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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Supplementary Material

Supplementary Table S1. Search strategy for the evaluation of liver safety and exposure to acetaminophen.

Area/objective	S. No.	Keywords	Results MEDLINE via PubMed
I. Intervention (acetaminophen)	1	N-Acetyl-p-aminophenol [tiab] OR Acetamidophenol [tiab] OR N-(4-Hydroxyphenyl)acetanilide [tiab] OR "Acetaminophen"[Mesh] OR Hydroxyacetanilide [tiab] OR APAP [tiab] OR Acetaminophen [tiab] OR p-Acetamidophenol [tiab] OR p-Hydroxyacetanilide [tiab] OR Acephen [tiab] OR Acetaco [tiab] OR Tylenol [tiab] OR Anacin-3 [tiab] OR "Anacin 3" [tiab] OR Anacin3 [tiab] OR Datril [tiab] OR Acamol [tiab] OR Algotropyl [tiab] OR paracetamol [tiab] OR Panadol [tiab]	29,414
II. Outcomes (liver safety)	2	"liver toxicity" OR "hepatic toxicity" OR hepatotoxicity OR "liver safety" OR ASAT OR ALAT OR aminotransferase OR "liver injury " OR "liver injuries" OR bilirubin	186,378
III. Study design (RCT)	3	random* [tiab] OR "Random Allocation"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR single blind method [tiab] OR double blind method [tiab] OR randomly [tiab]	1,364,326
IV. Final results	4	#1 AND #2	5,384
	5	#4 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	3,174
	6	#5 AND #3	143
	7	#6 AND Filters: English	139
	8	#5 AND Filters: Meta-Analysis, Systematic Review, English	28
	9	#7 OR #8	153

Supplementary Table S2. Inclusion criteria for the evaluation of liver safety and exposure to acetaminophen.

PICOS framework	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years), with no further restrictions regarding the disease type, healthy volunteers	In vitro/in vivo studies, animals' studies, children; patients who overdose paracetamol; patients consuming alcohol (including heavy/moderate drinkers, chronic drinkers etc.)
Intervention	Oral acetaminophen	Intravenous acetaminophen
Comparator	NA	
Outcomes	Hepatic aminotransferases (ALT and AST)	
Duration of therapy	At least two weeks	Less than two weeks (14 days)
Study types	RCTs	SLRs, non-RCTS, case studies, observational studies
Language	English	Others

ALT: alanine transaminase, AST: aspartate transaminase, NA: Not applicable, RCT: randomized clinical trials

Supplementary Table S3. Summary of selected liver safety studies stratified by treatment.

Treatment	Study	Arm	Threshold
Acetaminophen	15	17	>0-1 ULN, >1.5-2 ULN, >3 ULN
Acetaminophen+propylene glycol	1	1	>0-1 ULN
Diclofenac+misoprostol	1	1	>0-1 ULN, >1.5-2 ULN, >3 ULN
Ibuprofen	2	3	>0-1 ULN, >1.5-2 ULN, >3 ULN
Ibuprofen+acetaminophen	1	2	>1.5-2 ULN, >3 ULN
Levobunolol	1	1	>3 ULN
Naproxen	1	1	>1.5-2 ULN
Placebo	9	9	>0-1 ULN, >1.5-2 ULN, >3 ULN
Total	15	35	

