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Opinion paper

Personalised treatments for acute whiplash injuries: A pilot study of nested N-of-1 trials in a multiple baseline single-case experimental design

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ABSTRACT

Background: Whiplash associated disorder (WAD), a common and disabling condition, incurs huge burden and costs to Australia. Yet, current treatments for whiplash are not very effective; improved outcomes are urgently needed. Clinical guidelines recommend simple analgesia (paracetamol and non-steroidal anti-inflammatory drugs) but there have been no trials of guideline-recommended drugs. This study will investigate the effectiveness of evidence-based advice (EBA), paracetamol, naproxen, and both paracetamol and naproxen, in reducing daily neck pain and preventing chronic neck pain after whiplash injury.

Methods: This study is a pilot series of multi-cycle, double-blinded, randomised N-of-1 trials, nested in a multiple baseline design. The design will comprise three baselines of 5, 8 or 11 days duration. Post enrolment, participants will be randomly assigned to one of the baselines. Fifteen participants with acute (<2 weeks) Grade II WAD, experiencing at least moderate pain (NRS: $\geq$ 5/10), and at risk of poor recovery will be recruited from hospitals in Queensland, Australia, and through local physiotherapists. Patients will receive EBA plus a randomised sequence of three cycles of ten day treatment triplets (paracetamol designated as a C phase, naproxen, designated as a D phase, and both paracetamol and naproxen, designated as an E phase).

Discussion: We will test the effects of different treatments on the primary outcome of average neck pain intensity collected daily and at 4 and 7 months post-injury. Secondary outcomes, including disability, depression, post-traumatic stress symptoms, pain catastrophizing, and feasibility of study procedures, will also be evaluated. The results of this study will inform a larger trial aiming to strengthen the evidence on EBA and simple analgesics for WAD.

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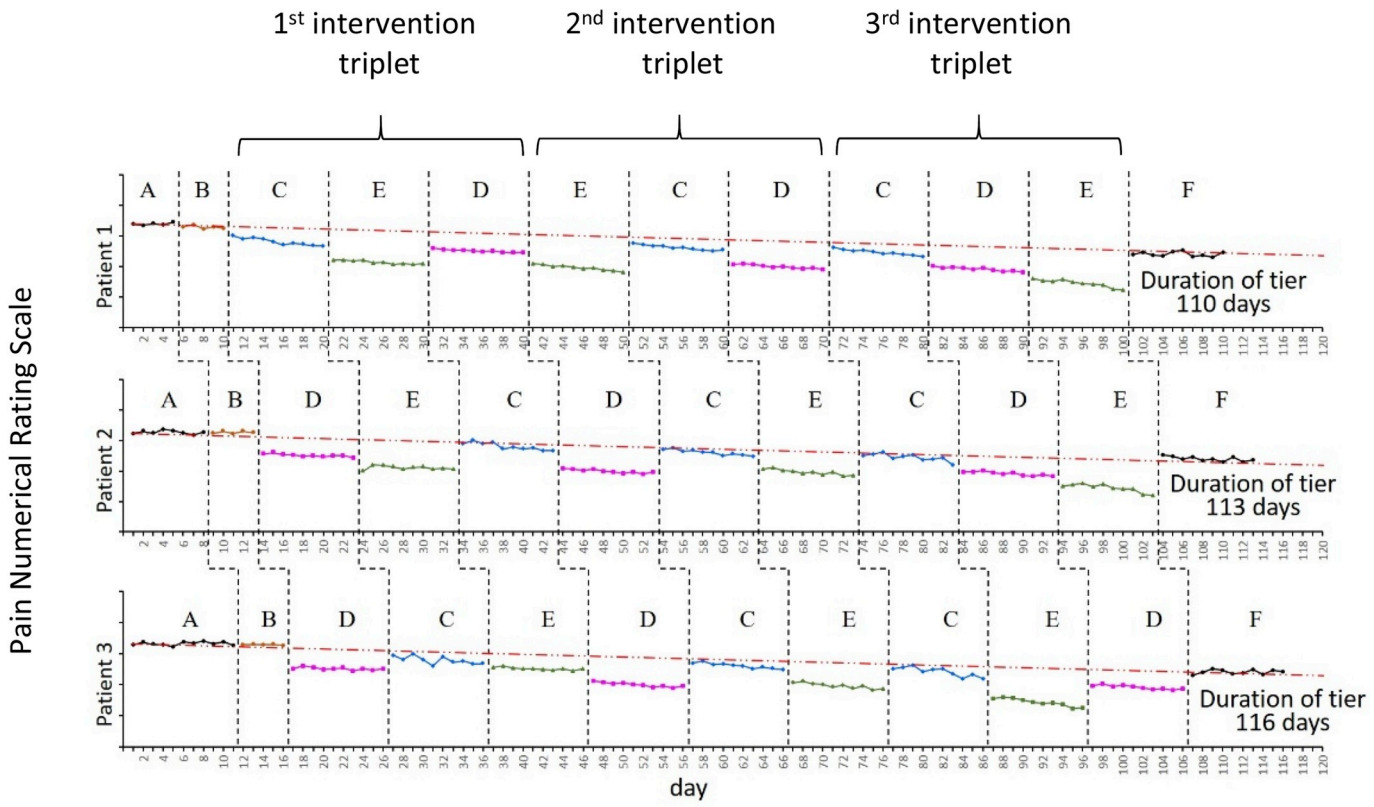

Fig. 1. Study design (simulated data). Phase A = initial baseline; Phase F = final baseline; Phase B = EBA; Phase C = paracetamol; Phase D = naproxen; Phase E = paracetamol + naproxen. Red line indicates expected natural recovery. Pain Numerical Rating Scale Score range = 0–10, 2 units per tick-mark. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

1. Introduction

Whiplash-associated disorder (WAD) is a common, costly and disabling condition. Up to 50% of those injured never fully recover [1] and up to 30% live with moderate to severe disability [2]. WAD accounts for the vast majority (85%) of submitted claims as well as the greatest incurred costs in the Queensland compulsory third party scheme [3]. In Australia, WAD comprise ~75% of all survivable road traffic collision (RTC) injuries with total costs of over $540 million annually [4].

