PHARMACOLOGY 2019
15–17 December | Edinburgh

SUBMIT AN ABSTRACT

- Participate in the UK's leading pharmacology event
- Share your research with over 1,200 attendees
- Apply for awards and attendance bursaries
- Have your work published in the British Journal of Pharmacology or the British Journal of Clinical Pharmacology

Deadline to submit 9 September

SUBMIT NOW

@BritPharmSoc  #Pharmacology2019
Medication safety in patients with hepatic impairment: a survey of community pharmacists’ knowledge level and their practice in caring for these patients

Short title: Medication safety in hepatic impairment

Rianne A. Weersink¹,²*, Marianna Abadier¹,³†, Anthonius de Boer³,⁴, Katja Taxis², Sander D. Borgsteede¹,⁵

* Rianne A. Weersink and Marianna Abadier should be considered joint first author.

Affiliations:
1. Department of Clinical Decision Support, Health Base Foundation, Houten, The Netherlands
2. Department of Pharmacy, Unit of Pharmacotherapy, -Epidemiology & -Economics, University of Groningen, Groningen, The Netherlands
3. Department of Pharmaceutical Sciences, University of Utrecht, Utrecht, The Netherlands
4. Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands
5. Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

† Marianna Abadier’s current affiliation: Mental Health Organisation Rivierduinen, Lisse and Leiden, The Netherlands

Correspondence to: Rianne A. Weersink. Email: r.a.weersink@rug.nl, telephone number: +31307400360, fax number: +31307400365

Principal investigator: The authors confirm that the Principal Investigator for this paper is Marianna Abadier.
Abstract

Aims: To study community pharmacists’ level of knowledge on medication safety in patients with hepatic impairment and their practice in caring for these patients.

Methods: Pharmacists from Dutch community pharmacies (n=1545) were invited to participate in an online survey. The survey consisted of 27 questions covering two main topics: knowledge and current practice. The level of knowledge was measured by a six-item knowledge test. Multiple linear regression was used to identify predictors of correctly answered responses.

Results: In total, 338 pharmacists (22%) completed the questionnaire. The mean knowledge score was 2.8 (SD 1.6). Only 30.3% of respondents were able to appropriately advise on use of analgesics in severe cirrhosis. Postgraduate education on hepatic impairment, knowledge of recently developed practical guidance, and fewer years of practice were associated with a higher level of knowledge. In total, 70.4% indicated to evaluate medication safety in a patient with hepatic impairment at least once weekly. In the past 6 months, 83.3% of respondents consulted a prescriber about a patient with hepatic impairment. Frequently encountered barriers in practice were insufficient knowledge on the topic and a lack of essential patient information (i.e., diagnosis and severity of the impairment).

Conclusion: Community pharmacists regularly evaluate the safety of a medicine in patients with hepatic impairment, yet their level of knowledge was insufficient and additional education is needed. Pharmacists experienced several difficulties in providing pharmaceutical care. If these issues are resolved, pharmacists can play a more active role in ensuring medication safety in their patients with hepatic impairment.

Keywords
Hepatology; medication safety; pharmacy; education

What is already known about this subject

- Patients with hepatic impairment have an increased risk of medication-related problems due to alterations in pharmacokinetics and pharmacodynamics of medicines.
- Pharmacists could play a key role in preventing and resolving medication-related problems in this vulnerable patient group.

What this study adds

- Community pharmacists frequently evaluated the safety of a medicine in patients with hepatic impairment.
- The level of knowledge of pharmacists on medication safety in patients with hepatic impairment was limited and more education on the topic is needed and wanted.
- Community pharmacists experienced limited access to relevant patient data (e.g., diagnosis and severity of hepatic impairment) which may adversely affect their practice.
Introduction

Patients with hepatic impairment are prone to develop adverse drug reactions due to changes in the pharmacokinetics and pharmacodynamics of medicines [1, 2]. Research showed that nearly 30% of patients with liver cirrhosis, the advanced stage of all chronic liver diseases, experience adverse drug reactions [3]. A Dutch study showed that almost two-thirds of patients with liver cirrhosis used potentially unsafe drugs [4]. In addition, a recent study among 57 patients with cirrhosis identified a median of six medication-related problems per patient [5]. Almost 60% of these problems could be resolved during a pharmacist-led medication review. This suggests that pharmacists, as medication experts, could play a key role in preventing and resolving medication-related problems in this vulnerable patient group.

