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# An observational study of paracetamol (acetaminophen) deprescribing in patients with cancer pain receiving opioids for moderate–to–severe pain

## Abstract

**Background.** The objective of the study was to investigate the utility of deprescribing paracetamol in cancer patients receiving opioids for moderate-to-severe pain.

**Material and methods.** Patients with well-controlled cancer pain (average pain intensity ≤ 4/10), who were receiving regular paracetamol and an opioid for moderate-to-severe pain, completed the Brief Pain Inventory — Short Form at baseline and at seven days post discontinuation of the paracetamol (or sooner if restarting the paracetamol). The study employed a Simon optimal two-stage design with the aim of reducing the number of subjects exposed to a "futile" intervention.

**Results.** Forty-four patients were enrolled, and 40 patients completed the study. Eighteen (45%) patients restarted the paracetamol, although another four patients reported a worsening of pain control and/or an increase in the use of rescue medication. The only factor associated with restarting paracetamol was the pathophysiology of the pain, with patients with mixed pain more likely to restart paracetamol than patients with nociceptive pain (P = 0.013).

**Conclusions.** On the basis of these results we would recommend a trial of discontinuing paracetamol in all patients receiving opioids for moderate-to-severe pain, who are deemed to be adequately pain controlled. The patients can be reassured that there is approximately a one in two chance of not needing to restart the paracetamol, and that if they do need to start the paracetamol, pain control can be re-gained within a very short period of time.

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**Key words:** paracetamol, acetaminophen, deprescribing, cancer pain, analgesics, opioid

## Introduction

Paracetamol (acetaminophen) is a non-opioid, which is recommended for use at step I (i.e. non-opioid +/– adjuvant), step II (i.e. opioid for mild-to-moderate pain + non-opioid +/– adjuvant), and step III (i.e. opioid for moderate-to-severe pain +/– non-opioid +/– adjuvant) of the World Health Organization three step analgesic ladder [1]. It is undoubtedly an effective analgesic, and it has an unrivalled adverse effect profile [2]. Nevertheless, a recent systematic review of the literature concluded that "there is insufficient evidence

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to support the use of paracetamol in combination with Step III opioids" in patients with cancer pain [3].

Most of the randomised controlled studies in the aforementioned systematic review investigated the effect of adding paracetamol to an analgesic regimen containing an opioid for moderate-to-severe pain [4–7]. However, Axelsson & Christensen [8] investigated the effect of removing paracetamol from such an analgesic regimen in 30 patients with well controlled pain (i.e. "average" pain intensity < 4/10); they reported no difference in pain intensity between the treatment period with paracetamol and the treatment period with placebo. It should be noted that 42 patients entered this study, but only 30 patients completed this study.

Subsequently, Axelsson et al. [9] reported an uncontrolled study of the effect of removing paracetamol from an analgesic regimen containing an opioid for moderate-to-severe pain; they reported that 68% of patients reported no difference in pain after discontinuing the paracetamol (with 6% of patients reporting less pain), and that 53% did not want to take paracetamol at the end of the study. The patients in this study were again well pain controlled (i.e. pain intensity < 4/10), and also on a stable analgesic regimen (i.e. no change in opioid dose in the past week). It should be noted, that only 34 patients completed this study.

The aim of the current study was to obtain further data about the utility of paracetamol in patients receiving opioids for moderate-to-severe pain that are deemed to be well pain controlled (and specifically whether or not paracetamol can reasonably be omitted in this situation). Indeed, Axelsson et al. [9] highlighted the need for additional data to support clinical decision making.

## Material and methods

The study was conducted at the Royal Marsden Hospital NHS Foundation Trust in the United Kingdom. The study was approved by the Royal Marsden Hospital Committee for Clinical Research, the local Research Ethics Committee, and the Medicines and Healthcare Products Regulatory Agency (MHRA).

The subjects were recruited from both inpatient wards and outpatient clinics. The inclusion criteria for the study were: a) age > 18 years; b) diagnosis of cancer; c) regular opioid for moderate-to-severe pain ("strong opioid") for preceding seven days; d) regular paracetamol for preceding seven days (i.e. ≥ 2 g/day); and e) average pain intensity ≤ 4/10 for preceding 24 hours. The exclusion criteria for the study were: a) estimated prognosis < 2 weeks; b) cognitive impairment; c) radiotherapy in preceding four weeks; and d) alteration in oncology therapy in preceding four weeks.

The patients were given a standard information sheet, time to consider the study, opportunity to discuss the study (with researchers / others), and asked to provide a formal written consent before the enrolment. On the first day of the study the patients were assessed by a researcher and asked to complete the Brief Pain Inventory — Short Form (BPI — SF) [10], and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) [11]; the researchers used the data from these tools and other information in the electronic patient record to determine the aetiology of the pain (i.e. cancer-related, cancer treatment-related, other cause), and the pathophysiology of the pain (i.e. nociceptive, neuropathic, mixed). The patients were then asked to discontinue taking paracetamol, and advised to contact the research team should there be any deterioration in their pain control.