Clinical guidelines recommend provision of evidence-based advice, encouraging return to usual activity, and exercise, but these provide only modest benefits [5] and have not significantly improved overall physical and mental health outcomes [6]. Recommendations from the Australian WAD management guidelines about pharmacological treatments for acute WAD are consensus-based and include simple analgesics as first line treatment, non-steroidal anti-inflammatory drugs (NSAIDs) if simple analgesics are ineffective, and opioids for severe pain [7]. There have been no trials of paracetamol and NSAIDs, and few trials on opioids for patients with WAD [8]. Despite this, opioids are frequently prescribed for WAD in both general practice (GP) [9] and emergency departments (EDs) [10]. In the US, inappropriate use of opioids for musculoskeletal (MSK) pain is a growing problem [11]. Medication trials in related conditions, soft tissue and musculoskeletal injury, have mostly been of single doses or short duration, and have not shown clear superiority of one simple analgesic regime over alternatives [12–16]. The effectiveness of the EBA booklet alone has not been studied before.

Clearly, urgent research on pharmacological treatments for acute WAD is needed. Paracetamol and NSAIDs are obvious choices for several reasons. The majority of people with WAD are managed in primary care; simple analgesics are cheap, easily administered, require little monitoring, commonly used, and available over the counter. The National Institute of Clinical Studies guidelines for pain management in EDs [17] and Australia and New Zealand College of Anaesthetists Acute Pain Management review [18] note that both paracetamol and NSAIDs are effective, but more effective if used together, for treating most mild to moderate acute MSK pain [19,20]. The pathophysiology of WAD remains uncertain but raised inflammatory biomarkers are found, especially in moderate-severe cases [21]; paracetamol, NSAIDs and selective cyclo-oxygenase (COX)-2 inhibitors all have effects on inflammation by inhibiting prostaglandin synthesis. Paracetamol and naproxen are also optimal treatments for N-of-1 trials as their plasma half-lives (paracetamol 1–4 h; naproxen 14 h [22]) leave no residual impact on target symptoms after three days cessation.

We will conduct a series of N-of-1 trials nested in a multiple baseline design, with Bayesian statistical modelling of prior data to account for natural recovery [2]. N-of-1 trials are individualised randomised controlled trials (RCTs), where each participant serves as their own control. They can determine the best therapy for an individual, as each participant receives all treatments. N-of-1 trials, being sensitive to individual differences, are a suitable design for a heterogeneous condition such as WAD [23]. When aggregated, N-of-1 trials provide population estimates of treatment effects akin to randomised controlled trials [24,25]. They are also cost-effective and efficient as they require fewer subjects than RCTs to achieve equivalent statistical power [26].

2. Aims and objectives

2.1. Primary aim

The primary aim of this pilot study is to conduct a series of N-of-1 trials comparing the effectiveness of 1) evidence-based advice (EBA), 2) paracetamol and EBA, 3) naproxen and EBA, and 4) both paracetamol, naproxen and EBA to reduce daily neck pain and to prevent chronic pain at 4 and 7 months following whiplash injury in 15 individuals at risk of

