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Protocol for evaluating the safety and dosing of drugs in patients with liver cirrhosis

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PROTOCOL FOR EVALUATING THE SAFETY AND DOSING OF DRUGS IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Introduction: Liver cirrhosis can have a major impact on drug pharmacokinetics and pharmacodynamics. Cirrhotic patients often suffer from potentially preventable adverse drug reactions. Guidelines on safe prescribing for these patients are lacking. The aim of this study is to develop a systematic method for evaluating the safety and optimal dosage of drugs in patients with liver cirrhosis.

Methods and analysis: For each drug, a six-step evaluation process will be followed. (1) Available evidence on the pharmacokinetics and safety of a drug in patients with liver cirrhosis will be collected from the Summary of Product Characteristics (SmPC) and a systematic literature review will be performed. (2) Data regarding two outcomes namely; pharmacokinetics and safety, will be extracted and presented in a standardized assessment report. (3) A safety classification and dosage suggestion will be proposed for each drug. (4) An expert panel will discuss the validity and clinical relevance of this suggested advice. (5) Advices will be implemented in all relevant Clinical Decision Support Systems in the Netherlands and published on a website for patients and health care professionals. (6) The continuity of the advices will be guaranteed by a yearly check of new literature and comments on the advices. This protocol will be applied in the evaluation of a selection of drugs: (A) drugs used to treat (complications of) liver cirrhosis, and (B) drugs frequently prescribed to the general population.

Ethics and dissemination: Since this study does not directly involve human participants, it does not require ethical clearance. Besides implementation on a website and in clinical decision support systems, we aim to publish the generated advices of one or two drug classes in a peer-reviewed journal and at conference meetings.

Strengths and limitations of this study

- This is the first protocol describing a six-step method to develop advices about the safety of drugs in patients with liver cirrhosis. The first four steps involve gathering evidence and an

assessment by an expert panel. Step five and six consist of implementing prescribing advice in all relevant clinical decision support systems in The Netherlands and regularly updating the advices.

- We have designed a safety classification to support health care providers and patients to efficiently judge drug safety in liver cirrhosis
- A potential limitation of this protocol is the number of published studies available concerning the use of drugs in patients with liver cirrhosis. However, the combination with expert opinion will make it possible to give specific advices.

INTRODUCTION

Liver cirrhosis is a slowly progressive disease characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules. Liver cirrhosis results from ongoing inflammation of the liver.[1] Clinical symptoms ensue because the hepatic architecture is affected which results in increased vascular resistance in the liver and portal hypertension.[1] Liver cirrhosis has an important impact on health care worldwide. In 2010, more than one million people died of liver cirrhosis, which was almost 2% of global deaths.[2,3] The Child-Pugh score classifies the severity of liver cirrhosis and predicts mortality.[4] It is also recommended by the medicine registration authorities in Europe and the United States for use in pharmacokinetic studies.[5,6]

The liver is the main organ for metabolism and detoxification of endogenous and exogenous substances. Several pathophysiological changes that occur in liver cirrhosis influence this detoxification of exogenous substances, i.e. drug pharmacokinetics.[7-9] Portal vein shunting increases oral absorption of some drugs through a bypass of the liver. Decreased plasma protein synthesis causes lower plasma protein concentrations and possibly a higher fraction of unbound drug. A reduction or impairment of drug-metabolizing enzymes in the liver may cause reduced metabolism. These changes often result in an elevated drug exposure, possibly causing side effects and toxicity.[7-9] It is also important to consider changes in pharmacodynamics. Hence, the efficacy of drugs could be different in patients with liver cirrhosis. Moreover, cirrhotic patients are more vulnerable to certain adverse drug reactions (ADRs), such as effects on coagulation or nephrotoxicity.[7,8]

In patients with liver cirrhosis 20% of drugs is dosed incorrectly and almost 30% of cirrhotic patients suffer ADRs.[10] It is estimated that nearly 80% of these ADRs could be prevented.[10] What is missing are guidelines on safe prescribing for those patients. Although there are reviews available summarizing the literature on this topic,[11,12] these get outdated and do not follow a systematic procedure.

This study wants to address this problem by developing advices for the safe use of medications in patients with liver cirrhosis. To guarantee the quality of these advices, it is important that the method for evaluating is performed in a uniform, transparent manner leading to a standardized report.[13] Furthermore, advices need to be manageable by health care professionals.[13] We intend to develop concrete and up-to-date advices to prevent alert fatigue and dissatisfaction by health care professionals. The aim of this study is to describe the systematic method used for evaluating the safety and optimal dosage of drugs in patients with liver cirrhosis.

METHODS

Six steps will be performed for evaluating a drug (Figure 1). Below, the six steps are described in detail. Step 1-3 will be performed by a pharmacist with experience in the evaluation of drug safety in the context of clinical decision support systems (RW). The critical steps are checked by a pharmacist/epidemiologist (SB).

Figure 1. Flowchart of the six-step process used per drug for evaluating the safety and optimal dosage in liver cirrhosis

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Step 1: Collection of evidence

Summary of Product Characteristics (SmPC)

Information concerning the pharmacokinetics of the drug in healthy volunteers and patients with liver cirrhosis will be collected from the official Product Characteristics as published by the responsible authorities EMA, FDA, and the Medicines Evaluation Board (MEB) in the Netherlands. For products registered by the EMA, the European Public Assessment Report (EPAR) will be searched on information about dosage in liver cirrhosis. Special warnings regarding the safety of the drug in patients with liver cirrhosis will also be collected.

Literature search in electronic databases

The search in electronic literature databases aims to review published literature about the alterations in pharmacokinetic parameters and the safety of the drug in patients with liver cirrhosis. Criteria for inclusion in the literature review are: (1) the study investigates patients with liver cirrhosis, (2) the study concerns the drug of interest, and (3) the outcome of the study is safety (i.e. adverse events) and/or (altered) pharmacokinetics. Studies with and without a control group will be included. If a drug is compared to another intervention, data about the control group will be included in the data extraction.

Exclusion criteria are: (1) animal studies, (2) cellular and molecular research, (3) studies in patients with other hepatic diseases, such as hepatocellular carcinoma, non-alcoholic fatty liver disease or primary biliary cholangitis that do not mention the inclusion of a subpopulation with liver cirrhosis and (4) studies about drug-induced liver injury in patients without liver cirrhosis.

