

# Management of Acetaminophen Hepatotoxicity: A Survey of Practicing Physicians

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- **Objective:** To assess and compare practicing gastroenterologist and primary care physician (PCP) knowledge of risk factors for, clinical management of, and attitudes toward liver transplantation for acetaminophen hepatotoxicity.
- **Participants and setting:** 333 PCPs and 64 gastroenterologists practicing in Michigan.
- **Outcome measures:** Knowledge of risk factors and management were measured by survey items and a summative knowledge index and a summative management index; attitude toward liver transplantation was measured by survey items.
- **Results:** Gastroenterologists were more likely than PCPs to have treated at least 1 patient with acetaminophen hepatotoxicity in the past year ( $P \leq 0.001$ ). Knowledge of acetaminophen hepatotoxicity risk factors was high in both groups. However, prolonged fasting was correctly identified as a risk factor by only 57% of all respondents. Gastroenterologists were significantly more likely to recommend N-acetylcysteine (NAC) in cases of nonintentional acetaminophen hepatotoxicity, refer patients with severe acetaminophen hepatotoxicity for liver transplant evaluation, and have higher management index scores compared with PCP respondents ( $P \leq 0.001$ ). Gastroenterologists were also more likely to endorse liver transplantation for patients with intentional acetaminophen hepatotoxicity compared with PCPs (74% versus 59%,  $P \leq 0.001$ ).
- **Conclusions:** Knowledge of risk factors for acetaminophen hepatotoxicity was high in both physician groups. As expected, gastroenterologists were more familiar with the clinical management of acetaminophen hepatotoxicity. In addition to further education of practicing physicians, assessment of consumer behavior and knowledge may be warranted to address the rising incidence of nonintentional acetaminophen hepatotoxicity in the United States.

consumed annually worldwide [1]. Large or excessive doses of acetaminophen taken over a short time period may result in life-threatening hepatotoxicity [2,3]. Intentional acetaminophen hepatotoxicity associated with suicidal behavior is the leading cause of acute liver failure in the United Kingdom, and an estimated 100,000 cases of intentional acetaminophen overdose are reported each year in the United States [4,5]. In addition, the incidence of nonintentional acetaminophen hepatotoxicity in patients receiving acetaminophen products for therapeutic intent is rising; these cases are associated with a high fatality rate [6–8]. Although the amount of acetaminophen ingested in many of these cases exceeds the recommended dose, several common clinical risk factors may predispose some patients to “therapeutic misadventures.” For example, chronic alcohol consumption and ingestion of medications that induce cytochrome P-450 enzyme activity have been implicated in predisposing some individuals to nonintentional acetaminophen hepatotoxicity [9–11]. Prolonged fasting with resultant depletion in hepatic glutathione stores also has been implicated as a risk factor in animal models and in patients with nonintentional acetaminophen hepatotoxicity [12,13].

Because many of these risk factors are commonly encountered in clinical practice, practicing physicians should be aware of the potential for untoward events when prescribing products that contain acetaminophen [14]. The primary aim of this study was to assess and compare practicing physicians’ knowledge of the risk factors and clinical management of acetaminophen hepatotoxicity. We also wanted to determine practicing physicians’ attitudes towards liver transplantation in patients with intentional and nonintentional acetaminophen hepatotoxicity. Based on prior experience and training, we hypothesized that practicing gastroenterologists would be more knowledgeable than PCPs of risk factors for acetaminophen hepatotoxicity and clinical management of suspected acetaminophen hepatotoxicity.

Currently, there are more than 200 over-the-counter products that contain acetaminophen, and it is estimated that more than 1 billion acetaminophen tablets are

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VIGNETTE 1  
(NONINTENTIONAL ACETAMINOPHEN  
HEPATOTOXICITY)

A 62-year-old woman receiving chronic phenytoin and Darvocet for trigeminal neuralgia develops an influenza-like illness with nausea, anorexia, and reduced oral intake. Following ingestion of 4 g of acetaminophen per day for 5 consecutive days, she presents to the emergency room with abdominal pain, metabolic acidosis, coagulopathy, and serum aminotransferase levels of 2000 U/L. Despite medical therapy, she develops worsening coagulopathy and encephalopathy, and the possibility of liver transplantation is raised.