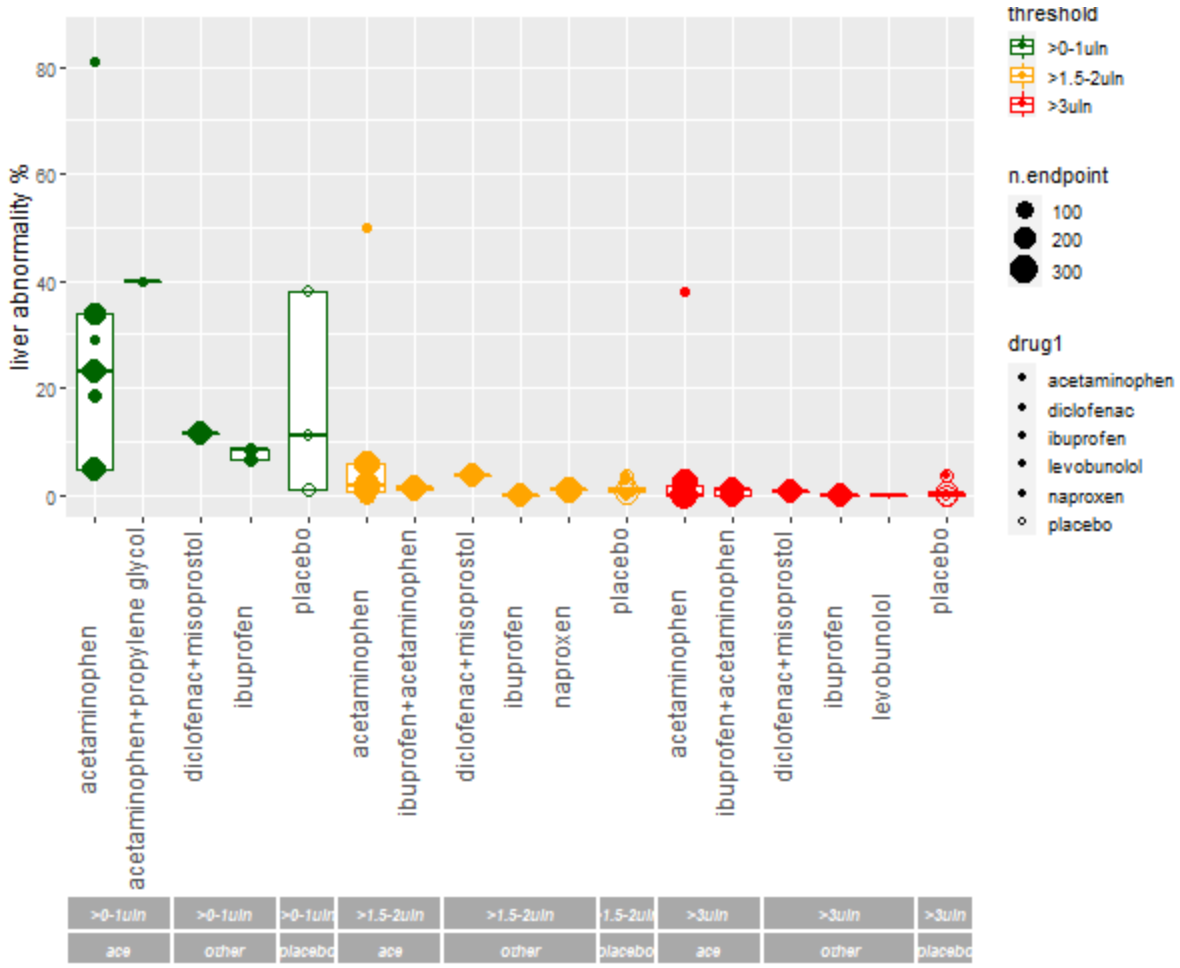
ULN: upper limit of normal

Supplementary Table S4. Simulated effect of acetaminophen monotherapy on % absolute liver abnormality event.