PubMed + EMBASE

These databases will be searched (this includes reviews published by the Cochrane library) by the search strategy outlined in Table 1. A more specific search will be performed if there is excessive literature. In this case, a stepwise search strategy will be used starting with PubMed as database. Filters that indicate studies with a high level of evidence will be used to limit the number of studies. The pharmacists responsible for the collection of evidence will judge whether sufficient data are collected to answer the research question and will discuss this with the expert panel.

Table 1. Proposed search strategy for PubMed and Embase

Database	Search query
PubMed	("Liver cirrhosis"[Mesh] OR cirrho*[ti] OR "hepatic impairment"[ti] OR "liver impairment"[ti] OR "hepatic dysfunction"[ti] OR "liver dysfunction"[ti] OR "hepatic insufficiency"[ti] OR "liver insufficiency"[ti]) AND ("X"[Mesh] OR "X"[tiab]) AND "humans"[MeSH Terms]
Embase	'liver cirrhosis'/exp OR cirrho*:ti OR 'hepatic impairment':ti OR 'liver impairment':ti OR 'hepatic dysfunction':ti OR 'liver dysfunction':ti OR 'hepatic insufficiency':ti OR 'liver insufficiency':ti AND ('X'/exp OR 'X':ab,ti) AND [humans]/lim

X= name of drug to be evaluated.

Citation tracking

Additional articles will be obtained through citation snowballing to locate primary sources.

Step 2: Data extraction and presentation

The following characteristics of included studies will be extracted: study design, number and characteristics of included patients and controls (e.g. severity of liver cirrhosis) and details on the intervention.

Concerning the outcome(s), the following data will be extracted:

- (altered) Pharmacokinetics: data on pharmacokinetic parameters (e.g. Area Under the Curve (AUC), elimination half-life and steady state concentration) of the drug in patients with liver cirrhosis, preferably compared with subjects without liver cirrhosis.
- Safety: data on the number of adverse events observed during use of the drug in cirrhotic patients and on the consequences of these adverse events (e.g. discontinuation of treatment, dose reductions), preferably compared with subjects without liver cirrhosis.

Data will be reported in summary tables for each outcome and sorted by level of evidence. The level of evidence of each study will be assessed according to the criteria for treatment harms of the Oxford Centre for Evidence-Based Medicine.[14] In a separate table, narrative reviews will be included as level 5 evidence to reflect on published expert opinions.

All data will be summarized in an assessment report. This standardized report will contain:

- Data from the SmPC
- Details on the electronic database search (search strategy, study selection process in a flowchart)
- Summary tables with pharmacokinetic and safety data
- References

Step 3: Classification and suggested dose

All information from the report will be used to suggest a safety classification and a dose per individual drug, if applicable sorted by severity of liver cirrhosis. The severity will be expressed using the Child-Pugh classification.[4]

Safety classification

To support health care providers and patients to efficiently judge drug safety in liver cirrhosis, we designed a safety classification (Table 2). For drugs in liver cirrhosis we will use the following categories: safe, no additional risks known, additional risks known, unsafe and unknown. Drugs that have not been evaluated are placed in the category 'not yet classified'.

Table 2. Safety classification of drugs used in liver cirrhosis

	Description	Action
Safe	The drug has been evaluated in patients with liver cirrhosis, and no increase in harm was found. The safety of the drug is supported by pharmacokinetic studies and/or safety studies over a long period. It might be necessary to use an adjusted dose.	This drug can be used by patients with liver cirrhosis.
No additional risks known	Limited data suggest that this drug does not increase harm in patients with liver cirrhosis in comparison with persons without cirrhosis. Drugs estimated as 'minor influenced by cirrhosis' based on pharmacokinetics* can also be classified in this category if the expert panel agrees. It might be necessary to use an adjusted dose.	The drug can be used in patients with liver cirrhosis. Adverse drug reactions need to be monitored.
Additional risks known	Limited data suggest an increase in patient harm in patients with cirrhosis compared with persons without cirrhosis. However, the number of studies is limited and/or the studies show contradicting results about the safety in patients with liver cirrhosis.	This drug should preferably not be used in patients with liver cirrhosis if there is a safer alternative available. Adverse drug reactions need to be monitored.
Unsafe	Data indicate this drug is not safe in patients with liver cirrhosis.	This drug should be avoided in patients with liver cirrhosis.
Unknown	For this drug insufficient data are available to evaluate the safety in patients with liver cirrhosis.	This drug should preferably not be used in patients with liver cirrhosis if there is a safer alternative available. Individual judgement of therapeutic need vs. additional risks in patients with liver cirrhosis. Adverse drug reactions need to be monitored.
Not yet classified	The drug has not been evaluated for safety in patients with liver cirrhosis.	No advice for action can be given

** Drugs are classified as 'minor influenced by cirrhosis' if they are cleared less than 20% by the liver.*[5]

Suggested dose

Pharmacokinetic data will be used to judge whether a dose adjustment is necessary in cirrhotic patients. It applies for most drugs that if the AUC is more than doubled, a dose reduction will be recommended.[5] Exceptions are for instance drugs that do not have a concentration-effect relationship or drugs with a small therapeutic range.

Step 4: Discussion and conclusion by the expert panel

An expert panel will evaluate the validity and clinical relevance of the initial classification, the suggested dose and the data extraction. Comments and opinions of the panel will be added to the initial report. The final report is a combination of the available evidence and expert opinions. The expert panel will conclude by consensus. If there are different interpretations within the expert panel, these will be included as 'expert comments' in the assessment report.

The expert panel consists of the following specialists: the pharmacist responsible for the data collection, extraction and initial evaluation (RW), two hepatologists (JD, HM), a clinical pharmacokinetics assessor of the Medicines Evaluation Board (MM), a general practitioner (MB), two hospital pharmacists (DB, NH), a clinical pharmacologist (DB), a community pharmacists (SvP) and two pharmacists working with the two national drug databases in the Netherlands (Pharmabase and G-Standard: MK, SB). Each expert has specific expertise in the treatment of patients with liver cirrhosis, in clinical pharmacology and/or the implementation of the outcomes. The general practitioner and community pharmacist will contribute to the implementation from the perspective of primary care. The pharmacists working for the national drug databases will assure that the advices can be implemented in clinical decision support systems.

Step 5: Implementation

Advices about the safety of a drug and the optimal dosage in patients with liver cirrhosis will be implemented in the two national drug databases in the Netherlands (Pharmabase and G-Standard).