VIGNETTE 2  
(INTENTIONAL ACETAMINOPHEN  
HEPATOTOXICITY)

An 18-year-old woman with a history of recent alcohol binge intentionally ingests 15 g of acetaminophen as a suicide gesture. In the emergency room, serum aspartate aminotransferase is 600 U/L, serum alanine aminotransferase is 250 U/L, and serum bilirubin level and prothrombin time are normal. Despite treatment, she develops confusion and somnolence with serum aminotransferase levels greater than 2000 U/L. Her family inquires about the possibility of liver transplantation.

## Methods

### Survey Population

A self-administered survey was mailed to 1000 primary care physicians (PCP) in southeastern Michigan and to 180 gastroenterologists practicing throughout the state of Michigan. The PCP participants were randomly selected from a large health maintenance organization affiliated with the University of Michigan Medical Center. The gastroenterology participants were identified from a hospital database of practicing gastroenterology physicians. Instructions for completing the survey and a stamped, self-addressed return envelope were sent to all addressees. In order to maintain respondent confidentiality, the survey was unmarked. Respondents were entered into a lottery to win a \$50 gift certificate. The initial survey was mailed to eligible participants in October 1999,

and a reminder postcard was mailed 1 week later. A second survey was mailed in November 1999, followed by a reminder postcard 2 weeks later. Follow-up telephone calls to nonresponders were made over several weeks, and a final survey was mailed in February 2000. The protocol was approved by the local Institutional Review Board.

### Survey Design

The questionnaire was designed to assess practicing physician knowledge in 3 areas: (1) risk factors for acetaminophen hepatotoxicity; (2) indications and relative safety of acetaminophen and nonsteroidal anti-inflammatory drug (NSAID) analgesics; and (3) clinical recognition and management of acetaminophen hepatotoxicity. We also set out to determine physician attitudes toward liver transplantation for intentional and non-intentional acetaminophen hepatotoxicity. The questionnaire consisted of 28 items (items were numbered 1 through 21; 1 item had 8 subitems) and took 10 minutes to complete. To pretest the questionnaire, we administered it to 60 internal medicine house officers at the University of Michigan Medical Center; following pretesting, we revised the questionnaire. Risk factor knowledge, knowledge of safety of acetaminophen and NSAID analgesics, and attitudes toward liver transplantation were assessed using 17 Likert-scaled items. Each item had 4 possible answers indicating strength of agreement that ranged from strongly agree to strongly disagree. Recognition and management of intentional and nonintentional acetaminophen hepatotoxicity were assessed using 2 case vignettes (**Sidebar**) and 5 multiple-choice items (1 of these items also assessed risk factor knowledge). The final section of the survey consisted of 6 demographic questions.

### Analysis

The responses to 14 Likert-scaled questions assessing physician knowledge of acetaminophen hepatotoxicity risk factors were used to construct a summative knowledge index. Item analysis resulted in a 10-item knowledge index that maximized internal consistency (Cronbach  $\alpha = 0.72$ ) [15]. This composite variable allowed us to compare overall knowledge levels between the 2 groups of physicians and predict factors contributing to variation in overall knowledge. Similarly, the responses to 6 questions assessing the management of acetaminophen hepatotoxicity were used to construct a summative management index. Item analysis resulted in a 5-item management index (Cronbach  $\alpha = 0.37$ ). Between-group comparisons of gastroenterology and PCP respondents were conducted using chi-square tests and *t* tests; bivariate analysis was used to identify predictors of the 2 summative indices. The ordinary least squares multiple regression approach was used to determine predictors of the knowledge and management indexes. Respondent age, sex, years in practice, practice setting, experience with acetaminophen

hepatotoxicity in the past year, and physician group were included in the regression models. Inclusion of covariates in the regression models was based on issues of multicollinearity rather than on bivariate statistical significance. *P* values less than 0.05 were considered statistically significant. All analyses were performed using STATA Version 6 (Stata Corporation, 1999, College Station, TX).

