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A Systematic Review of the Evidence Behind Use of Reduced Doses of Acetaminophen in Chronic Liver Disease

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Abstract

Acetaminophen is among the most commonly used nonopioid analgesics, but significant variation exists in its prescribing practices for cirrhosis patients. Our primary objective was to describe the quality of evidence supporting or refuting the use of acetaminophen in patients with hepatic dysfunction. A comprehensive literature review of PubMed, Cochrane Library, Web of Science, and International Pharmaceutical Abstracts using the search terms "acetaminophen," "paracetamol," "chronic liver disease," "cirrhosis," and "hepatic disease" for studies describing changes in acetaminophen metabolism in patients with hepatic dysfunction was conducted. Twelve studies and four abstracts were included. Ten studies and three abstracts were pharmacokinetic studies. Two studies and one abstract evaluated the association of acetaminophen use and decompensation in the cirrhotic patient. The level of certainty for dosing recommendations obtainable from reviewing the evidence is low due to a small number of studies meeting search criteria, small samples sizes, inadequate information regarding cirrhosis etiology and compensated versus uncompensated liver disease, and lack of information on patient centered health outcomes. High-quality trials are not available to support the use of decreased acetaminophen doses in compensated cirrhosis patients. Acetaminophen can be a safe analgesic in patients with compensated hepatic dysfunction after careful analysis of patient-specific factors.

Keywords

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

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Abstract:

Acetaminophen is among the most commonly used non-opioid analgesics, but significant variation exists in its prescribing practices for cirrhosis patients. Our primary objective was to describe the quality of evidence supporting or refuting the use of acetaminophen in patients with hepatic dysfunction. A comprehensive literature review of PubMed, Cochrane Library, Web of Science, and International Pharmaceutical Abstracts using the search terms "acetaminophen", "paracetamol", "chronic liver disease", "cirrhosis", and "hepatic disease" for studies describing changes in acetaminophen metabolism in patients with hepatic dysfunction was conducted. Twelve studies and four abstracts were included. Ten studies and three abstracts were pharmacokinetic studies. Two studies and one abstract evaluated the association of acetaminophen use and decompensation in the cirrhotic patient. The level of certainty for dosing recommendations obtainable from reviewing the evidence is low due to a small number of studies meeting search criteria, small samples sizes, inadequate information regarding cirrhosis etiology and compensated versus uncompensated liver disease, and lack of information on patient centered health outcomes. High quality trials are not available to support the use of decreased acetaminophen doses in compensated cirrhosis patients. Acetaminophen can be a safe analgesic in patients with compensated hepatic dysfunction after careful analysis of patient specific factors.

Keywords: acetaminophen, paracetamol, cirrhosis, chronic liver disease, dose

Introduction:

The United States opioid epidemic is a public health crisis that accounted for 42,249 deaths in 2016 and a five-fold increase in opioid overdoses since 1999 (1). The European Association for the Study of the Liver recommend against using NSAIDs (non-steroidal anti-inflammatory drug) in patients with cirrhosis and ascites due to concerns for increased rates of hepatorenal syndrome (2). This has prompted renewed interest in non-opioid analgesics such as acetaminophen for the treatment of acute and chronic pain. An estimated 50 million Americans use acetaminophen weekly and it is contained in more than 600 over-the-counter (OTC) and prescription products (3, 4).

Acetaminophen is well absorbed orally and therapeutic doses are biotransformed primarily in the liver (5). Two saturable pathways exist that produce non-toxic metabolites, the sulfation and glucuronidation pathways (5, 6). Under normal circumstances, 70-90% of acetaminophen is metabolized through these pathways, with a small portion excreted unchanged in the urine. The remainder is transformed to a highly reactive metabolite primarily via the cytochrome P450 (CYP) 2E1 enzyme system to a hepatotoxic moiety, N-acetyl-p-benzoquinoneimine (NAPQI), which is further metabolized to inactive and non-toxic cysteine and mercapturic acid conjugates. The glucuronidation pathway is not fully developed at birth, but increases with age until it reaches adult values at approximately age 10 (7). The rate of sulfation is unchanged with age and compensates for decreased glucuronidation capacity when metabolizing acetaminophen in children less than 10 years (8).   CYP2E1 enzyme activity increases at birth and approaches adult levels by 1-2 years of age (9).

Acetaminophen is the leading cause of acute liver failure (ALF) in the United States, accounting for approximately 50% of cases (10). Variability in acetaminophen prescribing practices exists in all patient populations, but is of greater significance in hepatically impaired patients who may be less likely to recover from drug induced liver injury (DILI) than healthy individuals (11). It was observed among ALF study group institutions that 48% of acetaminophen overdoses were unintentional (12). These statistics draw attention to the potential for harm among acetaminophen users.

