

# **Model-based meta-analysis supporting the combination of acetaminophen and topical diclofenac in acute pain: A therapy for mild-to-moderate osteoarthritis pain?**

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## Supplementary Material

Supplementary Table S1. Search strategy for studies on the combination of oral acetaminophen and oral or topical diclofenac in acute pain

Area/objective		No.	Key words	Results MEDLINE via PubMed
I. Intervention	<b>Ia. Diclofenac</b>	1	("Diclofenac"[Mesh]) OR (diclofenac [tiab] OR Diclophenac [tiab] OR Dicrofenac [tiab] OR Dichlofenal [tiab] OR "Diclofenac Sodium" [tiab] OR "Sodium Diclofenac" [tiab] OR Diclofenac, Sodium [tiab] OR "Diclonate P" [tiab] OR Feloran [tiab] OR Voltarol [tiab] OR Novapirina [tiab] OR Orthofen [tiab] OR Ortofen [tiab] OR Orthophen [tiab] OR SR-38 [tiab] OR "SR 38" [tiab] OR SR38 [tiab] OR Voltaren [tiab] OR "GP-45,840" [tiab])	13,438
	<b>Topical administration</b>	2	"Administration, Topical"[Mesh] OR topical* [tiab] OR cutaneous [tiab] OR dermal [tiab] OR transcutaneous [tiab] OR transdermal [tiab] OR percutaneous [tiab] OR skin [tiab] OR massage [tiab] OR embrocation [tiab] OR gel [tiab] OR ointment [tiab] OR aerosol [tiab] OR cream [tiab] OR creme [tiab] OR lotion [tiab] OR mousse [tiab] OR foam [tiab] OR liniment [tiab] OR spray [tiab] OR rub [tiab] OR balm [tiab] OR salve [tiab] OR emulsion [tiab] OR oil [tiab] OR patch [tiab] OR plaster [tiab]	1,525,339
	<b>Oral administration (systemic use)</b>	3	"systemic use" [tiab] OR "systemic treatment" [tiab] OR "systemic therapy" [tiab] OR "systemic administration" OR "systemic" [tiab] OR "Administration, Oral"[Mesh] OR "oral administration"[tiab] OR "Oral Drug Administration"[tiab] OR "oral use"[tiab] OR "oral therapy"[tiab] OR "oral treatment"[tiab] OR oral* [tiab] OR "Tablets"[Mesh] OR tablet*[tiab] OR "Capsules"[Mesh] OR "capsule*" [tiab] OR caplet* [tiab]	1,283,569
	<b>Ib. Acetaminophen</b>	4	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 Datriil [tiab] OR Acamol [tiab] OR Algotropyl [tiab] OR paracetamol [tiab] OR Panadol [tiab]	29,414
		5	#2 OR #3	2,666,226
		6	#1 AND #5	4,372
		7	#6 AND #4	317

Area/objective	No.	Key words	Results MEDLINE via PubMed
<b>II. Disease (pain)</b>	<b>8</b>	(("Pain"[Mesh] OR pain [tiab] OR Pains [tiab] OR "Physical Suffering" [tiab] OR "Physical Sufferings" [tiab] OR ache [tiab] OR aches [tiab] OR "joint pain" [tiab] OR "painful knee" [tiab] OR "painful joint" [tiab]) OR (Toothaches [tiab] or Odontalgia [tiab] or Odontalgia* [tiab] OR "Toothache"[Mesh] OR "dental pain" [tiab] OR "painful bunion" [tiab])) OR ((bunione* [tiab] OR dental [tiab]) AND ("Pain"[Mesh] OR pain [tiab]))	807,686
<b>III. Final results</b>	<b>9</b>	#7 AND #8	199
	<b>10</b>	#9 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	188
	<b>11</b>	#10 AND Filters: English	182

Supplementary Table S2. Inclusion criteria for studies on the combination of oral acetaminophen and oral or topical diclofenac in acute pain