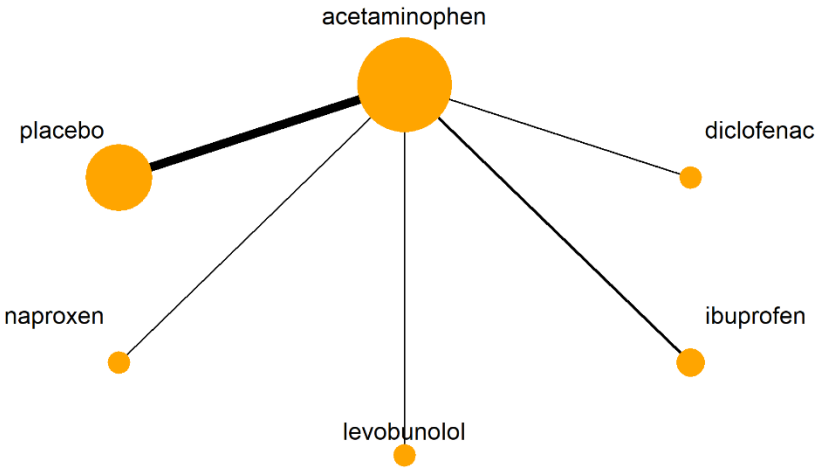
Treatment	Dose (mg/day)	Threshold	% Liver abnormality (95% CI)
Acetaminophen	1500-4000	>0-1 ULN	29.06 (24.31, 33.58)
Other drugs*	NA	>0-1 ULN	29.02 (24.29, 33.55)
Placebo/background	NA	>0-1 ULN	5.48 (3.73, 7.55)
Acetaminophen	1500-4000	>1.5-2 ULN	1.95 (1.15, 3.05)
Other drugs*	NA	>1.5-2 ULN	1.9 (1.1, 3.07)
Placebo/background	NA	>1.5-2 ULN	0.6 (0.36, 1.17)
Acetaminophen	1500-4000	>3 ULN	0.26 (0.08, 0.64)
Other drugs*	150	>3 ULN	0.22 (0, 0.66)
Placebo/background	NA	>3 ULN	0.25 (0.11, 0.54)

CI: confidence interval; ULN: upper limit of normal

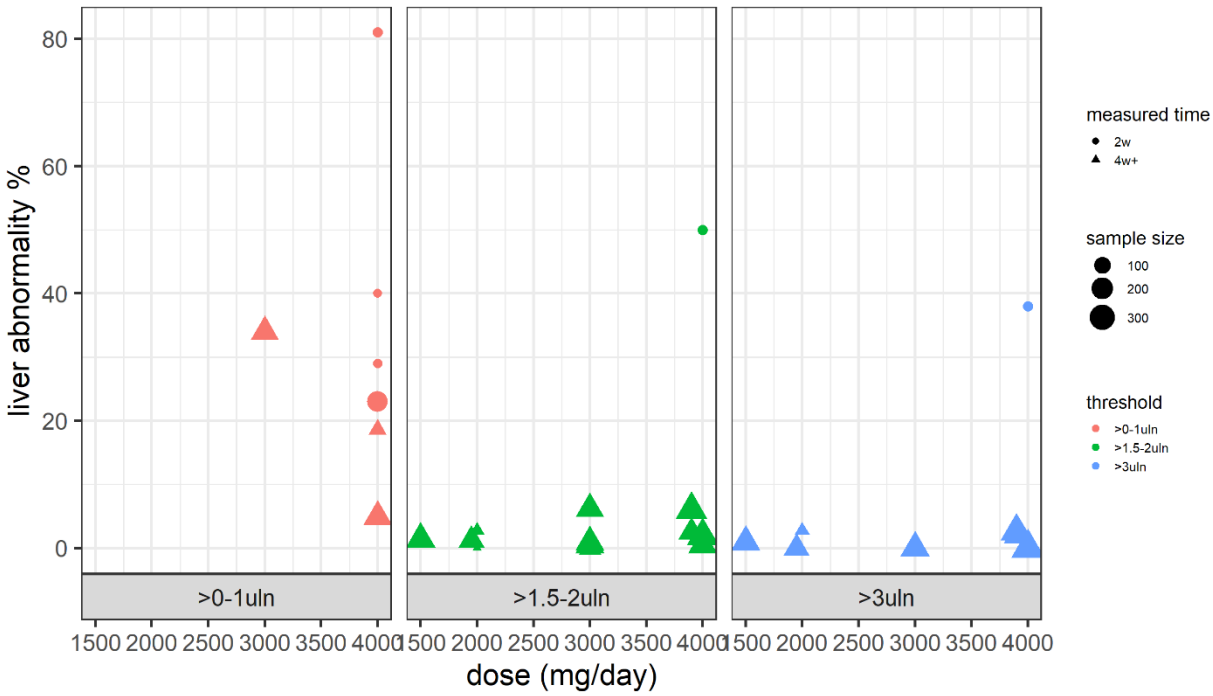
*Others drugs include diclofenac, ibuprofen, levobunolol and naproxen. Values are mean parameter estimates based on maximum likelihood model predictions, with 95% CI of resampling parameter estimates from the final model variance-covariance matrix 1000 times