This will generate specific alerts for health care professionals when they prescribe a drug with risks to a patient with liver cirrhosis. The advices will be published on a website available for patients and health care professionals. In both sources, a summary will be included to support the health care provider and describe background information of the advice. The full assessment report can be accessed through a hyperlink.

Step 6: Continuity

To assure up-to-date advices, literature searches will be saved and checked yearly for relevant literature. Comments from patients and professionals using the guidelines will be reviewed and included, if applicable. The expert panel will check yearly if the advices need to be up-dated based on their specific (clinical) expertise.

Drugs to be evaluated

A selection of drugs will be evaluated: (A) drugs used to treat (complications of) liver cirrhosis, such as ursodeoxycholic acid and beta-blockers and (B) drugs that are prescribed frequently to the general population, such as antibiotics and analgesics. An overview of the drugs that will be evaluated in this study is presented in Table 3.

Table 3. Drugs to be evaluated in the current study

Box A: drugs to treat (complications of) liver cirrhosis[15-20]		**Box B: most frequently used drugs in the general population***
Indication	**Drug (class)**	**Drug (class)**
Metabolic syndrome	Insulins	*Analgesics*
	Oral antidiabetics	Paracetamol
Dyslipidemia	Antilipemics	NSAIDs
(anti) Hepatitis B (anti) Hepatitis C	Nucleos(t)ide analogues	Opioids
	Interferon	*Antibiotics*
	Direct-acting antivirals	Tetracyclines
Primary biliary cholangitis/ autoimmune hepatitis	Corticosteroids	Sulfonamides and trimethoprim
	Ursodeoxycholic acid	Macrolides
	Azathioprine	Other antibiotics
	Mycophenolate mofetil	*Gastro-intestinal drugs*
Infections	Chinolons	Antacids
	Penicillins	H_2-receptor antagonists
Esophageal varices	Proton pump inhibitors	Propulsives
Portal hypertension	Beta blocking agents	Stimulant laxatives
Hepatorenal syndrome	Terlipressin	Bulk-forming laxatives
Ascites	Diuretics	*Cardiovascular drugs*
	Albumin	Antithrombotics
Hepatic encephalopathy	Osmotic laxatives	Calcium antagonists
	Rifaximin	RAS-inhibitors

* Based on number of users of prescribed drugs in the Netherlands according to the GIP-database 2013 (www.gipdatabank.nl).

DISCUSSION

We have developed a systematic method to evaluate the safety and optimal dosage of drugs in patients with liver cirrhosis. This method will produce a standardized assessment report per drug. It is important that this report contains the information health care professionals need for clinical decision making. To our knowledge, there are no studies available investigating the information needs of health care professionals to manage drug safety in patients with specific diseases, such as liver cirrhosis. In the development of an assessment report, we were inspired by a checklist that identifies the most important elements that should be included in drug-drug interaction management guidelines.[13] One of the main domains of the checklist was the 'management strategy'. We designed a safety classification to help health care professionals to efficiently judge the safety of a drug in a patient with cirrhosis. Safety classifications are used in other conditions where careful consideration is needed to judge the safety of a drug, such as Long QT-Syndrome,[21] porphyria[22] and pregnancy/lactation.[23] All classifications have in common that the number of categories is limited,

that a description is available why drugs are classified in a certain category, and that a category can be related to an advice towards a health care provider. We think our safety classification results in concrete advices and thereby preventing dissatisfaction and alert fatigue of health care professionals.

Strengths of our study are the combination of evidence from the literature and expert opinion, the implementation in clinical decision support systems and the continuity. First, the published evidence of drugs in liver cirrhosis is variable, and studies often have a limited scope or a selective patient population. Combination with expert opinion adds the clinical and pharmacological experience to the published literature. This combination will make it possible to give specific advices, which is even more relevant in case little published literature is available. Second, the advices will be implemented in the two main clinical decision support systems in the Netherlands, automatically reaching all hospitals, community pharmacies and general practices. Health care professionals will receive a notification if a contra-indicated drug is prescribed or dispensed to a patient with liver cirrhosis. This implementation can quickly result in a huge improvement in the medication safety of cirrhotic patients in the Netherlands. We believe that this Dutch approach of monitoring the safety of drug use is unique,[24] and hope to inspire others to implement this in their health care systems. Third, to safeguard continuity, it is important that this guideline will be updated regularly and that these updates will be included in new signals. The advices will get updated yearly if there is new literature or if we receive comments. This is a major advantage in comparison to all reviews published on this topic.

We expect that we will not perform a standard systematic review for all drugs.[25] Albumin, for example, has been safely used for a long period of time in patients with liver cirrhosis and many studies have been published, also in patients with liver cirrhosis. In this case, we will include literature from the highest level of evidence and stop extracting if we have sufficient information to

classify the drug. The expert panel will also decide whether sufficient information is collected to classify the drug. Another limitation is that we will evaluate a restricted number of drugs in this study. Future research can enlarge the amount of drugs evaluated. Also, this study will expose knowledge gaps in current literature with respect to the pharmacokinetics and safety of certain drugs in liver cirrhosis. Specific pharmacokinetic or pharmacodynamic studies can possibly fill this gap. Another interesting future research area is the implementation; Are patients and health care professionals using our website and getting the information they need? Do health care professionals follow our advices? And ultimately, does our study results in optimization of medication use, i.e. reduction in the number of adverse drug events experienced by liver cirrhosis patients?

In conclusion, this protocol describes a method to evaluate the safety and optimal dosage of drugs in patients with liver cirrhosis. This will lead to advices concerning the safety and optimal dosage of the drugs mostly used in liver cirrhosis and will reveal gaps in literature for future research.

ETHICS AND DISSEMINATION:

Since this study does not directly involve human participants, it does not require ethical clearance. The advices generated by the method described in this study will be published on a website and in two drug databases (see Implementation). We also aim to publish the generated advices of one or two drug classes in a peer-reviewed journal and at conference meetings.

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Contributions:

RW and SB wrote and drafted the protocol. MB, JD, NH, HM and SB contributed for an application for study funding. All authors contributed to the development of the study protocol and read and approved the final manuscript.

Competing interests statement:

RW: none to declare

MB: none to declare

DB: David Burger has received research grants from BMS, MSD and ViiV and has performed teaching for Abbvie, BMS, Gilead, MSD and ViiV, outside the submitted work.