The patients were reviewed after 48 hours and asked to complete the pain scales on the BPI — SF; the reviews were done either in person or on the telephone. On the last day of the study (seventh day), the patients were again assessed by a researcher and asked to complete the Brief Pain Inventory — Short Form (BPI — SF). The patients were also asked the questions: "Since stopping your paracetamol do you feel your pain control has got worse?" (option: yes or no); "Since stopping your paracetamol do you feel you have had to use more 'breakthrough' / 'rescue' painkillers?"(option: yes or no); "Do you want to restart your paracetamol?" (option: yes or no).

If a patient wanted to restart paracetamol before the end of the study (and contacted the research team), he was asked to complete the pain scales on the BPI — SF before restarting the paracetamol, and 48 hours after starting the paracetamol; the reviews were again done in person or on the telephone.

The study employed a Simon optimal two-stage design [12], which is frequently used in phase II oncology trials (with the aim of reducing the number of subjects exposed to a "futile" intervention). The sample sizes were based on a p0 (pre-specified null hypothesis response probability) = 0.5, a p1 (minimum desired response probability) = 0.7, an alpha = 0.05 and a power = 80%. Initially 15 patients were recruited, with a plan to stop the study if > 6 patients restarted the paracetamol; subsequently, a further 28 patients were recruited, with a plan to stop the study if > 16 patients restarted the paracetamol. [The plan was to recruit to a maximum of 80 patients, which would provide a 95% confidence interval of +/– 11% on the estimate of the proportion of patients restarting paracetamol].

The data were analysed using SPSS (Version 19) software. Binary logistic regression was used to determine the relationship between restarting paracetamol and demographics, aetiology of pain, pathophysiology of pain, baseline pain intensity scores, and baseline dose of regular opioid (i.e. morphine equivalent daily dose).

## Results

Forty-four patients were enrolled into the study, and 40 patients completed the study (Fig. 1). The median age of the subjects was 63 years (range 31––80 years). The other characteristics of the subjects are shown in Table 1. At baseline, the median "average" pain intensity was 2 (range 0–4), the median "least" pain was 0 (range 0–3), and the median "worst" pain was 3 (range 0–10) in the whole group.

Eighteen (45%; 95% confidence interval: 30–60%) patients restarted the paracetamol; 11 (61%) restarted before day seven (end of the study), whilst seven (39%) restarted on day seven. For the patients that restarted before the end of the study, the median time to restarting was three days (range one to six days). In eight of these patients, pain scores were obtained on the day of restarting the paracetamol and 48 hours later; seven of these eight patients reported improvement in pain scores after restarting the paracetamol (Tab. 2).

Twenty-two (55%) patients did not restart the paracetamol, although two reported that their pain control had got worse, and three stated that they had used more rescue medication during the study period. [One of the patients who reported that their pain had got worse also stated that he had used more rescue medication]. In total, therefore, 18 (45%) patients reported no negative effect on pain control following discontinuation of the paracetamol. On dayseven, the median "average" pain intensity was 1 (range 0–6), the median "least" pain was 0 (range 0–5), and the median "worst" pain was 2 (range 0–9) in this group.

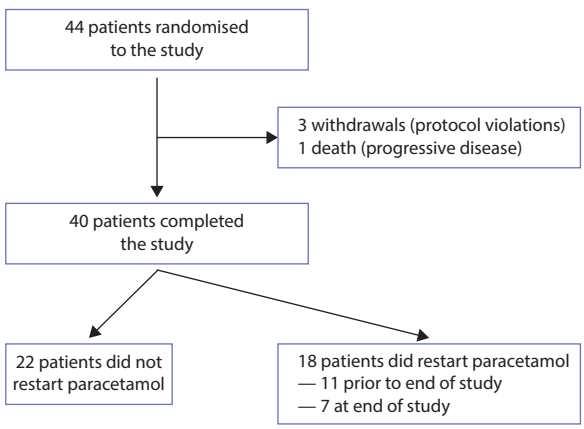


**Figure 1**. Study flow chart

**Table 1. Patient characteristics**

| Characteristic | Number patients (n = 44) |
|---|---|
| **Gender** | |
| Male | 25 (57%) |
| Female | 19 (43%) |
| **Cancer diagnosis** | |
| Breast | 5 (11.5%) |
| Gastrointestinal | 12 (27.5%) |
| Gynaecological | 3 (7%) |
| Haematological | 1 (2%) |
| Head & neck | 1 (2%) |
| Lung | 4 (9%) |
| Sarcoma | 1 (2%) |
| Urological | 17 (39%) |
| **Aetiology pain** | |
| Cancer-related | 42 (96%) |
| Cancer treatment-related | 1 (2%) |
| Unknown | 1 (2%) |
| **Pathophysiology pain** | |
| Nociceptive | 39 (88.5%) |
| — Somatic | –27 |
| — Visceral | –12 |
| Neuropathic | 0 (0%) |
| Mixed | 5 (11.5%) |

