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Use of Over-the-Counter Analgesics in Patients with Chronic Liver Disease

Physicians' Recommendations

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Abstract

Background: Over-the-counter analgesics (OTCAs), principally paracetamol (acetaminophen)-containing compounds and NSAIDs, are commonly used medications. Guidelines for the use of these agents in patients with chronic liver disease (CLD) are not available, despite the possibility that such patients may be more susceptible to the effects of an adverse reaction. Notwithstanding the lack of guidelines for healthcare providers, patients are often counselled to modify their use of these drugs. Therefore, the primary aim of this study was to assess healthcare providers' recommendations on how OTCAs should be used by patients with CLD.

Methods: An 11-question web-based survey was distributed via email to healthcare providers participating in four healthcare networks in the US, to determine what recommendations they make to patients with cirrhosis (compensated and decompensated) and chronic hepatitis regarding the use of paracetamol and NSAIDs. Healthcare providers were also queried about the recommendations they make to patients with cirrhosis regarding pain control, and on the use of paracetamol for patients who consume alcohol daily.

Results: Overall, a 12% response rate was obtained. Internal medicine, family practice, paediatrics, and gastroenterology were the most represented practice types. Recommendations against the use of NSAIDs were significantly less common than recommendations against paracetamol use, in cases of both compensated and decompensated cirrhosis ($p = 0.001$). Non-gastroenterologists and non-primary care physicians were the least likely to recommend against NSAID use ($p = 0.001$), while gastroenterologists were the least likely to recommend against paracetamol in these patients ($p = 0.001$). It was the recommendation of

most respondents that OTCAs should be avoided in patients with cirrhosis, and that paracetamol should be avoided or its dose reduced in the setting of daily alcohol use.

Conclusions: Significant variability exists among healthcare providers on their recommendations for OTCA use in the setting of chronic liver disease. Non-gastroenterologists are more likely to recommend against the use of paracetamol than NSAIDs, and patients with chronic liver disease may be under-treated for pain.

Introduction

Chronic liver disease (CLD) and cirrhosis alter the metabolism and effects of many drugs through a variety of mechanisms, including changes in pharmacokinetic behaviour, altered accumulation of free drug in plasma and end-organ response.[1] As such, the use of over-the-counter analgesics (OTCAs) in these patients should precipitate a heightened awareness among healthcare practitioners of the possibility of adverse events. Unfortunately, there are no established guidelines or systematic assessments of safety with regards to the use of OTCAs in this group of patients.

Despite the lack of clear guidelines, it has been recommended that patients with known CLD take lower than the usual doses of OTCAs, most notably paracetamol (acetaminophen), and that this group of patients be closely monitored for toxicity.[2,3] This recommendation stems from our understanding of the metabolism of paracetamol and the potential for hepatotoxicity in cases of ingestion of very high quantities, or when it is used in the setting of malnutrition or chronic alcohol consumption.[4-11] The recent work by Watkins et al.[12] has introduced new uncertainty as to the safety of paracetamol, even in healthy individuals. In that study, recommended doses of paracetamol taken for 14 days were found to lead to elevated transaminase levels in healthy patients.[12] However, the clinical significance of these findings remains uncertain.

In contrast to paracetamol, little is known about practitioners' perception of the risks associated with the use of NSAIDs in patients with CLD. However, risks of NSAID-induced end-organ damage as well as idiosyncratic hepatoxicity have been described.[13,14] A better understanding of the opinions of practicing healthcare providers and the recommendations they make regarding the use of OTCAs in patients with CLD will help direct efforts to develop standardized recommendations for their safe use in these patients. Therefore, we used a web-based survey of healthcare providers to assess their opinions with respect to OTCA use in this population.

Methods

Four healthcare networks based at academic hospitals were recruited to participate in this survey: Thomas Jefferson University, Temple University, Geisinger Health System and the University of Pennsylvania. All participating healthcare networks comprise multi-specialty, tertiary-care networks in the state of Pennsylvania, with all but one, Geisinger Health System, maintaining a significant presence in an urban setting. In order to participate, each healthcare network was required to have an intranet through which it could communicate with its healthcare providers.

