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ORIGINAL RESEARCH

Model-Based Assessment of the Liver Safety Profile of Acetaminophen to Support its Combination Use with Topical Diclofenac in Mild-to-Moderate Osteoarthritis Pain

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ABSTRACT

Introduction: The use of combination therapy of oral acetaminophen and topical diclofenac, having complementary mechanisms of action, is an attractive strategy to enhance the analgesic response in osteoarthritis (OA) pain. While topical diclofenac is considered as well tolerated due to its low systemic exposure, concerns of liver toxicity with acetaminophen at standard analgesic doses remain. Thus, this study aimed to assess the liver safety profile of acetaminophen, particularly in OA management, using a model-based meta-analysis (MBMA).

Methods: A literature review was conducted using the MEDLINE database to identify randomized clinical trials (RCTs) reporting liver toxicity on acetaminophen use. An MBMA was implemented to assess the deviation from the upper limit of normal (ULN) of alanine aminotransferase or aspartate aminotransferase, namely > 0–1 × ULN, > 1.5–2 × ULN, and > 3 × ULN representing mild, moderate, and severe risk of liver abnormality, respectively.

Results: A total of 15 RCTs were included in the MBMA, encompassing over 4800 subjects and exposure to acetaminophen ranging from 2 to 26 weeks. Of the 15 included studies, eight involved patients with OA pain, four involved healthy subjects and three were in patients with conditions such as asthma, glaucoma, chronic pain, and cardiovascular disease. Acetaminophen 1500–4000 mg/day was found to exhibit 23% (95% confidence interval (CI): 17.74–29.20), 1.35% (95% CI: 0.17–2.51) and 0.01% (95% CI: 0.00–0.32) increased risk for mild, moderate, and severe liver injury, respectively, versus placebo.

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Moreover, at therapeutic doses, no correlation was identified between acetaminophen intake and liver abnormality risk.
Conclusions: Overall, our analysis shows that short-term (∼ 8–16 weeks) acetaminophen use at therapeutically recommended doses is associated with a low risk of clinically relevant changes in liver enzymes. Given the good tolerability of topical diclofenac, the findings support the safety of the combination of acetaminophen and topical diclofenac, at least over the short term, as treatment for mild-to-moderate OA pain.

Keywords: Acetaminophen; Liver safety; Osteoarthritis; Pain; Topical diclofenac; Model-based meta-analysis

Key Summary Points

Why carry out this study?

Despite the availability of several pharmacological treatments, mild-to-moderate osteoarthritis (OA) pain remains inadequately managed. Combined use of acetaminophen and topical diclofenac, having complementary mechanisms of action, is an attractive approach to achieve effective analgesia in OA pain.

However, the tolerability of the combination remains to be investigated. Topical diclofenac is well tolerated, but concerns of liver toxicity with acetaminophen use have not been adequately addressed.

We conducted a model-based meta-analysis (MBMA) to evaluate the risk of increased liver enzymes (ALT, AST) associated with acetaminophen use at clinically recommended analgesic doses.

What was learned from this study?

Our study suggests acetaminophen exhibits a low risk of increased liver enzymes (ALT, AST) at clinically recommended analgesic doses and thus supports the safety of the combination of acetaminophen and topical diclofenac in mild-to-moderate OA pain.

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative disease of the joints and currently affects more than 527 million people globally, particularly the elderly population [1]. Chronic pain is the hallmark symptom of OA that results in significant disability and reduced quality of life in affected individuals and is also the major reason for them to seek medical care [2]. However, despite the huge burden associated with OA, pain management remains sub-optimal since current symptomatic therapies often exhibit modest efficacy (e.g., acetaminophen), unfavorable safety profile (e.g., oral non-steroidal anti-inflammatory drugs (NSAIDs)) and in some cases increased risk of addiction and overdose (e.g., opioids).

Growing evidence indicates that OA pain is a complex phenomenon which encompasses inflammatory and non-inflammatory pain pathways at peripheral and central levels of the nervous system [3]. While the identification of disease-modifying treatments is an ongoing endeavor in chronic conditions such as OA, a promising approach is the use of rational drug combinations, which act through different mechanisms to provide more effective pain relief with a favorable risk–benefit ratio [4, 5].

Acetaminophen is one of the most commonly used analgesic and antipyretic medications across the world and is also included on the World Health Organization's list of essential medicines as an effective and safe medicine [6]. Historically, it has been used as a first-line pain medication for OA [7], but recent reports from a wider range of clinical trials suggest that its use as a single agent results in modest efficacy [8, 9]. This finding may reflect its mechanism of action, which is mainly centrally mediated via the descending serotonergic pathways with minimal influence on peripheral pathways [10]. On the other hand, topical NSAIDs, including diclofenac, have emerged as useful treatment options for OA individuals with contraindications to oral NSAIDs [11]. They act primarily by targeting peripheral mechanisms of pain and inflammation by inhibiting cyclooxygenase in the skin and soft tissue, including cartilage

[12–14]. Combining acetaminophen and topical diclofenac represents therefore an attractive strategy to enhance the analgesic response, as their primary pharmacological effects are associated with complementary mechanisms of action. In addition, recent clinical guidelines provide recommendation to add topical NSAIDs to acetaminophen for patients still symptomatic after initial monotherapy treatment as first-line analgesic [15, 16]. Such an approach could help patients achieving adequate pain relief and potentially limit the overuse of acetaminophen, which may occur when analgesia is not sufficient or persisting over the dosing interval.

In this context, our research group hypothesized and showed lesser opioid use following combination therapy of oral acetaminophen and topical diclofenac when compared with acetaminophen monotherapy in OA pain (unpublished results). Despite such promising findings, the safety profile of this combination remains unclear in OA. In addition, there is a lack of clinical evidence on the combination in OA pain [17].