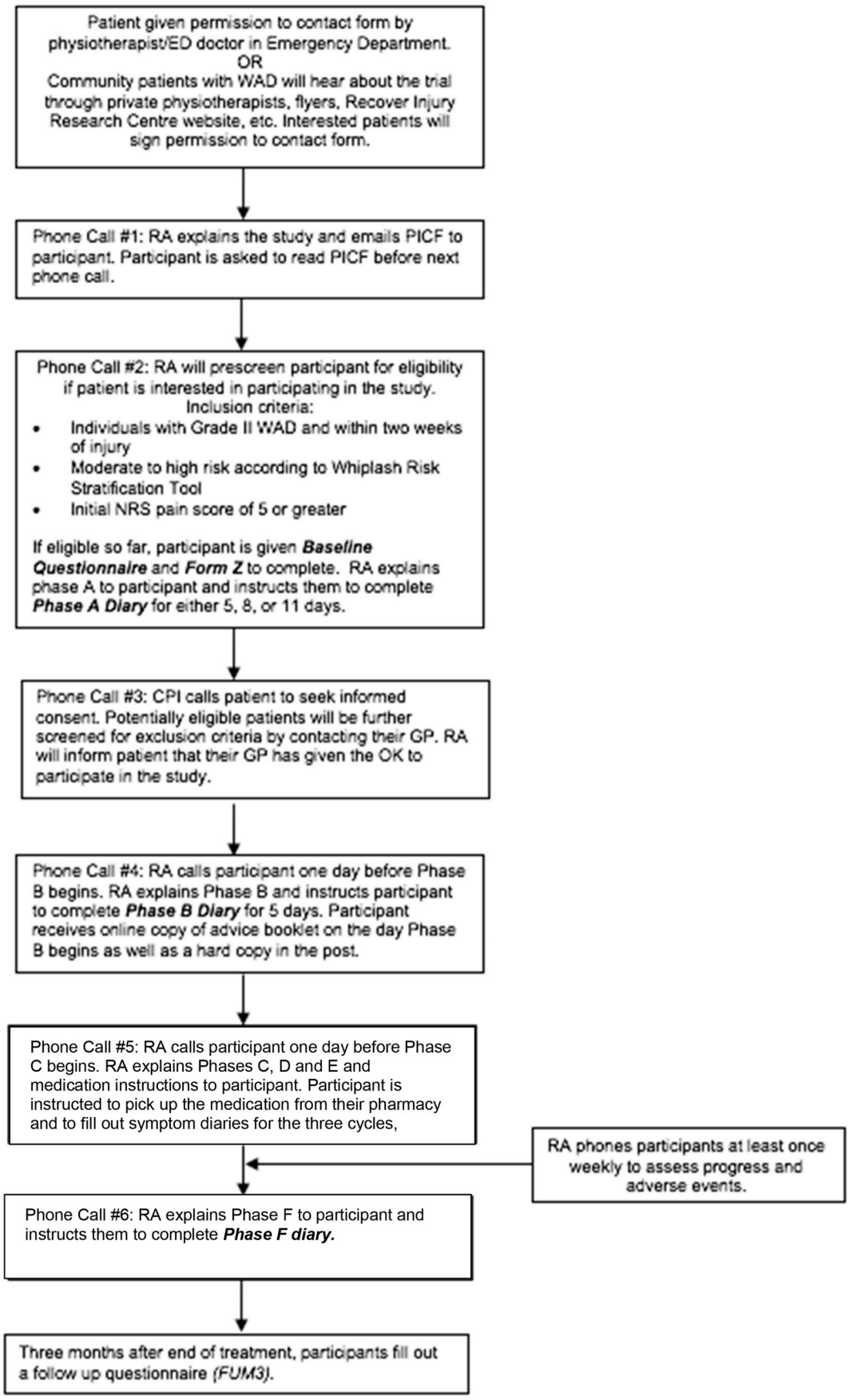

Fig. 2. Study flow.

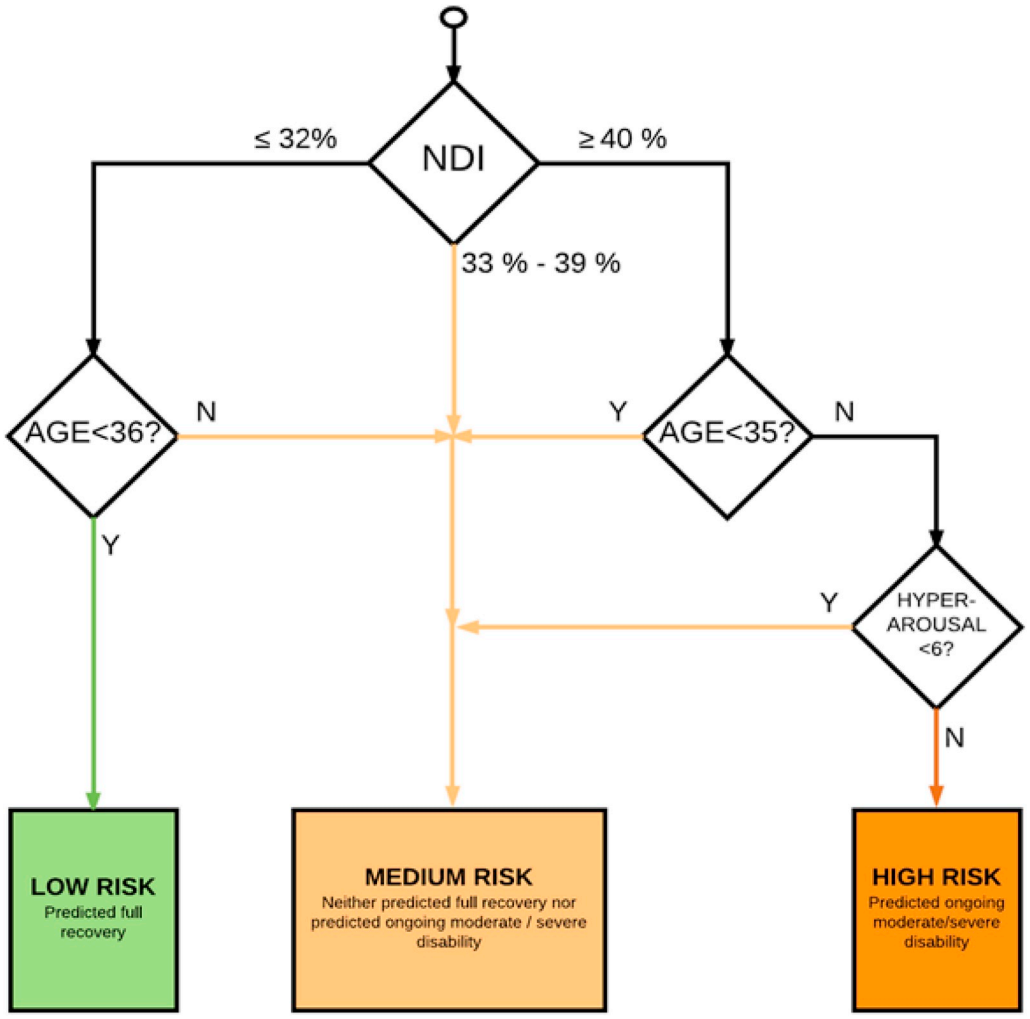

Fig. 3. Whiplash Risk Stratification Tool (WhipPredict) Algorithm31
The Neck Disability Index (NDI)33 is a ten item questionnaire that assesses neck pain related disability. Hyperarousal symptoms are measured using the hyperarousal subscale of the Posttraumatic Diagnostic Scale.34.

poor recovery. (Patients' use of the EBA booklet is continued during the pharmacological treatment phases).

2.2. Secondary aims: clinical

1) compare the effectiveness of EBA, paracetamol plus EBA, naproxen plus EBA, and both paracetamol and naproxen plus EBA in decreasing (1) disability, (2) depression, (3) posttraumatic stress symptoms and (4) pain catastrophizing at 4 and 7 months following whiplash injury in individuals at risk of poor recovery.
2) improve precision of individual clinical recommendations for simple analgesics in 'at-risk' adults with acute WAD
3) aggregate data to obtain group estimates of intervention effects.
4) to record management decision post-trial and management and compensation claim lodgment at 4 and 7 months post-injury.