PICOS framework	Inclusion criteria
<b>Population</b>	Patients (no age restrictions) suffering with pain
<b>Intervention</b>	Combination of oral paracetamol and topical/systemic diclofenac
<b>Comparator</b>	NA
<b>Outcomes</b>	Pharmacokinetic (PK) parameters (AUC, Cl, volume of distributions), Endpoints focused on the measurement of pain reduction expressed both as a rating scale or number of patients with none, mild, moderate, severe pain
<b>Study types</b>	Any
<b>Other</b>	English

Note that no specific exclusion criteria were defined for this combination search

Supplementary Table S3. Reported pain score reduction in studies on the combination of oral acetaminophen and oral or topical diclofenac in acute pain

Study	Arm	Drug 1	Drug 2	Endpoint	Endpoint	Baseline	Value	Change
Elzaki WM 2016	1	Ace		Pain score	NRS	8	2.25	-5.75
Elzaki WM 2016	2	Ace	Dic	Pain score	NRS	8	0.5	-7.5
Elzaki WM 2016	3	Placebo		Pain score	NRS	8	2.82	-5.18
Munishankar B 2008	1	Ace		Pain score	VAS at rest	NA	2	-6
Munishankar B 2008	2	Dic		Pain score	VAS at rest	NA	2	-6
Munishankar B 2008	3	Ace	Dic	Pain score	VAS at rest	NA	1.5	-6.5
Riad W 2007	1	Dic		Pain score	Pain rating scale (0-5) change	2.6	0.8	-1.8
Riad W 2007	2	Ace		Pain score	Pain rating scale (0-5) change	3.1	0.5	-2.6
Riad W 2007	3	Ace	Dic	Pain score	Pain rating scale (0-5) change	2.9	0.8	-2.1
Woo WW 2005	1	Dic		Pain score	VAS at rest	2.4	0.8	-1.6
Woo WW 2005	2	Ace		Pain score	VAS at rest	2	0.8	-1.2
Woo WW 2005	3	Ace	Dic	Pain score	VAS at rest	2.5	0.8	-1.7
Beck DH 2000	1	Ace		Pain score	VAS	NA	0.9	-1.6
Beck DH 2000	2	Ace		Pain score	VAS	NA	0.4	-2.1
Beck DH 2000	3	Ace	Dic	Pain score	VAS	NA	0.4	-2.1
Breivik EK 1999	1	Dic		Pain score	VAS	58	38	-20
Breivik EK 1999	2	Ace		Pain score	VAS	60	37	-23
Breivik EK 1999	3	Ace	Dic	Pain score	VAS	57	19	-38
Hannam JA 2014	1	Ace		Pain score	VAS	NA	NA	NA
Hannam JA 2014	2	Dic		Pain score	VAS	NA	NA	NA
Hannam JA 2014	3	Ace	Dic	Pain score	VAS	NA	NA	NA
Montgomery JE 1996	1	Ace		Pain score	VAS	NA	3.4	-4.6
Montgomery JE 1996	2	Dic		Pain score	VAS	NA	1.9	-6.1
Montgomery JE 1996	3	Ace	Dic	Pain score	VAS	NA	2.1	-5.9
Siddik SM 2001	1	Ace		Pain score	VAS at rest	NA	3.5	NA
Siddik SM 2001	2	Dic		Pain score	VAS at rest	NA	2.3	NA

Study	Arm	Drug 1	Drug 2	Endpoint	Endpoint	Baseline	Value	Change
<b>Siddik SM 2001</b>	3	Ace	Dic	Pain score	VAS at rest	NA	1.5	NA
<b>Siddik SM 2001</b>	4	Placebo		Pain score	VAS at rest	NA	3.2	NA
<b>Hiller A 2004</b>	1	Ace		Pain score	VAS (0-3)	2.25	1.4	-0.85
<b>Hiller A 2004</b>	2	Dic		Pain score	VAS (0-3)	1.5	1.65	0.15
<b>Hiller A 2004</b>	3	Ace	Dic	Pain score	VAS (0-3)	2	1.2	-0.8
<b>Matthews RW 1984</b>	1	Ace		Pain score	VAS	NA	NA	NA
<b>Matthews RW 1984</b>	2	Ace		Pain score	VAS	NA	NA	NA
<b>Matthews RW 1984</b>	3	Ace	Dic	Pain score	VAS	NA	NA	NA