Since topical NSAIDs are associated with lower risk of systemic (gastrointestinal (GI), renal, cardiovascular (CV) and hepatic) adverse events than oral NSAIDs due to their low systemic exposure, they are therefore generally regarded as safe in the management of OA [18]. On the other hand, while acetaminophen exhibits a low risk of CV, GI, and renal toxicity [19], concerns of liver toxicity with acetaminophen use have been frequently raised [20, 21]. Even though there are previous reviews on the liver safety profile of acetaminophen, they either analyze evidence derived primarily from observational studies or are outdated [8, 22]. Thus, there is a need to evaluate the risk of liver injury associated with acetaminophen using evidence from RCTs.

Model-based meta-analysis (MBMA) is an emerging statistical technique that can leverage published individual- and summary-level data, incorporate longitudinal data and the pharmacological concept of dose–response relationship, incorporating covariates in the analysis to inform key drug development decisions, such as the benefit–risk assessment of a treatment under investigation [23]. MBMA has already been applied to the drug development process across several therapeutic areas to compare efficacy and safety of drug treatments or determine an optimal dose against a comparator drug [23–28]. In addition, drug regulatory authorities have also started to recognize its importance as a predictive modeling approach [29, 30]. The objective of the present study is therefore to investigate the association between the use of acetaminophen and liver toxicity, particularly in OA management, using a model-based meta-analytical approach based on published summary-level data from RCTs identified through a literature search.

METHODS

Literature Search and Data Extraction

A literature review was conducted to identify RCTs investigating acetaminophen-associated liver toxicity, including primarily data from the OA patient population. The bibliographic database MEDLINE was searched from inception to April 2022 using key words for 'acetaminophen', 'liver' and 'toxicity' along with their spelling variants. The search was restricted to RCTs published in the English language. The detailed search strategy is presented in Supplementary Table S1. Studies were eligible for inclusion if they investigated the safety of oral acetaminophen on liver (including hepatic aminotransferases levels) in adult humans with or without any disease and were conducted for a duration of at least 2 weeks. The detailed list of inclusion exclusion criteria is presented in Supplementary Table S2. Each of the records identified during the search was assessed for relevance against predefined eligibility criteria.

Two independent researchers reviewed the abstracts to select potentially eligible studies. Disagreements were resolved through consensus. Full texts of the selected studies were retrieved and examined thoroughly for eligibility. Finally, one researcher reviewed all the selected publications in detail to extract all the relevant information related to study characteristics, while another researcher conducted

random checks to review the quality of data extraction.

Outcomes

The primary outcome was risk of liver abnormality defined by deviation in the upper limit of normal (ULN) in liver enzymes, e.g., alanine transaminase (ALT) or aspartate transaminase (AST). In addition, the definition of liver toxicity associated adverse events included ALT/AST elevation, liver injury, hepatic dysfunction, abnormality or organ failure reported from sources. Three threshold categories defined by different cut offs for exceeding upper limits of normal (ULN) of ALT and/or AST were further created: > 0–1 × ULN (including "0–1 × ULN" and " > 1 × ULN"); > 1.5–2 × ULN (including " > 1–1.5 × ULN", " > 1.5 × ULN", " > 2 × ULN", " ≥ 2 × ULN"); > 3 × ULN (including " > 3 × ULN", "ALT/AST > 2 × ULN, alkaline phosphatase (ALP) ≥ 718 × U/L", " > 3 × ULN ALT/AST, > 1.5 × ULN total bilirubin (TB)", "lack of definition; reported as serious AE").

Statistical Analysis

Model Development

An MBMA model was developed to quantify the relationship between drug exposure and the probability of exceeding ULN of ALT and/or AST, the most frequently reported definition of liver toxicity reported across studies, at the primary time point (time at which the endpoint is reported in the study) of RCTs. In order to make the best use of all the available information, a joint response model was developed to estimate the probability of patients exhibiting the three different thresholds k (> 0–1 × ULN, > 1.5–2 × ULN, > 3 × ULN of ALT/AST) of liver abnormality events within each treatment arm. The probability of an event was described as the sum of a non-parametric placebo or background response in trial *i* (eo_i) of threshold k and an event in active treatment arm *j* of trial *i* at the primary time point of RCTs (as shown in *Eq.* 1):

$$P(event)_{ijk} = eo_{ik} + f\left(Drug_{ij}, Dose_{ij}, \boldsymbol{\theta}\right) * f(X_{ij}, \boldsymbol{\beta}) \quad (1)$$

where $P(event)_{ijk}$ is the probability (%) of any given patient having a liver abnormality event for the k^{th} threshold in trial *I* and arm *j* and is described as a function of (i) a placebo effect (eo_{ik}) representing the placebo or background response for the k^{th} threshold in trial *i,* and defined using a fixed-effect model for every trial representing different thresholds of liver abnormality; (ii) a function $f(Drug, Dose, \boldsymbol{\theta}))$ characterizing the relationship between drug ($Drug_{ij}$) and dose ($dose_{ij}$) using fixed-effect model parameters (θ_i); and (iii) a function $f(X, \beta)$ describing the effect of covariates (X) (e.g. threshold) and their multiplicative effect using parameter $\boldsymbol{\beta}$. An additive effect across the thresholds was also tested. In the final model, two drug parameters were estimated.

A threshold-specific drug effect was estimated with a constant shift across different thresholds, as shown by the following term in Eq. (2):

$$\begin{aligned} f(threshold, \beta) = (1 + \pi_1 * (threshold'' > 1.5 \\ - 2ul'''') + \pi_2 \\ * (threshold'''' > 3u)) \end{aligned} \quad (2)$$

where π are coefficients of the drug effect for thresholds representing > 1.5–2 × ULN or > 3 × ULN relative to threshold for 0–1 × ULN elevation.