An 11-question, web-based, anonymous survey was distributed via email links on three repeat occasions within 7 days in the spring of 2005 to health-

Table I. Survey submitted to healthcare providers

Questions	Possible responses
How would you describe your practice?	(i) family practice; (ii) internal medicine; (iii) gastroenterology; (iv) paediatrics; (v) surgery; (iv) other
How many years have you been in practice?	(i) 1–5 years; (ii) 6–10 years; (iii) 11–15 years; or (iv) ≥16 years
Which best describes your practice?	(i) clinical/academic; (ii) clinical/private; or (iii) research
What do you think that patients with compensated cirrhosis should be told about the use of paracetamol (acetaminophen)?	(i) should use as directed on the product label; (ii) should use but take less than recommended on the product label; (iii) should not use at all; (iv) N/A
What do you think that patients with decompensated cirrhosis should be told about the use of paracetamol?	as above
What do you think that patients with compensated cirrhosis should be told about the use of non-steroidal anti-inflammatory drugs (NSAIDs)?	as above
What do you think that patients with decompensated cirrhosis should be told about the use of NSAIDs?	as above
What do you think that patients with chronic hepatitis without known cirrhosis should be told about the use of paracetamol?	as above
What do you think that patients with chronic hepatitis without known cirrhosis should be told about the use of NSAIDs?	as above
What do you think patients with history of daily alcohol use without recognized liver disease should be told about the use of paracetamol?	as above
In patients with cirrhosis and pain, what do you advise for pain control?	(i) paracetamol-containing products; (ii) NSAIDs; (iii) avoidance of all OTCAs; (iv) N/A

N/A = non-applicable; **OTCA** = over-the-counter analgesics.

care providers in each of the four different medical institutions (table I). Only one response from each recipient was analysed.

In the survey, healthcare providers were asked to describe their specialty, number of years in practice and practice focus (clinical/academic, clinical/private or research). The survey then queried physicians regarding their recommendation on the use of NSAIDs versus paracetamol in compensated and decompensated cirrhosis, chronic hepatitis (without known cirrhosis) and on the use of paracetamol in the setting of daily alcohol use (table I). Compensated cirrhosis was defined as being free from the complications associated with cirrhosis. Decompensated cirrhosis was defined as cirrhosis with complications such as ascites, bleeding or encephalopathy. Questions regarding healthcare providers' recommendations on the use of NSAIDs and paracetamol had the same four possible responses: (i) should use as directed on the product label; (ii) should use but take less than recommended on the product label; (iii) should not use at all; or (iv) non-applicable (N/A). In addition, one question queried healthcare providers about their recommendations for pain control in patients with cirrhosis; response options were: (i) paracetamol-containing products; (ii) NSAIDs; (iii) avoidance of all OTCAs; or (iv) N/A.

Responses were submitted via each institution's intranet and then forwarded to a central data repository at Thomas Jefferson University, where analysis of the aggregate data took place. For preliminary analyses, recommendations for the use of NSAIDs and paracetamol-containing analgesics were classified as 'do not use', 'use less than recommended' or 'use as recommended'. The response 'N/A' was excluded from analysis. Marginal homogeneity tests were used to compare recommendations regarding NSAIDs versus paracetamol-containing analgesics for compensated and decompensated cirrhosis, and for chronic hepatitis. In further analyses, logistic

regression models were applied to investigate the association between opinions on recommendations for analgesic use and a number of physician characteristics. These included physician practice type (classified as family practice/internal medicine, gastroenterology, paediatrics and 'other', which was defined as specialties other than paediatrics, gastroenterology, family practice or internal medicine), healthcare network site, practice focus (clinical/academic or clinical/private practice) and number of years in practice (1–5, 6–10, 11–15 or ≥16). In these analyses, recommendation for the use of OTCAs was defined as a dichotomous outcome ('do not use' vs 'use less than or as recommended'). Separate exact logistic regression models were fitted for each type of analgesic (NSAIDs or paracetamol) and for each hepatic condition, from which adjusted odds ratios, 95% CIs and p-values were computed. Statistical analyses were conducted in SAS 9.1 (SAS Institute Inc., Cary, NC, USA) and LogXact 5 (Cytel Corp., Cambridge, MA, USA).

Results

Surveys were sent to a total of 2391 healthcare providers: 700 were located at Geisinger Health System; 400 at Thomas Jefferson University Hospital; 291 at Temple University; and 1000 at the University of Pennsylvania. A total of 286 responses were received from all participating institutions, meaning an overall response rate of 12% (with response rates for each individual institution of 18%, 19%, 20% and 3%, respectively). The most represented practice types were internal medicine (18%), family practice (13%), paediatrics (8%) and gastroenterology (7%). The majority of responding healthcare providers reported being part of an academic practice.