 Several studies have drawn attention to the lack of understanding among patients about safe acetaminophen use in chronic liver disease (CLD) and physicians' disparate practices for maximum daily doses of acetaminophen. A recent study by Saab et al noted a significant knowledge deficit in liver disease patients about appropriate acetaminophen use (13). The investigators surveyed 401 outpatients regarding their understanding of acetaminophen dosing. A recommended maximum daily acetaminophen dose of < 3 g/day was identified by 7.5% of patients. Approximately 20% of surveyed patients believed that acetaminophen should be completely avoided in liver disease. Physician evaluation of potential harms caused by acetaminophen varies by specialty and experience. Rossi et al surveyed Philadelphia area physicians regarding their recommendations for acetaminophen use in cirrhosis and chronic hepatitis patients (14).   Survey respondents were more likely to advise their patients to avoid acetaminophen than a NSAID. Gastroenterologists were less likely than family medicine or internal medicine physicians to recommend avoiding acetaminophen use in compensated cirrhosis (OR: 0.09; 95% CI: 0.01-0.60), decompensated cirrhosis (OR: 0.05; 95% CI: 0.01-0.21), and chronic hepatitis (OR: 0.19; 95% CI: 0.01-1.07). Banerjee et al. reported similar survey

findings among gastroenterology fellows, internal medicine residents, and fourth year medical students in the Greater Washington D.C. area (15). Internal medicine and medical students noted their primary reason for using NSAIDs over acetaminophen was concern about worsening patients' CLD (16). When survey respondents did use acetaminophen in CLD patients they were more likely to prescribe < 2 g/day than 4 g/day regardless of liver disease severity (17). These studies highlight the inconsistent understanding of appropriate OTC analgesic use in CLD patients and the diverse prescribing practices among healthcare practitioners.

The FDA released a statement in 2003 regarding medication dosing and labeling recommendations in patients with impaired hepatic function (18). While acetaminophen's use in the United States predates this document by many years, this statement represents current best practices. Key aspects of these non-binding recommendations include use of the Child-Pugh classification for categorization of the severity of hepatic dysfunction and development of dose adjustments for medications if the pharmacokinetics (PK) are substantially altered by hepatic dysfunction. The FDA uses the example of a two-fold or greater increase in the area under the curve. This document does not provide further guidance for dosing in hepatic impairment and does not make specific recommendations for when dose adjustments should be made in pediatric patients.

Recommendations for appropriate acetaminophen use in chronic liver disease patients are further complicated by a lack of consensus from professional organizations. The American Liver Foundation issued a 2006 press release advising CLD patients to consult with their physician before taking acetaminophen, but did not offer guidance to prescribers on recommended regimens (19). Similarly, oral acetaminophen product labeling warns patients

with liver disease to seek physician guidance prior to starting acetaminophen, but does not provide specific dose recommendations (20). The American Geriatrics Society's (AGS) 2009 guideline on Pharmacological Management of Persistent Pain in Older Adults empirically suggests to decrease the maximum daily acetaminophen dose by 50-75% in patients with hepatic disease or a history of alcohol abuse (21). The guideline authors did not elaborate on this recommendation or reference supporting literature. The American Gastroenterological Association (AGA) and American Association for the Study of Liver Disease (AASLD) do not address acetaminophen dosing recommendations for CLD patients. Four review articles provide recommendations for acetaminophen use in cirrhosis patients. Chandok and Watt advised providers' treating patients with cirrhosis that acetaminophen use for greater than 14 days should not exceed 2-3 g/day, but 4g/day may be appropriate if use for less than 2 weeks is anticipated (22). Imani et al advocated for the same dosing in a 2014 review (23). Lewis endorsed use of the lowest effective acetaminophen dose in liver disease patients due to its narrow therapeutic index with a maximum daily dose (MDD) of 2-3g/day (11). Hayward et al published a comprehensive review of acetaminophen metabolism in patients with varying degrees and etiologies of liver disease (24). Their conclusions were that acetaminophen is a safe analgesic in all populations but made nonspecific recommendations for cautious prescribing based on individual patient characteristics. In light of these conflicting recommendations, our goal was to critically evaluate the quality of evidence used to formulate the acetaminophen dose recommendations for chronic liver disease patients.

Methods:

Relevant human studies published or in press before April 2018 were identified in PubMed, Cochrane Library, Web of Science Core Collection, and International Pharmaceutical Abstracts/EBSCOhost using the search terms "acetaminophen", "paracetamol", "chronic liver disease", "cirrhosis", and "hepatic disease". Additionally, we cross-referenced recent review articles to ensure we independently identified pertinent literature. The manufacturers of intravenous and branded acetaminophen were contacted for unpublished trials. We reviewed the U.S. National Library of Medicine ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for ongoing, unpublished, or previously overlooked trials. We reviewed ProQuest Dissertations & Theses Global, OpenSIGLE, OAIster, and the New York Academy of Medicine Grey Literature report that contains grey literature from 1999 to 2016. This search strategy was developed in conjunction with a research librarian.

Our literature review was narrowed to include adult and pediatric patients with diagnosed chronic liver disease. We excluded studies of patients with active alcohol use but without documented liver disease. Studies that were not published in English were also omitted. The authors met to review their findings and discussed their rating rationale until consensus was reached. Each author independently assessed the studies that met the inclusion criteria using a validated checklist to evaluate their quality. However, studies that were only published in abstract form were not analyzed with a validated checklist.

Multiple checklists exist to assess the quality of evidence of randomized, placebo controlled trials, but there are limited options for assessing the validity of pharmacokinetic studies. In 2015 a group of stakeholders released a checklist delineating optimal practices in reporting

pharmacokinetic studies (25). The ClinPK checklist (Table 1) was released in an effort to ensure

adequate information is described to draw unbiased conclusions from reported studies. The

checklist includes domains evaluating known pharmacokinetic data, study methodology,

presentation of results, limitations, and funding. While no standard cutoffs are defined to

demarcate high, intermediate, or low quality studies, the authors determined that it was

important to quantify the quality of information presented in the studies used to make dosing

recommendations in patients with CLD. Each study was evaluated to determine the number of

24 checklist items that were reported.

The assessment tool developed by Downs and Black is validated in both randomized and

nonrandomized trials to quantify study quality (26). We utilized it to analyze case control

studies that met our inclusion criteria. Clarity of reporting, internal validity, external validity,

and power are all assessed. Previous reviews utilizing this have suggested studies scoring from

26-28 are excellent, 20-25 are good, 15-19 are fair, and <14 are poor quality (27).