The effect of additive shift across threshold levels was also taken into account and, therefore, the Eqs. (1–2) were modified to the following form:

$$P(event)_{ijk} = eo_{ik} + (f\left(Drug_{ij}, Dose_{ij}, \boldsymbol{\theta}\right) + f\left(threshold_{ij}, \boldsymbol{\beta}\right)_{add}) \quad (3)$$

$$\begin{aligned} &f(threshold, \boldsymbol{\beta})_{add} \\ &= (\pi_{1.add} * (threshold = '' > 1.5\text{-}2\text{uln}\}) \\ &\quad + \pi_{2.add} * (threshold = '' > 3\text{uln}\})). \end{aligned} \quad (4)$$

When compared with Eqs. (1) and (2), the function $f(X_{ij}, \boldsymbol{\beta})_{add}$ in Eqs. (3) and (4) describes the effect of different threshold levels, whereas

the parameter β characterizes the additive effect on the baseline and π_{add} are the coefficients of the drug effect for threshold representing an elevation of > 1.5–2 $\times$ ULN or $> 3 \times$ ULN relative to 0–1 $\times$ ULN in liver abnormality on an additive scale.

The effect of oral acetaminophen treatment with another oral drug (e.g., ibuprofen) was also tested in the model as a separate parameter or shared with the overall effect of acetaminophen. The number of patients with liver abnormality event, defined by the three thresholds, in treatment arm *j* of trial *i* ($N_{event,ijk}$) was assumed to be binomially distributed with probability of event $P(event)_{ij}$ and sample size N_{ij} (Eq. 5):

$$N_{event,ijk} \sim binomial\left(N_{ijk}, P(event)_{ijk}\right) \quad (5)$$

Each observation was weighted based on the variance function for a binary endpoint in treatment arm *j* of study *i* with probability of event $P(event)_{ijk}$ and sample size $N_{ijk:}$

$$\sigma_{ik}^2 = P(event)_{ijk}(1 - P(event)_{ijk})/N_{ijk} \quad (6)$$

Since the true probability of the event $P(event)_{ijk}$ was unknown, the best estimates from the fitting algorithm were used in the model. The maximum likelihood estimates of the model parameters were obtained assuming a large sample size and normal approximation to the binomial likelihood.

Model Evaluation

Candidate models were evaluated using the maximum likelihood criteria [Akaike information criterion (AIC); *p*-value of < 0.05 defined the statistical significance level] and graphical diagnostics, with observed response plotted against population- and trial-specific predictions to evaluate the goodness-of-fit plots (precision, absence of bias). To determine the adequacy of the model, the percent relative standard error (RSE%) relating the standard error of a parameter as a percentage of the parameter estimate was also used; the lower the RSE% value, the greater the precision of the particular parameter. In addition, forest plots were used to compare model predictions for each study arm with their observed values. Partial residuals were also plotted as additional graphical assessment based on normalized observed values. To achieve consistency between model-predicted and observed data, residuals from the final model were used to normalize the actual observed values to the model predicted values. A total of 1000 sets of parameter estimates were re-sampled from the variance–covariance matrix of the final MBMA model to compute the confidence intervals (CI) for simulated outcomes. All analyses were conducted using the generalized least squares regression function (*gnls*) provided in the *nlme* package in R (version 3.5.3 or higher, 64 bit) running on Windows 10 Professional, SP1.

Compliance with Ethics Guidelines

The data used in this article were obtained from previously conducted studies and does not involve data generation in human participants or animal performed by any of the authors.

RESULTS

Study Inclusion and Characteristics

The literature review yielded 160 articles, 102 of which were excluded as they lacked relevant interventions or outcomes, were conducted in children, or were non-clinical or observational studies, resulting in 58 articles assessed for eligibility for full review. Of these, 40 were excluded after full text review. A total of 16 studies (18 sources), including 37 treatment arms reporting liver safety data were selected. Finally, a total of 15 studies were included which reported adverse events related to liver toxicity, defined as elevation in ALT/AST (Fig. 1). Of the 15 studies that met the inclusion criteria, eight were conducted in patients with OA pain, four in healthy subjects and the remaining three involved patients with other conditions such as asthma, glaucoma, chronic pain and cardiovascular disease. The total daily dose of