A barrier for pharmacists to fulfil this role was the lack of concrete prescribing recommendations for patients with hepatic impairment and deficiencies in the information for these patients in the product labels [6-9]. Yet, in 2018, practical guidance for safe drug use in this specific patient group was published [10, 11]. In the Netherlands, the website containing all guidance (www.drugsinlivercirrhosis.org) has been available since 2017. Furthermore, the guidance was integrated in all relevant Clinical Decision Support Systems (CDSS) used in Dutch community pharmacies. Implementing changes in practice may take time and pharmacists might encounter difficulties in practice [12]. For example, a substantial part of the recommendations depends on the severity of hepatic impairment, being expressed using the Child-Turcotte-Pugh (CTP) classification [10, 13]. Therefore, it is important that this severity class is registered in the medical and pharmaceutical record of a patient and exchanged between relevant healthcare providers. In addition, pharmacists need to be familiar with the recommendations and have sufficient knowledge about the topic to be able to interpret and apply the information in their practice.

Previous work focussed on knowledge and practices of physicians in prescribing analgesics for patients with chronic liver disease [14-16]. Little is known about the knowledge of community pharmacists on safe medication use in patients with hepatic impairment. Few studies described the care provided by pharmacists for a subgroup of patients: those with viral hepatitis C [17-19]. But those studies focussed on clinical pharmacists or described care in only one clinic. Therefore, this study aimed to determine the level of knowledge of community pharmacists on medication safety in patients with hepatic impairment and their practice in caring for this patient group.

Methods

Study setting

In the Netherlands, patients are usually registered with one general practitioner (GP) and one community pharmacy [20]. The GP keeps a medical record per patient and the pharmacist a pharmaceutical record. In general these are electronic records which operate a CDSS. Clinical risk management of medication use is an important activity of Dutch community pharmacists [21]. In case the CDSS generates a medication safety alert (e.g. contraindications, drug-drug interactions), the
pharmacist assesses the clinical relevance of the alert and if applicable, takes action (e.g. inform the patients, adjust the dose or switch drugs in cooperation with the GP).

Study population
We conducted a cross-sectional survey among pharmacists from the Utrecht Pharmacy Practice network for Education and Research (UPPER) network. The UPPER network consists of 1545 community pharmacies, representing 75% of all community pharmacies in the Netherlands at the time the survey was performed [22]. An invitation for the pharmacist to participate in the electronic survey was sent in March 2018, one and a half years after the implementation of the first safety and dosing advices in cirrhosis [10]. A reminder was sent two weeks later and the questionnaire was closed two weeks thereafter. As an incentive, all respondents were given the option to receive additional information about “pharmaceutical care in patients with hepatic impairment” by providing their email address at the end. The survey was conducted with Survey Monkey® software. It was approved by the UPPER Institutional Review Board of Utrecht University (number: UPF1801).

Survey
The survey consisted of 27 questions covering two main topics: knowledge and current practice and can be found in the Supplementary Data. The questionnaire was developed by the authors with expertise in hepatic impairment and pharmacy practice, and piloted among 13 pharmacists. We refined the questionnaire based on the pilot: we adjusted the formulation of some answers and changed the order of the questions slightly.

The topic knowledge was divided into self-perceived knowledge of pharmacists, questions on educational needs and a brief knowledge test. Self-perceived knowledge was tested by four statements where pharmacists recorded their agreement on a five-point Likert scale. To investigate educational needs, we asked the pharmacists about the training they received on medication safety in patients with hepatic impairment and if they wished to receive additional education. The knowledge test consisted of six multiple-choice questions and the participants were instructed to complete those without using reference works.

The topic of current practice was covered with questions on how often the pharmacists encountered a medication safety alert from their CDSS about a patient with hepatic impairment, the familiarity of pharmacists with the new recommendations and website [10], and questions about contact with other healthcare professionals. To include potential topics that were not covered by the survey, we added three open-ended questions about current practice and difficulties experienced in providing pharmaceutical care to patients with hepatic impairment at the end of the questionnaire.

