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Acetaminophen for Chronic Pain: A Systematic Review on Efficacy

Zandra Nymand Ennis[1,]
Dorthe Dideriksen[1,]
Henrik Bjarke Vægter[3,4] Gitte Handberg[3]
and Anton Pottegård[2]

(1) Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
(2) Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark
(3) Pain Research Group, Department of Anaesthesiology and Intensive Care Medicine, Odense University Hospital, Odense, Denmark
(4) Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

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Author for correspondence: Anton Pottegård, Clinical Pharmacology, University of Southern Denmark, J.B. Winsløws Vej 19, 2., DK-5000 Odense C, Denmark (e-mail: apottegaard@health.sdu.dk).

Abstract: Acetaminophen (paracetamol) is the most commonly used analgesic worldwide and recommended as first-line treatment in all pain conditions by WHO. We performed a systematic literature review to evaluate the efficacy of acetaminophen when used for chronic pain conditions.

Applying three broad search strategies for acetaminophen use in chronic pain in both Embase and PubMed, 1,551 hits were obtained. Following cross-reference searches of both trials and 38 reviews, seven studies comparing acetaminophen in continuous dosing regimens of more than

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two weeks with placebo were included. The review was conducted according to PRISMA guidelines.

All studies were conducted in patients with hip- or knee osteoarthritis and six out of seven studies had observation periods of less than three months. All included studies showed no or little efficacy with dubious clinical relevance.

In conclusion, there is little evidence to support the efficacy of acetaminophen treatment in patients with chronic pain conditions. Assessment of continuous efficacy in the many patients using acetaminophen worldwide is recommended.

Acetaminophen (paracetamol) has been widely endorsed as a first-line analgesic and is currently the most commonly used analgesic worldwide (1). As an example, 9.6% of all Danes obtained acetaminophen via prescription in 2013, with the prevalence rising to an astonishing 23% among 65-79 year olds and 45% among octogenarians (2). The recommendation of using acetaminophen has been generalized by the World Health Organization (WHO), suggesting acetaminophen as the first step in any pharmacological pain treatment (3). Similarly, acetaminophen is recommended as first-line treatment in many chronic pain conditions such as osteoarthritis (4) and for geriatric patients in general (5). The wide endorsement of acetaminophen is primarily attributable to a favourable safety profile compared with other treatment options (6), and the notion that acetaminophen has an efficacy comparable with Non-Steroid Anti Inflammatory Drugs (NSAIDs) – the latter primarily based on a highly cited study from 1991 by Bradley *et al.* (7).

While a solid evidence base exists for the use of acetaminophen in acute pain states such as dental and post-operative pain (8), post-partum pain (9) and migraine (10), the evidence supporting its use in more chronic pain conditions is less obvious. In a pivotal and often cited

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study from 1983, Amadio and Cummings showed that acetaminophen was superior to placebo in patients with osteoarthritis (OA) (11). While this cross-over study was only based on 25 patients, it has served as a basis for subsequent investigations, and as such later studies often compare acetaminophen directly to NSAIDs (12) or COX2 inhibitors (12), without including an arm receiving placebo.

Considering the widespread and often long-term use of acetaminophen, it is of major public health importance to ensure that this use is founded on solid evidence regarding efficacy. To this end, we conducted a systematic literature review to assess the efficacy of acetaminophen when used for chronic pain conditions.

Methods

Following the PRISMA guidelines for systematic review (13), two clinical pharmacists (AP and DD) and one clinical pharmacologist (ZNE), holding expertise on evidence-based counselling of health care professionals, conducted the literature search. The databases used included Pubmed (Medline) and EMBASE (Exerpta Medica, Elsevier; Ovid). Limits "human" and "English language" were applied. The databases were searched from their start to August 2014. An initial search using the keywords Chronic pain [MeSH] AND (Paracetamol OR Acetaminophen) resulted in four hits in PubMed, which led to a widening of the search strategy. We performed three separate literature searches:

Disease-specific search in PubMed

(Fibromyalgia[MeSH] OR Neuralgia[MeSH] OR Arthritis[MeSH] OR Low back pain[MeSH]) AND (Paracetamol OR Acetaminophen) AND Pain.