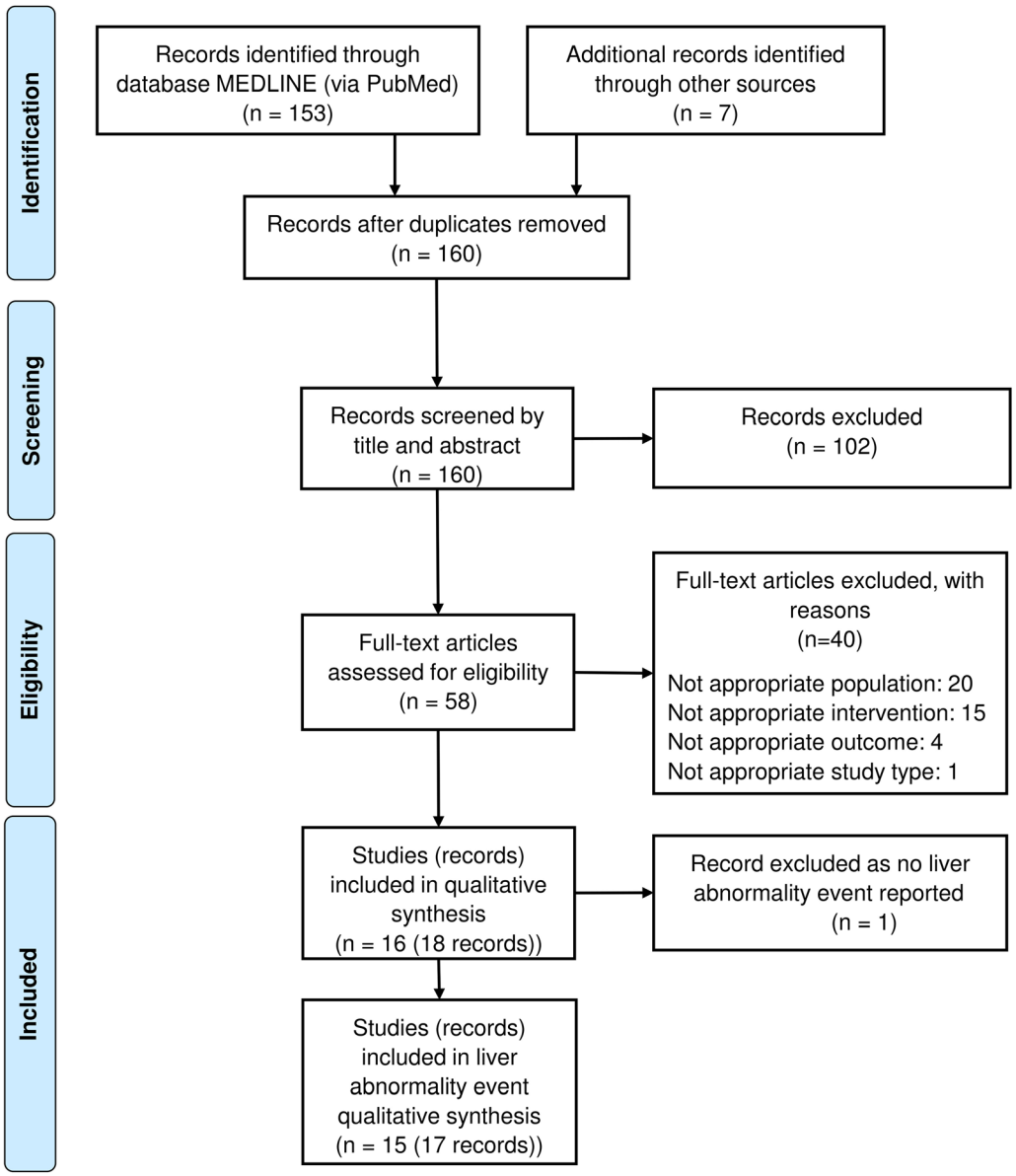

Fig. 1 Flow chart of the screening and selection process of RCTs investigating the hepatic safety profile of acetaminophen

acetaminophen was 1500 mg in one RCT, 2000 mg in three RCTs, 3000 mg in another three RCTs and 4000 mg in 11 RCTs (considering that some studies had more than one acetaminophen treatment arm). Treatment duration was short (2–4 weeks) in eight RCTs, intermediate (6–8 weeks) in two RCTs and relatively long (12–26 weeks) in five RCTs (Table 1).

A total of seven active randomized monotherapy or combination treatments were included. For combination treatment of diclofenac + misoprostol and ibuprofen + acetaminophen, only one and two study arms were available, respectively (Supplementary Table S3). However, these combination treatments did not exhibit any difference in liver abnormality when compared with data from monotherapy wih diclofenac or ibuprofen (Supplementary Figure S1). Thus, the following exploratory analysis focused on the primary or first treatment only, and the possible differences

Table 1 Summary of 15 RCTs included in the final analysis which reported liver safety data

Study	N	Age (mean years)	Study design	Study blinding	No. of arms	Treatments	Endpoint	Definition category	Duration (weeks)	Population
Pincus et al., 2001 [47]	454	61.5	Crossover	Double blind	2	Diclofenac + misoprostol, acetaminophen	AST elevation	> 0–1 × ULN, > 1.5–2 × ULN, > 3 × ULN	6	OA hip/knee
Altman et al., 2007 [48]	483	62.2	Parallel	Double blind	3	Acetaminophen, placebo	ALT/AST elevation	> 1.5–2 × ULN, > 3 × ULN	12	OA hip/knee
Bradley et al., 1991 [49]	195	56.5	Parallel	Double blind	3	Acetaminophen, ibuprofen	AST elevation	> 0–1 × ULN	4	OA knee
Doherty et al., 2011 [50]	892	60.6	Parallel	Double blind	4	Acetaminophen, ibuprofen, ibuprofen + acetaminophen	ALT elevation	> 1.5–2 × ULN, > 3 × ULN	13	OA knee
Ganetsky et al., 2019 [51]	50	29	Crossover	NA	2	Acetaminophen, acetaminophen + propylene glycol	ALT elevation	> 0–1 × ULN	2	Healthy volunteers
Herrero-Beaumont et al., 2007 [52]	212	64.2	Parallel	Double blind	2	Placebo, acetaminophen	ALT elevation	> 1.5–2 × ULN	26	OA knee
Heard et al., 2014 [45]	276	33	Parallel	Triple blind	2	Acetaminophen, placebo	ALT elevation	> 0–1 × ULN	2.3	Healthy volunteers
Ioannides et al., 2014 [53]	183	39.9	Parallel	Double blind	2	Acetaminophen, placebo	ALT elevation	> 1.5–2 × ULN, > 3 × ULN	12	Mild to moderate asthma

