardiovascular risk patients, including patients with heart failure and hypertension (see recommendation 15), but also in the following risk situations (Grade 1B): • a history of renal disease • reduced effective circulating volume (not only in patients with heart failure, but also, for instance, in patients with hepatic cirrhosis, chronic renal insufficiency and dehydration) • simultaneous use of drugs that may also compromise renal function, such as a RASI and/or a diuretic (the combination of these two drugs with an NSAID seems particularly hazardous)

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Table III. Contd

No.	Recommendation and grade of recommendation[a]
	Before prescribing an NSAID to a patient with a history of gout/hyperuricaemia, one should carefully assess the cardiovascular and renal risks because gouty arthritis is often associated with cardiovascular disorders (in which case NSAIDs should preferably be avoided – *cf.* recommendation 15), and because gout/hyperuricaemia has been associated with an increased risk of NSAID-induced renal insufficiency (Grade 1B)
	If an NSAID cannot be avoided in a patient at increased risk, the NSAID should be prescribed as short and as low as possible. Renal function should be checked before and 1 week after the start of the NSAID (Grade 1C). The patient receives oral and written information on how to recognize deterioration (Grade 2C)
Fractures due to fall incidents (section 5.1)[b]	
24	Psychotropic drugs (benzodiazepines and related agents, classical and atypical antipsychotic agents, tricyclic and non-tricyclic antidepressants) may only be started in elderly patients on strict indication (cave combinations) [Grade 1B]
	When patients are ≥70 years of age, the prescriber asks about fall incidents in the past year and assesses (on the basis of direct observation and the medical record) to which extent the patient has impaired mobility. If this assessment shows an increased risk of falling, the risk of fall injury should be examined more closely (Grade 1C)
25	The prescriber assesses periodically, in personal consultation with the elderly patient, whether it is still necessary to continue psychotropic drugs and those cardiovascular drugs that also increase the risk of falling (antiarrhythmic agents type Ia, digoxin, diuretics) (Grade 1B)
	The first reassessment of treatment should take place at 1–2 weeks after starting a benzodiazepine or antipsychotic agent, and at 4–6 weeks after starting an antidepressant (Grade 1C)
	If long-term treatment cannot be avoided, the use of all drugs that increase the risk of falling is reassessed at least annually (Grade 1C)
26	Elderly patients who have fallen repeatedly within 1 year and/or have visited an emergency department because of a fall, qualify for a multifactorial intervention that does not only encompass reconsideration of all drugs, which increase the risk of falling, but also pays sufficient attention to other risk factors (Grade 1C)
27	If a benzodiazepine (or related agent) is used to treat insomnia or anxiety for a longer period, one should try at least once to discontinue therapy by means of a minimal intervention strategy (such as a discontinuation letter or a derivative web application), or by means of gradual dose tapering (Grade 1B)
	If an elderly user does not succeed in complete discontinuation of the benzodiazepine, an attempt should be made to reduce the dose level (Grade 1B)
Fractures associated with glucocorticosteroids (section 5.2)[b]	
28	When a patient uses ≥7.5 mg prednisone equivalents per day for more than 3 months, the addition of a bisphosphonate is recommended in the following situations (Grade 1B):[e] • for doses >15 mg per day: always • for doses of 7.5–15 mg per day: when the patient is a postmenopausal female or a male >70 years of age, or when bone density is abnormally reduced
	Besides the bisphosphonate, an adequate intake of calcium and vitamin D is relevant (Grade 1B)
	The bisphosphonate is continued for as long as the corticosteroid therapy is continued, for a maximum of 5 years (Grade 1C)
	After discontinuation of the corticosteroid, the bisphosphonate can also be discontinued, unless the risk profile is still increased (Grade 1C)
	When a glucocorticoid is used in high intermittent doses of ≥15 mg prednisone equivalents per day, protective therapy should be emphatically considered, when the total cumulative exposure of the patient exceeds 1 g prednisone equivalents (Grade 2B)
Loss of diabetic control associated with blood glucose-lowering agents (section 5.3)[b]	
29	It is not advisable to prescribe glibenclamide to patients ≥70 years because the risk of a potentially serious hypoglycaemia is relatively high (Grade 1B)
30	Users of oral blood glucose-lowering sulfonylurea derivatives should be informed about the risks of unusual physical exercise, an irregular dietary pattern or reduced food intake, and also about how to manage these risks (Grade 2C)
	They should also receive oral and written information about the first symptoms of hypoglycaemia, especially when they are at increased risk of hypoglycaemia (e.g. because of renal insufficiency or a potential drug-drug interaction) [Grade 2C]
Loss of diabetic control associated with glucocorticosteroids (section 5.4)[b]	
31	When a glucocorticoid therapy with ≥7.5 mg prednisone equivalents per day is started, the blood glucose level should be checked (unless treatment consists of a single injection) [Grade 1C]. If necessary, blood glucose-lowering treatment is initiated or adapted under

