**Single Patient Multiple Cross-Over Studies To Determine The Effectiveness Of Paracetamol In Relieving Pain Suffered By Patients With Advanced Cancer Taking Regular Opioids:**

**a pilot study**

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Summary’

Paracetamol is a useful adjunct when used in combination with “weak opioids” for chronic

pain in palliative care patients with advanced cancer, however it is not certain that there is

continuing benefit when used in conjunction with “strong” opioids. N-of-1 trials allowed individual treatment decisions to be made for each participant: there was no added benefit for any of the participants, although no conclusion about the added benefit of paracetamol above regular opioids was possible for the group, due to insufficient numbers recruited. Paracetamol may not provide added benefit above regular opioids; this should assessed on a case by case basis to justify the extra tablet load.

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**Key words:** paracetamol, n-of-1 trial, palliative care, pain, opioids

**Background and rationale**

Chronic pain is the most feared symptom in palliative care (PC) patients. Whilst paracetamol is effective for mild to moderate pain and useful when used in combination with “weak opioids”, it is not certain that there is sufficient continuing benefit when used in conjunction with “strong” opioids for moderate to severe pain to justify the additional medication burden.

Although there have been several studies describing opioid-sparing effects of paracetamol, there

have been only a handful in patients with advanced cancer and pain despite strong opioids. A 2013 critical review concluded that the role of paracetamol in management of cancer pain remains controversial [19]. We conducted a series of n-of-1 trials to test the feasibility of using this methodology to obtain the per patient effectiveness of paracetamol in providing additional analgesia to regular opioids in people with advanced cancer experiencing moderate to severe pain.

**METHODS**

**Design**

We conducted three cycle, double blind, placebo-controlled multiple crossover n-of-1 trials.

Each treatment pair was 6 days; data from the first day of each 3-day period were discarded. The order of drugs in each cycle was determined by random allocation and blinded to clinician, investigator and patient. Within each treatment period, patients were randomised to either: slow release paracetamol 665 mg tabs (GlaxoSmithKline; over-encapsulated), or identical placebo, two capsules three times per day, in blocks of four prior to trial commencement.

Patient-completed daily diaries recorded BPI scores [21]. The trial result was compared to a predetermined clinically important change of 2.0 from baseline in BPI pain on average score over the last 24 hours [23]. Individual patient reports were generated to allow consultation between participant and clinician to decide whether to continue paracetamol.

**Study population**

Patients with advanced cancer taking opioids for chronic pain, in Queensland, Australia from May 2010 to September 2012.

**Institutional Ethics Committee Approval**

Approvals were obtained from Institutional Review Boards [IRBs] of participating hospitals, and

the University of Queensland Human Research Ethics Committee. All patients provided written

informed consent.

**Inclusion criteria**

a) aged ≥18 years

b) clinical diagnosis of chronic cancer-related pain with BPI average pain score of ≥ 3

over previous 24 hours;

c) taking regular dose of opioids (excluding codeine or tramadol) stable in 48 hours

prior

d) <= three doses of stable dose of breakthrough opioid/day in 48 hours prior

e) stable dose of other regular pain medications for at least 48 hours prior. Patients already

on paracetamol had to stop paracetamol 3 days prior;

f) no intervention that might alter pain levels during 2 weeks prior or plans to undergo

such on study;

g) intact gastrointestinal tract

**Exclusion criteria**

a) liver function (AST, ALT) >1.5x upper limit of normal, total bilirubin outside normal range;

b) paracetamol allergy

c) cognitive impairment

d) life expectancy < 6 weeks

e) poor understanding of English.

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**RESULTS**

Seven participants completed at least one cycle. Three patients completed 3 cycles; 1 completed 2 cycles; 1 completed 1 cycle, and 2 did not complete any cycles.

Individual patients’ mean differences in *BPI Pain on average* between paracetamol and placebo ranged from 0.2 to 0.3 with no patient having an important positive or negative response. Addition of paracetamol gave no added benefit above placebo. For three patients, paracetamol provided small additional pain relief in secondary outcomes, but this was not clinically significant.

**Adverse events**

There were 2 grade 1 adverse events (irregular heart beat) and 3 grade 2 adverse events

(constipation), unrelated to paracetamol. There were no reported serious adverse events.

**DISCUSSION**

Taking paracetamol was not worth the additional tablet burden for any of the patients.

We demonstrated the considerable advantage of participating in N-of-1 trials over RCTs: that participation gave useful evidence for every participant who completed at least one cycle.

We found recruitment to be far more difficult than expected. Barriers to recruitment were not related to the n-of-1 trial design, but to the strict inclusion criteria and the need to keep a stable opioid dose. Our patients were generally too advanced and pain control required frequent medication adjustments thereby excluding the majority from participating. The extent of this potential problem was not anticipated: it contributed to only 7 eligible participants being recruited. There were also other issues including time taken to obtain ethics and governance approval for each site. Therefore we decided not to proceed to a full trial. For future research in this area, we recommend targeting community patients earlier in the cancer trajectory, with less stringent eligibility criteria.

**Conflict of Interest Statement**

The authors declare that no conflicts of interest exist.

**Authors' contributions**

JH, GM, DC and JN conceived and participated in the design of the study. JN drafted the

manuscript. PS provided statistical advice and data analysis. All authors contributed to and

approved the final manuscript.

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