Results:

Twelve studies and four abstracts were identified as outlined in Figure 1. The population,

design, intervention, outcomes, and evaluation of the studies and abstracts that met our

criteria are described in Table 2 (6, 28-42). Ten studies were evaluated with the ClinPK checklist

(6, 28-32, 34, 36, 37, 42). Their scores ranged from 6 to 16 with a median score of 10.5. All the

studies met the ClinPK checklist criteria for study title, rationale, specific objectives, drug

preparation and administration characteristics, and results reporting (25). Per the ClinPK

checklist criteria eight of ten studies had an appropriate abstract, description of the

bioanalytical methods, commented on subjects lost to follow-up, and quantification of missing or excluded data. None of the studies satisfactorily reported concomitant medications, drug bioavailability, extracorporeal drug removal, covariates used in population pharmacokinetic models, and potential conflicts of interest as defined by the ClinPK checklist. Limited information describing relevant variables that would explain inter-patient pharmacokinetic differences was the most clinically significant ClinPK checklist omission for the purposes of our review. The study by Zapater et al. was the only study to describe its limitations, factors influencing PK variability, the formulas for calculated variables, and participant eligibility criteria according to the ClinPK checklist (42). Only one study described pharmacokinetic modeling methods/software (31). Two studies included the statistical modeling methods/software (31, 42) and funding sources (36, 42). Many of the omissions in the ClinPK checklist criteria reflect the changing standards for pharmacokinetic studies (25).

As a whole, the studies reported inconsistent endpoints most of which lack clinical significance. All studies used individual protocols regarding the number and timing of samples drawn. The majority of studies report urinary metabolites, acetaminophen concentrations, or changes in liver enzymes. Only the Arnman et al., El-Azab et al., and Zapater et al. studies report AUC in the placebo and intervention groups (29, 32, 42). None of the three studies meet the FDA AUC criteria for dose adjustment. All studies reporting AUC are single dose studies which prevents meaningful conclusions from being drawn from this data and do not contribute to determining if multiple dose regimens are appropriate in patients' with cirrhosis.

Current standards for staging liver disease severity and dosing medication advise use of the Child-Pugh score. The studies by Gelotte et al., Gunawan and Carey, and Zapater et al.

calculated the Child-Pugh score for participants, leaving questions about disease severity in the remaining studies (38, 39, 42). Few studies defined concurrent disease states, concomitantly administered medications, or confirmed cirrhosis diagnosis and severity.

Cormack et al., Fevery and de Groote, Gelotte et al., Leung et al. 1990, and Leung and Critchley 1991 do not report t1/2 of acetaminophen, but the remaining pharmacokinetic studies do (6, 31, 34, 38, 41). Unfortunately, there are no codified recommendations for dose adjustments based on this data. The Benson study and the abstract by Gunawan and Carey report changes to liver enzymes (30, 39). The studies by Forrest et al. 1979, Leung et al. 1990, and Leung and Critchley 1991 and the abstract by Gelotte et al. report urinary metabolite excretion (6, 37, 38, 41). While the studies that do not report AUC or t1/2 add to our body of knowledge, the other endpoints obtained can be difficult to use in routine clinical practice. The above limitations are compounded by the study investigators lack of elaboration on the clinical applicability of their findings.

The two retrospective case control studies by Khalid et al. and Fenkel et al. were assessed using the Downs and Black checklist and were determined to be fair quality (Table 1) (26, 33, 40). Both studies assessed the risk of decompensation in patients with cirrhosis who were taking over the counter analgesics. These studies relied on questionnaires to evaluate frequency, type, and dose of over the counter analgesics. The dependence on recall could introduce bias. The study by Fenkel et al. was the most comprehensive in delineating type of liver disease but did not calculate a Child-Pugh score for enrolled patients (33). The Khalid study was more comprehensive in that patients with decompensated cirrhosis, non-decompensated cirrhosis, and patients without cirrhosis were compared, which may eliminate some bias (40). There was

a much lower rate of concurrent alcohol use in the Fenkel study as compared to the Khalid study (33, 40).

Discussion:

A primary limitation to applying the results of pharmacokinetic studies to acetaminophen dosing recommendations lies with inherent interpatient variability within patients' in the same Child-Pugh class and poor differentiation of cirrhosis etiology Current drug dosing recommendations depend on the Child-Pugh score as a marker of the liver's capacity of the liver to metabolize medications. This score is a combined subjective and objective assessment of cirrhosis severity and likelihood of mortality (43). It assesses total bilirubin, albumin, PT/INR, ascites, and encephalopathy and segregates patients into three classes: A, B, and C. Class A patients have the lowest mortality, class C patients the highest. There is significant heterogeneity among patients with the same Child-Pugh class. Drug metabolism in cirrhosis is acknowledged to be impaired, but controversy exists in the significance and clinical utility of using predictive scores such as Child-Pugh to assess severity of metabolic changes. Kovarik et al. studied the pharmacokinetic changes of everolimus in patients with moderate hepatic dysfunction (defined as Child-Pugh scores 7-9) (44). The area under the curve (AUC) of everolimus ranged from 69-103 ng x h/ml in healthy patients to 146-328 ng x h/ml in a small number of patients with a Child-Pugh score of 7. Similar changes were seen in prolongation of half-life (t1/2) between the groups. The variability of these measures is notably greater in patients with hepatic impairment as compared to healthy patients. This variability in AUC is greater when patients with Child-Pugh scores of 8 or 9 are considered in the analysis. In contrast, Albarmawi et al. used Child-Pugh scores in patients with and without hepatic

dysfunction to evaluate pharmacokinetic variability of midazolam (43). These authors determined that the Child-Pugh score was an acceptable predictor of the CYP3A subfamily activity despite variation in midazolam $t_{1/2}$ within the same Child-Pugh class.