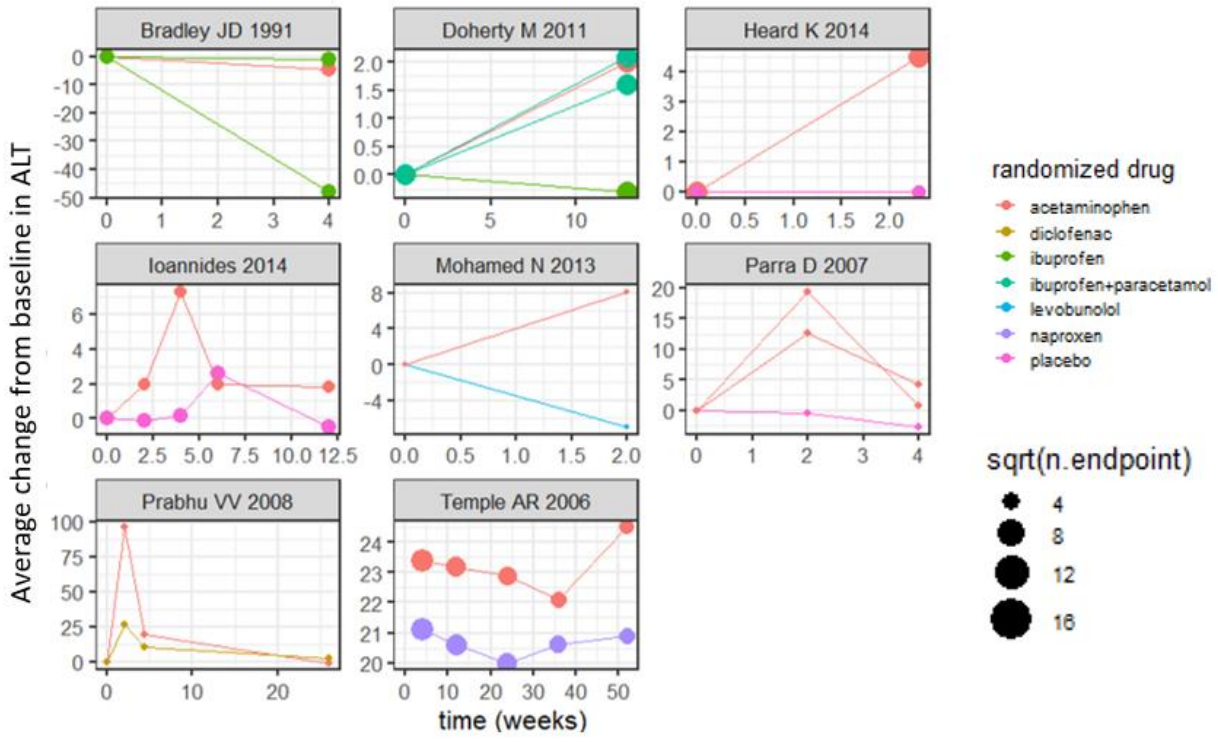
Supplementary Figure S1. Reported liver abnormality event rate, stratified by severity (threshold) and treatment arm. The box plot depicts the sample size weighted median. Dots describe each reported liver abnormality by treatment arm and threshold. Symbol size is proportional to the sample size in each 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.