JD: Joost Drenth has received research grants from Abbvie and Janssen and has been a member of advisory boards of AbbVie, BMS, Gilead, Janssen, and Merck, outside the submitted work.

NH: none to declare

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KT: none to declare

SD: none to declare

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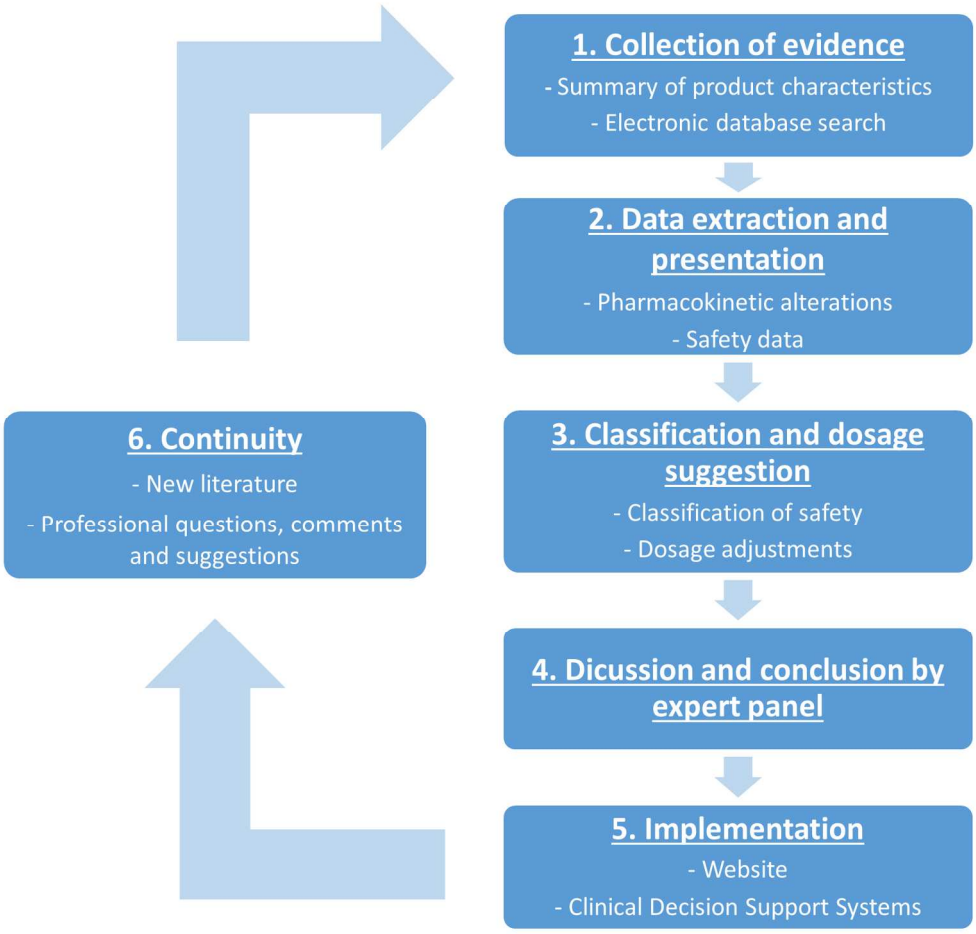

Figure 1. Flowchart of the six-step process used per drug for evaluating the safety and optimal dosage in liver cirrhosis

162x155mm (300 x 300 DPI)

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Evaluating the safety and dosing of drugs in patients with liver cirrhosis by literature review and expert opinion: a study protocol

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EVALUATING THE SAFETY AND DOSING OF DRUGS IN PATIENTS WITH LIVER CIRRHOSIS BY LITERATURE REVIEW AND EXPERT OPINION: A STUDY PROTOCOL

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ABSTRACT

Introduction: Liver cirrhosis can have a major impact on drug pharmacokinetics and pharmacodynamics. Cirrhotic patients often suffer from potentially preventable adverse drug reactions. Guidelines on safe prescribing for these patients are lacking. The aim of this study is to develop a systematic method for evaluating the safety and optimal dosage of drugs in patients with liver cirrhosis.

Methods and analysis: For each drug, a six-step evaluation process will be followed. (1) Available evidence on the pharmacokinetics and safety of a drug in patients with liver cirrhosis will be collected from the Summary of Product Characteristics (SmPC) and a systematic literature review will be performed. (2) Data regarding two outcomes namely; pharmacokinetics and safety, will be extracted and presented in a standardized assessment report. (3) A safety classification and dosage suggestion will be proposed for each drug. (4) An expert panel will discuss the validity and clinical relevance of this suggested advice. (5) Advices will be implemented in all relevant Clinical Decision Support Systems in the Netherlands and published on a website for patients and health care professionals. (6) The continuity of the advices will be guaranteed by a yearly check of new literature and comments on the advices. This protocol will be applied in the evaluation of a selection of drugs: (A) drugs used to treat (complications of) liver cirrhosis, and (B) drugs frequently prescribed to the general population.

Ethics and dissemination: Since this study does not directly involve human participants, it does not require ethical clearance. Besides implementation on a website and in clinical decision support systems, we aim to publish the generated advices of one or two drug classes in a peer-reviewed journal and at conference meetings.

Strengths and limitations of this study

- This is the first protocol describing a six-step method to develop advices about the safety of drugs in patients with liver cirrhosis. The first four steps involve gathering evidence and an

assessment by an expert panel. Step five and six consist of implementing prescribing advice in all relevant clinical decision support systems in The Netherlands and regularly updating the advices.

- We have designed a safety classification to support health care providers and patients to efficiently judge drug safety in liver cirrhosis
- A potential limitation of this protocol is the number of published studies available concerning the use of drugs in patients with liver cirrhosis. However, the combination with expert opinion will make it possible to give specific advices.