In addition to variability within patients with the same Child-Pugh class, the etiology of liver disease may have an effect on the activity of enzymes involved in acetaminophen metabolism (45). Patients' with non-alcoholic steatohepatitis have demonstrated higher expression of CYP2E1, which may lead to increased risk of hepatotoxicity with acetaminophen exposure. This variability has been further documented by George et al. (46). In their study of expression of the CYP enzymes, they determined that patients with hepatocellular disease had preserved levels of CYP2E1 while those patients with cholestatic dysfunction had reduced expression of the same enzyme. The authors further determined that the variability in this enzyme was 11-fold in healthy patients versus 44-fold in patients with advanced hepatic disease. The increased interpatient variation in enzymatic activity in patients with hepatic disease adds to the challenges of providing an optimized yet safe dose.

Multiple other factors limit the ability to draw robust conclusions regarding appropriate dosing from the evaluated studies. Factors affecting internal validity include short study duration, recruitment of small study populations, lack of subject randomization and poorly defined timeframes for subject enrollment. Patients received multiple doses of acetaminophen in the studies by Andreasen and Hutters, Benson, and the abstract by Gelotte et al. (28, 30, 38). We have observed in our clinical practice that many providers are willing to administer single doses of acetaminophen to compensated cirrhotic patients, the more valid clinical question relates to multiple dose regimens. Having only three studies addressing longer term use of

acetaminophen prevents strong conclusions from being drawn. External validity is limited by a heterogeneous and poorly defined population which is amplified by dated studies and changing standards for diagnosis and categorization of liver disease. Study population heterogeneity is often perceived as strengthening the external validity of data, but with small study populations, poorly defined etiology and severity of hepatic dysfunction, and inconsistent endpoints it is difficult to apply this data to specific patients.

Applying the ClinPK checklist to studies published well before the development of this quality measure highlights the changing standards for conducting pharmacokinetic research and reporting (25). We acknowledge applying current standards to older studies will lead to apparent lower scores. Many items on the list do not apply to the studies we identified (extracorporeal drug removal, bioavailability), but we chose to comprehensively assess all studies.

Other authors have suggested the absence of solid evidence can be reconciled with clinical practice by evaluation of risk factors. A review article by Lewis in 2002 provided suggestions for safe use of potentially hepatotoxic medications in CLD patients which included an evaluation of concomitant alcohol use, metabolic pathway inducers, and medications that decrease glutathione stores (11). Data on substances that reduce glutathione stores are limited, the Natural Medicines Comprehensive Database only identifies acetaminophen and alcohol consumption (47). The impact of glutathione levels in patients with cirrhosis is under debate. Two small studies have demonstrated conflicting results (48, 49). One study of 14 patients with cirrhosis reflects glutathione stores comparable to patients without hepatic impairment, while a study with 3 patients with cirrhosis had higher levels of glutathione than

placebo controls. If these study findings are valid, glutathione depletion may not be a risk factor for further hepatic damage in non-alcoholic patients with cirrhosis taking acetaminophen. Lewis recommended liver disease patients undergo more frequent liver function tests (LFTs) and clinical monitoring than healthy patients to detect trends indicating worsening liver function (11). The author did not specify a recommended frequency for LFT, clinical monitoring, or guidance on when to stop acetaminophen. Two studies of chronic acetaminophen use in OA and asthma patients without CLD suggest obtaining INR, albumin, and bilirubin labs if ALT and AST exceeds three times the upper limit of normal (ULN) (50, 51). These studies routinely monitored patients' ALT and AST as part of the study protocol, but no patients developed liver enzymes three times the ULN to provide clinical context on when to stop acetaminophen. Since the studies excluded CLD patients, the investigators' practice of monitoring ALT/AST does not have external validity for cirrhosis patients because they may not adequate viable hepatocytes to express liver enzymes with advanced disease (52). Further, routine practice does not dictate regular aminotransferase monitoring. The cases in supplement 1 provide two scenarios to consider the appropriateness of acetaminophen use in patients with chronic liver disease through application of the patient specific factors discussed above (2, 45, 53).

This risk benefit analysis should include consideration of the paucity of evidence suggesting that chronic scheduled use of the maximum recommended doses of acetaminophen provide better pain relief than lower doses. At the time of this writing there is no available literature evaluating improved analgesia with acetaminophen 4 g/day compared to < 3 g/day. In a 2006 systematic review McQuay and Moore reported a number needed to treat (NNT) of 9 (95% CI: 6-20) to achieve at least 50% maximum total pain relief for a single dose of acetaminophen

1000mg compared to a 500-650mg dose (54). This finding is similar to the results of a 2008 Cochrane Database Systematic Review which noted a NNT of 3.5 (95% CI: 2.7-4.8) for a single acetaminophen 500mg dose, NNT of 4.6 (95% CI: 3.9-5.5) for acetaminophen 600-650mg, and NNT of 3.6 (95% CI: 3.4-4) for acetaminophen 1000mg to achieve at least 50% pain relief in post-operative patients (55). These dose response results suggest that empiric acetaminophen dose reductions may not result in a clinically significant decrease in pain control regardless if a patient has CLD or normal hepatic function. Therefore CLD patients may not have compromised analgesia when adhering to an expert opinion maximum daily acetaminophen dose of 2-3 g/day. Documented increases in t1/2 and AUC, potential equianalgesic effects of reduced doses, and an emphasis on patient safety coupled with clinical judgement make reductions in the maximum daily dose reasonable.