Data analysis
We used both descriptive and inferential statistics to analyse the data. Due to missing values, the number of respondents per question varied and, where appropriate, the absolute number of respondents per questions was listed. In total, less than 5% of items was missing. Due to the low rate scoring of some of the multiple-choice questions, we merged responses from selected questions into
fewer categories. The statements on knowledge were recoded from a five-point Likert scale into a three-level scale: “strongly disagree/disagree”, “neutral”, “agree/strongly agree”. The answers on the frequency of a medication safety alert were recoded into “often” (daily/weekly) and “rarely” (monthly/less than once a month). The answers “countryside” and “village” from the variable “location of pharmacy” were combined into “village or countryside”. Answers to the question about the community pharmacy registration were merged into “registered as community pharmacist” and “not (yet) registered as community pharmacist”.

The outcome of the knowledge test was the number of correctly answered questions, with a maximum of 6. Univariate analyses were performed for all potential explanatory variables. The variables age and years of practice were highly correlated and therefore only one variable (i.e. years of practice) was included in the analysis. After univariate analyses, variables with p-values <0.25 were included in multiple linear regression analysis. Cases with missing data were deleted pairwise. A p-value <0.05 was considered statistically significant. The analyses were performed with Statistical Package for Social Sciences (SPSS), version 25.

Results

In total, 338 pharmacists (22%) completed the survey of the 1545 pharmacies the invitation was sent to. The characteristics of the respondents are presented in Table 1. Respondents were predominantly female pharmacists, working in a community pharmacy in an urban area.

Knowledge

Respondents were asked about their self-perceived knowledge on medication safety in hepatic impairment (Figure 1). A minority of pharmacists (20.4%) perceived their knowledge about the influence of hepatic impairment on medication as sufficient, and 29.0% indicated that they were able to interpret hepatic laboratory values. In total, 69.6% (n=218) of respondents received prior education on medication safety in hepatic impairment. Almost half (44.1%; n=138) of pharmacists received training while in pharmacy school, and 18.2% (n=57) during their two-year registration period as community pharmacist. A total of 42.8% (n=134) received education during a postgraduate course or a pharmacotherapy meeting. Almost all respondents (90.7%; n=284) expressed a wish for additional education on this topic.

The mean score of the respondents on the knowledge test was 2.8 (SD 1.6) correct answers out of six questions (mode 2.0). Fifteen respondents (4.7%) were able to answer all six questions correctly, and 6.3% answered all incorrectly (n=20). As can be seen in Table 2, 77.6% of pharmacists did not know which laboratory parameters are used to assess hepatic function, and 69.7% were not able to give a proper analgesic advice in a patient with severe cirrhosis. On the other hand, 64.0% of the pharmacists were familiar with the Child-Pugh classification, and 61.8% knew that medication adjustments are only needed in patients with cirrhosis and not (yet) in patients with viral hepatitis or steatosis.

In multiple linear regression analysis three variables were associated with the total knowledge score (Table 3). Higher knowledge scores were associated with postgraduate education or a
pharmacotherapy meeting on hepatic impairment (p<0.001) and familiarity with the new recommendations or website (p<0.001). A higher total knowledge score was also negatively correlated to years of practice (p<0.001).

Current practice
Seventy percent of pharmacists indicated to encounter at least once a week a medication safety alert from their CDSS concerning a patient with hepatic impairment (Table 4). A proportion of 53.4% were familiar with the new alerts in their CDSS. A total of 55.4% were aware of the website with advice about medication safety in cirrhosis.

Among healthcare professionals, the GP was most often consulted with a question about a prescription in a patient with hepatic impairment. A total of 71.3% of respondents contacted a prescriber in the past 6 months to retrieve the severity of a patient’s hepatic impairment. More than half of these respondents experienced difficulties during that contact. In an open question, pharmacists explained these difficulties. A frequently mentioned remark was the lack of relevant patient information (e.g., severity of hepatic impairment or diagnosis of cirrhosis): "General practitioners become irritated when I ask for a patient’s renal function, let alone when I also ask which patients have cirrhosis." [Female, 63 years old]. Respondents also indicated that there was a lack of knowledge on this topic: "My general practitioners have no idea what hepatic impairment exactly means. The contraindication hepatic impairment is registered while the patient 'only' had an increase in ALAT and / or ASAT." [Female, 36 years old].