## Results

### Respondent Demographics

Surveys mailed to 77 PCPs and 4 gastroenterologists were returned due to improper address labeling, leaving a total of 1099 eligible participants (923 PCPs, 176 gastroenterologists). The participant response rate did not significantly differ between the PCP (333/923, 36.5%) and gastroenterologist (64/176, 36.4%) groups. The 333 PCP respondents included 163 family practitioners, 90 internists, 65 pediatricians, and 15 other PCPs.

Gastroenterologists were significantly more likely to be male and to have treated at least 1 patient with acetaminophen hepatotoxicity in the past year than were PCP respondents (Table 1). Nearly two thirds of gastroenterologists had treated at least 1 patient in the past 12 months compared with one quarter of the PCP respondents. The mean age and number of years in practice did not significantly differ between the 2 groups. Respondents predominantly characterized their practice setting as "suburban" (73%), with a few respondents indicating a "rural" (18%) or "inner city" (9%) practice setting; no significant differences in practice setting were noted between groups.

### Risk Factor, Epidemiology, and Safety Knowledge

Table 2 shows the percentage of each physician group that correctly recognized 8 potential risk factors for acetaminophen hepatotoxicity by physician group. Overall, correct recognition of these risk factors was high. More than 95% of respondents in both groups correctly categorized chronic alcohol consumption exceeding 3 drinks per day and total dose of acetaminophen consumed as potential risk factors for acetaminophen hepatotoxicity. PCP respondents showed significantly greater awareness of cirrhosis as a potential risk factor for acetaminophen hepatotoxicity ( $P \leq 0.001$ ). A smaller but similar proportion of respondents in both groups properly recognized anticonvulsant use and prolonged fasting as potential risk factors.

The majority of respondents in both groups were aware that annual mortality due to chronic NSAID use is higher than annual mortality due to acetaminophen hepatotoxicity (Table 2). About half of the respondents in both groups correctly recognized that the majority of acetaminophen hepatotoxicity cases result from intentional overdose. Almost exactly half of each physician group correctly identified the

Table 1. Respondent Demographics

	PCP Group (n = 333) %	GI Group (n = 64) %	$\chi^2_{(1)}$	P Value
Age, yr			0.626	NS
Up to 50	60.4	65.6		
51 or more	39.6	34.4		
Sex			20.186	$P \leq 0.001$
Male	68.7	95.3		
Female	31.3	4.7		
Years in practice			0.014	NS
Up to 15	49.2	48.4		
16 or more	50.8	51.6		
Practice location			1.402	NS
Suburban	70.9	78.1		
Inner city or rural	29.1	21.9		
Treated ACM hepatotoxicity patients in past year			39.047	$P \leq 0.001$
At least 1	24.6	64.1		
None	75.4	35.9		

ACM = acetaminophen; GI = gastroenterologist; NS = not significant; PCP = primary care physician;  $\chi^2_{(1)}$  = Pearson chi-square with 1 degree of freedom.

relationship between daily NSAID use and the development of gastrointestinal toxicity. Approximately half of the physicians in both groups were also aware that acetaminophen is preferred and recommended over NSAIDs in patients with osteoarthritis. However, gastroenterologists were significantly more likely to recognize that acetaminophen is preferred over NSAIDs in patients with cirrhosis ( $P \leq 0.001$ ).

The responses to items 1 through 9 and 14 in Table 2 were used to construct a summative knowledge index. The knowledge index scores ranged from a low of 0 ( $n = 1$ ) to a high of 10 ( $n = 18$ ); the mean was 7.52. We found no significant difference in knowledge index scores between PCPs and gastroenterologists. More specifically, out of a total possible score of 10, the mean PCP score of 7.46 ( $n = 333$ ) was similar to the mean gastroenterologist score of 7.81 ( $n = 64$ ). Furthermore, regression analyses of demographic variables and management index scores demonstrated that only management index scores significantly influenced knowledge index scores ( $P \leq 0.001$ ) (data not shown).