INTRODUCTION

Liver cirrhosis is a slowly progressive disease characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules. Liver cirrhosis results from ongoing inflammation of the liver.[1] Clinical symptoms ensue because the hepatic architecture is affected which results in increased vascular resistance in the liver and portal hypertension.[1] Liver cirrhosis has an important impact on health care worldwide. In 2010, more than one million people died of liver cirrhosis, which was almost 2% of global deaths.[2,3] The Child-Pugh score classifies the severity of liver cirrhosis and predicts mortality.[4] It is also recommended by the medicine registration authorities in Europe and the United States for use in pharmacokinetic studies.[5,6]

The liver is the main organ for metabolism and detoxification of endogenous and exogenous substances. Several pathophysiological changes that occur in liver cirrhosis influence this detoxification of exogenous substances, i.e. drug pharmacokinetics.[7-9] Portal vein shunting increases oral absorption of drugs with a high hepatic extraction ratio through a bypass of the liver. Decreased plasma protein synthesis causes lower plasma protein concentrations and possibly a higher fraction of unbound drug. A reduction or impairment of drug-metabolizing enzymes in the liver may cause reduced metabolism. These changes often result in an elevated drug exposure, possibly causing side effects and toxicity.[7-9] It is also important to consider changes in pharmacodynamics. Hence, the efficacy of drugs could be different in patients with liver cirrhosis. Moreover, cirrhotic patients are more vulnerable to certain adverse drug reactions (ADRs), such as effects on coagulation or nephrotoxicity.[7,8]

In patients with liver cirrhosis 20% of drugs is dosed incorrectly and almost 30% of cirrhotic patients suffer ADRs.[10] It is estimated that nearly 80% of these ADRs could be prevented.[10] There are studies available describing the pharmacokinetic alterations for a wide range of drugs in cirrhotic patients.[8,10-14] All these studies are of great value and can be very useful for healthcare professionals. However, they can be difficult to obtain and interpret for a busy health care professional not frequently dealing with cirrhotic patients. What is missing is the translation of all literature into a,

regularly updated, and easy manageable source of information on safe prescribing in patients with liver cirrhosis.[15]

This study wants to address this problem by developing advices for the safe use of medications in patients with liver cirrhosis. To guarantee the quality of these advices, it is important that the method for evaluating is performed in a uniform, transparent manner leading to a standardized report.[16] Furthermore, advices need to be manageable by all health care professionals dealing with patients with liver cirrhosis.[16] We intend to develop concrete and up-to-date advices to prevent alert fatigue and dissatisfaction by health care professionals. The aim of this study is to describe the systematic method used for evaluating the safety and optimal dosage of drugs in patients with liver cirrhosis.

METHODS

Six steps will be performed for evaluating a drug (Figure 1). Below, the six steps are described in detail. Step 1-3 will be performed by a pharmacist with experience in the evaluation of drug safety in the context of clinical decision support systems (RW). The critical steps are checked by a second pharmacist/epidemiologist (SB).

Figure 1. Flowchart of the six-step process used per drug for evaluating the safety and optimal dosage in liver cirrhosis

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Step 1: Collection of evidence

Summary of Product Characteristics (SmPC)

Information concerning the pharmacokinetics of the drug in healthy volunteers and patients with liver cirrhosis will be collected from the official Product Characteristics as published by the responsible authorities EMA, FDA, and the Medicines Evaluation Board (MEB) in the Netherlands. For

products registered by the EMA, the European Public Assessment Report (EPAR) will be searched on information about dosage in liver cirrhosis. Special warnings regarding the safety of the drug in patients with liver cirrhosis will also be collected.

Literature search in electronic databases

The search in electronic literature databases aims to review published literature about the alterations in pharmacokinetic parameters and the safety of the drug in patients with liver cirrhosis. Criteria for inclusion in the literature review are: (1) the study investigates patients with liver cirrhosis, (2) the study concerns the drug of interest, and (3) the outcome of the study is safety (i.e. adverse events) and/or (altered) pharmacokinetics. Studies with and without a control group will be included. If a drug is compared to another intervention, data about the control group will be included in the data extraction. There will be no limit to the time periods searched.

Exclusion criteria are: (1) animal studies, (2) cellular and molecular research, (3) studies in patients with other hepatic diseases, such as hepatocellular carcinoma, non-alcoholic fatty liver disease or primary biliary cholangitis that do not mention the inclusion of a subpopulation with liver cirrhosis and (4) studies about drug-induced liver injury in patients without liver cirrhosis.

PubMed + EMBASE

These databases will be searched (this includes reviews published by the Cochrane library) by the search strategy outlined in Table 1. A more specific search will be performed if there is excessive literature. In this case, a stepwise search strategy will be used starting with PubMed as database. Filters that indicate studies with a high level of evidence will be used to limit the number of studies. The pharmacists responsible for the collection of evidence will judge whether sufficient data are collected to answer the research question. This step is checked by another pharmacist and will be discussed and finally confirmed by the expert panel.

Table 1. Proposed search strategy for PubMed and Embase

Database	Search query
PubMed	("Liver cirrhosis"[Mesh] OR cirrho*[ti] OR "hepatic impairment"[ti] OR "liver impairment"[ti] OR "hepatic dysfunction"[ti] OR "liver dysfunction"[ti] OR "hepatic insufficiency"[ti] OR "liver insufficiency"[ti]) AND ("X"[Mesh] OR "X"[tiab]) AND "humans"[MeSH Terms]
Embase	'liver cirrhosis'/exp OR cirrho*:ti OR 'hepatic impairment':ti OR 'liver impairment':ti OR 'hepatic dysfunction':ti OR 'liver dysfunction':ti OR 'hepatic insufficiency':ti OR 'liver insufficiency':ti AND ('X'/exp OR 'X':ab,ti) AND [humans]/lim

X= name of drug to be evaluated.

Citation tracking

Additional articles will be obtained through citation snowballing to locate primary sources.

Step 2: Data extraction and presentation

The following characteristics of included studies will be extracted: study design, number and characteristics of included patients and controls (e.g. severity of liver cirrhosis) and details on the intervention. Concerning the outcome(s), the following data will be extracted:

- (altered) Pharmacokinetics: data on pharmacokinetic parameters (e.g. Area Under the Curve (AUC), elimination half-life and steady state concentration) of the drug in patients with liver cirrhosis, preferably compared with subjects without liver cirrhosis.
- Safety: data on the number of adverse events observed during use of the drug in cirrhotic patients and on the consequences of these adverse events (e.g. discontinuation of treatment, dose reductions), preferably compared with subjects without liver cirrhosis.

Data will be reported in summary tables for each outcome and sorted by level of evidence. The level of evidence of each study will be assessed according to the criteria for treatment harms of the Oxford Centre for Evidence-Based Medicine.[17] In a separate table, narrative reviews will be included as level 5 evidence to reflect on published expert opinions. The summary tables will be checked by a second pharmacist.

