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## Paracetamol for low back pain: the state of the research field

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### ABSTRACT

**Introduction:** Paracetamol is one of the most frequently used analgesics for people with low back pain, but despite its frequent use there is still debate regarding its efficacy and safety for this indication.

**Areas covered:** We describe the origin of paracetamol and its proposed mechanisms of action. We focus in on low back pain and describe the evidence it has on the efficacy of paracetamol (taken by patients orally) and current insights on its side-effects. When searching for relevant publications we focused mainly on recent Cochrane reviews and published RCTs. We found that there is increasing evidence that shows paracetamol is not more effective than placebo in patients with acute low back pain. Concerning patients with subacute and chronic back pain, the evidence for or against the efficacy of paracetamol vs placebo is lacking and would need more research.

**Expert opinion:** We argue that we still need better evidence on the efficacy of paracetamol for acute and chronic back pain. Until that evidence becomes available paracetamol should still be considered as an option for patients with back pain. However, we suggest that a strategy focusing on non-pharmacological management as the first treatment option in low back pain may be equally effective with less side effects.

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Paracetamol; low back pain; effect; review

## 1. Introduction

Paracetamol (P) has been available for the management of pain for more than 100 years. It is reported that it was already synthesized in the year 1878 [1,2]. The initial clinical results of paracetamol were published in 1893 by a German physician but were not positive. Von Mering reported that adverse effects of paracetamol were elevated blood levels of methemoglobin which could lead to dangerous tissue hypoxia [3]. Because of this serious adverse event and due to the availability of another drug, namely aspirin (since 1899), paracetamol did not receive much attention.

This situation changed around 1948 when Merings' claims were disputed by British and American scientists who suggested that paracetamol could well be used as an analgesic and antipyretic [4–6]. These scientist showed that the previously found methemoglobin in patients that used paracetamol was attributed to contamination of the paracetamol; purified paracetamol did not yield this dangerous side-effect. Paracetamol subsequently entered the market in the 1950s in the USA and since then its popularity strongly increased. Around 1980 paracetamol was sold more often over the counter than aspirin in the United Kingdom [1]. In 2014, more than 200 million packs of paracetamol were sold in the UK [7]. Nowadays paracetamol is amongst the most frequently used drugs worldwide and presents in most households for the treatment of acute and chronic pain conditions. This review article summarizes the mechanism of action of paracetamol

and describes the evidence from RCTs regarding the efficacy of paracetamol (via oral route) for people with low back pain as compared to placebo and NSAIDs. Hereafter, we described the outcomes of the PACE-trial, which is the largest RCT evaluating the efficacy of paracetamol versus placebo for people with acute low back pain. Next, we present data regarding potential harms of paracetamol. Subsequently, we consider which recommendations regarding the prescription of paracetamol are included in recent clinical guidelines for the management of low back pain. After a short summary of the efficacy and harms of NSAIDs, which are regarded as an alternative for paracetamol, we present our own opinion. When searching for relevant publication we were mainly looking at recent (Cochrane) reviews and published RCTs (e.g. the PACE-study).

## 2. Mechanism

For decades it was assumed that paracetamol inhibits pro-inflammatory prostaglandin (PG) synthesis via the inhibition of cyclooxygenase enzyme (COX). However, current studies demonstrate low inhibitory action of P both on COX-1 and COX-2, though its clinical efficacy is high and is associated with pronounced antipyretic and analgesic effect, compared to other compounds [8,9]. This fact makes the elucidation of the mechanism of action of paracetamol challenging but explains almost complete absence of anti-inflammatory action

**Article highlights**

- Paracetamol is one of the most frequently used analgesic
- The efficacy and safety of paracetamol are still under debate
- There is increasing evidence that paracetamol is not more effective than placebo for people with acute low back pain
- The efficacy of paracetamol for people with subacute or chronic low back pain is unknown
- NSAIDs do not appear to be significantly more effective than paracetamol for people with back pain
- A non-pharmacological treatment strategy as first treatment choice for people with back pain is advised.

of the drug (anti-inflammatory action of a number of drugs is associated with COX-2 inhibition).

Recently, two mechanisms of paracetamol action were hypothesized. Graham et al. [10] report, that paracetamol has almost negligible action on COX-1 and COX-2 in vitro, but postulate that in vivo paracetamol blocks biological effects of PGs in intact cells directly by decreasing the concentration of arachidonic acid. Paracetamol action on PG synthesis may be realized through the modulation of stimulating action of pro-inflammatory cytokines [10].