The results for respondents' recommendations on the use of NSAIDs and paracetamol-containing products for the spectrum of CLD (daily alcohol use, chronic hepatitis and cirrhosis, compensated or decompensated) are summarized in table II. Overall, recommendations against the use of paracetamol were significantly more common than recommendations against the use of NSAIDs for compensated cirrhosis, decompensated cirrhosis and chronic hepatitis. These differences were statistically significant. Specifically, for patients with compensated cirrhosis, 26% of respondents recommended against the use of NSAIDs, versus 40% against the use of paracetamol ($p = 0.001$). For patients with decompensated cirrhosis, 67% recommended against the use of NSAIDs versus 84% against the use of paracetamol ($p = 0.001$). For patients with chronic hepatitis, 14% recommended against the use of NSAIDs versus 24% against the use of paracetamol ($p = 0.001$). The differences remained statistically significant even after exclusion of the 22 paediatricians, who may not have had a significant exposure to patients with CLD ($p = 0.001$ for all three hepatic conditions). With regard to the use of paracetamol in patients who consume alcohol daily, 32% of healthcare providers responded that paracetamol should be avoided altogether, and 41% responded that paracetamol should be used at doses less than those indicated. The remaining 28% of respondents were of

Table II. Physicians' recommendations regarding the use of NSAIDs and paracetamol (acetaminophen), by hepatic condition

Physician recommendations [n (%)]	Compensated cirrhosis		Decompensated cirrhosis		Chronic hepatitis		Daily alcohol consumption
	NSAIDs (n = 274)	APAP (n = 278)	NSAIDs (n = 277)	APAP (n = 278)	NSAIDs (n = 280)	APAP (n = 279)	APAP (n = 279)
Do not use	71 (25.9)	112 (40.3)	186 (67.1)	234 (84.2)	38 (13.6)	66 (23.7)	88 (31.5)
Less than indicated	130 (47.4)	129 (46.4)	52 (18.8)	38 (13.7)	124 (44.3)	126 (45.2)	113 (40.5)
Use as indicated	73 (26.6)	37 (13.3)	39 (14.1)	6 (2.2)	118 (42.1)	87 (31.2)	78 (28.0)

APAP = *N*-acetyl-*p*-aminophenol, chemical name of paracetamol.

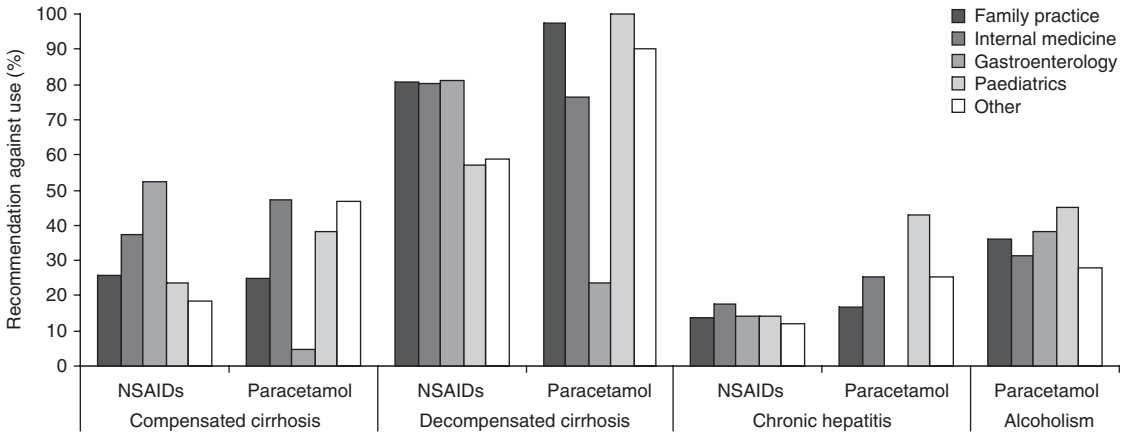

Fig. 1. Recommendations against the use of NSAIDs and paracetamol (acetaminophen) for each hepatic condition, by physician practice type. 'Other' physicians were defined as belonging to specialties other than family practice, internal medicine, paediatrics or gastroenterology.

the opinion that full doses of paracetamol should be recommended for patients consuming alcohol daily (table II).