2.3. Secondary aims: feasibility

1) To assess the applicability of N-of-1 trials when there is natural recovery from a disease/injury
2) Proportion of screened patients eligible
3) Proportion of eligible patients enrolled
4) Enrolment rate (i.e. number of enrolments per month)
5) Logistic model for recruitment to a full trial, including staff requirements and strategies to overcome any barriers identified.
6) Feedback from ED clinicians, local GPs, trial GPs, and patients on their experience with the trial and areas for improvement, to inform a full scale trial.

3. Methods/design

3.1. Design overview

This is a series of N-of-1 trials nested in a multiple-baseline design (MBD). Each tier of the design includes a baseline (phase A). Four different interventions are then compared for 15 patients with recent onset WAD:

1) intervention 1, phase B: evidence-based advice (EBA)
2) intervention 2, phase C; paracetamol + EBA
3) intervention 3, phase D: naproxen + EBA
4) intervention 4, phase E: paracetamol + naproxen + EBA.

Effectiveness of the interventions will be evaluated using a series of MBDs across 3 participants at a time [27]; that is, each MBD will contain 3 tiers, one per participant (Fig. 1; simulated data). Baseline NRS pain scores will be collected daily during a no intervention phase (phase A).

Intervention 1 (phase B) will start immediately after phase A, and as soon as possible, within 2 weeks of injury. Following phase B there will be three triplets of pharmacological interventions. Each triplet will consist of intervention 2 (phase C), intervention 3, (phase D) and intervention 4 (phase E). The duration of each of these interventions is 10 days. In order to control for sequencing effects, the sequence of interventions within each triplet will be randomised. Moreover, sequence within triplet will be randomised independently for each tier (see also Randomisation section below). The intervention sequences in the triplets shown in Fig. 1 are only an example of possible randomisation sequences for the three interventions in a given triplet.

Having different duration of initial baseline phases (phase A) across the participant tiers is a critical design feature of the multiple-baseline design [27]. Having different phase lengths bolsters the scientific rigor of the study because the different lengths control for threats to internal validity (e.g., maturation, history). In other words, if the initial baseline phase lengths were equal, then an extraneous event (due to history, maturation) could occur at a particular point in time that coincided with the phase change. In that case, it is not possible to know whether the change in behaviour was due to the intervention, or due to the extraneous event. Having different phase A lengths reduces the probability of such an event occurring at precisely the phase change time given that this differs in "real time" across the tiers. Phase A is either 5, 8 or 11 days because of the multiple baseline design – it is as short as possible to get treatment started as soon as possible, but long enough to obtain at least 5 observations, for maximum rigor [28]. Phase B is 5 days because it is as short as possible, but long enough to obtain at least 5 observations, for maximum rigor. Phase F is a 10 day observation phase, the same as the treatment phases, using a double dummy design, so the timing of doses does not unblind.

Secondary outcomes will be measured at baseline, the end of each treatment cycle, post-trial observation period, and three month follow up. Study flow is illustrated in Fig. 2.

The trial protocol conforms to the *Single-Case Reporting guideline In BEhavioural* interventions [29] and Consort Extension for reporting N-of-1 trials guidelines [30] and adheres to IMMPACT recommendations for design of clinical trials for chronic pain prevention [31].

3.2. Setting

Community patients recruited via EDs of Royal Brisbane and Womens' Hospitals and Caboolture hospitals, Brisbane, online via social media/websites, and through local physiotherapists.

3.3. Participants

3.3.1. Inclusion criteria

- Individuals with Grade II WAD and within 2 weeks of injury.
- Moderate to high risk according to the Whiplash Risk Stratification Tool (WhipPredict), a validated tool for predicting ongoing moderate/severe disability following acute whiplash injury [32]. See Fig. 3 for the algorithm used by WhipPredict to predict the risk of disability following acute whiplash injury.
- Initial Numerical Rating Score (NRS) pain score [33] of 5 or greater.

3.3.2. Exclusion criteria

- Pre-existing serious spinal pathology (e.g. metastatic disease of the spine);
- Confirmed fracture or dislocation at time of injury (WAD IV);
- WAD III (neurological compromise eg decreased reflexes, muscle power);
- Previous whiplash injury or neck pain condition requiring treatment, and still symptomatic;
- Long term use of Paracetamol or NSAIDs for other chronic conditions (e.g. back pain, joint pain/arthritis)
- Long term analgesics such as opiates, tramadol, etc and adjunctive analgesics for neuropathic pain such as pregabalin, amitriptyline, etc.
- Known hypersensitivity to paracetamol or naproxen or to any excipients (hives, blisters, rash, dyspnea and wheezing);
- Asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs;
- History of renal insufficiency (eGFR$<$60 ml/min/1.73 m^2 or ACR $>$3 mg/mmol)
- Patients on diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers
- Severe active liver disease that in the clinician's judgement excludes the patient;
- Patients who are severely malnourished, anorexic, septic, have a low body mass index or are chronic heavy users of alcohol.
- Women who are pregnant or breastfeeding
- History of severe or uncontrolled psychiatric illness or substance abuse
- Patients who are smokers or obese (BMI $>$ 30)
- Inability to speak and write in English (participants will be required to complete questionnaires written in English only)
- Older than 65 years
- Use of concomitant drugs that increase the risk of upper GI bleeds/perforation e.g. anticoagulants, antiplatelet drugs, or corticosteroids
- Current H. pylori infection or past infection where the clinician considers a risk of upper GI bleeding persists.
- Prior history of peptic ulcer disease and/or gastrointestinal bleeding
- History of inflammatory bowel disease
- Uncontrolled hypertension, symptomatic heart failure and persistent peripheral edema.
- Cardiovascular risk/history $\geq$10% within 5 years or history of established CVD (eg unstable angina or MI, not including hypertension).
- Patients undergoing or planning to have surgery during the next three months.