### Recognition and Management of Hepatotoxicity

Regarding treatment of an acetaminophen overdose, 58.6% of the PCPs and 62.5% of the gastroenterologists recognized that N-acetylcysteine (NAC) treatment might be of benefit when administered more than 12 hours after ingestion.

**Table 2.** Physician Knowledge of Acetaminophen Hepatotoxicity Risk Factors, Epidemiology, and Safety

	PCP Group (n = 333) % correct	GI Group (n = 64) % correct	$\chi^2_{(1)}$	P Value
<b>Risk factors</b>				
1. Coadministration with food	90.4	98.4	4.830	$P \leq 0.05$
2. Total acetaminophen dose consumed	96.4	96.9	0.612	NS
3. Chronic alcohol consumption*	96.7	95.3	1.402	NS
4. Smoking	61.0	85.9	14.718	$P \leq 0.001$
5. Cirrhosis	94.9	79.7	17.772	$P \leq 0.001$
6. Concomitant use of anticonvulsant	74.8	68.7	1.617	NS
7. Concomitant use of antibiotics	75.1	67.2	1.752	NS
8. Prolonged fasting	58.0	54.7	0.931	NS
<b>Epidemiology</b>				
9. Annual NSAID toxicity deaths exceed those due to ACM hepatotoxicity	61.0	68.7	1.385	NS
10. The majority of ACM hepatotoxicity cases result from intentional overdose	46.5	54.7	1.426	NS
11. Alcohol potentiates the gastrointestinal toxicity of NSAIDs (eg, bleeding, ulcers)	95.2	85.9	7.797	$P \leq 0.01$
12. Fewer than 1% of patients receiving daily NSAIDs for 2 months develop significant gastrointestinal toxicity (eg, bleeding, ulcers)	54.0	50.0	0.355	NS
<b>Indications and safety</b>				
13. ACM is preferred to NSAID analgesics in patients with cirrhosis	38.1	65.6	16.589	$P \leq 0.001$
14. ACM is preferred to NSAID analgesics in patients with osteoarthritis	52.5	43.7	1.66	NS

ACM = acetaminophen; GI = gastroenterologist; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; PCP = primary care physician;  $\chi^2_{(1)}$  = Pearson chi-square with 1 degree of freedom.

\*More than 3 drinks per day.

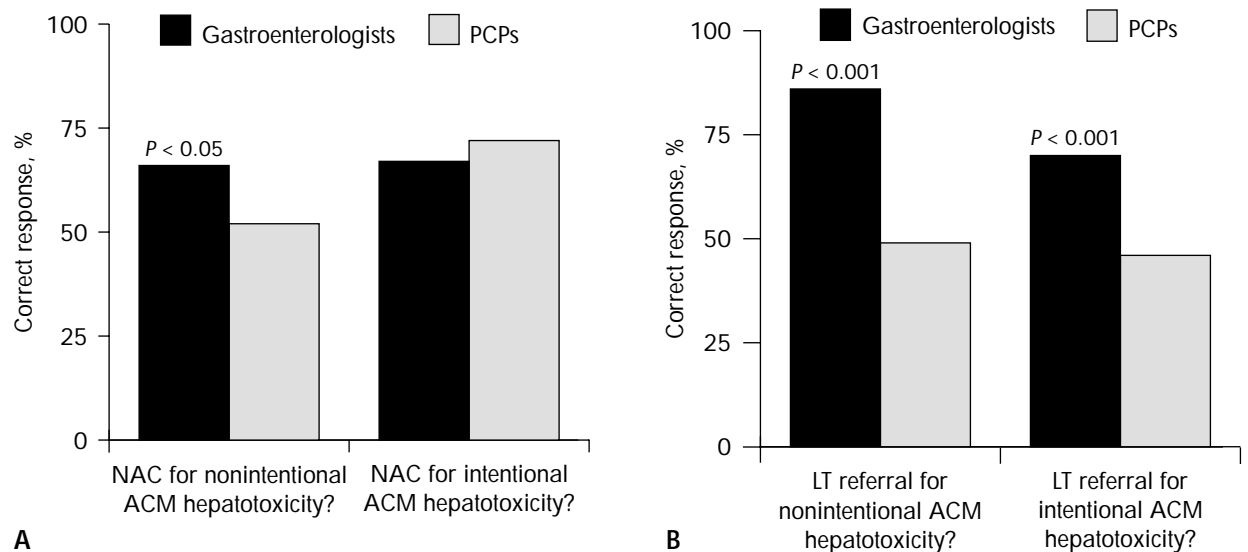
However, gastroenterologists were more likely to recommend NAC therapy in vignette 1 ( $P \leq 0.05$ ) (Figure 1). In addition, the gastroenterologist group was significantly more likely to refer the patient in vignette 1 and vignette 2 for liver transplant evaluation than was the PCP group ( $P \leq 0.001$ ). However, there was no difference in the use of NAC therapy in vignette 2 ( $P = 0.459$ ). Only 34% of physicians in both groups correctly identified prolonged fasting as a risk factor for acetaminophen hepatotoxicity in vignette 1. Furthermore, only 51% of those who correctly identified prolonged fasting as a risk factor in Table 2 (item 8) were able to identify prolonged fasting as a risk factor in vignette 1.

