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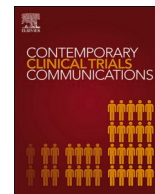
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Comparing pregabalin and gabapentin for persistent neuropathic pain: A protocol for a pilot N-of-1 trial series

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ABSTRACT

Background: Evidence-based management of neuropathic pain is commonly ineffective due to the large variability in response between cases. Patients often have to trial several drugs before finding one that provides adequate relief, leading to increased costs and worsened outcomes. There is thus a need for tools to guide and streamline prescribing decisions in neuropathic pain. N-of-1 trials provide a potentially precise and economical method of selecting between multiple interventions in an individual patient, and merit a feasibility assessment for use in clinical pain practice.

Aims: We aim to evaluate the feasibility of N-of-1 trials to compare pregabalin and gabapentin for individual presentations of neuropathic pain.

Methods: This is a double-blinded multiple crossover study, with recruitment from existing patients at an outpatient pain clinic in New South Wales, Australia. Participants will undergo three 4-week treatment pairs, comprising 2 weeks of pregabalin (150–600 mg/day) and 2 weeks of gabapentin (900–3600 mg/day), in an individually randomised order. Intervention doses will be derived from participants' existing treatment dose. Medications will be taken orally three times daily. The primary outcome will be pain intensity; measures will be self-reported daily in patient diaries. After completing all three cycles, participants and their physicians will be presented with the results of the trial to form an informed decision about their treatment.

Discussion: As a stable yet debilitating condition, neuropathic pain is especially amenable to an N-of-1 study design. A successful trial would represent a significant quality of life improvement for the patient, possibly extending over the course of their lifetime.

1. Background

1.1. Neuropathic pain

Neuropathic pain is pain caused by disease or dysfunction of the somatosensory system [1,2]. It is a common complication of various neurological pathologies, including post herpetic neuralgia, diabetic neuropathy, and stroke [3,4]. Presentations of neuropathic pain are often chronic, and tend to respond poorly to conventional analgesics such as paracetamol or NSAIDs [3]. Neuropathic pain is associated with a range of comorbidities, including sleep disturbance, depression, anxiety and disability [5]. With an estimated Australia-wide prevalence of 8.5% [6], neuropathic pain thus represents a significant public health

burden.

1.2. Antiepileptics in neuropathic pain

Evidence-based guidelines recommend the anti-epileptics gabapentin and pregabalin as first-line medications for neuropathic pain [3, 5,7,8]. They are administered orally, and achieve pain attenuation by binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels [9]. Both drugs demonstrate confirmed but modest efficacy compared to placebo. The number needed to treat is 7.7 for pregabalin and 6.3 for gabapentin [10]. Pregabalin and gabapentin are generally well-tolerated, and feature similar adverse effect profiles [3]. Dizziness and somnolence are the most common findings, occurring in approximately 25% of patients

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[9,11]. While many trials have studied pregabalin and gabapentin against placebo, there are few high-quality studies that directly compare the two [3,12]. Furthermore, the individual response to these agents has been shown to vary greatly between patients [13]. This highlights the need for trials exploring individual as well as group based effects [14].

1.3. N-of-1 trials: an introduction

Clinical approaches to pain management have conventionally focused on systematic review of high-quality RCTs. However, these studies measure effectiveness as a population average, and do not accurately predict individual responses to pain interventions. This is especially pertinent given the variability observed in neuropathic pain profiles [15]. Furthermore, in the pursuit of conclusive and well-controlled data, neuropathic pain trials disproportionately enlist patients with 'pure', uncomplicated presentations and sparse comorbidity profiles [5]. As such, generalising study results to daily practice is often challenging [16].

N-of-1 trials are randomised, double-blinded, multiple crossover trials of effect [17], which offer a robust and flexible alternative to RCTs for the assessment of individual patients [18–20]. They have been used in neuropsychology [16,21], palliative care [19], and cardiology [22], among other fields. Data from a series of N-of-1 trials can be analysed to provide an estimate of the corresponding population-level response [23].