3.4. Recruitment and screening

Community patients with WAD will be informed of the trial through private physiotherapists, flyers, RECOVER Injury Research Centre website, social media and Emergency Departments of Royal Brisbane and Womens' Hospital and Caboolture Hospitals, Brisbane. Patients diagnosed with grade II WAD by doctors will be referred to ED physiotherapists, who will inform them of the study and present them with a permission to contact form if interested. By signing this form, patients consent to be contacted by research staff to explain the study. Those who wish to be involved will provide informed consent and will be prescreened by research staff for inclusion and exclusion criteria. Eligible participants will be further screened by the trial GP or their own GP (i.e. more extensive exclusion criteria). The GP will also provide the medication script.

3.5. Randomisation

The randomisation codes in variable block sizes of 4–6 will be generated by the study statistician following standard statistical procedures and sent to the study dispensing pharmacy. Each individual receives interventions 2, 3 and 4 in a randomised sequence within a triplet, over three treatment triplets, which controls for sequencing effects. The order of interventions within a given triplet is randomised independently such that the order of interventions in a given triplet is independent on the order of interventions in the previous triplet. Triplets in each tier are randomised separately. The randomisation procedure for each patient's MBD is independent of the others. Fig. 1 illustrates

a hypothetical randomisation sequence. The schedule of treatment order in each triplet/tier will be kept in a sealed envelope in a locked filing cabinet in the pharmacy, and will be in the 24hr on-call bag after hours in case unblinding is needed. Study medication will be prepared according to the randomisation schedule by an independent pharmacist, and sealed in medication kits. Following baseline assessment, research staff will provide the next kit to the participant.

3.6. Study interventions

3.6.1. Evidence-based advice booklet

All patients will be provided by the research team with an evidenced-based advice booklet *Whiplash Injury Recovery: A Self Help Guide (2*nd *edition),* co-authored by MS, after completing the baseline period. The research team will explain the evidence-based advice (EBA) booklet, which is based on recommendations of the current Australian Guidelines for Whiplash Management. It provides information about whiplash; assurance about prognosis; advice to stay active and resume working; information on correct posture and resuming functional daily activities; pictorial descriptions of specific exercises for the neck and upper limbs, and an exercise program proven to reduce neck pain.. This second edition of the booklet was written based on consumer and health care professional feedback via focus groups. Any effect size from this booklet itself as an intervention is unknown, although there is some evidence for small effects from staying active and doing specific exercises for the neck and upper limbs [36].

Patients can subsequently use the booklet to follow the EBA and do the exercises as suggested, whenever they choose throughout the rest of the study. That is, use of the EBA booklet is continued during the pharmacological treatment phases. The daily surveys ask patients to record any advice they implemented from the booklet that day.

3.6.2. Medications

There will be 3 cycles of 10-day triplets of paracetamol 1g four times daily (phase C) or naproxen sodium 275 mg four times daily (phase D) or both (phase E) (90 days active treatment), then a 10-day observation phase (phase F), using a double dummy design, so the timing of doses does not unblind. Data from first 3 days of each treatment period will be discarded to ensure no carryover. Given that the treatment phases (i.e., phases C, D, and E) are of 10 days duration, this will still provide at least 5 observations per phase in order to meet design standards [28]. To ensure blinding of doctors, research staff and participants, both Paracetamol and Naproxen tablets will be identical in every way by using encapsulation.

3.7. Co-interventions

Participants who experience high levels of continuing or worsening pain will be able to contact research staff to return for an earlier review with the GP. In some instances, rescue medication (oxycodone 5 mg prn) can be provided in addition to the study medicine. These medications are consistent with current clinical practice guidelines for WAD management. Patients will be provided with the rescue medication if they have continuing and worsening pain that is debilitating in nature (in the short term) or continuing high levels of pain that have not improved after 2 days of treatment, despite following the trial regimen. Participants will be provided with rescue medication for 2 days duration.

At the end of the trial, in respect of the compensable nature of a whiplash injury, the patients will be permitted to seek further treatment if required. We cannot prevent patients having treatment – both for ethical reasons and as the patients may submit a compensation claim through the compulsory third party system. Information about any additional treatments sought by participants (eg additional medication, physiotherapy etc.) will be gained via patient diaries at the follow-up time points and controlled for during analysis.

3.8. Adherence to study medication

Adherence with the study medications will be assessed in three ways: (1) daily self-recorded medication intake, (2) the trial staff will ask about adherence during the planned telephone-based reviews starting at 1 week post randomisation and (3) counts of returned tablets following the completion of treatment. Participants will be asked to return all unused tablets for counting at the end of the treatment period in a reply paid post satchel.

3.9. Study outcome measures

Primary outcomes: assessed daily during baseline, during the intervention trials, at end of trial and at 3-month follow-up Table 1 (see Table1).

1. Daily neck pain intensity: patients' self-report of average pain intensity during the previous 24 h on Numeric Rating Scale (NRS) 0–10 [37]. Participants will be asked to select the number that best represents their pain during the previous 24-h on a scale of 0–10; with 0 indicating *no pain* and 10 indicating *worst possible pain.* Evidence indicates that Numeric Pain Rating Scales have a sufficient level of discriminative validity to differentiate pain intensity in people with chronic pain [38].
2. A custom single-item question, adapted from Nicholas et al., 2007[39], on patients' self-report of confidence to perform daily activities in the presence of neck pain using a scale ranging from 0, meaning not at all confident, to 6, meaning completely confident [39].
3. Adverse events and severity using National Cancer Institutes of Health: Common Terminology Criteria for Adverse Events [40].