All data will be summarized in an assessment report. This standardized report will contain:

- Data from the SmPC

- Details on the electronic database search (search strategy, study selection process in a flowchart)
- Summary tables with pharmacokinetic and safety data
- References

Step 3: Classification and suggested dose

All information from the report will be used to suggest a safety classification and a dose per individual drug, if applicable sorted by severity of liver cirrhosis. The severity will be expressed using the Child-Pugh classification.[4]

Safety classification

To support health care providers and patients to efficiently judge drug safety in liver cirrhosis, we designed a safety classification (Table 2). For drugs in liver cirrhosis we will use the following categories: safe, no additional risks known, additional risks known, unsafe and unknown. Drugs that have not been evaluated are placed in the category 'not yet classified'.

Table 2. Safety classification of drugs used in liver cirrhosis

	Description	Action
Safe	The drug has been evaluated in patients with liver cirrhosis, and no increase in harm was found. The safety of the drug is supported by pharmacokinetic studies and/or safety studies over a long period. It might be necessary to use an adjusted dose.	This drug can be used by patients with liver cirrhosis.
No additional risks known	Limited data suggest that this drug does not increase harm in patients with liver cirrhosis in comparison with persons without cirrhosis. Drugs estimated as 'minor influenced by cirrhosis' based on pharmacokinetics* can also be classified in this category if the expert panel agrees. It might be necessary to use an adjusted dose.	The drug can be used in patients with liver cirrhosis. Adverse drug reactions need to be monitored.
Additional risks known	Limited data suggest an increase in patient harm in patients with cirrhosis compared with persons without cirrhosis. However, the number of studies is limited and/or the studies show contradicting results about the safety in patients with liver cirrhosis.	This drug should preferably not be used in patients with liver cirrhosis if there is a safer alternative available. Adverse drug reactions need to be monitored.
Unsafe	Data indicate this drug is not safe in patients with liver cirrhosis.	This drug should be avoided in patients with liver cirrhosis.
Unknown	For this drug insufficient data are available to evaluate the safety in patients with liver cirrhosis.	This drug should preferably not be used in patients with liver cirrhosis if there is a safer alternative available. Individual judgement of therapeutic need vs. additional risks in patients with liver cirrhosis. Adverse drug reactions need to be monitored.
Not yet classified	The drug has not been evaluated for safety in patients with liver cirrhosis.	No advice for action can be given

** Drugs are classified as 'minor influenced by cirrhosis' if they are cleared less than 20% by the liver.*[5]

Suggested dose

Pharmacokinetic data will be used to judge whether a dose adjustment is necessary in cirrhotic patients. It applies for most drugs that if the AUC is more than doubled, a dose reduction will be recommended.[5] Exceptions are for instance drugs that do not have a concentration-effect relationship or drugs with a narrow therapeutic range. Both the proposed classification and suggested dose are checked by a second pharmacist, before discussion by the expert panel.

Step 4: Discussion and conclusion by the expert panel

An expert panel will evaluate the validity and clinical relevance of the initial classification, the suggested dose and the data extraction. This panel will meet five times during the study to discuss the assessment reports. Comments and opinions of the panel will be added to the initial report, such as recommendations for therapeutic drug monitoring or extra monitoring of liver function tests and/or clinical response. The final report is a combination of the available evidence and expert opinions. The expert panel will conclude by consensus. If there are different interpretations within the expert panel, these will be included as 'expert comments' in the assessment report.

The expert panel consists of the following specialists: the pharmacist responsible for the data collection, extraction and initial evaluation (RW), professionals with expertise regarding our two main outcomes; altered safety or pharmacokinetics in patients with liver cirrhosis (DB, NH), representatives of the specialists responsible for prescribing: hepatologists (JD, HM), general practitioner (MB), representatives of specialists responsible for dispensing: clinical pharmacists (DB, NH), a community pharmacist (SvP), a clinical pharmacokinetics assessor of the Medicines Evaluation Board (MM) and two pharmacists working with the national drug databases in the Netherlands (Pharmabase and G-Standard: MK, SB). Each expert has specific expertise in the treatment of patients with liver cirrhosis, in clinical pharmacology and/or the implementation of the outcomes. The general practitioner and community pharmacist will contribute to the implementation from the perspective of primary care. The pharmacists working for the national drug databases will assure that

the advices can be implemented in clinical decision support systems. There is also an epidemiologist (SB) in the expert panel who will pay attention to the methodology.

All conflicts of interest of the members of the expert panel will be identified, disclosed and published on the website (see implementation). The chair of the expert panel (SB) has no conflicts of interest.

Step 5: Implementation

Advices about the safety of a drug and the optimal dosage in patients with liver cirrhosis will be implemented in the two national drug databases in the Netherlands (Pharmabase and G-Standard). This will generate specific alerts for health care professionals when they prescribe or dispense a drug with risks to a patient with liver cirrhosis.

The advices will also be published on a website. On this website, a summary will be included which starts with the key recommendations (i.e. safety classification of drug and dosing advices) and describes background information on the advice and the body of evidence (i.e. number of studies retrieved, number of participants and level of evidence of the studies). The full assessment report can be accessed through a hyperlink. The advices will be in Dutch, since they will be implemented in national clinical decision support systems. The summary of finding tables derived from the (English) literature will be left in English. Conflicts of interest of the members of the expert panel will be mentioned on the website.

There will also be a part on the website intended for patients with liver cirrhosis. This part will contain a simple, patient friendly, version of the advices with directions to consult their doctor or pharmacist in case of further questions. These advices will be made in collaboration with the Dutch Liver Patients Association. Before publication of the website, the finding and understanding of the content will be tested by patients and health care professionals. Via user testing a group of patients and a group of health care professionals will test the website.[18] If issues emerge from this testing, these issues will be solved and the process will be repeated until no more issues emerge.

Step 6: Continuity

To assure up-to-date advices, literature searches will be saved and checked yearly for relevant literature. Comments from patients and professionals using the guidelines will be reviewed and included, if applicable. The expert panel will check yearly if the advices need to be up-dated based on their specific (clinical) expertise.

Drugs to be evaluated

A selection of drugs will be evaluated: (A) drugs used to treat (complications of) liver cirrhosis, such as ursodeoxycholic acid and beta-blockers and (B) drugs that are prescribed frequently to the general population, such as antibiotics and analgesics. An overview of the drugs that will be evaluated in this study is presented in Table 3.