Other researchers suggest that paracetamol is a specific and unique COX-3 inhibitor [9]. It is assumed that COX-3 plays a role in later phases of inflammatory process via the modulation of the synthesis of endogenous anti-inflammatory mediators [11,12]. Paracetamol action may be associated also with central mechanisms that is mediated through activation of descending serotonergic pathways and through an active metabolite influencing cannabinoid receptors, other than downregulation of PG synthesis [13]. A recent FMRI study also suggests a central effect of paracetamol in cerebral areas known to be associated with pain [14]

### 3. Low back pain

Low back pain is a musculoskeletal condition for which paracetamol is prescribed and used regularly. Low back pain occurs frequently and is responsible for a substantial burden of illness. It is the number one condition responsible for years lived with disability (YLDs) [15]. Almost everybody, up to 80–90% of the population, will experience an episode of low back pain during their life. In most cases with acute low back pain, the prognosis is favorable and the pain and related disability will diminish within a few weeks. In a small percentage (5–10%), however, the low back pain persists and develops in a chronic pain disorder. Low back pain is also characterized by its recurrences. After recovery of a low-back pain episode the complaints often (up to a third of the cases) return in the following year [15].

In most people with low back pain, the precise cause of the pain is unknown. In only a small proportion (up to 5–10%) of patients presenting in primary care underlying pathologies, such as malignancies, fracture, infections can be identified. When specific pathologies explaining the back pain are not present, the complaints are labeled as being nonspecific. It hampers adequate treatment that in most cases no cause of

the pain can be found, since no causal treatment can thus be applied. Consequently, many treatments for low back pain are focused on reduction of symptoms. There are many treatments available for people with back pain. This includes non-pharmacological treatments (patient education, exercises, manual therapies) and pharmacological treatments (mostly pain medications, including paracetamol) [16]. Some patients suffering from low back pain also receive surgery. Especially patients with persisting radicular pain (>6–8 weeks) in the leg due to a herniated disk are regarded as surgical candidates. At the same time, there is good evidence that recovery rates after 1 and 2 years follow up are more or less similar between patients receiving disc surgery or prolonged conservative care [17]

### 4. Analgesics for low back pain

Analgesics are frequently prescribed for people with back pain. An estimated 55% of the patients with low back pain use analgesics [18]. In a cohort study in elderly people presenting with back pain in primary care this percentage was 72% [19]. Data from Australia shows that 892 analgesics were recommended per 1000 spinal pain problems [20]. In Switzerland a study showed that the most prescribed medications for low back pain were non-steroidal anti-inflammatory drug (NSAIDs) in 97.4% of the respondents followed by paracetamol in 94.4% of the respondents [21]; other drugs that are often recommended for low back pain are opioids, muscle relaxants and anti-depressants [22]. Bearing in mind that these data concern prescriptions and not over-the-counter medications, the actual use of analgesics, including paracetamol, in people with back pain is very common. Of concern, especially because of the frequent use of analgesics such as paracetamol and NSAIDs, are the potential harms of these drugs. The harms of paracetamol are described elsewhere in this review. The potential harms of NSAIDs, the increased risk of gastrointestinal side effects, are well known and should be considered when managing elderly patients.

### 5. Evidence of benefits

#### 5.1. Paracetamol versus placebo

The Cochrane review (2016) on paracetamol for low back pain summarized the available evidence on the efficacy [23]. This Cochrane review only included placebo-controlled studies and initially identified three studies. One study [24] was a large study from Australia, the second study [25] was from the United States and the third study [26] was from Austria. However, the last study [26] has been retracted from the literature (one of the authors had not consented to submission and publication of the study). Meta-analysis was not possible in the Cochrane review because the study by Nadler did not report results for the placebo group. The main conclusion of the Cochrane review was that in patients with acute low back pain, paracetamol was not better than placebo and there was uncertainty regarding the effect in patients with chronic low back pain.