3.9.1. Secondary outcomes

1. *At end of each of the 3 cycles, end of trial and at* 3-month *follow-up*:
   a. **Neck Disability Index** – the NDI is a valid, reliable and responsive measure of neck pain related disability [34]. The questionnaire has 10 items concerning pain and activities of daily living including personal care, lifting, reading, headaches, concentration, work status, driving, sleeping and recreation. An overall score (out of 100) will be calculated by totaling responses to 10 questions, each with 6 potential Likert-type responses (e.g., 0 indicating no disability to 5 indicating total disability), and multiplying the sum by 2 to yield a percentage.
   b. **Patient global rating of change (GRC)** [41]– GRC is a self-report measure recommended by IMMPACT to assess perceived efficacy of treatment in chronical pain clinical trials [42]. The scale ranges from −5 (vastly worse) to +5 (completely recovered), with 0 indicating no change. Higher GRC scores have been found to be significantly associated with greater pain improvement [43].
   c. **Global Satisfaction scale of Treatment Satisfaction Questionnaire for Medication (TSQM)** [44]- this composite comprises of two items from the TSQM survey and will be used to assess the overall level of satisfaction or dissatisfaction with medication. The Global Satisfaction scale of TSQM is a reliable (Cronbach's alpha = 0.86), valid, and psychometrically sound measure of patient satisfaction with medication [44].
   d. **Pain Catastrophising Scale (PCS)** – PCS will be used to assess catastrophizing behaviours associated with pain (catastrophizing defined as *"an exaggerated negative mental set brought to bear during an actual or anticipated painful experience"*) [45]. The PCS is a 13-item instrument relating to the degree to which participants experienced 13 thoughts or feelings when experiencing pain on a 5-point scale, with 0 indicating *not at all* and 4 indicating *all the time.* The measure provides a total pain catastrophizing score and a scale for three subscales including rumination, magnification

and helplessness. The sum of responses yields a score out of 52 with higher scores indicating greater pain catastrophizing. A PCS total score ≥24 indicates a high level of pain catastrophizing. The PCS has been shown to have adequate internal consistency (coefficient alphas: total PCS = .87, rumination = .87, magnification= .66, and helplessness = .78)[46].

e. **PTSD Checklist for DSM-5 (PCL-5)** - PCL-5 is a 20-item self-administered measure of PTSD symptoms, corresponding with the diagnostic criteria for PTSD in DSM-5 [35]. The instrument uses a 5 point Likert scale, with 0 indicating *not at all* and 4 indicating *extremely*. An overall score of 0–80 can be calculated by summing the responses to the 20 questions, with higher scores denoting greater symptom severity. PCL-5 is psychometrically sound with good internal consistency, convergent and discriminant validity, and test-retest reliability [47].

f. **Depression & Anxiety Stress Scales (DASS-21)** – DASS-21 is a widely used, valid, and reliable self-administered tool that is designed to assess symptoms of three negative emotional states: depression, anxiety, and stress [48]. The 21-item self-administered survey contains three subscales: depression, anxiety, and stress. Each subscale contains 7-items. There are 4 response options for each item with 0 indicating *did not apply to me at all, never* and 3 indicating *applied to me very much or most of the time, almost always.* Scores are totaled for each subscale [49]. Higher scores on each subscale indicate increased symptom severity.

g. **EQ-5D-5L** - this survey is a generic measure of health status, comprising of a descriptive system assessing five dimensions of health (mobility, personal care, usual activities, pain/discomfort, and anxiety/depression), and a visual analogue scale. Evidence shows that EQ-5D-5L is a sensitive, valid, and reliable (Cronbach's alpha = 0.78) tool to measure health related quality of life [50, 51].

2. *At post-trial F/U*: Management decision at review 2 weeks post N-of-1 trial; compensation claim lodgement.
3. *At* 3-month F/*U only*: Concordance with post N-of-1 trial decision; compensation claim lodgement.

3.10. Sample size

We will recruit 15 participants for this pilot study. Sample size calculations were not undertaken as this is a pilot study using a design that has not been utilised previously. Feasibility of recruitment and retention is the main issue we will be assessing.

3.11. Unblinding

The trial participants, investigators, clinicians and research staff will be blinded to the treatment allocation. The Principal Investigator (JN) and GM will be able to unblind individual cases if the following criteria are met:

1. Emergency Unblinding - To make a clinical treatment decision or when an unexpected serious adverse event occurs.
2. During an unmasked analysis in accordance with the study analysis plan or at the request of the Data Safety Monitoring Board.
3. At the conclusion of each patient's study to determine the effect of intervention.

If GM (medically qualified investigator) requires emergency unblinding, he will quote, participant initials, participant date of birth and trial title to the Principal Investigator, who will contact the pharmacy. The pharmacy will unblind for the specific participant only. The medically qualified investigator will talk to and unblind the participant.

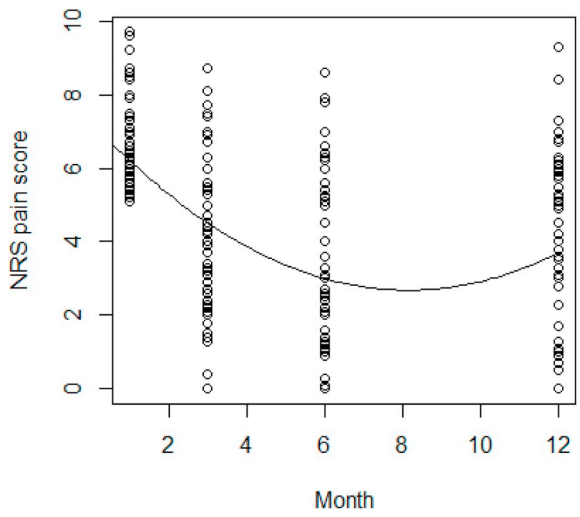

Fig. 4. Bayesian Model of NRS Pain Scores for Moderate to High Risk Groups over time (months)2.

3.12. Adverse events

Information about adverse effects of the medication will be sought from all participants using open-ended questioning at weekly intervals following randomisation during their contact with the research assistant. Participants will be able to contact trial staff at any time of the day if they have questions or concerns about the medication. In the event that a participant reports an adverse event or side effect, the trial staff will liaise with the trial GP. The doctor will then call the participant to assess further and to make a determination on what action should be taken. This may include dose alteration or withdrawal from the study if deemed necessary. All adverse events will be reported to the relevant ethics committees. The most common side effects reported with paracetamol usage are nausea, vomiting, constipation and with naproxen, gastrointestinal (heartburn, abdominal pain, constipation) and central nervous system symptoms (headaches, somnolence, tinnitus, vertigo).