Another open-ended question asked about the role of pharmacists in caring for patients with hepatic impairment. Overall, there was a sense of willingness amongst respondents to take responsibility in ensuring optimal medication use in patients with hepatic impairment: “Our role is to provide information about the use of medication when a patient has hepatic impairment and the possible consequences.” [Female, 57 years old].

Discussion
This study is unique in assessing community pharmacists’ level of knowledge on medication safety in patients with hepatic impairment and their practice in caring for these patients. We demonstrated that 70% of the respondents evaluated at least once a week the safety of a medicine in a patient with hepatic impairment and more than 80% consulted a prescriber in the past 6 months with a medication safety question. Yet, the pharmacists’ knowledge level – subjective and objective – was insufficient and they expressed a wish for additional education. Furthermore, pharmacists experienced difficulties in caring for these patients due to problems in the contact with prescribers and limited access to essential patient data, like the severity of hepatic impairment.

Pharmacists had limited knowledge on different topics of pharmaceutical care in hepatic impairment. Strikingly, only about one fifth of respondents knew which laboratory parameters are used to evaluate hepatic function. In addition, a large proportion of pharmacists was not able to give correct advice on analgesic use in severe cirrhosis. Knowledge of pharmacists on this topic does not seem to have been assessed previously, yet a few studies evaluated physicians’ practices in prescribing...
analgesics in patients with cirrhosis [14-16]. These studies found similar results: an overall limited knowledge on the topic. Possible explanations for this finding are that medication safety in hepatic impairment is a rather complex topic. Gastroenterologists, specialized in caring for these patients, also knew more often which analgesic was safe to prescribe compared to non-gastroenterologists [14]. In addition, the former lack of practical guidance possibly contributed to the low knowledge level. This lack of guidance probably also limited the quantity and quality of education on the topic: less than half of the respondents in our survey had some training in hepatic impairment during their pharmacy degree. These results mark the need for additional or higher quality education about medication safety in hepatic impairment. The respondents in our study that took a postgraduate course also had a higher score on the knowledge test, possibly indicating the effect of additional education. However, we do not know how recently the respondents took this course and how often they took a postgraduate course on this topic.

Pharmacists with less years in practice scored higher on the knowledge test. Previous studies assessing healthcare professionals’ knowledge on other topics (e.g., (pharmaco)genetics) also showed that more recent graduation was related to higher knowledge scores [23, 24]. Recent graduates probably remember most from the education received during pharmacy school or their registration period and may be more willing to learn. Notable was also the association between familiarity with the new recommendations in the CDSS or the website and a higher score on the knowledge test. Participants familiar with the website or recommendations are possibly more interested in the topic and might have read background information about medication safety in patients with hepatic impairment.

When consulting prescribers about patients with hepatic impairment, more than half of the pharmacists experienced difficulties during that contact. One of the difficulties mentioned was the lack of relevant patient information, i.e. data on the diagnosis and the severity of hepatic impairment. This can partly be explained by the complex classification used to grade the severity of hepatic impairment (i.e., the Child-Pugh classification [13]). This classification consists of five parameters and two of these include clinical symptoms (i.e., degree of ascites and of hepatic encephalopathy). Pharmacists cannot determine the severity of hepatic impairment themselves and need the information from physicians. Exchange of relevant patient data between physicians and pharmacists is therefore necessary. Warholak et al. showed that pharmacists were able to give better pharmaceutical support when they had a more complete overview of a patient’s medical record [25]. Furthermore, a review on clinical decision support noted that drug-disease interaction alerts could only work if the diagnoses and conditions of a patient, even as the degree of impairment have been accurately entered into the medical or pharmaceutical record of a patient [26]. Efforts are needed to improve exchange of these patient data.