When asked about pain control in patients with cirrhosis, 32% of healthcare providers were of the opinion that NSAIDs should be recommended for the control of pain versus 23% who were of the opinion that paracetamol should be recommended. However, 45% responded that they would advise avoidance of any OTCA in this group of patients.

Practice Type

When analysis was conducted by practice type, we found significant differences in recommendations regarding NSAID use in patients with compensated cirrhosis and those with decompensated cirrhosis (figure 1). Paediatricians and 'other' physicians were less likely to recommend against the use of NSAIDs in both compensated ($p = 0.028$) and decompensated cirrhosis ($p = 0.001$) compared with family practice/internal medicine physicians. There was no statistically significant difference between gastroenterologists and family practice/internal medicine physicians regarding recommendations against NSAID use for either compensated or decompensated cirrhosis ($p = 0.153$ and 0.999, respectively). Regarding recommendations against NSAIDs for chronic hepatitis, there was no statistical difference across physician practice types ($p = 0.645$). With respect to paracetamol, recommendations for use differed significantly across physician practice types for compensated cirrhosis ($p = 0.001$), decompensated cirrhosis ($p = 0.001$) and chronic hepatitis ($p = 0.006$). Specifically, gastroenterologists were least likely to recommend against the use of paracetamol than any other physicians. With regard to paracetamol and daily alcohol use, there was no statistical difference across practice types in the recommendation that patients should be advised against the use of this drug ($p = 0.633$).

Multivariable analyses investigated the independent association between the various healthcare provider characteristics (healthcare network site, practice type and focus, years in practice) and the recommendations against NSAID or paracetamol in patients with CLD. These results are summarized for NSAIDs and paracetamol in tables III and IV, respectively.

Recommendations on the use of NSAIDs remained significantly different across practice types

Table III. Multivariable logistic model of factors influencing opinions on recommendations against the use of NSAIDs, by hepatic condition[a]

	Compensated cirrhosis (n = 273)		Decompensated cirrhosis (n = 276)		Chronic hepatitis (n = 279)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Practice type						
Family/internal medicine	Reference	0.002	Reference	0.001	Reference	0.798
Gastroenterology	2.53 (0.81, 7.78)		1.18 (0.31, 5.38)		0.91 (0.14, 4.25)	
Other	0.48 (0.24, 0.95)		0.33 (0.15, 0.65)		0.74 (0.32, 1.80)	
Practice focus						
Academic	Reference	0.074	Reference	1.000	Reference	0.056
Private	0.49 (0.21, 1.11)		0.98 (0.47, 2.03)		0.37 (0.11, 1.04)	
Years in practice						
1–5	Reference	0.121	Reference	0.001	Reference	0.065
6–10	1.45 (0.51, 3.97)		1.77 (0.75, 4.20)		0.88 (0.14, 3.84)	
11–15	1.35 (0.50, 3.68)		2.23 (0.92, 5.39)		1.40 (0.34, 5.30)	
≥16	2.40 (1.10,5.17)		4.58 (2.24, 9.67)		2.82 (1.08, 7.87)	

a Site was included in the analysis, but was not significant in any model and is not shown here.

OR = odds ratio.

in patients with compensated and decompensated cirrhosis (p = 0.002 and 0.001, respectively); 'other' physicians, including paediatricians, were less likely to recommend against NSAID use than family practice/internal medicine physicians (table III). For patients with chronic hepatitis, recommendations remained similar across all practice types (p = 0.798).

With regard to paracetamol, there were significant differences across practice types in compensated and decompensated cirrhosis, as well as chronic hepatitis (p = 0.001, 0.001 and 0.003, respectively). Gastroenterologists were far less likely than family practice and internal medicine physicians to recommend against paracetamol use for these patients (table IV). For patients with daily alcohol use, recommendations against the use of paracetamol did not differ across physician practice types (p = 0.621).

Practice Focus

Healthcare providers in private settings were less likely to recommend against the use of NSAIDs for patients with compensated cirrhosis and chronic hepatitis (p = 0.074 and 0.056, respectively), but not for patients with decompensated cirrhosis (table III). With regard to recommendations against the use of paracetamol, there were no significant differences across practice types.