Conclusion:

As clinicians, we are seeking robust data to draw from in making evidence-based recommendations for patient care. The limited side effect profile at therapeutic doses and low cost make acetaminophen an attractive non-opioid analgesic option for pain management in many patients. While the studies have significant limitations, the body of evidence suggests that acetaminophen is an acceptable option in a compensated cirrhotic patient, particularly when incorporating the expert opinion dosing and monitoring recommendations advocated above. The specific recommendation of limiting acetaminophen doses to less than 2-3 grams per day is not supported by high quality trials, particularly when acetaminophen is used chronically. There is insufficient evidence to arbitrarily reduce doses or avoid the use of acetaminophen in cirrhosis patients.

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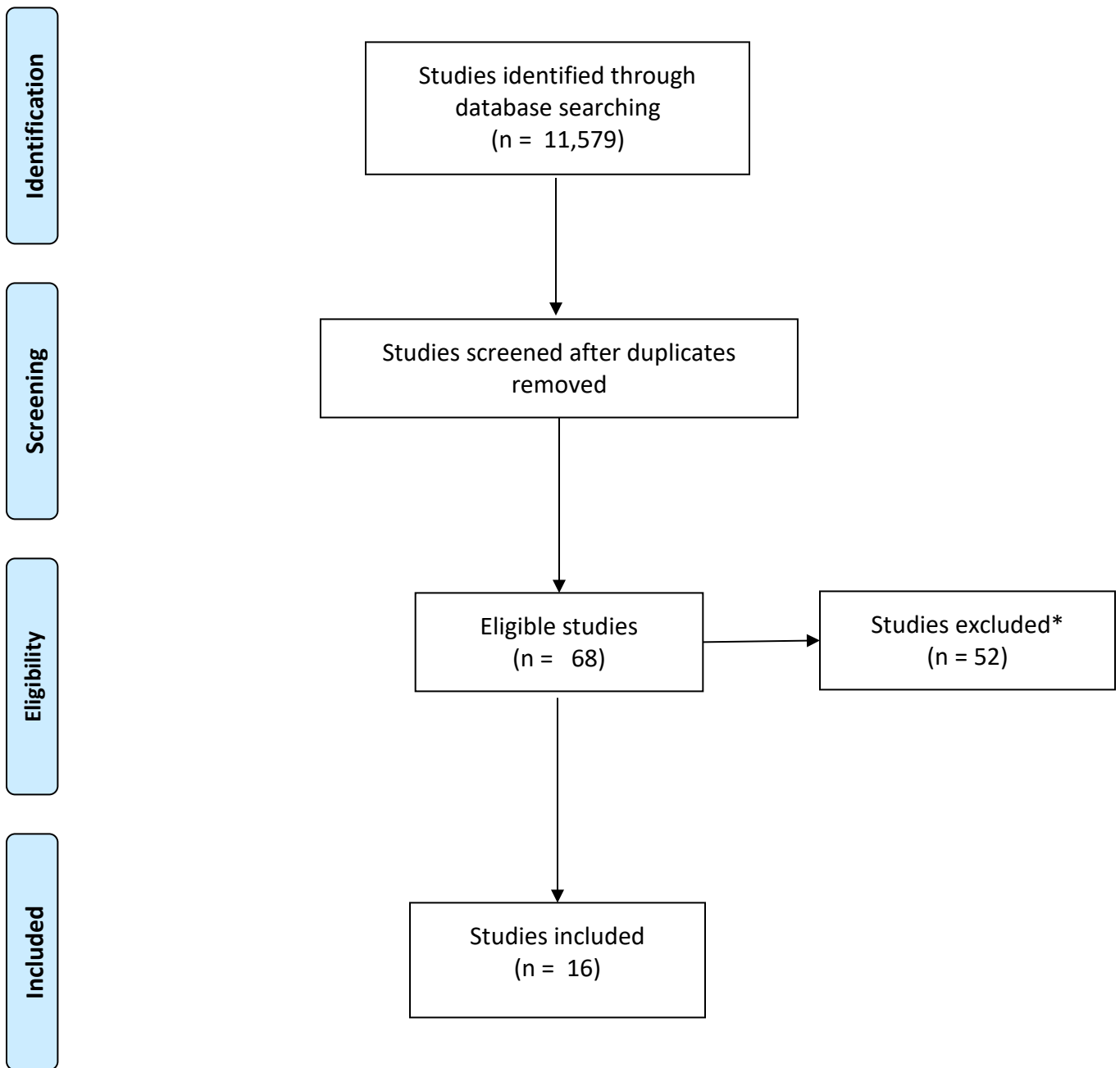knee. Arthritis Care Res (Hoboken). 2012;64(4):465-74.

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Figure 1: PRISMA flow diagram of studies identified, excluded, and included in systematic review.