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Free Text search in PubMed

Chronic pain AND (Paracetamol OR Acetaminophen).

Disease-specific search in EMBASE

Keywords similar to the disease-specific search in PubMed, including all subheadings stated under each keyword.

The three searches resulted in 594, 493 and 464 hits, respectively.

The subsequent review and selection process was divided into two rounds. This process was initially planned using input from two specialists in the treatment of pain (GH and HBV), and was further developed and refined via two initial tests, each consisting of 50 abstracts (from the wide PubMed search) that were screened by all three reviewers.

In the first round, articles were screened by their titles and abstracts independently by two reviewers (discrepancies were solved via consensus). In this round, studies were eligible for inclusion if they met all of the following criteria, as judged via the abstract: (1) reporting original data on human use of acetaminophen from a controlled study; (2) the use of acetaminophen should be compared to either placebo or a non-pharmacological intervention; and (3) the studies should report an outcome related to efficacy or effectiveness. Studies using acetaminophen as rescue medication or only as combination therapy with other drugs were excluded together with investigations in patients with acute pain (pain lasting less than 3 months), studies of pregnancy-related pain or dental pain. Further, we excluded abstracts and conference proceedings. Lastly, if no abstract was available, the title should indicate that the study concerned the efficacy of acetaminophen or otherwise the publication was discarded.

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In the second round, we required studies to meet the same inclusion and exclusion criteria as mentioned above, as judged by the full-text read. Furthermore, we required that (4) the study had included individuals above 18 years of age; and (5) individuals should receive acetaminophen in a continuous dose regimen lasting more than 14 days with an average daily intake above 2 grams.

In addition to the original studies, we also included reviews included in all three literature searches, provided they concerned the efficacy or evidence base for use of acetaminophen (judged via the abstract). Reviews concerning the use of acetaminophen among patients with specific co-morbidities (e.g. renal insufficiency or cardiovascular complications) were not included. Included reviews were subsequently scanned for additional references on original studies. Similarly, the guidelines issued by the American Pain Association (14), the Canadian Pain Society (15) and the British Pain Society (16) were searched for eligible references.

Lastly, we cross-reference-searched all included original publications for additional original publications. If more than one study or updated data were available from the same cohort, the study holding the most recent data was chosen.

Results

From the literature search, we identified seven eligible trials (**fig. 1**). The median duration of the trials was 6 weeks (range 3 weeks - 6 months) and they included a median of 108 (range 22-405) patients in the arm receiving acetaminophen. Despite our broad search strategy also included terms specific to other chronic pain conditions (see methods), all seven studies concerned patients with osteoarthritis of the knee and/or hip. A full overview of the studies can be found in **table 1**.

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While all seven studies met our inclusion criteria, the trials were subdivided into two groups. The first group (n=4) comprised studies that were specifically designed to evaluate the effect of acetaminophen compared to placebo (11,17–19). The second group (n=3) comprised studies that, although including both an acetaminophen and a placebo arm, was found to be of lesser relevance: One study was primarily designed to evaluate the effect of glucosamine (20), one study also evaluated a thorough rehabilitation programme (21), and lastly one study primarily aimed to evaluate high *versus* low dose acetaminophen and further specifically required participants to have a positive prior experience with acetaminophen treatment (22).