Limitations
The current study achieved a response rate of 22%. Because there are also general pharmacy email addresses included in the UPPER network mailing list, this percentage could be lower if more than one pharmacist per pharmacy filled out the questionnaire. The response rate is considered low for
web-based questionnaires [27, 28]. Though, it is reasonable for the UPPER network with a usual response rate of 10-15% in their surveys [22, 29]. Non-response bias was possible: pharmacists with limited interest and knowledge on this topic possibly did not participate resulting in a higher average knowledge score. On the other hand, participants received additional information on the topic as incentive, which could have attracted pharmacists with limited knowledge resulting in a lower mean level of knowledge. When comparing characteristics of respondents with Dutch national data from 2004, a high frequency of female pharmacists was noted in our sample [30]. A likely explanation is that in the past 15 years, the male/female ratio among community pharmacists in the Netherlands has changed, as described by the Dutch Foundation for Pharmaceutical Statistics [31].

To test the level of knowledge of participants, we used six multiple-choice questions. Thus, the score on the knowledge test only gives a global impression about the pharmacists’ knowledge. Nevertheless, in our opinion, the designed questions represent minimal requirements for providing proper care in these patients.

Implications for practice and future research

The results of this study point to a compelling need for more education on medication safety in patients with hepatic impairment. It is recommended to provide basic knowledge and create awareness for this patient group during the pharmacy and medicine undergraduate studies and provide more advanced practice-based education in a postgraduate course. In a couple of years, this study and especially the knowledge test could be repeated to evaluate improvement. In further research, one could also study the actual care provided by the pharmacists. For example, by assessing how pharmacists manage alerts in their CDSS on medication safety in patients with hepatic impairment or by examining if pharmacists ask their customers about liver disease before they recommend a NSAID.

To improve medication safety in patients with hepatic impairment, pharmacists and prescribers can be supported by their CDSS [26]. The practical guidance on medication safety in patients with hepatic impairment was published in English, yet only integrated in CDSS in the Netherlands [10]. This study provides valuable insights for other countries that want to integrate decision support for safe use of medication in hepatic impairment. To make optimal use of clinical decision support, the exchange of the diagnosis and severity of hepatic impairment between healthcare professionals needs to be improved. Pharmacotherapy meetings between GPs and pharmacists can help. These meetings could be used to discuss practicalities limiting the exchange of the diagnosis and severity of hepatic impairment and to improve involvement and knowledge among participants. Previous studies have shown the positive impact of high quality pharmacotherapy meetings in optimizing pharmacotherapy [32, 33].

Medication-related problems are very common in patients with cirrhosis. A recent single-centre trial showed that more than half of medication-related problems could be resolved by a pharmacist-led medication review [5]. These results are promising and the guidance we developed can support pharmacists. Yet, for large-scale implementation of pharmacists-led medication reviews in these patients, there are still some barriers to overcome as we demonstrated in this study.
Conclusion

We showed that the level of knowledge of community pharmacists on medication safety in patients with hepatic impairment is low and that additional education is needed and wanted. The majority of pharmacists encounter patients with hepatic impairment regularly; however, when providing care in these patients they frequently experience difficulties in the contact with other healthcare professionals and lack essential patient information. If these issues are resolved, pharmacists can play a more active role in ensuring safe and optimal medication use and prevention of medication-related problems in patients with hepatic impairment.