Table 1 presents the currently available randomized clinical trials evaluating paracetamol vs placebo in patients with acute

**Table 1.** RCTs evaluating paracetamol vs placebo in patients with acute low back pain.

Author(s), year	patients	interventions	Outcomes/follow-up	Results	Remarks
Nadler 2002 [25]	Acute LBP (n = 371)	(1) heat wrap (2) ibuprofen (1200 mg/d) (3) paracetamol (4000 mg/d) (4) placebo (5) unheated back wrap All interventions for 2 days	Pain relief (NRS 0–5); Disability (RMDQ 0–24)	No data on the placebo group presented. Pain relief after 3–4 days: group 2 (1.68) group 3 (1.95) Disability after 3–4 days: group 2 (2.7) group 3 (2.9)	
Williams 2014 [24]	Acute LBP (n = 1653)	(1) paracetamol regular (3990 mg/d) (2) paracetamol as needed (max 4000 mg/d) (3) placebo All interventions max 4 weeks	Pain (NRS 0–10); Disability (RMDQ 0–24)	No difference in outcome between the 3 groups. Pain intensity after 2 weeks: Group 1 (2.6) Group 2 (2.6) Group 3 (2.5) Mean disability after 2 weeks: Group 1 (5.2) Group 2 (5.4) Group 3 (5.3)	Median days to recovery Group 1 (17) Group 2 (17) Group 3 (16)
Friedman 2020 [27]	Acute LBP (n = 120)	(1) Ibuprofen (600 mg) + paracetamol (2000–4000 mg) (2) Ibuprofen (600 mg) + placebo Both interventions for 7 days	Disability (RMDQ 0–24) Pain (4-point scale)	No difference in outcome between the 2 groups Pain after one week none/mild: Group 1 (72%) Group 2 (72%) Improvement disability: Group 1 (11.1) Group 2 (11.9)	

low back pain. The studies by Nadler, and Williams were included in the Cochrane review [23–25]. The study by Friedman was published afterward [27]. Table 1 illustrates the overall limited evidence available comparing paracetamol versus placebo. In total, only three trials were conducted in patients with acute low back pain, for one of which no data were presented on the placebo group. The two remaining trials show that there is no difference in effect of paracetamol versus placebo. This holds true for paracetamol taken regularly, as needed and as addition to Ibuprofen [24,27]. For chronic low back pain, there was only one trial, but the publication of this study has been retracted [26], thus for chronic low back there is no good evidence for or against the efficacy of paracetamol available.

### 5.2. Paracetamol versus NSAIDs

The previous Cochrane review on NSAIDs for low back pain (2008) covered acute as well as chronic low back pain [28]. This review has subsequently been split up in one review focusing on acute low back pain [29], one on chronic low back pain [30,31] and one on sciatica [32,33].

There are only limited trials available comparing NSAIDs with paracetamol. Table 2 shows three trials in acute low back pain and one in chronic low back pain. Most of the studies are relatively old, show methodological shortcomings (e.g. a drop-out rate of 45%) and are carried out in specific study populations (e.g. young soldiers who were prescribed bedrest). The three trials in people with acute low back pain show no significant differences in effect (pain and disability) between NSAIDs and paracetamol [25,34,35]. There is only one trial in people with chronic low back pain in which an NSAID is compared to paracetamol. In this relatively old study (1982), diflunisal (1000 mg/day) was compared to paracetamol (4000 mg/day). The study had a small sample size (n = 30)

and did not find significant differences between the NSAID and paracetamol [36]. The authors of the Cochrane review (chronic low back pain) conclude that it remains unclear whether NSAIDs are more effective than other drugs, including paracetamol [30,31].

### 5.3. The PACE – trial

Overall, Tables 1 and 2 show a limited number of relatively old trials with small sample sizes and methodological shortcomings. There is one more recent Australian trial which stands out regarding size and methodological quality and also regarding the impact on recommendations in clinical guidelines as well as on clinical practice. This so-called PACE-trial was published in 2014 in the Lancet [24]. Up to that date, there was no good evidence available regarding the efficacy of paracetamol for acute low back pain, despite the fact that paracetamol was recommended in most (inter)national clinical guideline for the management of low back pain as the preferred first choice of pain medication, if prescription of pain medication was considered [37,38]. The PACE trial was conducted in Sydney, Australia and included 1652 people with acute low back pain. Patients had a new episode of low back pain with or without leg pain of at least moderate intensity. Patients were randomly allocated to three groups; (1) paracetamol (two tablets of 665 mg modified release paracetamol three times a day) regularly (n = 550); (2) paracetamol (two tablets of 500 mg immediate release tablets taken up to four times a day) as needed (n = 549) or (3) placebo (n = 553) for a maximum of four weeks or until recovery, if this happened before the four-week time point. Patients, clinicians and researchers were blind regarding the treatment allocation. Patients received instruction to use the study medications until they had experienced seven consecutive days with no or limited pain (0 or 1 on a 0–10 pain scale) or for maximum of