Identification

Studies identified through database searching
(n = 11,579)

Screening

Studies screened after duplicates removed

Eligibility

Eligible studies
(n = 68)

Studies excluded*
(n = 52)

Included

Studies included
(n = 16)

* Reasons that studies were excluded: wrong comparator group (n=2), wrong patient population (active alcohol use) (n=11), wrong study design (n=11), wrong outcomes (n=8), background information (n=16), non-English studies (n=4)

Table 1: ClinPK Checklist

	Checklist Item	
	Title/Abstract	Reported on Page Number
1	The title identifies the drug(s) and patient population(s) studied.	
2	The abstract minimally includes the name of the drug(s) studied, the route of administration, the population in whom it was studied, and the results of the primary objective and major clinical pharmacokinetic findings.	
	Background	
3	Pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion) that is known and relevant to the drugs being studied is described.	
4	An explanation of the study rationale is provided	
5	Specific objectives or hypotheses is provided	
	Methods	
6	Eligibility criteria of study participants are described	
7	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described	
8	Drug preparation and administration characteristics including dose, route, formulation, infusion duration (if applicable) and frequency are described.	

9   Body fluid or tissue sampling (timing, frequency and storage) for quantitative drug measurement is described.

10 Validation of quantitative bioanalytical methods used in the study are referenced or described if applicable.

11 Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first or mixed order).

12 For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described.

13 Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced.

14 The specific body weight used in drug dosing and pharmacokinetic calculations are reported (i.e., ideal body weight vs. actual body weight vs. adjusted body weight)

15 Statistical methods including software used are described

Results

16 Study withdrawals or subjects lost to follow- up (or lack thereof) are reported.

17 Quantification of missing or excluded data is provided if applicable.

18 All relevant variables that may explain inter- and intra-patient pharmacokinetic variability (including: age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and

pertinent co-morbidities) are provided with appropriate measures of variance.

19 Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95% confidence intervals)

20 Studies in patients receiving extracorporeal drug removal (i.e., dialysis) should report the mode of drug removal, type of filters used, duration of therapy and relevant flow rates.

21 In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, Cmax (maximal concentration) and Tmax (time to maximal concentration) should be reported.

Discussion/Conclusion

22 Study limitations describing potential sources of bias and imprecision where relevant should be described

23 The relevance of study findings (applicability, external validity) is described

Other Information

24 Funding sources and conflicts of interest for the authors are disclosed.

Table 2: Study Characteristics and Outcomes

Reference (Author/year)	Study population	Study design	Intervention	Outcome(s) (p-value/CI)	Checklist score
Andreasen and Hutters (1979) [30]	Pilot phase: Cirrhosis (n=11); controls (n=12)	PK study	Paracetamol 1000 mg PO x 1 dose	$t_{1/2}$ (hr): • cirrhotics: 3.7 ± 0.8 • controls: 2.1 ± 0.6 ($p<0.01$)	ClinPK 10
	Follow-up: Cirrhosis (n=4); controls (n=9)	PK study	Paracetamol 1000 mg PO TID x 5 days	Plasma acetaminophen concentration before second daily dose (mcg/ml): • cirrhotics 9.2 • controls: 3.2 ($p<0.01$) $t_{1/2}$: values not reported ($p =$ ns)	
Arnman and Olsson (1978) [31]	Cirrhosis (n=21); secondary liver cancer (n=4); controls (n=15)	PK study	Paracetamol 15 mg/kg PO x 1 dose	$t_{1/2}$ (hr): • controls: 2.9 ± 1.5 • cirrhotics 4.75 ± 2.4 • liver cancer: 4.7 ± 1.6 $p<0.01$ for controls vs cirrhotics AUC (6 hour): • controls: 2.8 ± 0.9 mcg x min/ml • cirrhotics: 4.2 ± 1.1 mcg x min/ml $p<0.001$ for controls vs cirrhotics	ClinPK 12

Benson (1983) [32]	Pilot phase: Cirrhosis (n=6)	PK study	Acetaminophen 1000 mg PO four times daily X 5 days	Mean acetaminophen $t_{1/2}$ (hr): 3.42 $\pm$2.5	ClinPK 11
	Follow-up: Stable, chronic liver disease (n = 20)	Prospective, double-blind placebo controlled crossover PK study	1000 mg PO four times daily X 13 days	SGOT (units) (AST): • baseline: 42.5 (SD 26.3) • acetaminophen period: 39.5 (SD 23.1) • placebo period: 55.0 (SD 71.6) SGPT (units) (ALT): • baseline: 58.6 (SD 55.7) • acetaminophen period 53.3 (SD 48.8) • placebo period 77.3 (SD 126.2) Reported as no difference	
Cormack et al. (2006) [33]	Patients age 3-15 with CLD (n=16)	PK study	Acetaminophen 40 mg/kg PR X 1 dose (rounded to combinations using 60, 125, 240, or 500 mg. Doses >1000 mg were given).	Mean acetaminophen C_{max}: 11.4 mg/L	ClinPK 15
El-Azab et al. (1996) [34]	Young healthy controls (n=4),	PK study	Acetaminophen 1000 mg PO X 1 dose	Mean acetaminophen plasma $t_{1/2}$ (hr):	ClinPK 10

	elderly healthy controls (n=4), young CLD (n=4), elderly CLD (n=4)				• young healthy controls = 2.4 $\pm$ 0.3 • young CLD = 4.1 $\pm$ 0.1 (p < 0.05) • elderly healthy controls = 2.8 $\pm$ 0.2 • elderly CLD = 4.2 $\pm$ 0.2 (p < 0.05) AUC $_{(0-\infty)}$(mcg•min/mL): • young healthy controls = 3.55 $\pm$ 0.12 • young CLD: 4.60 $\pm$ 0.29; (p < 0.05) • elderly healthy controls = 2.46 $\pm$ 0.15 • elderly CLD: 3.47 $\pm$ 0.14; (p < 0.05)	
Fenkel et al. (2010) [35]	Cirrhotic cases admitted to hospital with liver associated events (n=90) Controls: outpatients with a diagnosis of cirrhosis without a hospitalization for 3 months (n=126)	Case control	Recall of acetaminophen, ibuprofen, naproxen, aspirin, and alcohol use in last 30 days	Rate of acetaminophen use prior to hospitalization: • cirrhotic cases: 34% • controls: 26% (p=NS) APAP use in last 30 days not associated with hospitalization (OR: 0.59, 95% CI: 0.25-1.24, p=0.161)	Downs and Black 15