References

1. Delco F, Tchambaz L, Schlienger R, Drewe J, Krahenbuhl S. Dose adjustment in patients with liver disease. Drug Saf 2005; 28: 529-45.
2. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008; 64: 1147-61.
3. Franz C, Egger S, Born C, Rätz Bravo A, Krähenbühl S. Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis. Eur J Clin Pharmacol 2012; 68: 179-88.
4. Weersink RA, Taxis K, Drent JPH, Houben E, Metselaar HJ, Borgsteede SD. Prevalence of Drug Prescriptions and Potential Safety in Patients with Cirrhosis: A Retrospective Real-World Study. Drug Saf 2018: 1-8.
5. Hayward KL, Patel PJ, Valery PC, Horsfall LU, Li CY, Wright PL, Tallis CJ, Stuart KA, Irvine KM, Cottrell WN, Martin JH, Powell EE. Medication-Related Problems in Outpatients With Decompensated Cirrhosis: Opportunities for Harm Prevention. Hepatol Commun 2019; 3: 620-31.
6. Hilscher MB, Odell LJ, Myhre LJ, Prokop L, Talwalkar J. The pharmacotherapy of cirrhosis: concerns and proposed investigations and solutions. J Clin Pharm Ther 2016; 41: 587-91.
7. Chang Y, Burckart GJ, Lesko LJ, Dowling TC. Evaluation of Hepatic Impairment Dosing Recommendations in FDA-Approved Product Labels. J Clin Pharmacol 2013; 53: 962-66.
8. Failings in treatment advice, SPCs and black triangles. Drug Ther Bull 2001; 39: 25-27.
9. Hayward KL, Powell EE, Irvine KM, Martin JH. Can paracetamol (acetaminophen) be administered to patients with liver impairment? Br J Clin Pharmacol 2016; 81: 210-22.
10. Weersink R, Bouma M, Burger D, Drent J, Harkes-Idzinga S, Hunfeld N, Metselaar H, Monster-Simons M, Taxis K, Borgsteede S. Evidence-Based Recommendations to Improve the Safe Use of Drugs in Patients with Liver Cirrhosis. Drug Saf 2018; 41: 603-13.
11. Weersink RA, Bouma M, Burger DM, Drent JPH, Harkes-Idzinga SF, Hunfeld NGM, Metselaar HJ, Monster-Simons MH, Putten SAW, Taxis K, Borgsteede SD. Safe use of proton pump inhibitors in patients with cirrhosis. Br J Clin Pharmacol 2018; 84: 1806-20.
12. Watkins K, Wood H, Schneider CR, Clifford R. Effectiveness of implementation strategies for clinical guidelines to community pharmacy: a systematic review. Implement Sci 2015; 10: 151.
13. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-9.

14. Rossi S, Assis DN, Awsare M, Brunner M, Skole K, Rai J, Andrel J, Herrine SK, Reddy RK, Navarro VJ. Use of over-the-counter analgesics in patients with chronic liver disease. Drug Saf 2008; 31: 261-70.

15. Nguyen D, Banerjee N, Abdelaziz D, Lewis JH. Trainees’ attitudes and preferences toward the use of over the counter analgesics in patients with chronic liver disease. Adv Pharmacoepidemiol Drug Saf 2014; 3: 1052.1000167.

16. Hong YM, Yoon KT, Heo J, Woo HY, Lim W, An DS, Han JH, Cho M. The Prescription Pattern of Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs in Patients with Liver Cirrhosis. J Korean Med Sci 2016; 31: 1604-10.

17. Gauthier TP, Moreira E, Chan C, Cabrera A, Toro M, Carrasquillo MZ, Corentin M, Sherman EM. Pharmacist engagement within a hepatitis C ambulatory care clinic in the era of a treatment revolution. J Am Pharm Assoc 2016; 56: 670-76.

18. Kolor B. Patient education and treatment strategies implemented at a pharmacist-managed hepatitis C virus clinic. Pharmacotherapy 2005; 25: 1230-41.

19. Mohammad RA, Bulloch MN, Chan J, Deming P, Love B, Smith L, Dong BJ. Provision of clinical pharmacist services for individuals with chronic hepatitis C viral infection: Joint Opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks of the American College of Clinical Pharmacy. Pharmacotherapy 2014; 34: 1341-54.

20. Mark MP. The general pharmacy work explored in The Netherlands. Pharm World Sci 2008; 30: 353-59.

21. van de Pol JM, Geljon JG, Belitser SV, Frederix GWJ, Hövels AM, Bouvy ML. Pharmacy in transition: A work sampling study of community pharmacists using smartphone technology. Res Soc Admin Pharm 2019; 15: 70-76.

22. Koster ES, Blom L, Philbert D, Rump W, Bouvy ML. The Utrecht Pharmacy Practice network for Education and Research: a network of community and hospital pharmacies in the Netherlands. Int J Clin Pharm 2014; 36: 669-74.

23. Roederer MW, Van Riper M, Valgus J, Knaff G, McLeod H. Knowledge, attitudes and education of pharmacists regarding pharmacogenetic testing. Per Med 2012; 9: 19-27.

24. Baars MJH, Henneman L, ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. Genet Med 2005; 7: 605.

25. Warholak-Juarez T, Rupp MT, Salazar TA, Foster S. Effect of patient information on the quality of pharmacists’ drug use review decisions. Journal of the American Pharmaceutical Association (1996) 2000; 40: 500-07.

26. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, Classen DC, Bates DW. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007; 14: 29-40.
27. Nulty DD. The adequacy of response rates to online and paper surveys: what can be done? Assess Eval High Edu 2008; 33: 301-14.

28. Cunningham CT, Quan H, Hemmelgarn B, Noseworthy T, Beck CA, Dixon E, Samuel S, Ghali WA, Sykes LL, Jetté N. Exploring physician specialist response rates to web-based surveys. BMC Med Res Methodol 2015; 15: 32.

29. Heringa M, Floor-Schreuder A, Wouters H, De Smet PAGM, Bouvy ML. Preferences of Patients and Pharmacists with Regard to the Management of Drug–Drug Interactions: A Choice-Based Conjoint Analysis. Drug Saf 2018; 41: 179-89.

30. Kooy MJ, Dessing WS, Kroodsma EF, Smits SRJG, Fietje EH, Kruijtbosch M, De Smet PAGM. Frequency, nature and determinants of pharmaceutical consultations provided in private by Dutch community pharmacists. Pharm World Sci 2007; 29: 81-89.

31. Foundation for Pharmaceutical Statistics. Openbaar Apotheker wordt Vrouwenberoep. Pharm Weekbl 2015; 150: 9.

32. Eimers M, van der Aalst A, Pelzer B, Teichert M, de Wit H. Leidt een goed FTO tot beter voorschrijven? Huisarts Wet 2008; 51: 340-45.

33. Florentinus SR, Hulten Rv, Kloth MEM, Heerdink ER, Griens AMGF, Leufkens HGM, Groenewegen PP. The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners. Ann Pharmacother 2007; 41: 319-24.
### Table 1. Characteristics of the respondents

| Characteristic                                               | n (%)     |
|--------------------------------------------------------------|-----------|
| Gender                                                       |           |
| Female                                                       | 207 (66.6)|
| Male                                                         | 104 (33.4)|
| Age in years, mean ± SD                                      | 42 ± 11   |
| Registered as community pharmacist                            |           |
| Yes                                                          | 274 (89.8)|
| No or not yet                                                | 31 (10.2) |
| Years of practice, median (IQR)                              |           |
| ≤ 10                                                         | 112 (36.7)|
| 11-20                                                        | 98 (32.1) |
| 21-30                                                        | 67 (22.0) |
| > 31                                                         | 28 (9.2)  |
| Practice setting                                             |           |
| Community pharmacy                                           | 295 (94.9)|
| Outpatient pharmacy                                          | 16 (5.1)  |
| Location of pharmacy                                         |           |
| Urban area                                                   | 190 (62.3)|
| Village or countryside                                       | 115 (37.7)|

SD, standard deviation; IQR, interquartile range. a. number of respondents is 311, b. number of respondents is 305
Table 2. An overview of the knowledge test containing the questions, the correct and incorrect answers (n=317)