**Table 2.** RCTs evaluating paracetamol vs NSAIDs in patients with acute or chronic low back pain.

Author(s), year	patients	interventions	Outcomes/follow-up	Results	Remarks
Wiesel 1980 [34]	Acute LBP (n = 45)	(1) aspirin (625 mg – 4 times/d) (2) phenylbutazone (100 mg- 4times/d) (3) paracetamol (1 tablet (?mg) 2 times/d) All intervention for 5 days	Pain; No days before return work/follow-up 2 weeks	No significant differences. Mean number of days before return work group 1 (5.7) group 2 (6.5) group 3(5.7)	(1)concerns soldiers (age 17–34) (2)phenylbutazone is taken of the market
Nadler 2002 [25]	Acute LBP (n = 371)	(1) heat wrap (2) ibuprofen (1200 mg/d) (3) paracetamol (4000 mg/d) (4) placebo (5) unheated back wrap All interventions for 2 days	Pain relief (NRS 0–5); Disability (RMDQ 0–24)/ follow up 4 days	No difference (2) vs (3) regarding pain and disability Pain relief after 3–4 days: group 2 (1.68) group 3 (1.95) Disability after 3–4 days: group 2 (2.7) group 3 (2.9)	
Miki 2018 [35]	Acute LBP (n = 127)	(1) loxoprofen (60 mg-3 times/d) (2) paracetamol (600 mg-4 times/d) Both intervention for 4 weeks	Pain (NRS)/follow up 4 weeks	No significant differences Mean difference l pain score Group 1 (–0.5) Group 2 (0)	High drop-out rate of 45%
Hickey 1982 [36]	Chronic LBP (n = 30)	(1) diflunisal (1000 mg/d) (2) paracetamol (4000 mg/d) Both intervention for 4 weeks	No. of patient with none/mild back pain	No difference between the groups. No. of patient with none/mild back pain after 2,4 weeks Group 1 (11,13) Group 2 (9,7)	More patients rated (1) as good or excellent (10 out of 16 vs 4 out of 12)

four weeks. On the primary outcome measure, which was time to recovery, no difference in effect between the three groups was found; the median time to recovery was 17 days in the regular group, 17 days in the as-needed group and 16 days in the placebo groups. Also on the secondary outcome measures, including pain intensity, disability, health-related quality of life the study showed no significant and/or clinically relevant difference between the three study groups [24].

#### 5.4. Replication of the PACE-trial

Due to the importance and impact of the PACE trial for patients and clinicians, replication of the study and its results are important. Unfortunately, a subsequent attempt to replicate the PACE-trial, namely the PACE-plus trial was discontinued due to problems with patient recruitment [37]. It was however, possible to conduct a re-analysis of the original data of the PACE study using the predefined and published protocol of the PACE-plus study, including its statistical analysis plan [39]. In this so-called inferential reproducibility study, conducted by an independent group, a different primary outcome was chosen, namely pain intensity (0–10 NRS), data from pain diaries were used instead of data from follow-up questionnaires, a different statistical approach was used and pre-planned exploratory subgroup analyses (based on severe pain intensity NRS >7 and severe impairment of physical functioning (RMDQ > 16)) were included. The re-analysis showed that paracetamol, either taken regular or as needed, was not more effective than placebo in reducing the pain intensity (primary

outcome) and secondary outcomes such as physical functioning and health-related quality of life and time to recovery. These results (i.e. no difference between paracetamol vs placebo) were also found in the subgroups of patients with severe pain-intensity and severe impairment of physical functioning. Overall, the re-analysis confirmed the original analysis and results of the PACE-trial and strengthen its conclusions [40].