Table 1 continued

Study	N	Age (mean years)	Study design	Study blinding	No. of arms	Treatments	Endpoint	Definition category	Duration (weeks)	Population
Maeda et al., 2020 [46]	242	30	Parallel	Single blind	2	Placebo, acetaminophen	ALT elevation, liver injury	> 0–1 × ULN, > 1.5–2 × ULN, > 3 × ULN	4	Healthy volunteers
Mohamed et al., 2013 [54]	18	55	Parallel	Open label	2	Levobunolol*, acetaminophen	liver injury	> 3 × ULN	2	Open angle glaucoma
Pincus et al., 2004 [55]	638	63.4	Crossover	Double blind	2	Placebo, acetaminophen	liver enzymes elevation	> 3 × ULN	6	OA hip/knee
Parra et al., 2007 [56]	36	70.3	Parallel	Double blind	3	Placebo, acetaminophen	ALT elevation	> 1.5-2 × uln	4	Patients stabilized on warfarin therapy
Prior et al., 2007 [57]	542	61.7	Parallel	Double blind	2	Placebo, acetaminophen	ALT/AST elevation, ALT/AST/TB elevation	> 1.5–2 × ULN, > 3 × ULN	12	OA hip/knee
Temple et al., 2006 [58]	581	59.3	Parallel	Double blind	2	Acetaminophen, naproxen	ALT elevation, ALT/AST elevation	> 1.5–2 × ULN	4	OA hip/knee
Watkins et al., 2006 [59]	67	33.4	Parallel	Single blind	2	Placebo, acetaminophen	ALT elevation	> 0–1 × ULN, > 1.5–2 × ULN, > 3 × ULN	2	Healthy volunteers

*Levobunolol was administrated topically; remaining treatments were administrated orally. *ALT* alanine transaminase, *AST* aspartate transaminase, *NA* Not applicable, *TB* total bilirubin, *OA* osteoarthritis, *ULN* upper limit of normal

arising due to combination treatment were to be tested in the MBMA analysis.

Exploratory Analysis

Table 2 provides a summary of liver abnormality thresholds reported by various primary treatments in the 15 studies. Primary treatments other than acetaminophen (e.g., diclofenac, ibuprofen, levobunolol and naproxen) were included to further inform acetaminophen effect with different liver abnormality thresholds by ensuring the development of a network MBMA analysis as shown in the network plot (Supplementary Figure S2). Figure 2 shows the percentage of liver abnormalities along with their associated ULN thresholds for the various primary treatments. There were generally lower event rates for liver enzyme elevations > 1.5 ULN from baseline. In addition, large variation was observed in > 0–1 ULN elevation particularly in the acetaminophen and placebo arms. Moreover, higher liver abnormality event rate was not observed with increasing daily dose of acetaminophen across the different ULN thresholds (Supplementary Figure S3).

It is worth mentioning that 9 studies reporting the time course of plasma ALT/AST showed a transient rise in liver enzymes: an initial peak, typically two weeks after start of acetaminophen treatment, which subsequently returned to near normal levels (Supplementary Figure S4 and Supplementary Figure S5). However, large variation in the levels of ALT/AST across the limited number of studies prohibited any further quantitative assessment of these patterns.

Model Development and Assessment of Risk of Liver Injury

Out of the 15 selected RCTs (including 35 treatment arms) assessing liver safety endpoints and reporting event rate of liver abnormality, six studies (including 13 treatment arms) reported 0–1 ULN threshold, ten studies (including 24 treatment arms) reported > 1.5–2 ULN threshold and nine studies (including 21 treatment arms) reported > 3 ULN threshold. There were three studies reporting all three thresholds, four studies reporting two thresholds and 8 studies reporting either one of the three thresholds (Table 2). The liver abnormality event defined by these three thresholds were reported at primary time point across 15 studies, which varied from 2 to 26 weeks (mean ~ 7.5 weeks).

Due to the limited number of studies and no distinct differences in the reported liver abnormality event rates for drugs other than acetaminophen, the effect of diclofenac, ibuprofen, levobunolol and naproxen was estimated with a common shared effect on liver safety endpoints (Fig. 2). One treatment arm with ibuprofen plus acetaminophen combination did not exhibit any significant effect on the risk of liver abnormality versus acetaminophen, when separated drug effect was tested in the model. Therefore, this combination treatment arm was treated as acetaminophen in the final analysis. However, no dose response for liver abnormality was observed for the acetaminophen dose range (1500–4000 mg/day). In general, the model demonstrated adequate performance when predicting the event rates for the different thresholds. The observed event rates fell within the 95% prediction intervals (Fig. 3). The potential impact of time to liver abnormality outcome, population type (healthy vs. diseased) and age across studies were further evaluated in the model as covariates. However, no significant effect was observed.

Simulations based on the final model showed an increased risk of 23.58% (95% CI: 17.74–29.20) for 0–1 ULN elevation in ALT/AST following treatment with acetaminophen, which corresponds to mild liver abnormality. On the other hand, acetaminophen intake was associated with an extremely low risk of moderate and severe liver abnormality (1.35% (95% CI: 0.17–2.51) and 0.01% (95% CI: 0.00–0.32) elevation in > 1.5–2 ULN and > 3 ULN, respectively) when compared with background/placebo (Table 3). The simulated absolute risk of liver abnormality is presented in Supplementary Table S4, where background/placebo were associated with 5.48% (0–1 ULN), 0.6% (> 1.5–2 ULN), and 0.25%

Table 2 Summary of ULN elevation thresholds of liver abnormality events reported across the 15 studies included in the MBMA

Drug	Patients	Trials	Arms	Trials (> 0–1 ULN)	Arms (> 0–1 ULN)	Trials (> 1.5–2 ULN)	Arms (> 1.5–2 ULN)	Trials (> 3 ULN)	Arms (> 3 ULN)
Acetaminophen	2920	15	20	6	7	10	14	9	12
Diclofenac	227	1	1	1	1	1	1	1	1
Ibuprofen	353	2	3	1	2	1	1	1	1
Levobunolol*	9	1	1	0	0	0	0	1	1
Naproxen	291	1	1	0	0	1	1	0	0
Placebo	1069	9	9	3	3	7	7	6	6
Total	**4869**	**15**	**35**	**6**	**13**	**10**	**24**	**9**	**21**

*Levobunolol was administrated topically; other treatments were administrated orally. *ULN* upper limit of normal. Arms here mean treatment arms across the trials exhibiting a given ULN elevation

(> 3 ULN) risk of liver abnormality, respectively, for different thresholds.