The four studies (11,17–19) we found relevant to the efficacy of acetaminophen had different findings. Case *et al.* (18) found a difference at -74.6 ± 300 points in the total WOMAC score after 12 weeks treatment (p=0.19) among the 29 patients allocated to acetaminophen 4g/day. In the placebo group (n=28), the difference was -118±348.9 (p=0.08). The pre-defined clinical significance level at >20% improvement in the WOMAC scale was not met, and the authors concluded that acetaminophen was not superior to placebo. In the study by Miceli-Richard *et al.* (19), 779 patients were randomized to either acetaminophen 4g/day (n=405) or placebo (n=374) in a 6-week treatment regimen. Responders were defined as having >30% decrease in the global pain intensity as evaluated by the VAS scale. It was concluded that acetaminophen was not superior to placebo, as no difference was shown between the groups who both presented a mean decrease from baseline at 23 mm after 6 weeks treatment (p=0.84). Pincus *et al.* (17) conducted a three-arm cross-over study in 556 patients. Among the 239 patients randomized to acetaminophen *versus* placebo or placebo *versus* acetaminophen, 167 completed per protocol. The study showed superiority of acetaminophen to placebo in the Paces-b study, quantified by a decrease by -3.08 (SE 1.10) in the WOMAC score (p=0.005). However, the similar comparison was not found statistically significant in the identical Paces–a study which found a decrease by -2.09 (SE 1.20) in WOMAC score (p=0.080). Both Paces studies failed to demonstrate clinically

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relevant improvements, pre-defined as >20% decrease in the WOMAC index score. Lastly, the study by Amadio and Cummings (11) included 25 patients and found acetaminophen to be superior to placebo when looking at the primary outcome (50-foot walk time). A change from baseline at 17.56 sec. to 14.91±0.82 sec. in the acetaminophen group *versus* 17.41±1.22 sec. in the placebo group was demonstrated after three weeks (p=0.05). Among the secondary outcomes, tenderness, pain at rest and in motion, acetaminophen was superior to placebo, too. The outcomes swelling and heat did not differ. Secondary outcomes were evaluated by a three-point scale; "acetaminophen better", "placebo better" or "no difference". Only nine patients completed per protocol and no threshold for clinical relevance was included in the manuscript.

Among the three studies found to have lesser relevance to the evaluation of acetaminophen efficacy, one study (22) tested the efficacy of extended-release formulation (ER) of acetaminophen in 483 patients. Patients were treated for 12 weeks with either acetaminophen ER 1950 mg /day (n=158), Acetaminophen ER 3900 mg/day (n=160) or placebo (n=165). The study found the efficacy of acetaminophen was statistical superior to placebo. A decrease in WOMAC index of -24.5 and -18.6 for acetaminophen ER 3900 mg/day and placebo respectively was demonstrated (p=0.015) and the authors concluded that acetaminophen ER 3900 mg/day was effective in treating OA pain. Importantly, however, the protocol required participants to have "a prior response to acetaminophen" (22) prior to enrollment, which limits the generalizability of the finding to all OA patients. Another study in 44 patients waiting for total joint replacement (21), investigated the efficacy of acetaminophen combined with rehabilitation (n=22) versus rehabilitation alone (n=22). After a three weeks treatment regimen a decrease in VAS score at -39 mm and -25 mm respectively was showed. The authors interpreted on variations in VAS scores between the groups rather than changes in absolute values, however, it was concluded that variations were statistically significant (p= 0.035). The authors concluded that the efficacy of this rehabilitation programme was augmented by acetaminophen. The third

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study tested glucosamine sulfate *versus* placebo, using acetaminophen as a side-comparator in 318 patients during six months. Enrolled patients were allocated to either glucosamine sulfate 1500 mg/day (n= 106), acetaminophen 3g/day (n=108) or placebo (n=104). The study showed a -2.7 and -2.0 point decrease in the Lequesne index and a -16.0 and -11.7 decrease in the total WOMAC index score for acetaminophen and placebo, respectively, among the 150 per-protocol completers. The study failed to show statistical significant changes between acetaminophen and placebo using both Lequesne index (p=0.26) and WOMAC score (p=0.08). Statistical significant changes between glucosamine and placebo was demonstrated in both Lequesne index (p=0.01) and WOMAC score (p=0.018) and the authors concluded that glucosamine was efficient in treating OA symptoms (20). The findings of the three secondary studies were considered of a clinical relevant magnitude, although the threshold for clinical relevance was not predefined in any of the studies.

Discussion

Despite multiple broad literature searches, this systematic review has only identified seven studies regarding the efficacy of acetaminophen towards chronic pain. All eligible studies pertained specifically to OA patients and of seven eligible studies only four were found relevant. No studies relevant to other chronic pain conditions were identified.