Ace: acetaminophen, Dic: diclofenac, NRS: numerical rating scale, VAS: visual analog scale, NA: no value reported

Supplementary Table S4. Summary of model development steps for the evaluation of opioid sparing effect in acute pain

Model development steps	Model number	Reference model	p-value versus reference model	AIC	logLik
<b>base mod</b>	2		-	115	-51
<b>mod2 + interaction term*</b>	2.1	2	0.028	113	-48

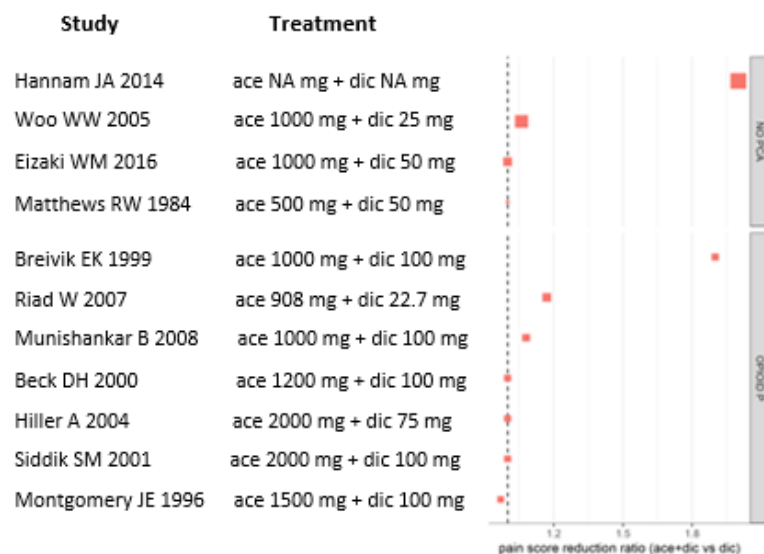
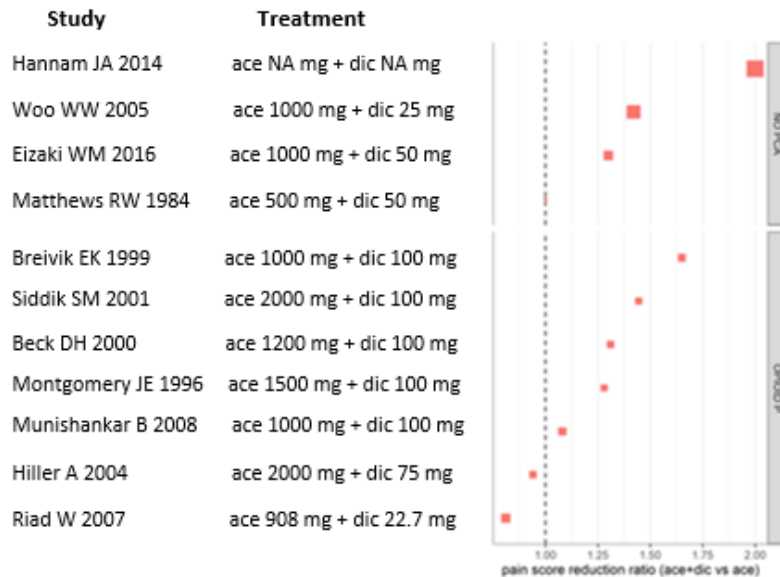
\*final model

Supplementary Table S5. Typical treatment effect on mean opioid PCA consumption difference from placebo, and percent difference from acetaminophen.