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Table III. Contd

No.	Recommendation and grade of recommendation[a]
	guidance of these test results. In more severe cases of hyperglycaemia, insulin is preferable to an oral blood glucose-lowering agent (Grade 1C). Patients are advised to be attentive to symptoms of hyperglycaemia (thirst, dry mouth, increased diuresis, fatigue) and to consult their physician if necessary (Grade 2C) When there is no evidence that the patient has diabetes, the glucose level is checked before therapy is started and 3–7 days after its start. When a risk factor is present (e.g. a renal disease or a high corticosteroid dose of ≥15 mg prednisone equivalents per day) one or more additional checks should be considered (Grade 2C)
	When the patient is known to have diabetes or develops hyperglycaemia during corticosteroid use, it is advisable to check the glucose level more frequently (every 1–2 weeks at the beginning of therapy) [Grade 2C]
32	When blood glucose-lowering treatment has been started or adapted because of glucocorticoid-induced hyperglycaemia, the risk that hypoglycaemia may develop when corticosteroid treatment is again discontinued should be considered (Grade 1A)
	Bradycardia associated with digoxin and/or sotalol (section 5.5)[b]
33	When digoxin and/or sotalol are given to elderly users, risk factors for the development of bradycardia should be carefully considered: • renal function should be checked before the start of treatment, before each dose increase, and subsequently at least once a year (Grade 1B) • combinations with other cardiovascular agents that can enhance their effects (such as verapamil and diltiazem) should only be given on strict indication (Grade 1B) • sotalol should only be combined with another β-blocker on strict indication (Grade 1B) • the risk of drug-drug interactions between digoxin and potentiating non-cardiovascular drugs (macrolides, itraconazole, ketaconazole) should be carefully controlled (Grade 1B) • when digoxin is added to a potassium-losing diuretic without the addition of a potassium-sparing agent (RASI, potassium-sparing diuretic), the potassium level should be checked before the start of therapy, before each increase in dose, and subsequently at least once a year (Grade 1C)
	Severe constipation associated with opioids (section 5.6)[b]
34	Each opioid user should be simultaneously treated with a laxative, except when there is a good reason not to do so (e.g. a joint decision by prescriber and patient to effectuate this measure not immediately). In such cases, the prescriber records the specific reason and periodically reassesses the need for a laxative (Grade 1C)
	The prescriber who selects an osmotic laxative (e.g. lactulose or macrogol) as monotherapy regularly enquires whether this agent is effective and adds a contact laxative (e.g. sennosides or bisacodyl) if necessary (Grade 1C)

a Recommendations are graded according to the system of the GRADE Work Group.[12-14] Each recommendation is provided with a code that is composed of a number to indicate the power of the recommendation (1 = strong; 2 = weak) and a letter for the methodological quality of the underlying evidence (A = high-quality evidence from RCTs without important limitations or exceptionally strong evidence from observational studies; B = moderate quality evidence from RCTs with important limitations [inconsistent results, methodological flaws, indirect or imprecise], or very strong evidence from observational studies; C = low-quality evidence from observational studies with at least one critical outcome, case series or from RCTs with serious flaws or indirect evidence).

b The section numbers refer to the sections of the full report.[15]

c It is advisable to submit these recommendations for further cost-effectiveness analyses as they are only based on clinical considerations. One has to realize that lower gastrointestinal complications cannot be prevented by the addition of a gastric protective agent.

d Risk factors for hyperkalaemia during RASI use are:[36] advanced age (when users continue a RASI in spite of hyperkalaemia, an age above 70 years is a significant risk factor for the development of serious hyperkalaemia);[37] chronic kidney disease (particularly if the glomerular filtration rate is <30 mL/min); co-morbidities (heart failure, diabetes mellitus); hypovolaemia (cave intercurrent acute events that may lead to dehydration);[38] co-medications (non-selective NSAIDs, COX-2 selective inhibitors, β-blockers, calcineurin inhibitors [ciclosporin, tacrolimus], heparin, ketoconazole, potassium-sparing diuretic, trimethoprim, pentamidine); potassium supplements (including salt substitutes and certain herbs rich in potassium [such as noni juice (*Morinda citrifolia*), alfalfa (*Medicago sativa),* dandelion (*Taraxacum officinale),* horsetail *(Equisetum arvense)* and nettle *(Urtica dioica)*].

e It is recommended the BMD be measured in all other patients who will be treated for more than 3 months with ≥7.5 mg PE. Patients with a Z-score lower than −1 or a T-score lower than −2.5 should be treated with a bisphosphonate.[39]

AT_1 = angiotensin 1; **BMD** = bone mineral density; **COX-2** = cyclooxygenase-2; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **INR** = international normalized ratio; **LMWH** = low molecular weight heparin; **OTC** = over-the-counter; **PAI** = platelet aggregation inhibitor; **PE** = prednisone equivalents; **PPI** = proton pump inhibitor; **RASI** = renin angiotensin system inhibitor; **RCT** = randomized clinical trial; **SSRI** = selective serotonin reuptake inhibitor; **UGIE** = upper gastrointestinal event; **VKA** = vitamin K antagonist.

recognize their importance and stimulate better communication between healthcare professionals.