Years in Practice

There were no significant differences in NSAID recommendations across years of practice for patients with compensated cirrhosis, although there was a trend for physicians who were in practice longer to be more likely to recommend against NSAID use (table III). This trend was more apparent for patients with decompensated cirrhosis and chronic hepatitis (p = 0.001 and 0.065, respectively).

Regarding recommendations on the use of paracetamol, physicians who were in practice longer also tended to recommend against the use of parace-

Table IV. Multivariable logistic model of factors influencing opinions on recommendations against the use of paracetamol (acetaminophen), by hepatic condition[a]

	Compensated cirrhosis (n = 277)		Decompensated cirrhosis (n = 277)		Chronic hepatitis (n = 278)		Alcohol (n = 278)	
	OR (95% CI)	p-value	OR (95%CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Practice type								
Family practice/internal medicine	Reference	0.001	Reference	0.001	Reference	0.003	Reference	0.621
Gastroenterology	0.09 (0.01, 0.60)		0.05 (0.01, 0.21)		0.19 (0.01, 1.07)		1.01 (0.32, 3.06)	
Other	1.43 (0.80, 2.59)		2.16 (0.87, 5.53)		1.50 (0.78, 3.03)		0.77 (0.41, 1.44)	
Practice focus								
Academic	Reference	0.741	Reference	0.203	Reference	0.715	Reference	0.129
Private	0.87 (0.44, 1.72)		2.07 (0.65, 7.69)		1.16 (0.52, 2.57)		0.57 (0.28, 1.21)	
Years in practice								
1–5	Reference	0.332	Reference	0.016	Reference	0.075	Reference	0.564
6–10	1.13 (0.49, 2.64)		6.60 (1.36,47.73)		1.13 (0.37, 3.31)		1.47 (0.63, 3.48)	
11–15	1.17 (0.74, 3.88)		4.31 (1.10, 22.72)		1.60 (0.56, 5.35)		1.42 (0.61, 3.27)	
≥16	1.65 (0.87, 3.22)		1. 99 (0.80, 5.18)		2.42 (1.11, 5.40)		0.96 (0.47, 1.89)	

a Site was included in the analysis, but was not significant in any model and is not shown here.

OR = odds ratio.

tamol in patients with compensated cirrhosis and chronic hepatitis, although this was not statistically significant. There was a significant difference across years of practice for decompensated cirrhosis ($p = 0.016$), with physicians who were in practice for 6–10 years more likely to recommend against the use of paracetamol (table IV).

Discussion

Through a web-based survey across four different healthcare networks, we queried healthcare providers on the recommendations they make regarding the use of two common analgesics, paracetamol and NSAIDs, to patients with varying degrees of CLD. Our goal was to assess such opinions, and their potential clinical implications. In doing so, we aimed to demonstrate that there is a need for initiatives to standardize recommendations for use of these agents in patients with CLD.

Our results show that healthcare providers frequently were more likely to recommend against the use of paracetamol than NSAIDs in patients with CLD; even in patients with decompensated cirrhosis, physicians were more likely to recommend against the use of paracetamol than against the use of NSAIDs. An inference of this observation is that healthcare providers may regard NSAIDs as less dangerous than paracetamol for use in patients with CLD.

The fact that paracetamol is the most common drug implicated in fulminant hepatic failure in the US today is likely to have led to the perception that it may be dangerous in patients with CLD.[15,16] The recently published study by Watkins et al.,[12] which identifies paracetamol as a cause of significant transaminase elevations in healthy subjects, may contribute to the notion that this drug could be especially toxic to a patient with underlying liver disease. Despite these perceptions, it should be noted that the laboratory abnormalities in that study of paracetamol in healthy subjects were not associated

with any clinical manifestations of liver disease. In addition, there have been numerous studies to suggest that even the prolonged metabolism of paracetamol in patients with CLD rarely has clinically significant consequences.[1,17,18] In fact, a recent literature analysis[19] concluded that paracetamol is a safe and effective OTCA for use in patients with CLD, especially in light of the potential deleterious effects of NSAIDs.[19-21]

It is important to point out the special circumstance involving patients who are chronically using alcohol because there is evidence to suggest that paracetamol at therapeutic to supra-therapeutic doses may be hepatotoxic in these patients.[22-24] The mechanism for this increased potential hepatotoxicity in the setting of chronic alcohol use has been linked to the induction of the cytochrome P450 in combination with the depletion of glutathione stores. This in turn leads to increased levels of the toxic metabolite of paracetamol, N-acetyl-p-benzoquinoneimine, which is responsible for hepatocyte injury.[24,25] However, much of these data are in the form of retrospective studies, and more recent data have challenged the role of alcohol in paracetamol-induced liver injury.[19,22] The majority of healthcare providers responding to this survey were of the opinion that paracetamol can be given to patients using alcohol daily, either at a full or reduced dose. These results affirm that there is no consensus as to the best advice for patients with significant alcohol intake with regard to paracetamol use.