Though the included studies were performed exclusively in OA patients, the populations showed some heterogeneity as some studies included patients presenting symptoms of inflammation (11,17), who were excluded in other studies and one study only included patients having positive prior experience with acetaminophen (22). Further, of the four primary studies, the longest treatment period was 12 weeks. As such, it is questionable whether the results mirror effectiveness among chronical users of acetaminophen. Furthermore, direct comparison by

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meta-analysis or otherwise is made difficult since the studies have different study designs, different populations and apply different outcome measures. Some studies quantify efficacy by using validated specialized tools for assessing pain and function in OA patients; WOMAC (23), OARSI (24) and the Lequesne index (25). Other studies are quantifying efficacy via measures with dubious generalizability such as patient preference, patient assessment and global assessment.

Differences in adherence to allocated regimen varied among the studies with drop-out rates ranging from 0-64 % (11,21). In general, the studies allowing more extensive use of rescue medication showed higher adherence. Non-steroid anti-inflammatory drugs were the most commonly used rescue medication, while some studies allowed opioids; either tramadol in doses up to 400 mg/day or Codeine 30 mg/day (17,21). All studies demonstrated high tolerability and a favourable safety profile, in line with previous literature on the overall safety of acetaminophen (6). However, it should be noted that the safety of acetaminophen in specific populations, e.g. alcoholics and malnutritioned individuals, is still of concern (26).

The primary strength of our study is the multiple broad search strategies designed to include original data on either chronical pain or conditions associated with chronic pain. All literature was assessed by two persons, ensuring the validity of the literature search. Furthermore, reviews were included to undergo a manual reference search to further ensure a more complete capture of published studies.

When evaluating pain study outcomes, it is important to distinguish between clinically relevant and statistically significant (27). While the efficacy of acetaminophen in spinal pain was statistically significant in a recent meta-analysis, the greatest observed effect size of -3.7 points in a 0-100 point VAS scale falls short of the minimal clinically relevant change of -9.0 points (28). However, unlike our study, this review included patients presenting acute pain conditions (29), and studies using single-dose regimens (30). Extrapolating data from single-dose or intermediate

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duration treatment regimens (treatment duration less than 3 months) to that of chronic use (more than 6 months continuous treatment) is questionable as earlier studies have shown loss of analgesic efficacy during long-term follow-up (31,32). A similar mechanism cannot be rejected in long-term treatment with acetaminophen. Human pain exerts significant complexity; the cognition of pain is dependent on both sensory and affective processing, and it is known that the cognition of pain is confounded by several factors such as socio-economic status, co-morbidity, concomitant medication, physical inadequacy and cognitive disturbances (33). This complicates the conduct of clinical studies of analgesics.

These problems have been acknowledged by WHO, whose generally approved pain ladder initially published in 1986 still holds acetaminophen as a universal first-line treatment in all pain conditions. In 2007, a conference was held, trying to establish the need for more specific treatment guidelines in patients suffering from chronical pain conditions (34). However, no specific guidelines on the topic have yet been published.

In conclusion, the amount of literature on the long-term efficacy of acetaminophen in chronic pain is scarce. The few available studies that are limited to an OA population suggest negligible efficacy with doubtful clinical relevance. Considering these findings, continuous assessment of efficacy in the many long-term users of acetaminophen worldwide is recommended.