#### 5.5. Influence of compliance in the PACE-trial

One point of discussion after the publication of the PACE trial was the potential influence of (non)compliance regarding medication intake on the study results. Non-adherence was discussed in the original publication of the trial as well as in subsequent commentaries. There were reports that up to 70% of patients in PACE were non-adherent (depending on the definition of non-adherence) during the study period and the overall adherence to guideline recommended care was considered as poor [41]. In order to investigate the influence of noncompliance on the outcomes in the PACE trial a Complier Average Causal Effect (CACE-)analysis was carried out. In a CACE-analysis, patients randomized to the intervention group who are compliant are compared to patients randomized to the control group, who would have been compliant if they had been randomized to the intervention group. In the CACE-analysis of the PACE study, data were used of the patients randomized to the regular paracetamol treatments versus the patients in the placebo group. Compliance

was defined as taking at least an average of four out of six prescribed tablets (corresponding to 2660 mg in total) per participant per day during the first two weeks after inclusion in the PACE trial. Based on this definition 394 (72%) compliers were identified in the regular paracetamol group. The results showed that for the primary outcome measure pain intensity (0–10 NRS) the mean difference between the regular paracetamol group and the placebo group was 0.068 (95% CI –0.37, 0.50) in the propensity weighted CACE-analysis, 0.23 (95% CI –0.16, 0.62) in the Joint Modeling CACE-analysis and 0.11 (95% CI –0.20, 0.42) in the Intention-to-treat analysis. All these differences were not statistically nor clinically significantly different. The analysis of the secondary outcome measures, disability, physical functioning, global change showed similar findings. These results showed that even in patients compliant to the treatment regimen paracetamol was not more effective than placebo [42].

## 6. Evidence of harms of paracetamol

When considering the value of medication, it is important to consider the potential benefits as well as the potential harms. Traditionally, paracetamol has been considered to be a relatively safe type of medication which is one of the reasons why it has been recommended as the first step in the pain ladder of the World Health Organization (WHO) and also as the recommended first choice of pain medication in (inter)national clinical guidelines for the management of back pain [37]). In the efficacy studies presented above, only limited data on side-effects are included and presented. These studies are not set up, nor have the size to validly and reliably estimate the safety of paracetamol for patient with back pain. The prevalence and severity of harms should preferably come from other sources such as large cohort studies, patient registries, (inter)national surveillance studies. A recent review article summarized long-term adverse effects of paracetamol [1]. They reported that there is evidence for an increased risk of gastrointestinal bleeding (paracetamol taken regularly at doses >2–3 g per day) and a small increase in systolic blood pressure (4 mmHg), but these associations need further confirmation including in randomized clinical trials. The authors conclude that in the management of chronic pain disorders paracetamol can be regarded as the least worse option, when compared with other options, such as NSAIDs and opioids [1].

In a review of eight cohort studies Roberts et al. report on increased risk of side effects of paracetamol. Four of these studies reported on cardiovascular side-effects and showed

a dose–response with one study reporting an increased risk ratio of all cardiovascular side-effects ranging from 1.19 (0.81 to 1.75) to 1.68 (1.10 to 2.57). One cohort study reported on increased risk of gastrointestinal side effects and reported a dose–response (an increased risk ranging from 1.11 (1.04 to 1.18) to 1.49 (1.34 to 1.66)). Four cohort studies reporting renal side effect, of these three reported a dose–response with one reporting an increasing OR of  $\geq 30\%$  decrease in estimated glomerular filtration rate from 1.40 (0.79 to 2.48) to 2.19 (1.4 to 3.43). The authors of the review mention the observational nature of the data and the possibility of channeling bias, but (based on the found dose–response relationships) they warn for the increased risk of side-effects, especially when using higher analgesic dosages [43]. In 2011 the FDA recommended that the paracetamol dosage unit for a prescription should be 325 mg or less. Since January 2014 this is obligatory for manufacturers [44]. There seems to be consensus that the maximum daily dosage of paracetamol should not exceed 4000 mg. Also, in all RCTs, including the large PACE-trial, described in this review and presented in Tables 1 and 2 the prescribed daily dosages of paracetamol not higher than 4000 mg.