NSAIDs can have deleterious effects on patients with advanced CLD, through indirect end-organ damage as well as through idiosyncratic hepatotoxicity.[1,13,14,26,27] In particular, NSAIDs impart deleterious effects on the kidneys by the inhibition of prostaglandins, which leads to a decrease in renal perfusion and subsequent reduction in glomerular filtration rate. In addition, NSAIDs have also been shown to inhibit renal water metabolism, and may cause mucosal bleeding in patients who are already at increased risk of bleeding as a result of thrombocytopenia and coagulopathy associated with advanced liver disease.[13,28-32] Furthermore, an elevated risk of gastrointestinal bleeding in all patients who use NSAIDs has been well described, even in those without underlying CLD or who take only over-the-counter doses.[33] Despite a recent study suggesting that cyclo-oxygenase 2-selective inhibitors may cause less toxicity than non-selective NSAIDs in CLD,[20] the overall recommendation remains that NSAIDs should be avoided in patients with advanced liver disease.[1]

Our findings suggest that gastroenterologists are more aware that there is a lack of data to prevent the use of labelled doses of paracetamol in patients with CLD.[9,16] This is in contrast to their responses about recommendations on the use of NSAIDs, which were not significantly different from those made by healthcare providers from other specialties. This finding also highlights the possibility that even gastrointestinal specialists may not be sufficiently cautioning patients with liver disease against the potential harm of NSAIDs.

An important observation of our study was that healthcare providers in general are of the opinion that it may be unsafe to use any OTCAs to treat pain in patients with cirrhosis. The obvious implication of this finding is that patients with liver disease may be under-treated for pain. Certainly, the decision to advise a patient with CLD on the use of an analgesic must be made with caution, given the potential for unpredictable drug pharmacokinetics and pharmacodynamics. However, the possibility that patients with CLD are needlessly being under-treated for pain demonstrates the need for development and implementation of standardized guidelines for practicing healthcare providers caring for these patients.

The main limitation of this study is the relatively low overall response rate to the survey (12%). However, the diversity of physician practices did allow for a meaningful comparison of recommendations

between gastroenterologists, primary care physicians and other specialists. One potential bias rests in the fact that the majority of responding physicians belonged to an academic practice, therefore our results may be less reflective of healthcare providers' recommendations in community medical practice settings. Other potential limitations of this study include the grouping of a wide variety of provider specialties into a single category for analysis, and the inclusion of paediatricians (who are less likely to encounter patients with CLD) in the study. However, with respect to paediatricians, the differences in recommendations made by healthcare providers remained statistically significant even after their exclusion from the analysis and therefore we feel confident that the results are unbiased by their responses. The inclusion of healthcare providers from varied specialties is justified since these physicians are certainly in contact with patients with CLD, albeit less frequently than gastroenterologists and primary care physicians. These physicians may be less familiar with OTCA risks in this population and more likely to make harmful recommendations to such patients. One final limitation of the study was the reliance on physicians' responses to the questionnaire without direct observation or measurement of their actual behaviour and recommendations in a clinical setting.

The results of our study invoke a concern that healthcare providers, overall, may be underestimating the potential hepatotoxicity associated with OTCAs, specifically NSAIDs. Subsequently, they may be recommending their use in the place of paracetamol in patients with advanced CLD, regardless of whether alcohol is a contributing factor in the decision.

Conclusion

Our results call into question the appropriate use of over-the-counter analgesics in patients with varying degrees of liver disease. We found that overall recommendations against the use of NSAIDs were significantly less common than recommendations against the use of paracetamol. This was especially true for non-gastroenterologists and non-primary care physicians. In addition, there appears to be hesitancy in recommending OTCAs in patients with liver disease. The establishment of guidelines which provide some advice on the safe use of OTCAs in patients with CLD should be further explored.

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