Univariate analysis of the potential factors associated with restarting paracetamol demonstrated a significant difference in terms of the pathophysiology of the pain, with all five (out of five) patients with mixed pain restarting, compared with 13 (out of 35) patients with nociceptive pain [Fisher's Exact Test: P = 0.013]. However, univariate analysis found no relationship between restarting paracetamol and demographics, aetiology of pain, the baseline pain intensity scores, or the baseline dose of regular opioid (i.e. morphine equivalent daily dose / MEDD). The median MEDD for the group that restarted paracetamol was 120 mg (range 40–720 mg), whilst the median MEDD for the group that did not restart paracetamol was 95 mg (range 40–600 mg).

## Discussion

Paracetamol is commonly used to treat cancer pain [13], and is recommended for use at all levels of the World Health Organization three step analgesic ladder [1]. Many patients start paracetamol at step I or II, and continue with paracetamol at step III (even though there is often little evidence of a clinically significant analgesic effect). However, paracetamol's mechanism of action is somewhat different from that of opioids (and non-steroidal anti-inflammatory drugs) [14], which means that it can have an additive effect (and, potentially, an opioid-sparing effect) [15].

Table 2. Pain intensity scores of patients that restarted paracetamol prior to end of study

| Patient ID | "Average pain" (0–10 NRS) on day paracetamol restarted | "Average pain" (0–10 NRS) two days after paracetamol restarted | "Worst pain" (0–10 NRS) on day paracetamol restarted | "Worst pain" (0–10 NRS) two days after paracetamol restarted | "Least pain" (0–10 NRS) on day paracetamol restarted | "Least pain" (0–10 NRS) two days after paracetamol restarted |
|---|---|---|---|---|---|---|
| Patient 5 | 5 | 2 | 5 | 3 | 5 | 2 |
| Patient 10 | 4 | 2 | 4 | 3 | 0 | 0 |
| Patient 15 | 4 | 3 | 9 | 7 | 0 | 0 |
| Patient 28 | 5 | 3 | 7 | 5 | 4 | 0 |
| Patient 30 | 4 | 3 | 6 | 4 | 2 | 2 |
| Patient 31 | 2 | 2 | 3 | 4 | 1 | 0 |
| Patient 39 | 7 | 6 | 9 | 8 | 6 | 0 |
| Patient 42 | 4 | 1 | 5 | 2 | 2 | 0 |

NRS — numerical rating scale

The results of this study confirm that paracetamol does have a role in the management of cancer pain in patients receiving opioids for moderate-to-severe pain, but that many (~ 50%) of these patients could stop taking paracetamol without negative effects on their pain control. Our results are similar to those of Axelsson et al. [9], who reported that 53% of their patients wanted to stop taking regular paracetamol. Moreover, Axelsson et al. also found no association between restarting paracetamol and demographics, aetiology of pain, or the baseline dose of regular opioid.

Paracetamol has few adverse effects or drug interactions. Thus, the major downside of taking paracetamol is the tablet burden, i.e. 8 tablets per day if the patient is taking 1 g four times a day (utilising 500 mg tablets) [16]. Discontinuing paracetamol and reducing the patients tablet burden may improve adherence with other medication (and so improvement in other symptoms). Furthermore, discontinuing paracetamol will also result in significant financial savings for the patients and the healthcare service (even though the drug is relatively inexpensive).

On the basis of these results (and those of Axelsson et al. [9]), we would recommend a trial of discontinuing paracetamol in all patients receiving opioids for moderate-to-severe pain who are adequately pain controlled. The patients can be assured that there is approximately a one in two chance of not needing to restart the paracetamol, and that if they do need to start the paracetamol, the pain control can be re-gained within a very short period of time (i.e. less than 48 hours).

However, we would not recommend routinely discontinuing paracetamol in patients receiving opioids for moderate-to-severe pain who are inadequately pain controlled (unless there is an issue around tablet burden / adherence). Moreover, we would suggest that patients receiving opioids for moderate-to-severe pain who are inadequately pain controlled, and who are not receiving regular paracetamol, should be given a therapeutic trial of this unique non-opioid analgesic.

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## *Conflict of interest*

None of the authors have any relevant conflict of interest.

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