3.13. Data management

Data will be collected at RECOVER Injury Research Centre, The University of Queensland, using Survey Monkey and analysed using SPSS. Statistical modelling will be conducted using R.

3.14. Data analyses

A Bayesian linear mixed effects model has been developed for the pain trajectory of natural recovery for the moderate to high-risk group (Whip-Predict [32]) with initial NRS ≥ 5 (Fig. 4). Data are from a prospective longitudinal study of prognostic factors for poor functional recovery [53] and from the control arm (usual care) of an RCT [23]. This model allows us to predict the expected natural recovery of each patient in this trial, and thus allows us to assess whether there has been significant improvement in each outcome measure when the patient is on a given treatment. Fig. 5 shows actual data for individual pain trajectories for those in the moderate to high-risk group (Whip-Predict [32]) with initial NRS>=5. The developed model has the following form:

$$y_{ij} = \theta_{0i} + \theta_1 t_j + \theta_2 t_j^2 + \varepsilon_{ij},$$

where $\theta_{0i} = \theta_0 + b_{0i}$, $(\theta_0, \theta_1, \theta_2)$ are the population parameters, y_{ij} is NRS pain score at time t_j, $b_{0i} \sim N(0, \sigma_b^2)$ are random effects that account for repeated measures over time. They will be assumed to vary normally with zero mean and between subject variance σ_b^2 and $\varepsilon_{ij} \sim N(0, \sigma^2)$ are residual errors, for $i = 1, \ldots, N$ (the number of patients) and $j = 1, \ldots, n_i$

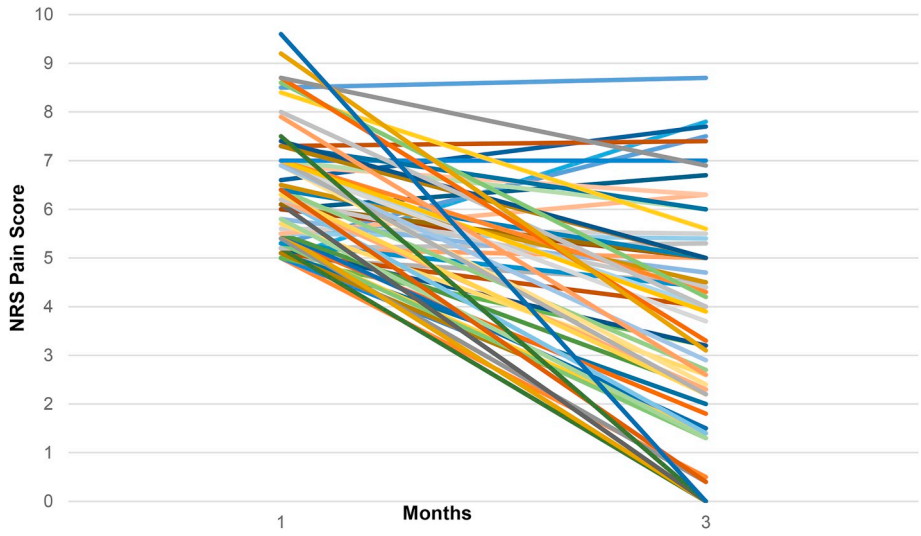

Fig. 5. Nrs pain scores for moderate to high risk Group31.

(the number of observations for patient *i*). Uninformative priors derived as proposed in Dansirikul et al. (2005) [52] will be considered for this model.

As the patients in Sterling et al. (2010) are different from those in this study, we cannot assume our empirical model will be directly transferrable. Demographics of our sample will be compared to those of the moderate to high risk group with NRS>=5 from Sterling et al. (2010). Further, we will calibrate the model using data from phase A to ensure our model for natural recovery is applicable to this study.

For estimating the effect of paracetamol, naproxen and both paracetamol and naproxen with respect to EBA, a Bayesian linear mixed effects model will also be considered, and will have the form as specified above with the addition of three population/random effect parameters relating to these treatment differences. Accordingly the random effects $(b_{0i}, b_{3i}, b_{4i}, b_{5i})$ will be assumed to follow a multivariate normal distribution with a zero mean vector and a variance-covariance matrix Ω. Again, uninformative priors for this model will be considered as derived in Dansirikul et al. (2005). With this formulation, when a patient is on an intervention, the outcome will be compared to what is predicted by the empirical model for a given point in time. Thus, treatment difference will be assessed with respect to EBA with natural recovery over time.

Unfortunately, it is unknown how (or if) each intervention will affect pain. Typically, in N-of-1 trials where natural recovery does not need to be accounted for, treatment effects are assumed to be additive (and this additive model is what is described above). Such an effect will be explored in our analysis but we will also consider including treatment effects in other ways (eg treatment effect may depend on severity, and thus multiplicative effects would be appropriate). Such a decision is a problem of model choice, and, as no prior data are available to inform this problem, we will be guided by information that will be available in the data, adopting formal model selection techniques from Bayesian statistics to determine the preferred model. The inclusion of additional covariates (eg age, gender) will also be explored again through formal model choice procedures. When estimating the model for natural recovery and appropriately including intervention effects, overall participant response against natural recovery will be calculated as follows: **1)** posterior mean differences in population and individual expected outcomes compared to natural recovery at the end of the trial and at 3 months follow up will be evaluated with associated 95% credible intervals; and **2)** the posterior probability that the intervention effect is>=average of 1.5 NRS points better than natural recovery will be estimated. We will take>=1.5 points on NRS scale to be a clinically significant difference [31]. For each intervention, a patient will be deemed a responder to that intervention if the corresponding individual level difference to natural recovery is>=1.5 NRS points. If there is>=1.5 NRS points difference between two interventions, they will be deemed to respond better to that intervention.