DISCUSSION

The present study was designed with the objective to characterize the risk of liver abnormality associated with the use of therapeutic doses of acetaminophen using published summary-level data extracted from RCTs conducted in patients with OA, healthy subjects and patients with a range of conditions associated with analgesic and anti-inflammatory drug use. Our goal was to establish whether the use of acetaminophen is associated with unacceptable risk of liver abnormalities, which would result in an unfavorable benefit–risk balance for its use in combination with topical diclofenac, which is generally well-tolerated, in patients affected by mild-to-moderate OA.

Based on the findings from this MBMA including 15 RCTs, with a representative sample of over 4,800 subjects, it appears that acetaminophen use at $\leq$ 4 g/day is associated with a 23%, 1.35% and 0.01% increased risk of mild, moderate, and severe liver toxicity, respectively, versus placebo. These results have significant implications have significant implications as serum liver transaminases remain the most reliable and sensitive indicators of hepatocellular injury [31, 32]. Although a 23% increased risk appears numerically large, mild elevation in transaminases is frequently observed in clinical practice due to many non-drug factors such as obesity, and is often not a clinical concern because of liver self-healing capacity [33]. The magnitude of the effects is, generally, in line with two recent reviews which showed higher risk of abnormal results on liver function tests in patients taking acetaminophen than control subjects, while acknowledging that the clinical relevance of the findings remains uncertain with respect to patient outcomes [8, 9]. Moreover, the MBMA estimated risk of liver injury with acetaminophen is very low when compared with the risk of GI and CV toxicity and renal insufficiency posed by oral NSAIDs or the risk of delirium, falls/fractures, physical dependence and addiction posed by opioids [34]. Therefore, acetaminophen is still maintained and included in OA clinical practice guidelines and suggested to be used in combination with topical NSAIDs to achieve better efficacy and safety outcomes in OA [15, 16, 35, 36]. Moreover, in individuals with limited treatment options due to intolerance of or contraindications to the use of other types of OA

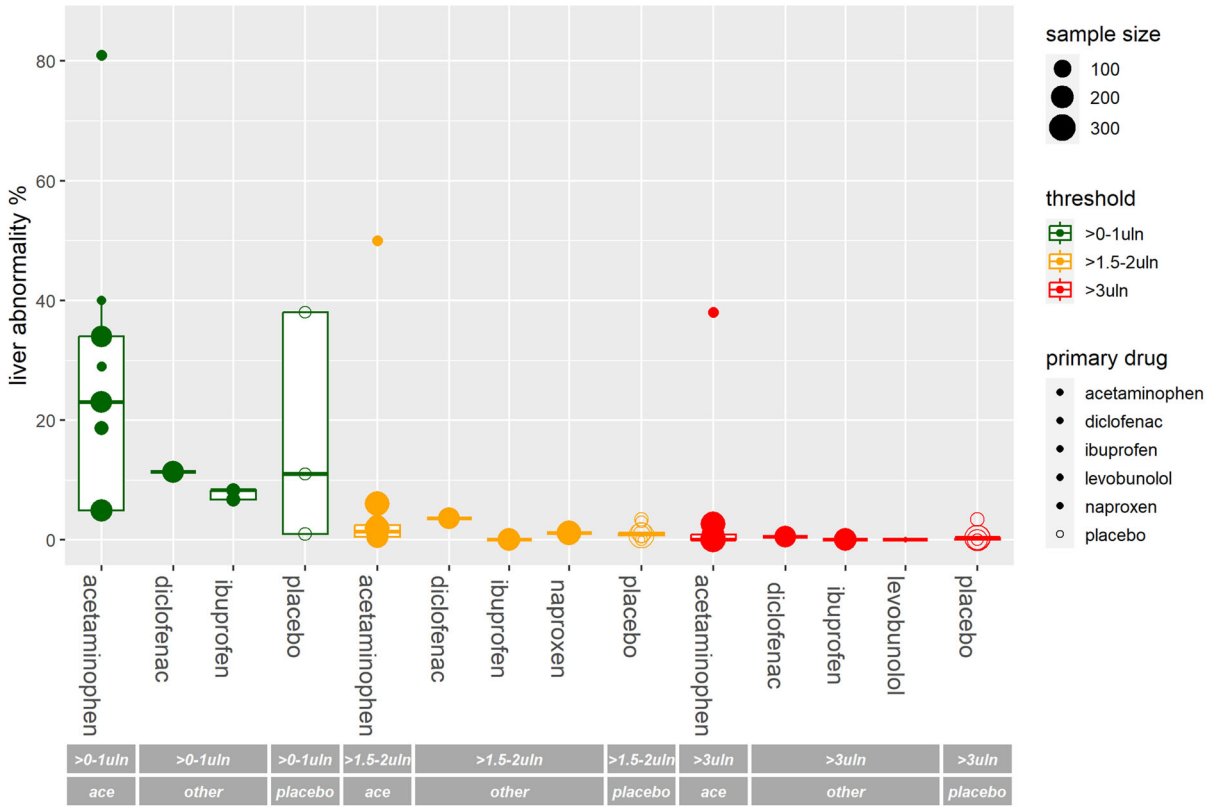

Fig. 2 Reported liver abnormality event rate at primary time, stratified by threshold and primary treatments. *Box plot* presents sample size weighted median. *Dot* presents each reported liver abnormality by treatment arm and threshold. Symbol size is proportional to the sample size in each treatment arm. *Green symbol*: > 0–1 × ULN elevation; *yellow symbol*: 1.5–2 × ULN elevation; *red symbol*: > 3 × ULN elevation. *ULN* upper limit of normal, *ace* acetaminophen

medications, acetaminophen remains conditionally appropriate and recommended [36].