1.4. Justification for the current study

N-of-1 trials offer potential clinical utility in informing and personalising prescription decisions for individuals with refractory neuropathic pain. A previous series of N-of-1 trials successfully assessed the

effectiveness of gabapentin against placebo in neuropathic pain on a case-by-case basis [24]. We aim to evaluate whether N-of-1 trials are feasible to compare gabapentin and pregabalin for patients with neuropathic pain. Application of N-of-1 trials to this clinical niche has strong potential to improve patient outcomes and reduce costs [25]. As a secondary objective, individual trials from this study can be aggregated to provide further comparative data on pregabalin and gabapentin for neuropathic pain [26].

2. Methods

2.1. Study design

This study comprises a series of N-of-1 trials in patients currently prescribed gabapentin for neuropathic pain. The trials will utilise a randomised, double-blinded, multiple crossover design using pregabalin as the intervention and gabapentin as the comparator.

Each 12-week trial will consist of three 4-week cycles, divided into two blocks of 2 weeks each for gabapentin and pregabalin respectively. Treatment cycles will be individually randomised for each patient. Fig. 1 demonstrates a sample trial. Medications will be administered three times daily, with doses derived from the participant's existing gabapentin use. Review appointments will be held at the conclusion of Cycles 1 and 2, allowing each participant to discuss the progress of the trial; return their patient diary and any unused medications; and report any adverse effects. Participants will also be advised to contact their treating physician as needed for questions or clarification, or in the incidence of any serious or novel adverse effects.

This protocol meets the CENT (CONSORT extension for N-of-1 trials) guidelines [27].