## 7. Recommendations in clinical guidelines

Many national clinical guidelines contain recommendations regarding the use of paracetamol for symptomatic pain treatment in patients with back pain. For decades, paracetamol was the undisputed analgesic of first choice, if prescription of pain medication was considered [22,37,45]. More recently, there appears to be more variation in the recommendations. While in some guidelines paracetamol remains a first choice, in other guidelines paracetamol is not recommended (any more). It is of interest to see which recommendations are included in guidelines issued from 2016 onwards. The PACE trial was published in 2014 and its results could well have influenced the recommendations in the guidelines published in 2016 and more recently [22,45]. Table 3 presents an overview of the recommendations regarding paracetamol in these recently issued clinical guidelines. In four out of eight guidelines paracetamol is not recommended, whereas in three guidelines it is still recommended and in one guideline it is considered optional, but it is mentioned that there is evidence of a lack of effect. Based on the same body of evidence, Table 3 thus shows that guideline committees decided to give different and sometimes even opposite recommendations. The new evidence, especially from the large PACE-trial

**Table 3.** Paracetamol recommendation in recent (2016 onwards) clinical guidelines for back pain.

Country	Recommendation concerning paracetamol for back pain
Australia, 2016	Recommended for acute low back pain – but information is included that there is evidence that paracetamol may not be more effective than placebo
Belgium, 2017	Not recommended as single pain medication
Canada, 2017	Recommended as first choice pain medication for acute and chronic back pain. NSAIDs are second choice.
Denmark, 2018	Only after careful consideration in patients with acute low back, because of evidence of no short term effect
Germany, 2017	Not recommended due to new evidence of lack of effect compared to placebo
The Netherlands, 2017	May be prescribed regularly or as-needed; NSAIDs may not be more effective than paracetamol
UK, 2017	Not recommended
US, 2017	Not recommended due to new evidence indicating that paracetamol is not more effective than placebo

certainly resulted in a less favorite role of paracetamol in many recent guidelines.

## 8. Alternatives for paracetamol

### 8.1. NSAIDs

In many clinical guidelines NSAIDs are recommended as second choice pain medication for patients with back pain. In a few guidelines, NSAIDs have replaced paracetamol as first option. NSAIDs are often prescribed but are also available over the counter [46].

### 8.2. NSAIDs vs placebo

The Cochrane review on NSAIDs for acute low back pain included 9 trials comparing NSAIDs with placebo [29]. The results showed that NSAIDs were significantly more effective than placebo. However, the mean difference in pain intensity score between NSAIDs and placebo (based on statistical pooling of four trials) was about 7 points (i.e.  $-7.29$  (95% CI  $-10.98$  to  $-3.61$ ) on a 0 to 100 pain scale. Also regarding physical functioning as measured with the Roland Morris Disability Questionnaire (RMDQ) NSAIDs were found to be significantly, but only marginally more effective than placebo. The mean difference (based on two trials) was about 2 points (i.e.  $-2.02$  (95% CI  $-2.89$  to  $-1.15$ ) on a scale from 0 to 24. The Cochrane review concludes that NSAIDs are (slightly) more effective than placebo regarding pain intensity and disability.

The Cochrane review on NSAIDs for chronic low back pain (2016) included six trials comparing NSAIDs with placebo [30,31]. The results showed that NSAIDs were significantly but clinically only marginally more effective than placebo. The mean difference in pain intensity score between NSAIDs and placebo was only about 7 points (i.e.  $-6.97$  (95% CI  $-10.74$  to  $-3.19$ ) on a 0 to 100 pain scale. Also regarding physical functioning as measured with the Roland Morris Disability Questionnaire (RMDQ) in four studies, NSAIDs were found to be significantly, but only marginally more effective than placebo. The mean difference was less than 1 point (i.e.  $-0.85$  (95% CI  $-1.30$  to  $-0.40$ ) on a scale from 0 to 24. The Cochrane review concludes that NSAIDs are (slightly) more effective than placebo regarding pain intensity and disability. However, the magnitude of the effects is small and if only RCTs with a low risk of bias are considered, the differences in effect between NSAIDs and placebo are even smaller [30,31].

The safety profile of NSAIDs in general is considered to be less favorable compared to paracetamol. Therapeutic effects of NSAIDs are associated with their ability to block COX-2, whereas the most common adverse effects (digestive system disorders, renal damage, impairment of platelet aggregation, etc.) – with decreased COX-1 activity. Among the most widely used NSAIDs those with selective action on COX-2 are associated with 3-4-fold fewer gastro-intestinal side-effects, compared to nonselective NSAIDs

Of importance is to mention the value of an evaluation of the cytochrome P450 (CYP450) system. Some patients with deficit enzyme defects may not benefit from the NSAIDs which use the CYP450-2C9 or CYP450-3A4 as substrates [44].