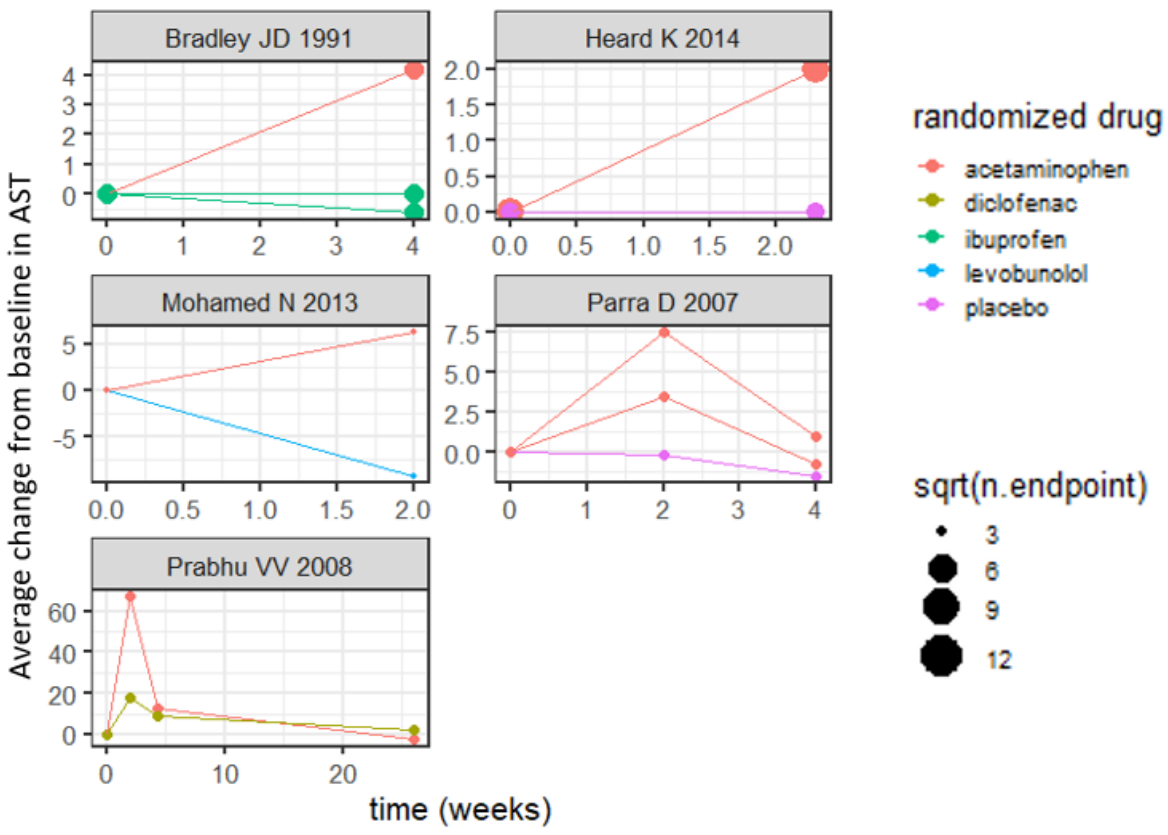
Supplementary Figure S2. Primary/first treatment network plot of included 15 RCTs reporting liver abnormality. Levobunolol was administered topically; remaining treatments were administered orally. The width of solid lines represents the number of clinical trials.



Supplementary Figure S3. Reported liver abnormality event by acetaminophen daily dose across 20 treatment arms. Red symbol: >0-1 ULN elevation; green symbol: >1.5-2 ULN elevation; blue symbol: >3 ULN elevation. ULN: Upper limit of normal



Supplementary Figure S4. Time course of changes in liver ALT concentrations in plasma for various studies with acetaminophen. Study “Temple AR 2006” reported absolute ALT value at given time points and hence reported no change from baseline due to missing baseline value. ALT: alanine transaminase



Supplementary Figure S5. Time course of changes in liver AST concentrations in plasma for various studies with acetaminophen. AST: Aspartate transaminase