4. Discussion

The development of chronic pain and disability following road traffic crash injuries such as WAD is common and incurs enormous costs worldwide. Currently recommended treatments offer only modest benefit [5,6] and improved outcomes are of great public interest. This trial will assess the effectiveness of commonly used simple early interventions that are recommended by clinical guidelines, despite the lack of evidence for their use. The intervention will be delivered to individuals at risk of poor recovery recruited through Emergency Departments and physiotherapy practices using an innovative design, N-of-1 trials nested in a MBD.

The evidence gap on pharmacological treatment of whiplash is of concern, particularly in the light of recent work on low back pain, which shows that paracetamol is not effective [14], and NSAIDs are of limited benefit (effect sizes are small and not clinically significant) [15].

N-of-1 trials (individualised randomised controlled trials) are a subtype of single-case experimental design (SCED), where the patient serves as their own control. N-of-1 trials have unique properties, which are well known in chronic, stable conditions. This study is innovative in testing the method for use in an acute condition which is changing due to natural recovery [2]. If N-of-1 trials are feasible to use in acute settings, there are implications for trial design to test other treatments for WAD, and for other acute conditions where natural recovery occurs, eg in rehabilitation (stroke, Traumatic Brain Injury), postoperative pain, and deteriorating chronic conditions with changing baselines. Some of these are suitable for using observation periods rather than relying on prior data, which may not exist.

4.1. Strengths

Each participant receives both study medication and placebo/comparator, and thus learns which treatment works best specifically for him/her. They are a patient-oriented and clinically relevant method to optimise individual treatment. When aggregated, N-of-1 trials are of equivalent strength to RCTs yet need fewer subjects because of greater statistical power [26], so results can be obtained more quickly. Collecting their own data and receiving feedback empowers patients [54]. All patients receive each medication, avoiding patients declining because they may get placebo.

Nesting an N-of-1 design in a MBD improves overall scientific rigor. MBDs, one of the four prototypical types of SCED, are used to study treatment effects by replicating effect of a treatment variable across multiple participants, settings or behaviours. Initial baselines in each tier are established by repeated observation over time of the untreated target symptom. Interventions are then implemented in a temporally staggered sequence across participants, settings or behaviours in each tier [27]. MBDs have been used in Traumatic Brain Injury, stroke, etc, where baselines are changing over time because of natural recovery [55]. Advances in Bayesian statistical techniques now provide a powerful way to adjust for changing baselines, allowing application of N-of-1 trials to acute conditions that change over time.

Our results will give a probability of response and side effects to each treatment, which can guide treatment recommendations for each individual for this costly and treatment resistant condition.

The results of this study will inform a larger trial, which if successful, will provide evidence for effective simple interventions for a costly and treatment resistant condition. This would have the potential to confirm or change current practice on how care for WAD is provided at a national and international level.

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Availability of data and materials

Not applicable.

Composition, roles, and responsibilities

A Trial Steering Committee, including the principal investigator, co-investigators, and statistician, will govern this study and ensure that Good Clinical Practice is adhered to throughout. An independent DSMB, involving experts in the field of study, will also be constituted to evaluate the safety aspects of the study.

Coordinating centre – Recover Injury Research Centre, The University of Queensland.

Steering Committee – JN, MS, GM, SJ.

Data management team – JN, SJ.

Declaration of competing interest

Nil declared.

Abbreviations

AE	Adverse Event
COX	Cyclo-oxygenase
DASS	Depression and Anxiety Stress Scales
EBA	Evidence-based advice
ED	Emergency Department
GP	General Practice
MBD	Multiple baseline design
MSK	Musculoskeletal
NDI	Neck Disability Index
NSAID	Non-steroidal inflammatory drug
NRS	Numerical rating score
PCS	Pain Catastrophising Scale
PGIC	Patient Global Impression of Change
RCT	Randomised controlled trial
RTC	Road traffic collision
SAE	Serious adverse event
SCED	Single Case Experiment Design

Table 1
List of outcome measures used.

Outcome	Tool	Frequency of measurement
Neck pain intensity	NRS	Daily
Adverse events	Adverse event form	Every ten days
Confidence to perform daily activities	Confidence scale (0–6)	Daily
Neck disability	NDI	Every ten days
Impression of change	Patient global impression of change	Every ten days
Satisfaction with medication	Global Satisfaction Scale	Every ten days
Pain Catastrophising	PCS	Every ten days
Post-traumatic stress	PCL-5	Every ten days
Depression, anxiety, and stress	DASS-21	Every ten days
Health status	EQ-5D-5L	Every ten days

TSQM	Treatment Satisfaction Questionnaire for Medication
WAD	Whiplash Associated Disorder

Author's contributions

JN: designed protocol; coordinating principal investigator; contributed expertise on primary care research and clinical trial (including N-of-1 and SCED) methodology and conduct. GM: input to design of study; contributed expertise in general practice and primary care research. JM: input into statistical aspects of design of study; expert in biostatistics. RT: expert input into N-of-1 design and SCED design. MP: input into design of study. CF: input into pharmaceutical aspects of the trial and study protocol. MWT: input into pharmaceutical aspects of the trial and study protocol. SJ: Set up of study and recruitment. MS: input into design of study; contributed expertise in management of whiplash. All authors contributed to and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval has been granted by Darling Downs Hospital and Health Service (HREC/18/QTDD/36) and The University of Queensland (#2018001497). The study has been registered with Australian and New Zealand Clinical Trials Registry (ACTRN12618001291279). The trial protocol conforms to the Single-Case Reporting Guideline In BEhavioural Interventions and adheres to IMMPACT recommendations for design of clinical trials for chronic pain prevention. Prior to enrollment into the study, research staff will provide potential trial participants the Patient Information Sheet and inform them of the purposes, methods, possible risks and benefits of participating in the study. Written informed consent, complying with ethical standards, will be obtained .

Consent for publication

Not applicable.

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