Topical NSAIDs, especially topical diclofenac, are generally considered safe in the management of OA [11, 37] and are, therefore, recommended as first-line by most OA clinical practice guidelines before the use of oral NSAIDs [15, 16]. In spite of the recent reports questioning the efficacy of acetaminophen in OA pain [8, 9] the combination of acetaminophen and topical diclofenac could help patients achieve adequate pain relief and potentially limit repeated supratherapeutic ingestion of acetaminophen in case of insufficient analgesia, which is associated with worse clinical outcomes than isolated acetaminophen overdose [20, 38]. In addition, the safety profile of acetaminophen is not affected by topical NSAIDs [39]. Taken together with the good tolerability profile of diclofenac [40], this combination may prevent progression of patients to oral NSAIDs and opioids, especially the elderly with comorbidities. Furthermore, it can be anticipated that the more favorable safety profile of the combination would ensure greater adherence [41]. As such, the findings from the current study may be helpful to a range of stakeholders in the field of OA including clinicians, specialists and researchers.

The current MBMA could not identify any dose–response relationship between the use of acetaminophen and the liver abnormality within the analyzed dose range of 1500–4000 mg/day for 2–26 weeks of treatment. Interestingly, a meta-analysis based on long-term observational studies identified

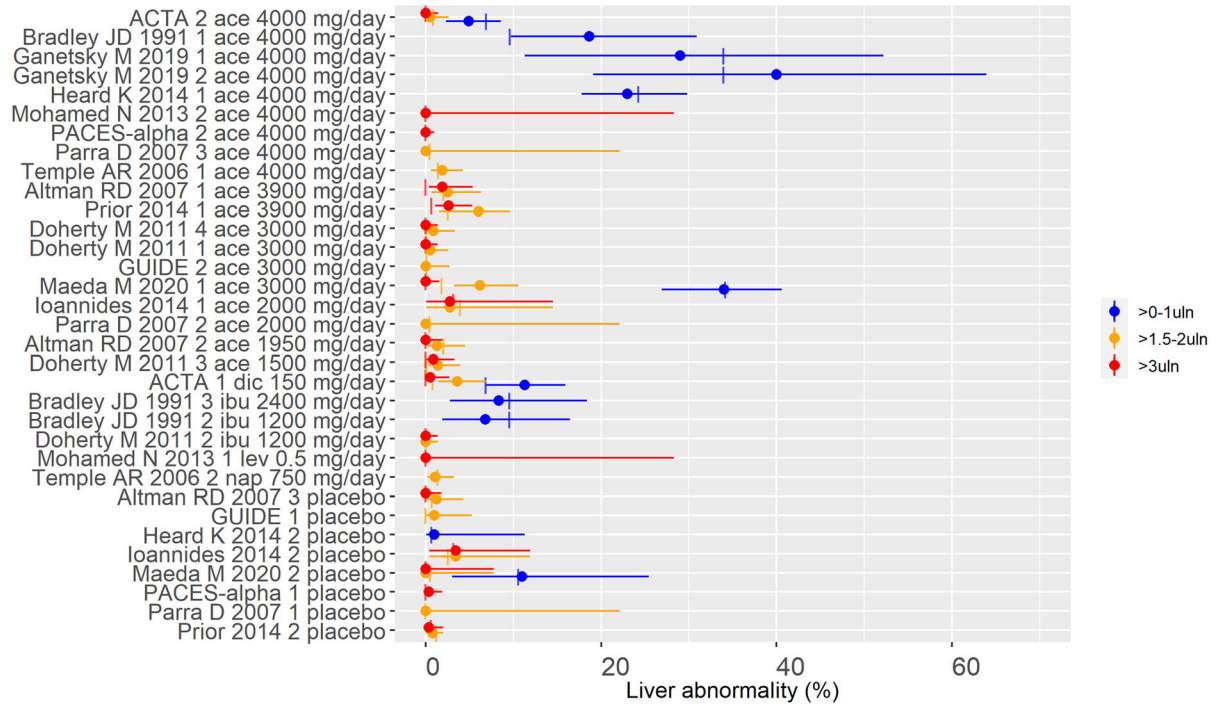

Fig. 3 Observed (*circle*) and model-estimated (*vertical bar*) liver abnormality (± 95% CI) by study/treatment arm at primary time. *Colors* represent the different elevation thresholds for ALT/AST (*blue*: > 0–1 × ULN, *orange*: > 1.5–2 × ULN, *red*: > 3 × ULN). The *horizontal lines* present the respective 95% CIs or reported event rate. *ace* acetaminophen, *CI* confidence interval, *dic* diclofenac, *ibu* ibuprofen, *lev* levobunolol, *nap* naproxen, *plc* placebo