Table 3. Drugs to be evaluated in the current study

Box A: drugs to treat (complications of) liver cirrhosis[19-24]		**Box B: most frequently used drugs in the general population***
Indication	**Drug (class)**	**Drug (class)**
Metabolic syndrome	Insulins	*Analgesics*
	Oral antidiabetics	Paracetamol
Dyslipidemia	Antilipemics	NSAIDs
(anti) Hepatitis B (anti) Hepatitis C	Nucleos(t)ide analogues	Opioids
	Interferon	*Antibiotics*
	Direct-acting antivirals	Tetracyclines
Primary biliary cholangitis/ autoimmune hepatitis	Corticosteroids	Sulfonamides and trimethoprim
	Ursodeoxycholic acid	Macrolides
	Azathioprine	Other antibiotics
	Mycophenolate mofetil	*Gastro-intestinal drugs*
Infections	Chinolons	Antacids
	Penicillins	H_2-receptor antagonists
Esophageal varices	Proton pump inhibitors	Propulsives
Portal hypertension	Beta blocking agents	Stimulant laxatives
Hepatorenal syndrome	Terlipressin	Bulk-forming laxatives
Ascites	Diuretics	*Cardiovascular drugs*
	Albumin	Antithrombotics
Hepatic encephalopathy	Lactitol	Calcium antagonists
	Lactulose	RAS-inhibitors
	Rifaximin	

* Based on number of users of prescribed drugs in the Netherlands according to the GIP-database 2013 (www.gipdatabank.nl).

DISCUSSION

We have developed a systematic method to evaluate the safety and optimal dosage of drugs in patients with liver cirrhosis. Our method combines systematic literature review with expert opinion and contains many aspects of the development of guidelines. We used the AGREE Reporting Checklist to ensure that important issues are included in the study protocol.[25] Our approach will produce a standardized assessment report per drug. It is important that this report contains the information health care professionals need for clinical decision making. In the development of an assessment report, we were inspired by a checklist that identifies the most important elements that should be included in drug-drug interaction management guidelines.[16] One of the main domains of the checklist was the 'management strategy'. We designed a safety classification to help health care professionals to efficiently judge the safety of a drug in a patient with cirrhosis. Safety classifications are used in other conditions where careful consideration is needed to judge the safety of a drug, such as Long QT-Syndrome,[26] porphyria[27] and pregnancy/lactation.[28] All classifications have in common that the number of categories is limited, that a description is available why drugs are classified in a certain category, and that a category can be related to an advice towards a health care provider. We think our safety classification results in concrete advices and thereby preventing dissatisfaction and alert fatigue of health care professionals.

Strengths of our study are the combination of evidence from the literature and expert opinion, the implementation in clinical decision support systems and the continuity. First, the published evidence of drugs in liver cirrhosis is variable, and studies often have a limited scope or a selective patient population. Combination with expert opinion adds the clinical and pharmacological experience to the published literature. This combination will make it possible to give specific advices, which is even more relevant in case little published literature is available. Second, the advices will be implemented in the two main clinical decision support systems in the Netherlands, automatically reaching all hospitals, community pharmacies and general practices. Health care professionals will receive a notification if a contra-indicated drug is prescribed or dispensed to a patient with liver

cirrhosis. This implementation can quickly result in a huge improvement in the medication safety of cirrhotic patients in the Netherlands. We believe that this Dutch approach of monitoring the safety of drug use is unique,[29] and hope to inspire others to implement this in their health care systems. Third, to safeguard continuity, it is important that this guideline will be updated regularly and that these updates will be included in new signals. The advices will get updated yearly if there is new literature or if we receive comments. This is a major advantage in comparison to all reviews published on this topic.

We expect that we will not perform a standard systematic review for all drugs.[30] Albumin, for example, has been safely used for a long period of time in patients with liver cirrhosis and many studies have been published, also in patients with liver cirrhosis. In this case, we will include literature from the highest level of evidence and stop extracting if we have sufficient information to classify the drug. The expert panel will also decide whether sufficient information is collected to classify the drug. Another limitation is that we will evaluate a restricted number of drugs in this study. Future research can enlarge the amount of drugs evaluated. Also, this study will expose knowledge gaps in current literature with respect to the pharmacokinetics and safety of certain drugs in liver cirrhosis. Specific pharmacokinetic or pharmacodynamic studies can possibly fill this gap. Another interesting future research area is the implementation; do health care professionals follow our advices? How can the information obtained in our study be used to improve official drug labeling? And ultimately, does our study results in optimization of medication use, i.e. reduction in the number of adverse drug events experienced by patients with liver cirrhosis?

In conclusion, this protocol describes a method to evaluate the safety and optimal dosage of drugs in patients with liver cirrhosis. This will lead to advices concerning the safety and optimal dosage of the drugs mostly used in liver cirrhosis and will reveal gaps in literature for future research.

ETHICS AND DISSEMINATION:

Since this study does not directly involve human participants, it does not require ethical clearance. The advices generated by the method described in this study will be published on a website and in two drug databases (see Implementation). We also aim to publish the generated advices of one or two drug classes in a peer-reviewed journal and at conference meetings.

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Contributions:

RW and SB wrote and drafted the protocol. MB, JD, NH, HM and SB contributed for an application for study funding. All authors contributed to the development of the study protocol and read and approved the final manuscript.

Competing interests statement:

RW: none to declare

MB: none to declare

DB: David Burger has received research grants from BMS, MSD and ViiV and has performed teaching for Abbvie, BMS, Gilead, MSD and ViiV, outside the submitted work.

JD: Joost Drenth has received research grants from Abbvie and Janssen and has been a member of advisory boards of AbbVie, BMS, Gilead, Janssen, and Merck, outside the submitted work.

NH: none to declare

MK: none to declare

MM: none to declare

SVP: none to declare

HM: Herold Metselaar has received research grants from AbbVie, Astellas, Novartis and Gilead and has been a member of advisory boards of AbbVie, Astellas and Novartis, outside the submitted work.