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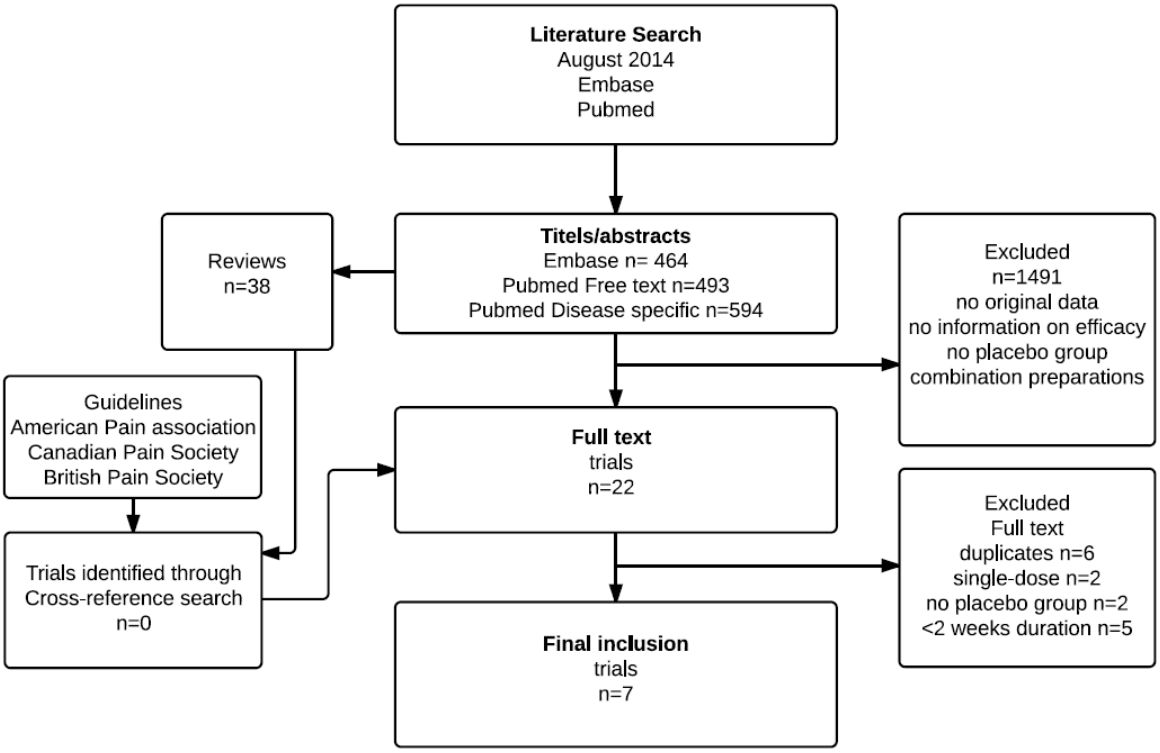
Figures

Figure 1: Flow chart of literature search



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Main author	Pub. year	Study-design	Study participants	Paracetamol dose [mg/day]	Treatment duration	No. Included *	Primary Outcome	Efficacy
Casale	2012	Randomized, open-label, parallel-group	OA knee/hip	3000	3 weeks	ITT: 44 PP: 44	VAS	APAP-39 vs. PL-25
Altman	2007	Randomized, double-blind, parallel-group	OA knee/hip	1950 ER or 3900 ER	12 weeks	ITT: 483 PP: 347	WOMAC	APAP-24.5 vs. PL-18.6
Herrero-Beaumont	2007	Randomized, parallel-group, double-dummy, double-blind,	OA knee	3000	6 months	ITT: 212 PP: 150	Lequesne	APAP-2.7 vs. PL-2.0
Miceli-Richard	2004	Randomized, double-blind, parallel-group	OA knee	4000	6 weeks	ITT: 779 PP: 560	VAS	APAP-23 vs. PL-23
Pincus	2004	Randomized, double-blind, double-dummy, cross-over	OA knee/hip	4000	6 weeks	ITT: 239 PP: 167	WOMAC	Paces-a: APAP-8.4 vs. PL-4.8 and APAP-4.5 vs. PL-3.6 Paces-b: APAP-8.4 vs. PL-4.6 and APAP-8.7 vs. PL-2.0
Case	2003	Randomized, double-blind, parallel-group	OA knee	4000	12 weeks	ITT: 57 PP: 41	WOMAC	APAP-74.6 ± 300 vs. PL-118±348.9
Amadio	1983	Randomized, double-blind, cross-over	OA knee	4000	3 weeks	ITT: 25 PP: 9	50 foot walk time/sec	APAP-2.65±0.82 vs PL-0.15±1.22

Table1: Characteristics of included studies NOTE: ITT = Intention-to-treat analysis; PP = Per protocol analysis

APAP: Acetaminophen, PL: Placebo * Only counting individuals using either acetaminophen or placebo.

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