Although the Netherlands is a country with a high level of computerized information in community pharmacies and GP practices, we still identified a clear need to expand and improve current software systems to support the comprehensive implementation of our recommendations (see table II, particularly recommendation 7). It is obvious that the availability of hardware and software systems in other countries will be an important general determinant of how manageable it will be to organize computer support for the implementation of our recommendations there.

Limitations

To identify the most relevant ADEs, we combined data from the IPCI and HARM studies, even though these studies had used different methods of data collection. In the IPCI study, a single research team retrospectively gathered data from electronic medical records of GPs and hospital discharge letters. The quality of these data thus depended directly on the quality of these data sources.[3] In the HARM study, 21 researchers in 21 different hospitals prospectively performed the inclusion of patients on the basis of a preconceived trigger list, which may have led to incompleteness of and variability in the selection of patients.[6] Despite such differences, we considered it acceptable to combine the IPCI and HARM cases because both studies closely followed each other in time, looked at unplanned, potentially drug-related hospitalizations in a representative population of Dutch outpatients and applied similar approaches for the systematic assessment of causality and avoidability. By combining their results, we obtained a more robust number of cases (although admittedly the contribution of the HARM study was substantially larger than that of the IPCI study). The combination of study results may also have reduced, to some extent, the selection and information bias of the individual original studies. For instance, while the IPCI way of data retrieval tended to miss over-the-counter (OTC) use, the HARM researchers specifically enquired whether patients had been using NSAIDs or aspirin on their own initiative. Conversely, the discharge letters from the IPCI study were often more rich in detail than the crude tabulated data we received from the HARM researchers.

Implementation

Although economic analyses were beyond the assigned scope of the Task Force, the time has come to vigorously execute implementation strategies that are as much evidence-based as possible; to target barriers to change and their underlying causes; to recognize and distinguish risk medications, risk patients, risk processes and risk healthcare providers; and to consider that different prescribers may require different methods of implementation.[41] It should be emphasized that many of the recommended actions cannot be postponed until the next medication review but should already be carried out as soon as a treatment is started or changed.[40] Although these recommendations are especially developed to reduce hospital admissions related to medication in outpatients, it may be clear that many of the recommendations are also valid for hospitalized patients.

The beneficial and adverse effects of the recommended interventions should be monitored, not only to assess the progress of implementation but also to increase our current evidence base. When interpreting the results of monitoring, it is not realistic to expect total success since individual HARMs may be less preventable in practice than in theory. Moreover, prescribers may have a sound reason to disregard advice in an individual patient. If this is the case, the reason for the deviation should be recorded to facilitate transfer of patient data, to advance quality assessment and to enrich future scientific analyses.[40]

Conclusions

Two independent studies (the IPCI study and the HARM study) have shown that 5.1–5.6% of all unplanned hospital admissions in the Netherlands are medication related.[2,3,6,7] Pooling of their data yielded a total of 829 HARMs, of which 44% were judged as potentially preventable.

Seven types of pharmacologically predictable adverse effects with ten long-existing drug classes were identified. Thirty-four drug-specific recommendations and nine general issues were developed. More often than not, recommendations could not be based on definitive randomized trials but had to be derived from well designed observational studies and general pharmacological common sense.

More than 50% of the potentially preventable HARMs are associated with ten well known old drug classes. As these HARMs constitute a significant public health problem, the Task Force underlines the need to implement its recommendations into current clinical practice.

Further research is still needed to assess the cost consequences and cost effectiveness of some recommendations, and to monitor the implementation of the recommendations and their effect on the incidence of potentially preventable HARMs.

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Peter De Smet contributed to conception and study design. Patricia van den Bemt and Miriam Sturkenboom provided access to the anonymized crude data of the HARM and IPCI studies. Margaretha Warlé-van Herwaarden and Peter De Smet combined these into a single database and used it for further analysis. Peter De Smet collected and aggregated the background literature. The Task Force (including Patricia van den Bemt, Miriam Sturkenboom, Margaretha Warlé-van Herwaarden, Cees Kramers and Peter De Smet) interpreted the data and developed the recommendations. All authors contributed to the drafting of the manuscript and approved the final version of the report.

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Correspondence: Professor *Peter A.G.M. De Smet*, IQ Healthcare, Radboud University Nijmegen Medical Centre, Geert Grooteplein 21, 6525 EZ Nijmegen, the Netherlands. E-mail: pdesmet@knmp.nl