The summative management index consisted of the 4 management questions from the vignettes (Figure 1) and the item assessing the potential benefit of NAC when given more than 12 hours after acetaminophen ingestion. Management index scores ranged from a low of 0 ( $n = 16$ ) to a high of 5 ( $n = 47$ ); the mean was 2.89. The mean gastroenterologist score of 3.5 ( $n = 64$ ) was significantly higher than the mean PCP score of 2.7 ( $n = 333$ ) ( $P \leq 0.001$ ). In regression analysis, gastroenterologists had significantly higher management index scores than PCPs; similarly, physicians practicing for less than 15 years had significantly higher management index scores than those practicing for 15 years or more ( $P < 0.001$ ). In addition,

younger physicians (under age 50 years) registered higher management index scores relative to older physicians ( $P \leq 0.001$ ). Knowledge index scores were positively associated with management index scores ( $P \leq 0.01$ ), as was having treated at least 1 acetaminophen overdose patient in the past year ( $P \leq 0.01$ ). Respondent gender and practice setting, however, were not associated with management index scores (data not shown).

### Opinions Toward Liver Transplantation

Both PCP and gastroenterologists strongly endorsed liver transplantation for patients with nonintentional acetaminophen hepatotoxicity (Figure 2). However, both groups were less likely to support liver transplantation for intentional acetaminophen hepatotoxicity, with gastroenterology physicians favoring liver transplantation more frequently than PCPs ( $P \leq 0.001$ ). Overall, about 33% of all physicians endorsed liver transplantation for nonintentional acetaminophen hepatotoxicity but not for subjects with intentional acetaminophen hepatotoxicity. Of the 218 physicians who recommended liver transplantation in vignette 1, 98% ( $n = 213$ ) also agreed that patients with nonintentional acetaminophen hepatotoxicity are suitable candidates for liver transplantation. In vignette 2, 83% ( $n = 165$ ) of the 198 physicians recommending liver



**Figure 1.** Gastroenterology and primary care physician (PCP) respondents who correctly answered that (A) N-acetylcysteine (NAC) is appropriate for acetaminophen (ACM) hepatotoxicity, and (B) liver transplantation (LT) referral is appropriate for ACM hepatotoxicity.

transplantation also approved of liver transplantation for patients with intentional acetaminophen hepatotoxicity. These findings suggest that there is consistency between physician opinion regarding selection criteria for liver transplantation and physician behavior when recommending treatment for a patient with severe acetaminophen hepatotoxicity.