Fevery and de Groote (1969) [36]	Controls (n=8) Hepatitis (n=12) Cirrhosis (n=14)	PK study	N.A.P.A 10 mg/kg	Serum levels unconjugated N.A.P.A. at 3 hrs (mcg/ml): - Controls: 1.29 $\pm$ 0.78 - Hepatitis: 1.92 $\pm$ 1.01 - Cirrhosis: 2.80* $\pm$ 1.25 Serum levels unconjugated N.A.P.A. at 6 hrs mcg/ml): - Controls: 0.76 $\pm$ 0.5 - Hepatitis: 1.22 $\pm$ 1.01 - Cirrhosis: 2.36* $\pm$ 1.36 $p < 0.01$ for cirrhosis compared to controls	ClinPK 6
Forrest et al. (1975) [37]	CLD patients who received acetaminophen (n=14)	PK study	Paracetamol 1500mg PO X 1 dose	10/14 CLD patients who received acetaminophen had a prolonged $t_{1/2}$ (hr) mean CLD $t_{1/2}$ (hr): 3.15 (Range: 1.5-7)	Unable to evaluate, published in abstract form only
Forrest et al. (1977) [38]	CLD (n=23)	PK study	Paracetamol 1500 mg PO X 1 dose	Mean paracetamol plasma $t_{1/2}$ (hr): - CLD = 2.9 $\pm$ 0.3 - healthy controls* = 2.0 $\pm$ 0.4	ClinPK 9
Forrest et al. (1979) [39]	Severe CLD (n=7), mild CLD (n=8), and healthy controls (n=8)	PK study	Paracetamol 1500 mg PO X 1 dose	Mean paracetamol plasma $t_{1/2}$ (hr): - healthy controls = 2.43 $\pm$ 0.19 - mild CLD = 2.16 $\pm$ 0.54 - severe CLD = 4.25 $\pm$ 1.15 ($p < 0.001$)	ClinPK 12

| | | | | Mean urine cysteine conjugate (% of dose):
• healthy controls = 3.8 ± 0.1
• mild CLD = 4.4 ± 0.6
• severe CLD: 4.2 ± 0.9

Mean urine mercapturate conjugate (% of dose):
• healthy controls = 4.8 ± 0.2
• mild CLD = 4.3 ± 0.7
• severe CLD: 4.2 ± 0.6
Reported as no difference for cysteine or mercapturate conjugates. | |
| Gelotte et al. (2007) [40] | Hepatocelluar cirrhosis secondary to hepatitis C and/or alcohol abuse with Child-Pugh: 7-9 (n=12); healthy matched controls (n=13) | PK study | Acetaminophen 1000mg PO four times daily X 4 days | Increased total acetaminophen clearance from first to final doses
• hepatic impaired (p=0.037)
• matched controls (p<0.001)

Fractional amount of glucuronide excreted
• hepatic impaired: 40.2±13.3% to 52.1±16.4% (p<0.001) | Unable to evaluate, published in abstract form only |

				• matched controls: 49.0±7.4% to 60.8±11.1% (p=0.008)	
Gunawan and Carey (2002) [41]	Patients in hepatology and liver transplant clinics (n=217 total; n = 174 used acetaminophen; n = 43 no acetaminophen use	Survey	Survey regarding acetaminophen use in last 4 days; advice received about acetaminophen use, change in severity of cirrhotic complications, Medical records: LFTs, CLD etiology, presence of cirrhosis or severe fibrosis, Child-Pugh Score	• 96 patients had cirrhosis or severe hepatic fibrosis • 55% of patients told to avoid acetaminophen by a provider • 29% of patients told to avoid acetaminophen from a non-medical source • No increases in LFTs or cirrhosis complications in patients using acetaminophen 4g/day versus those who did not use acetaminophen • Child-Pugh score was not higher in cirrhosis or severe hepatic fibrosis patients who used acetaminophen versus those who did not use acetaminophen	Unable to evaluate, published in abstract form only

Khalid et al. (2009) [42]	Hospitalized cirrhotic cases (n=91), non-hospitalized cirrhotic controls (n=153), non-cirrhotic hospitalized controls (n=89)	Retrospective case-control study	Recall of OTC medication use over previous 30 days	Rate of acetaminophen use: • cirrhotic cases: 19% • non-hospitalized cirrhotic controls: 25% • non-cirrhotic controls: 42% ($p = 0.001$ for all comparisons)	Downs and Black 19
Leung et al. (1990) [43]	Cirrhosis secondary to hepatitis B (n=29); cirrhosis secondary to chronic alcohol consumption (n=13), untreated hepatocellular carcinoma (n=8)	PK study	Paracetamol tablets 1.5 g PO x 1 dose	Urine cysteine conjugate (%): • cirrhosis secondary to HBV: 5 ± 2 • cirrhosis secondary to EtOH: 4 ± 2 • HCC: 11 ± 3 Urine mercapturic acid conjugates (%): • cirrhosis secondary to HBV: 4 ± 1 • cirrhosis secondary to EtOH: 4 ± 2 • HCC: 9 ± 3 ($p < 0.05$ for HCC compared to patients without malignancy)	Unable to evaluate, published in abstract form only
Leung and Critchley (1991) [6]	Cirrhosis secondary to CHBV (n=39); HCC (n=19); healthy controls (n=26)	PK study	Paracetamol 1500 mg PO x 1 dose	Urine cysteine conjugate (%): • controls: 4 ± 1 • CHBV: 5 ± 2 • HCC: 12 ± 3 ($p < 0.0001$ for HCC compared to CHBV or controls)	ClinPK 10