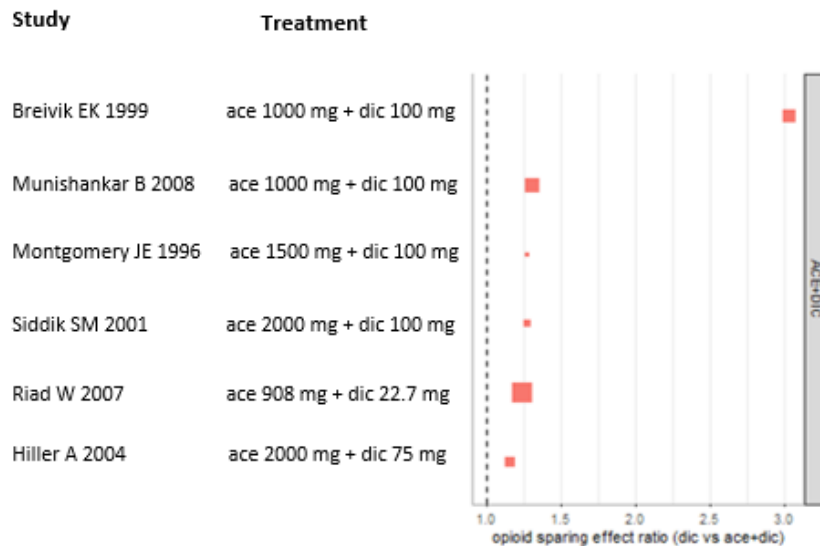
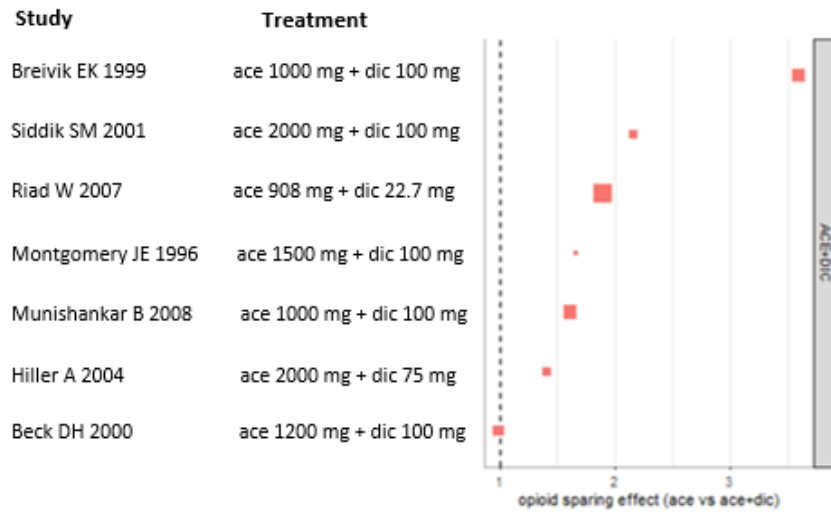
Treatment	Model predicted mean opioid PCA difference from placebo (mg) with 95% CI	Percent difference from acetaminophen (%)
<b>Systemic acetaminophen</b>	-18.93 ( -29.47, -8.33)	-
<b>Systemic acetaminophen + diclofenac</b>	-33.87 ( -44.43, -22.26)	-32.62 ( -47.59, -19.1)
<b>Systemic diclofenac</b>	-28.41 ( -39.15, -17.68)	-20.7 ( -32.86, -8.45)

Values are mean parameter estimates based on maximum likelihood model predictions, with 95% confidence interval of resampled parameter estimates from the final model variance-covariance matrix 1,000 times. CI: confidence interval; PCA: patient-controlled analgesia