**Discussion**

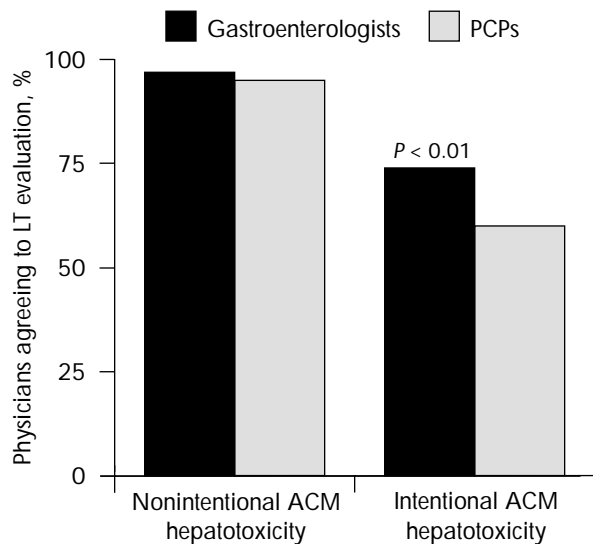
Acetaminophen is a safe and highly effective analgesic when used in recommended doses. However, acetaminophen is also a well-characterized, dose-dependent hepatotoxin that can lead to life-threatening acute liver failure when excessive doses are ingested [5]. Our study results demonstrate that overall practicing physician knowledge of recognized risk factors for acetaminophen hepatotoxicity is high, as assessed by individual questions and the summative knowledge index. The lack of a difference in the 2 respondent groups was somewhat surprising in light of the greater clinical experience with acetaminophen hepatotoxicity in the past year among gastroenterologists compared with PCP respondents. Furthermore, gastroenterologists would be expected to have greater knowledge of a specific liver disease due to subspecialty training. It is possible that PCPs have expanded their fund of knowledge of acetaminophen hepatotoxicity in light of recent well-publicized reports and changes in acetaminophen product labeling [6,9,16].

The overall response rate to our survey of 36.1% is comparable to that reported in other studies of PCP and gastroenterologist knowledge of *Helicobacter pylori* infection (30%) and chronic hepatitis C (33%) [17,18]. The low response rate observed might be due in part to the targeting of practicing

physicians who have limited time to complete mail surveys [19–21]. While a higher response rate would have minimized the likelihood of respondent bias, our primary objective was to compare knowledge and attitudes between the 2 physician groups. In this sense, the lack of significant variation in response rates in the physician groups allows for an unbiased estimation of between-group differences. Furthermore, the age and gender profiles of our respondents were representative of the targeted physician groups [22,23]. Therefore, we feel that the surveyed respondents are representative of PCPs and gastroenterologists practicing in the United States.

Both groups of respondents clearly recognized that chronic alcohol consumption exceeding 3 drinks per day and the total acetaminophen dose consumed are potential risk factors for acetaminophen hepatotoxicity [9,10,12]. In addition, both groups of respondents recognized that other patient behaviors such as concomitant antibiotic use or coadministration of acetaminophen with food do not increase the risk of acetaminophen hepatotoxicity. However, the increased likelihood of acetaminophen hepatotoxicity developing in individuals with prolonged fasting was correctly identified by only approximately 50% of the respondents in both groups [12]. In addition, prolonged fasting was correctly recognized as a risk factor in vignette 1 by only 34% of respondents. The low level of awareness of this risk factor may be due to the frequent lack of inquiry regarding fasting in an outpatient medical interview compared with inquiry about alcohol intake [24,25]. In addition, there is limited published information on the clinical association of fasting with acetaminophen hepatotoxicity, and the potential hazards of prolonged fasting were not mentioned in the recent

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**Figure 2.** Gastroenterology and primary care physician (PCP) respondents who agreed that patients with nonintentional acetaminophen (ACM) hepatotoxicity and patients with intentional ACM hepatotoxicity are suitable candidates for liver transplantation (LT) evaluation.

product-label revisions for over-the-counter acetaminophen products [12,16].