				Urine mercapturic acid conjugates (%): - controls: 3 ± 1 - CHBV: 5 ± 2 - HCC: 10 ± 3 ($p < 0.0001$ for HCC compared to CHBV or controls)	
Zapater et al. (2004) [44]	CLD (n=14), healthy controls (n=7)	PK study	Acetaminophen 1000 mg PO X 1 dose	Mean acetaminophen plasma $t_{1/2}$ (hr): - healthy controls = 2.0 ± 0.4 - all CLD = 3.8 ± 1.1; ($p = 0.01$) - mild-moderate CLD = 3.7 ± 1.3 - severe CLD = 4.0 ± 0.6 $AUC_{(0-6h)}$ (mg•h/L): - healthy controls = 38.8 ± 4.3 - all CLD: 67.4 ± 22.4; ($p < 0.05$) - mild to moderate CLD = 64.6 ± 25.0 - severe CLD: 72.0 ± 18.5	ClinPK 16

Legend:
CHBV = chronic hepatitis B virus infection
CLD = chronic liver disease

EtOH = alcohol
HCC = hepatocellular carcinoma
N.A.P.A. = N-acetyl-p-aminophenol (acetaminophen)
OTC = over the counter
PK = pharmacokinetic
PO = by mouth
PR = per rectum
APAP = acetaminophen or paracetamol
SUL = sulfates
GUL = glucuronides
SGOT = serum glutamic oxaloacetic transaminase
SGTP = serum glutamic pyruvic transaminase
ALT = alanine aminotransferase
AST =aspartate amino transferase
*= healthy controls from previous studies

Supplement 1:

Case 1:

A 66 year-old female patient with a past medical history significant for nonalcoholic fatty liver disease, cirrhosis (Child-Pugh class B), hypertension, stage 3 chronic kidney disease, and osteoporosis presents to her primary care physician with worsening bilateral knee pain. The patient reports that her knee pain is impairing her ability to comfortably ambulate. She self treats her knee pain with as needed OTC naproxen approximately three times a week. The patient has not been hospitalized in over a year. She does not drink alcohol. Her home medications include torsemide, spironolactone, and lisinopril. The patient's most recent labs are significant for international normalized ratio (INR): 1.6 (0.9-1.1), total bilirubin: 2.4 mg/dL (0.3-1.0 mg/dL), serum albumin: 3.1 g/dL (3.5-5 g/dL), serum creatinine: 1.45 mg/dL (0.7-1.5 mg/dL), AST: 38 units/L (8-42 units/L), ALT: 29 units/L (0-35 units/L). It was determined that she is not a liver transplant candidate. She decided to place a few limitations on her care after the transplant evaluation including do not resuscitate, do not intubate, and no artificial nutrition orders. Her advance directive choices indicate that she is trending towards a more palliative approach to her medical care.

This patient has compensated cirrhosis as evidenced by her lack of recent hospitalizations. She is a candidate for chronic acetaminophen 1 g by mouth three times a day to treat her OA knee pain Acetaminophen is a preferred analgesia for knee OA (57). The suggested dose regimen is consistent with recent expert opinion recommendations. However it is unclear if the patient would experience a clinically significant difference in analgesia or be at a higher risk for decompensation if a 2 g/day or 4 g/day regimen was chosen. The patient would be at increased risk of hepatorenal syndrome and acute kidney injury with continued NSAID use given her

Child-Pugh class B cirrhosis, stage 3 CKD, and diuretic use. The patient is at increased risk of hepatotoxicity due to increased CYP2E1 activity in NASH patients (47). She should be counseled to stop acetaminophen and immediately contact her physician if she develops any signs and symptoms suggestive of decompensated cirrhosis as defined by EASL (e.g. ascites, bleeding, encephalopathy, or jaundice) (2). It would be reasonable to obtain an INR, total bilirubin, albumin, electrolytes, and serum creatinine if this patient is develops decompensated cirrhosis and/or is hospitalized.

Case 2:

A 45 year old male with cirrhosis secondary to alcohol use disorder is admitted to the hospital for shortness of breath secondary to tense ascites. Other than the complaints listed above, the only other significant history is chronic back pain which has kept the patient out of work for the last several years. The patient had been admitted approximately twice a month for the past year for episodes of tense ascites. The patient's home medications are lactulose, rifaximin, spironolactone, furosemide, nadalol, ciprofloxacin, and acetaminophen 1000 mg PO TID; all have been restarted in the hospital. The patient's compliance to his home medication regimen is uncertain and the patient endorses continuing to drink a pint or more of vodka daily. The patient has a Child-Pugh score of 13 (Class C) and while not considered a transplant candidate, has a MELD score of 38.

Due to the severity of liver disease, uncertainty of the adequacy of all metabolic pathways, and the possibility of reduced glutathione stores and CYP2E1 induction secondary to continued alcohol use acetaminophen should be discontinued. NSAIDs would not be an appropriate analgesic option for this patient due to concerns with hepatorenal syndrome and potential

additional fluid retention. The patient should be referred to physical therapy or could be

considered for an opioid if an appropriate patient safety agreement could be developed.