dose–response relationship between acetaminophen use and major adverse events such as mortality, CV, GI, or renal toxicity [21]. It also noted that such long-term dose–response observed for most endpoints suggests a considerable degree of acetaminophen toxicity especially at the upper end of the recommend analgesic doses. Thus, we acknowledge the differences between RCTs and the potential value of using long term observational studies in assessing the safety of acetaminophen. The majority of RCTs included in the current analysis were generally of relatively short duration (mean study duration = 7.4 weeks, range of 2–26 weeks) and used narrow dose range of acetaminophen across different liver toxicity thresholds, which limited the ability of MBMA to identify statistically significant dose–response relationship. However, most clinical guidelines for OA management suggest short-term or episodic use of acetaminophen at < 3 g/day and/or not exceeding 4 g/day, e.g., in elderly subjects, with joint consideration of its analgesic effect and potential safety issues [15, 16, 35, 36]. Our analysis also supports the above consideration by showing short-term standard acetaminophen use (≤ 4 g/day) to be associated with low risk of clinically relevant liver enzyme elevations. On the other hand, the long-term impact of mild liver abnormality might raise concern in clinical practice; elevation of liver transaminases can be resolved rapidly by reducing the dose and/or the duration of treatment [42]. Eventually, ALT/AST monitoring may need to be considered in patients who are at higher risk of liver toxicity.

It should be clear that we have also included 7 RCTs conducted in healthy subjects and in subjects with other disease conditions (e.g., asthma, glaucoma) in order to increase the precision of parameter estimates describing drug effects. Of note is that studies conducted in

Table 3 Simulated placebo-adjusted liver abnormality events associated with acetaminophen monotherapy

Drug	Dose (mg/day)	Threshold	Percent of placebo-adjusted liver abnormality (95% CI)
Acetaminophen	1500–4000	> 0–1 × ULN	23.58 (17.74, 29.20)
Other drugs*	NA	> 0–1 × ULN	23.54 (17.79, 29.08)
Acetaminophen	1500–4000	> 1.5–2 × ULN	1.35 (0.17, 2.51)
Other drugs*	NA	> 1.5–2 × ULN	1.30 (0.13, 2.46)
Acetaminophen	1500–4000	> 3 × ULN	0.01 (0.00, 0.32)
Other drugs*	150	> 3 × ULN	0.00 (0.00, 0.35)

*"Others" includes diclofenac, ibuprofen, levobunolol, and naproxen. Values are mean parameter estimates based on maximum likelihood model predictions, with 95% CI obtained by resampling of the parameter estimates from the final model variance–covariance matrix 1000 times. *CI* confidence interval, *ULN* upper limit of normal

healthy adults generally involved younger subjects (mean age = 31.7 years) when compared with studies involving patients (mean age = 60 years). There was no significant trend suggesting increased risk of liver abnormality with increasing age or underlying disease condition (e.g., healthy vs OA). This finding contradicts existing evidence which shows ageing and frailty to be associated with increased risk of acetaminophen hepatotoxicity [43]. However, reduced liver size in the elderly may also lead to significantly less increase in transaminases than younger population [44]. In addition, RCTs conducted in healthy subjects reported higher risk of elevated ALT/AST than diseased subjects with few subjects experiencing a transient ALT elevation with 4 g/day of acetaminophen, after a mean duration of 2 weeks that did not increase any further and was mostly resolved on discontinuation of acetaminophen [45, 46]. Therefore, we cannot fully rule out the impact of such transient elevation in studies of < 4 weeks duration that might prevent the MBMA to account for the potential effect of age or disease on acetaminophen associated risk of liver toxicity. In addition, the relatively short study duration of the included RCTs, in general, also prevented the assessment of the impact of acetaminophen on long term liver safety.

In addition to the points highlighted previously, our analysis has several limitations. First, the model does not allow any prediction of risk of liver abnormality with acetaminophen doses above 4000 mg/day. Second, the effect of age as a covariate is not accounted for in the model due to limited number of studies, despite the fact that the population analyzed here ranges from 29 to 70 years. Third, the duration of the studies and the effect of long-term acetaminophen use (> 26 weeks) on the underlying liver abnormality risk remains unclear. However, the likelihood that this pattern persists beyond 26 weeks is very high with the exception of ageing, in which case the susceptibility to liver abnormality will increase. Fourth, we could not differentiate single and repeated liver abnormality events due to acetaminophen, as the data source did not allow us to conduct such analysis. Fifth, given the use of published data, there is a potential for publication bias, but even more importantly, there is heterogeneity in the way liver toxicity is defined. Lastly, we acknowledge that other definitions of liver toxicity, such as transaminases in combination with total bilirubin or ALT/ALP ratio could have been more suitable. However, we were restricted to the use of ALT/AST elevation since it was the most commonly reported outcome for liver safety across studies when compared with other measures.

CONCLUSIONS

The current MBMA demonstrates that short-term (~ 8 to 16 weeks) acetaminophen use at standard analgesic doses (≤ 4000 mg/day) is associated with a low risk of clinically relevant liver injury. Given the high safety profile of topical diclofenac, one can consider the use of acetaminophen as safe when co-administered with topical diclofenac, at least over a short-term, as treatment for mild-to-moderate OA. Whilst additional studies are desirable to further characterize the long-term safety of acetaminophen, it is plausible to assume that at therapeutic doses and recommended dosing regimen, acetaminophen will show comparable safety profile in OA patients.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Vidhu Sethi: employee and shareholder of Haleon. Oscar Della Pasqua: employee and shareholder of GlaxoSmithKline. Li Qin: employee and shareholder of Certara. Eugène Cox: former employee and shareholder of Certara; current employee of University Leiden, the Netherlands. Luke Van der Laan and Iñaki F. Trocóniz: No competing interests to disclose.

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