| QUESTION                                                                 | n (%)          |
|--------------------------------------------------------------------------|----------------|
| 1. Which laboratory parameters are used to assess liver function?        |                |
| Correct: Albumin, bilirubin and INR                                      | 71 (22.4)      |
| Incorrect:                                                               | 246 (77.6)     |
| • Gamma-GT and Alkaline Phosphatase                                      | 17 (5.4)       |
| • ASAT and ALAT                                                          | 210 (66.2)     |
| • Lactate dehydrogenase and ammonia                                      | 1 (0.3)        |
| • I do not know                                                          | 18 (5.7)       |
| 2. Which classification is used to estimate the severity of hepatic impairment? |                |
| Correct: Child-Pugh                                                      | 203 (64.0)     |
| Incorrect                                                                | 114 (36.0)     |
| • ASAT / ALAT ratio                                                      | 31 (9.8)       |
| • Hy’s Law                                                               | 0 (0)          |
| • None of the above answers                                               | 7 (2.2)        |
| • I do not know                                                          | 76 (24.0)      |
| 3. In which of the following diseases is the impairment of hepatic function clinically relevant for medication use? |                |
| Correct: Liver cirrhosis                                                 | 196 (61.8)     |
| Incorrect                                                                | 121 (38.2)     |
| • Viral hepatitis                                                        | 1 (0.3)        |
| • Steatosis hepatis (fatty liver)                                        | 2 (0.6)        |
| • All three answers mentioned                                            | 80 (25.2)      |
| • None of the above answers                                               | 2 (0.6)        |
| • I do not know                                                          | 36 (11.4)      |
| 4. What do you do if a GP adds the contraindication “hepatic impairment” in the medical record of a patient because of a liver cyst? |                |
| Correct: The contraindication is irrelevant, I remove it in consultation with the GP | 165 (52.1)     |
| Incorrect                                                                | 152 (47.9)     |
| • The contraindication is relevant, I do not do anything                 | 19 (6.0)       |
| • I do not know what to do                                               | 133 (42.0)     |
| 5. A physician asks your advice on pain relief in a patient with arthrosis and severe liver cirrhosis. Which analgesic would you certainly not recommend? |                |
| Correct: Diclofenac                                                      | 96 (30.3)      |
| Incorrect                                                                | 221 (69.7)     |
| • Acetaminophen (paracetamol)                                            | 140 (44.2)     |
| • Tramadol                                                               | 12 (3.8)       |
| • Morphine                                                               | 19 (6.0)       |
| • I do not know                                                          | 50 (15.8)      |
| 6. Which pharmacokinetic process(es) are affected by hepatic impairment? |                |
| Correct: All of the pharmacokinetic processes                            | 158 (49.8)     |
| Incorrect                                                                | 159 (50.2)     |
| • Absorption                                                             | 0 (0)          |
| • Distribution                                                           | 0 (0)          |
| • Metabolism                                                             | 125 (39.4)     |
| • Excretion                                                              | 19 (6.0)       |
| • No influence on pharmacokinetics                                       | 0 (0)          |
| • I do not know                                                          | 15 (4.7)       |

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GP, general practitioner; GT, glutamyltransferase
Table 3. Multiple linear regression analysis of variables associated with total knowledge score. Variables predicting knowledge levels of pharmacists in a multiple linear regression model (n=305).

| Predictors                                         | Coefficient (β) | SE  | 95% CI       | p-value |
|----------------------------------------------------|-----------------|-----|--------------|---------|
| [Intercept]                                        | 2.019           | 0.192 |              |         |
| Years of practice\textsuperscript{a}              | -0.029          | 0.008 | -0.045, -0.014 | <0.001  |
| Postgraduate education course or pharmacotherapy meeting | 0.720           | 0.161 | 0.403, 1.037  | <0.001  |
| Familiar with new recommendations or website       | 1.372           | 0.171 | 1.035, 1.709  | <0.001  |

Adjusted $R^2$=0.27. SE, standard error; 95% CI, 95% confidence intervals of the coefficients. a. years of practice was included as continuous variable in the analysis.

Table 4. Current practice among pharmacists in caring for patients with hepatic impairment.

|                                                                 | Often (daily/weekly) | Rarely (monthly or less) |
|-----------------------------------------------------------------|----------------------|--------------------------|
| How often do you encounter a “hepatic impairment” medication safety alert in your CDSS? | 238 (70.4)           | 100 (29.3)                |
| Familiarity with new CDSS alerts or website                    |                      |                          |
| Yes                                                             | 218 (69.6)           | 95 (30.4)                 |
| No                                                              |                      |                          |
| Are you familiar with the new CDSS alerts?                     | 167 (53.4)           | 146 (46.6)                |
| Are you familiar with the website?                             | 173 (55.4)           | 139 (44.6)                |
| In the past 6 months, have you consulted one of the following prescribers with a question about medication safety in a patient with hepatic impairment? | 279 (83.3)           | 56 (16.7)                 |
| General practitioner                                           | 262 (78.2)           | 73 (21.8)                 |
| Gastroenterologist                                             | 86 (25.7)            | 249 (74.3)                |
| Other prescriber                                               | 54 (16.1)            | 281 (83.9)                |
| In the past 6 months, have you consulted a prescriber about a patient’s severity of hepatic impairment? | 239 (71.3)           | 96 (28.7)                 |
| If yes, did you encounter difficulties during that contact?    | 135 (56.7)           | 103 (43.3)                |

Number of respondents varied per question from 312-338 and n=238 for the last question. CDSS, clinical decision support system.
Figure 1. Self-perceived knowledge on medication safety in hepatic impairment among pharmacists (n=338)