## 9. Ongoing studies

A check on ongoing studies evaluating the efficacy of paracetamol for back pain on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) revealed that most of the current studies focus on combination drugs, e.g. tramadol hydrochlorine/paracetamol; codeine/paracetamol; orphenadrine, caffeine, diclofenac sodium/paracetamol; or hydrocodone/paracetamol. Studies evaluating (oral) paracetamol as mono-drug for back pain are hardly conducted.

## 10. Expert opinion

This review concerning the current status of paracetamol shows the different views that clinicians and guideline developers have on its value in the management for patients with back pain. This review showed that there is increasing evidence that paracetamol is not more effective than placebo in patients with acute low back pain. The large and well conducted Australian PACE-trial found no difference in effect of regular paracetamol, paracetamol as-needed and placebo. Subsequently, independent re-analysis of the data confirmed the conclusion of no effect and also in subsequent analyses focusing on compliant patients, no effect could be demonstrated. The PACE trial gives a strong message. At the same time, it remains a single trial, conducted in a single country and setting only. In order obtain a stronger evidence regarding the evidence of paracetamol for acute low back pain a replica study with new data in a another setting/country would be welcome. The recent trial by Friedman et al. also found no difference in effect of paracetamol versus placebo, but their study design (e.g. both paracetamol and placebo were given in combination with Ibuprofen) and setting was quite different from the PACE-trial hampering statistical pooling of the results of both trials.

Concerning patients with subacute (between 6 and 12 weeks) and chronic (>12 weeks) back pain, the evidence for or against the efficacy of paracetamol vs placebo unfortunately is lacking. We cannot simply generalize the finding in patients with acute back pain to those with subacute and chronic back pain. Further high quality evidence from randomized clinical trials in patients with subacute and chronic back pain is clearly needed.

An important issue is whether paracetamol should be recommended (e.g. in clinical guidelines) and used in clinical practice in the management of back pain. At least 2 questions are relevant for this issue: (1) What are the alternatives? and (2) What is the magnitude of the placebo-effect?

- (1) When considering the alternatives, the option of non-pharmacological care, i.e. not prescribing or taking pain medication is an important one. Especially for patients with acute back pain, it is known that their prognosis is favorable as illustrated by the median recovery rates (about 17 days) in the PACE trial. For many patients, it holds that with adequate patient education and reassurance and with their pain diminishing relatively quickly over time there is no need for taking pain medications. In the American guidelines, non-pharmacological care is explicitly recommended as the first option in the management of back

pain. For those patients in which pain medication is considered (if the non-pharmacological was insufficient), NSAIDs are proposed as alternative for paracetamol and are thus recommended as first option as pain medication in some clinical guidelines. The present review, however, showed that effect of NSAIDs on pain and disability were very small and most likely not clinically relevant. Moreover, in head-to-head comparisons, NSAIDs have not shown to be clearly better than placebo, although the number of trials investigating this contrast is rather limited. Given these findings and because the safety profile of NSAIDs is less favorable than the safety profile of paracetamol, it is not obvious that NSAIDs should be preferred.

- (2) In research, we often want to separate specific effects of medications from nonspecific effects or placebo effects. In clinical practice, this distinction may be less relevant. Medication is prescribed to and used by patients and the end-results may be caused by the specific as well as the nonspecific effect of the drug – the more effect the better. By discarding paracetamol as pain medication for patients with back pain we also lose the potential of the nonspecific effects. While indeed there are ethical issues involved in prescribing placebo it is important to acknowledge that placebo-effects are true and measurable effects. There are even open-label placebo trials in the field of back pain, in which patients are told that they would receive placebo, which show positive effects on pain and disability [47,48]. On the other hand, we know that placebo-effects in trials may be exceeding 30% of the total observed effect, and that these placebo effects may not be reflected in clinical practice [49]. Much is still unclear about the clinical relevance of the placebo effect.

In conclusion, we argue that we still are in need of better evidence on the efficacy of paracetamol for acute and chronic back pain. Until that evidence becomes available paracetamol should still be considered as an option for patients with back pain if pharmacological management is strictly necessary. However, a strategy focusing on non-pharmacological management as the first treatment of choice in low back pain, as proposed by the American clinical practice guideline may be equally effective with less side effects [50].

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