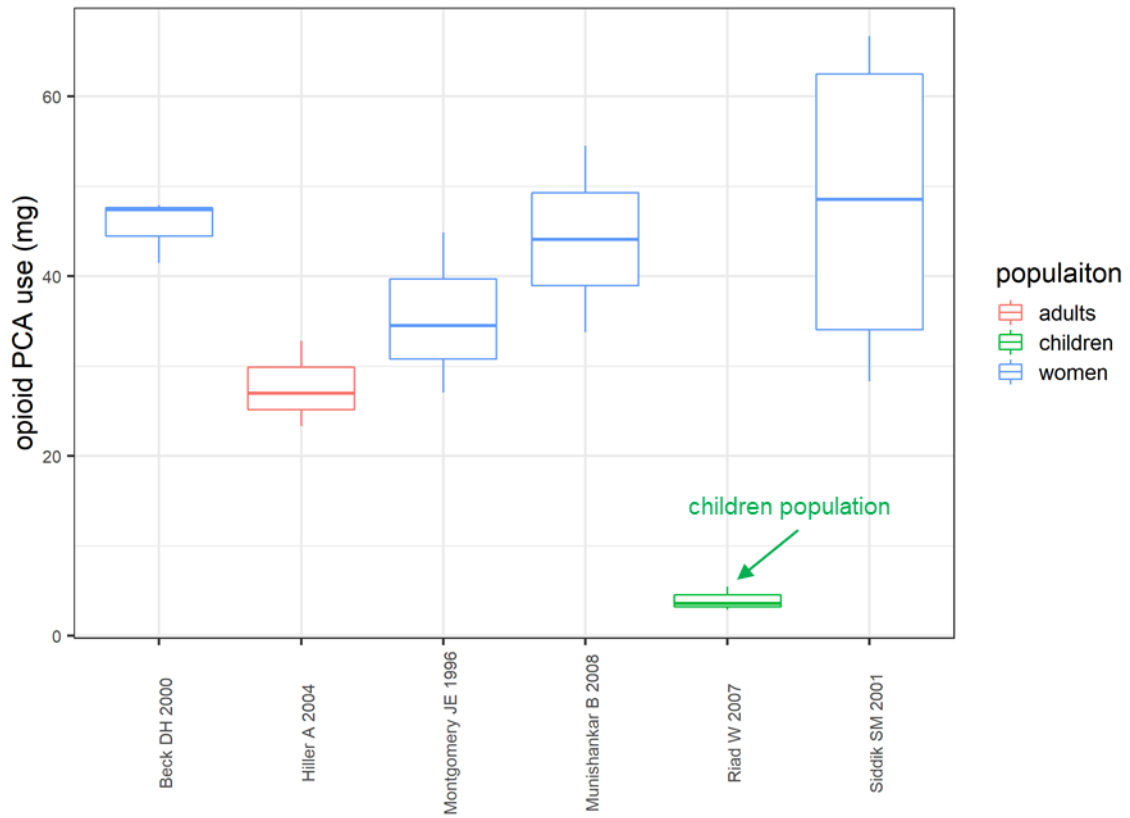




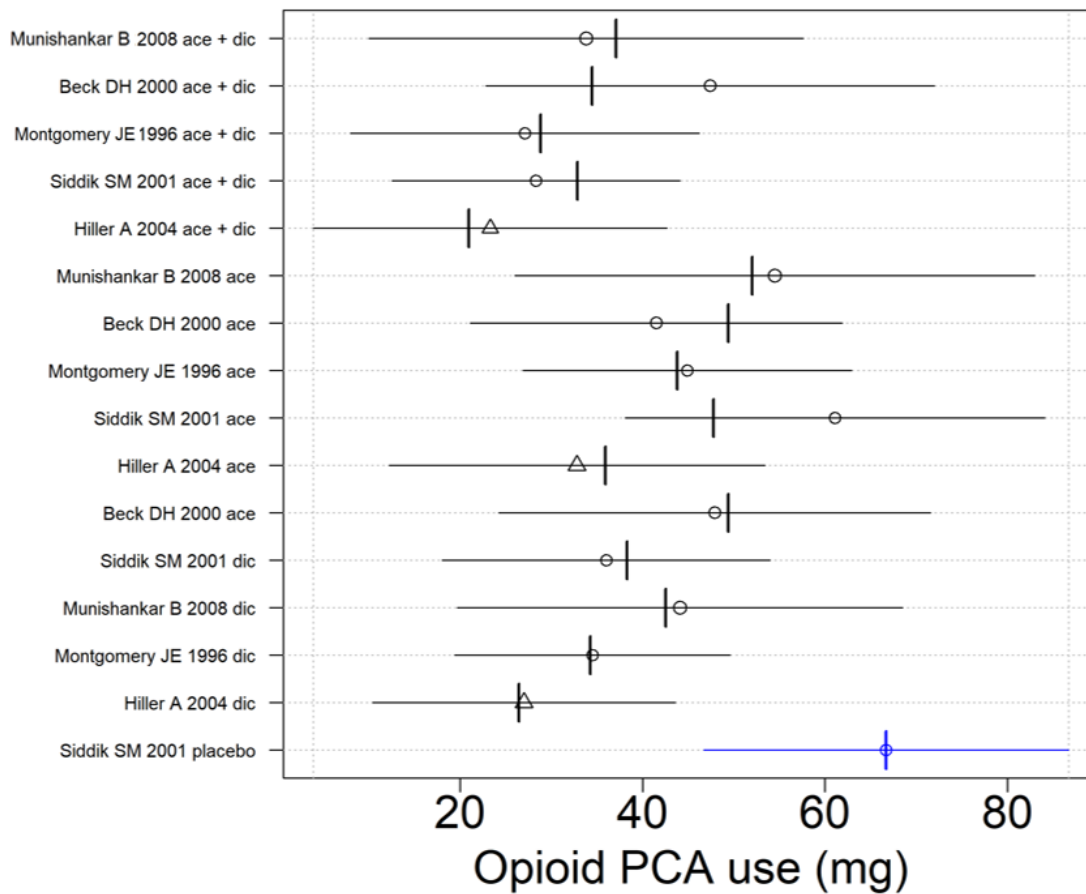
Supplementary Figure S1. The observed ratio of the beneficial effect of systemic ace+dic on pain score reduction at 6 to 72 hours, compared to either drug alone across 11 acute pain studies by use of opioid patient-controlled analgesia (PCA) vs. no PCA. The vertical dashed line (ratio=1) indicates no beneficial effect of combination compared to either drug alone in the same study. The size of the squares represents the sample size in the study arm. ace: acetaminophen; dic: diclofenac; OPIOID P: Opioid PCA; NA: not applicable



Supplementary Figure S2. The observed ratio of the beneficial effect of systemic ace+dic on opioid sparing effect at 6 to 72 hours, in comparison to either drug alone in seven acute pain studies allowing opioid patient-controlled analgesia. The vertical dashed line (ratio=1) indicates no beneficial effect of combination compared to either drug alone within study. PCA: patient-controlled analgesia. The size of symbol represents the sample size in the study arm. ace: acetaminophen; dic: diclofenac



Supplementary Figure S3. Reported mean opioid use (mg) across the six studies in an acute pain setting. Study “Riad 2007” study was conducted in children and the remaining 5 studies were conducted in adult population. PCA: patient-controlled analgesia



Supplementary Figure S4. Observed (circle) and model-predicted (vertical bar) use of opioid PCA (mg) for included treatment arms. The symbols represent the mean reported response rate in the various trials and treatment arms. Circle size is proportional to sample size of each arm. The horizontal lines represent the 95% confidence intervals. The vertical tics depict model predictions. Blue is placebo, and black is active treatment arm; circles describe gynecological surgery, and triangle represents tonsillectomy. PCA: patient-controlled analgesia, ace: acetaminophen, dic: diclofenac