Gastroenterologists did not consider cirrhosis a risk factor for acetaminophen hepatotoxicity as frequently as PCP respondents (Table 2). This discrepancy may be due to controversial issues in the medical literature regarding the risk of acetaminophen hepatotoxicity in patients with chronic liver disease [26,27]. Gastroenterologists may be more aware of the preservation of hepatic glucuronidation activity in patients with cirrhosis, allowing for the safe metabolism of acetaminophen through nontoxic pathways [28]. In addition, gastroenterologists may be more familiar with the data confirming the safe use of low-dose acetaminophen in patients with chronic liver disease [29–31]. Gastroenterologists were significantly more likely to recognize that acetaminophen is preferred over NSAIDs in patients with cirrhosis due to the potentially severe gastrointestinal and renal toxicity of NSAIDs [32,33]. Therefore, gastroenterologists may have felt that patients with cirrhosis are not at marked risk for acetaminophen hepatotoxicity if a low total daily dose of acetaminophen is consumed.

Management index scores reflecting practicing physician knowledge of the recognition and management of acetaminophen hepatotoxicity were significantly higher in gastroenterologists compared to PCPs. Although a comparable proportion of gastroenterologists and PCPs recognized that NAC may have therapeutic benefit when administered more than 12 hours after an acetaminophen overdose [34–36], gastroen-

terologists were significantly more likely to recommend NAC for a critically ill patient with nonintentional acetaminophen hepatotoxicity (vignette 1) (Figure 1). In addition, gastroenterologists were more likely to recommend evaluation for liver transplantation in patients with both nonintentional and intentional acetaminophen hepatotoxicity. These data suggest that gastroenterologists are more adept at managing patients with acetaminophen hepatotoxicity, as proposed in our hypothesis. Nonetheless, our study results suggest that further education of both physician groups of the potential benefit of early NAC therapy in patients with known or suspected acetaminophen hepatotoxicity is needed to improve clinical outcomes.

The high level of physician support for liver transplantation in nonintentional acetaminophen hepatotoxicity (Figure 2) may be due to the iatrogenic nature of many of these cases [37,38]. Although ethical guidelines indicate that liver transplant candidates should be selected solely on the basis of medical need and not on behavioral issues, PCPs and gastroenterologists may be less supportive of liver transplantation for intentional acetaminophen hepatotoxicity due to a bias against candidates with psychiatric or substance abuse disorders [39,40]. In addition, respondents may be unaware of published data regarding favorable outcomes in selected patients with severe acetaminophen hepatotoxicity undergoing liver transplantation [41].

In conclusion, PCP knowledge of risk factors for acetaminophen hepatotoxicity was excellent and similar to that of gastroenterologists despite significantly less clinical experience in the past year. However, as expected, gastroenterologists had higher management index scores indicative of greater familiarity with the recognition and management of acetaminophen hepatotoxicity. Although overall knowledge level was high in both groups, a greater awareness of the potential benefit of NAC therapy in patients with suspected acetaminophen hepatotoxicity is needed. Repackaging of acetaminophen-containing products into blister packs and limiting the total number of acetaminophen tablets dispensed have recently been implemented in the United Kingdom to reduce the incidence and severity of acetaminophen hepatotoxicity [42,43]. Although concerns regarding the inconvenience and cost of these measures have been raised, preliminary data suggest that these efforts may be effective [44–46]. If other studies confirm our findings of a relatively high level of practicing physician knowledge of acetaminophen hepatotoxicity risk factors, further investigation of consumer behavior and knowledge may be warranted in light of the increasing incidence of nonintentional acetaminophen hepatotoxicity being reported in the United States [6–8].

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*Financial disclosures: none.*

*Author contributions: conception and design, LQ, TS, RF; analysis and interpretation of data, LQ, JB, TS, RF; drafting of the article, LQ, JB, RF; critical revision of the article for important intellectual content, TS, RF; final approval of the article, TS, RF; provision of study materials or patients, RF; obtaining of funding, RF; administrative, technical, or logistic support, LQ, TS, RF; collection and assembly of data, LQ, JB, RF.*

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