KT: none to declare

SD: none to declare

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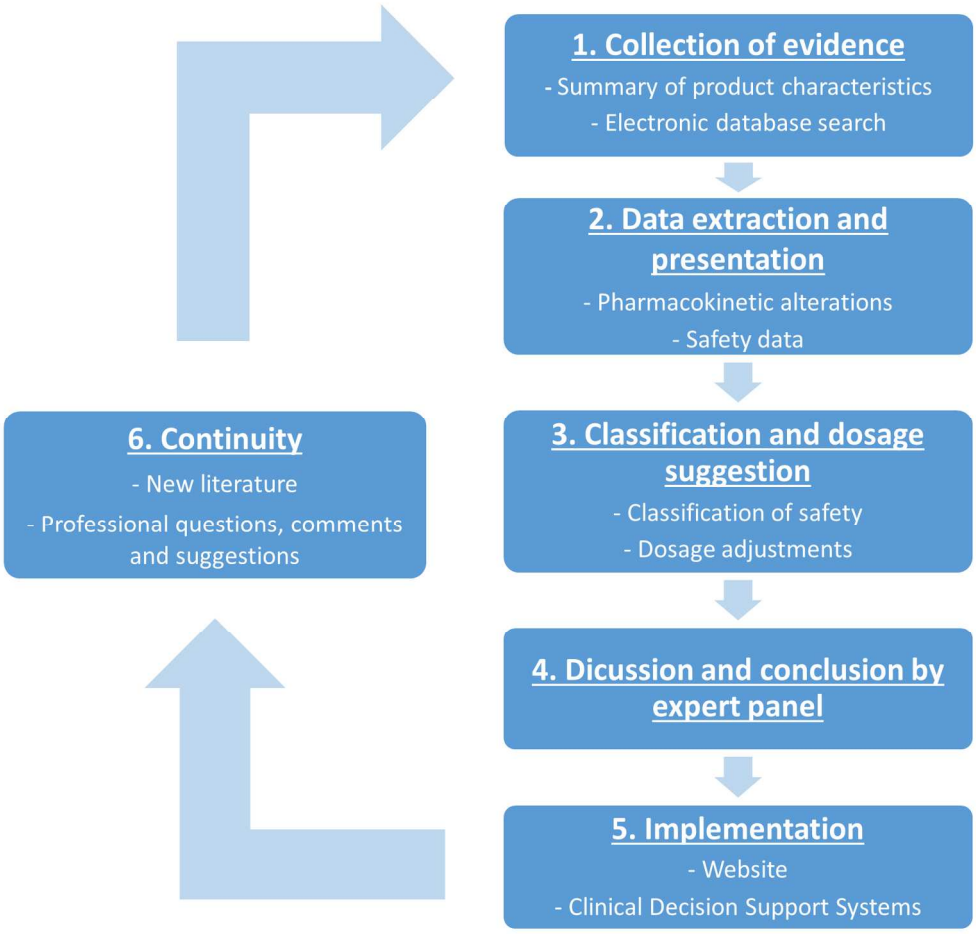

Figure 1. Flowchart of the six-step process used per drug for evaluating the safety and optimal dosage in liver cirrhosis

162x155mm (300 x 300 DPI)

AGREE Reporting Checklist
2016

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page # and explanation
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☒ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	Page 4 and 5
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☐ Health care setting or context	Page 4, 5, 8-10 Health care setting/context is not applicable
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	Page 6,8. Our advice applies to all patients with cirrhosis, irrespective of sex and age.
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☒ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☒ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	Page 1, 10-11. We added data on the description of the members' roles in the guideline development group.
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☒ Outcomes/information gathered on patient/public information ☒ How the information gathered was	Page 11 There are several ways we sought information about the experiences and expectations of the target population. Some are beyond the scope of our article, but we will explain them here: - For study funding we composed a project group containing a board member of the Dutch Liver Patients association. She contributed towards study funding and can be consulted for patient-related questions.

	used to inform the guideline development process and/or formation of the recommendations	- We conducted a study to assess the medication information needs of cirrhotic patients (not published yet) and will use the results for the development of the patient part of the website - We will test the text on our website via performance-based testing with the target populations (i.e. health care professionals and patients); see page 11
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	Page 5, 11 We added extra words on page 5 to specify the target users of the guideline
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	Page 5-7 In addition, we included details on the time periods searched (page 6)
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	Page 6-8
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	Not all items are applicable (i.e. Magnitude of benefit versus magnitude of harm). Page 7,8. We used the Oxford Centre 2011 levels of evidence table to grade our evidence. Page 10. The interpretation (consistency and direction) of the results will be discussed in the expert panel. Page 11. We added a sentence on how we describe the body of evidence per advice
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures	On page 10 the process of recommendation development is described even as the outcomes.

to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.	that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	Not applicable. Our study is primarily focusing on the safety of medication, not the efficacy. For this reason, this item is not applicable.
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	Page 7-9 We designed a safety classification, based on the amount and strength of available literature. For each advice, summery tables will be made summarizing the evidence.
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	Our advices will not be externally reviewed before publication. However, they will be published on a website from which we will gather comments from users (see page 11/12 'continuity') and reflect on these. Comments will be included in the annual review process.
14. UPDATING	☒ A statement that the guideline will be	Page 11 and 12.

PROCEDURE *Describe the procedure for updating the guideline.*	updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	Page 9, our safety classification gives specific recommendations about our relevant population (i.e. patients with liver cirrhosis). The two last points are in our opinion not (yet) applicable, since we do not have recommendations yet.
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	Not applicable, because our study is designed to give advice per drug there are no different options.
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	Page 11. Extra information added where the key recommendations can be found. The recommendation about the safety and the dosing advices are grouped at the beginning of each report.
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the	Page 11: The advices will be implemented in all (relevant) clinical decision support systems in the Netherlands, which is a facilitator for its application. Barriers are described in the discussion section (page 14) and also on page 11. We added extra information on the method of testing the website (pilot). The pilot testing is still to be done, so we do not have information on point 3 and 4 yet.

	guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned	Page 11-14. As stated before, the advices will be implemented in the relevant clinical decision support systems, automatically reaching all hospitals, community pharmacies and general practices. The generated alerts will provide a link to the freely available website.
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	Not applicable, the recommendations will not require additional resources in order to be applied.
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	On page 14 we describe some ideas for further research; to assess the adherence to the recommendations and the impact of the advices. These are just ideas; we do not specify how this should be measured.
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	Page 16. More information about the funding body was provided and the statement was included.
23. COMPETING INTERESTS *Provide an explicit statement that all group members have*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought	Page 11, 15, 16. Information was provided on how the competing interests will be managed.

declared whether they have any competing interests.	☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	

From:
Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.