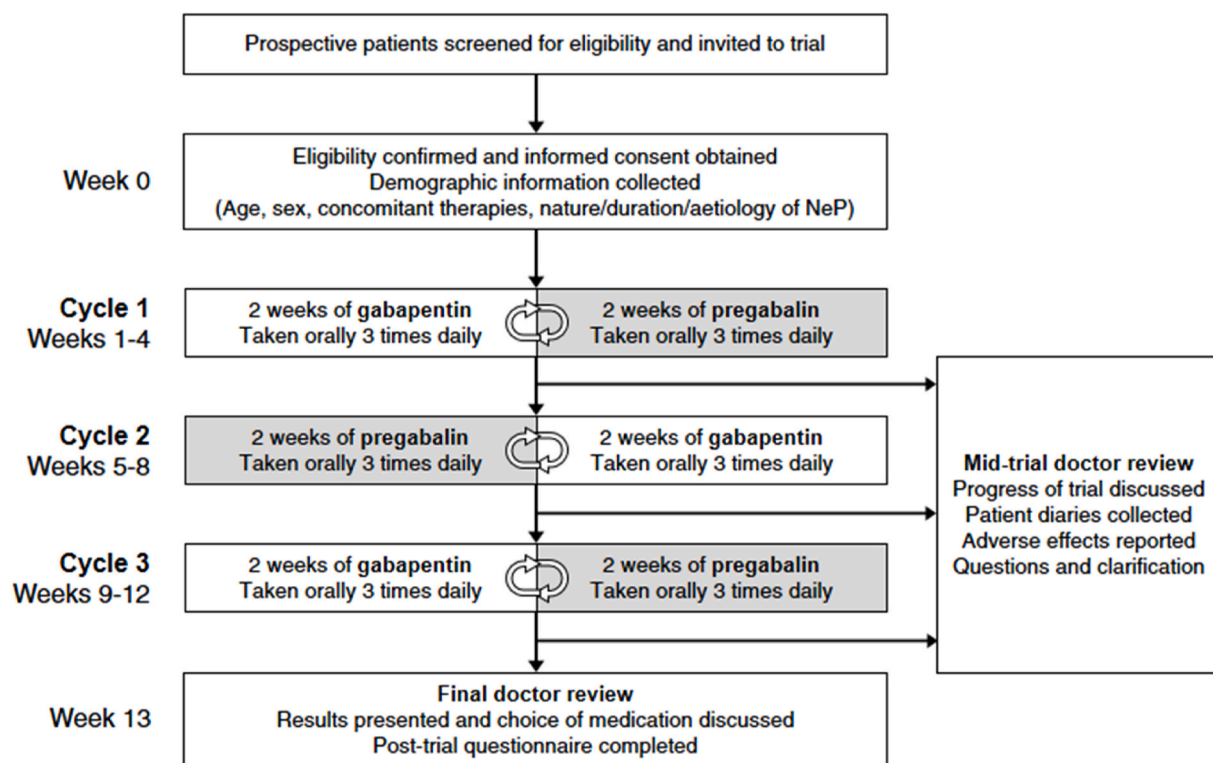


Fig. 1. Study design for individual N-of-1 trials.

2.2. Study setting

This study will be undertaken in the Illawarra-Shoalhaven Chronic Pain Service (I-SCPS), an outpatient clinic at the Port Kembla Hospital in New South Wales, Australia. Ethical approval for this study is pending following minor revision from the Illawarra and Shoalhaven Local Health District Ethics Committee (2020/ETH00096). This study is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12618001762246p).

2.3. Study enrolment

I-SCPS physicians will screen for prospective participants from their regular pool of patients, and inform them of the trial and its aims. Volunteers will subsequently undergo a detailed history check to confirm their eligibility. Informed consent will be obtained.

Participants will be recruited according to the following inclusion criteria:

1. Registered at the I-SCPS of Port Kembla Hospital.
2. Aged 18 years or greater.
3. Diagnosed with chronic and stable neuropathic pain.
4. Currently prescribed gabapentin (900–3600 mg/day) for neuropathic pain.
5. Able to consistently maintain pain medications and treatments for the duration of the trial.
6. Able to provide informed consent and complete forms in English.
7. Able to be reliably contacted by telephone.

The exclusion criteria are as follows:

1. Breastfeeding, pregnancy or planned pregnancy during the trial.
2. Gabapentin or pregabalin sensitivity.
3. Active or past history of seizures in the last 12 months, or clinically considered to be at high risk of seizures.
4. Creatinine clearance less than 30 mL/min.
5. Likelihood of surgical intervention within the duration of the trial.
6. Inability to attend review visits due to prolonged absence from the region.

3. Interventions

Gabapentin and pregabalin in identical capsules will be orally administered three times daily. Drugs will be sourced from the Port Kembla Hospital pharmacy, which will group and order the medications for each N-of-1 trial according to the participant's randomised sequence. At the start of each trial, participants will receive 12-week medication kits, divided into six labelled 14-day blocks.

Gabapentin will be prescribed at the participant's existing gabapentin dose. Pregabalin will be prescribed at one-sixth the participant's existing gabapentin dose, in accordance with accepted drug equivalence ratios [11,28–30] (see Table 1).

Table 1
Sample calculation of pregabalin dose from existing gabapentin dose.

Existing/daily gabapentin dose (mg)	Daily pregabalin dose (mg)
900 (300 TDS)	150 (50 TDS)
1800 (600 TDS)	300 (100 TDS)
3600 (1200 TDS)	600 (200 TDS)

3.1. Randomisation

Each 4-week cycle will contain 2-week blocks of gabapentin and pregabalin in a randomly determined order. Block randomisation, with a block size of 2, will be used to generate random sequences of three cycles – e.g. AB-BA-AB or BA-BA-AB – for each individual N-of-1 trial. This will ensure that an equal number of participants begin the trial on either pregabalin or gabapentin [31]. Randomisation will be conducted by a statistician from the University of Queensland.

The resulting sequences will be provided to the hospital pharmacy for preparation and labelling of the medication kits. These will subsequently be dispensed by each participant's treating physician, along with instructions for their use.

3.2. Blinding

This study will be double-blinded. Medications will be re-encapsulated into identical capsules. Equivalent amounts of the hypo-allergenic and efficient excipient methylcellulose will be used as necessary for volume correction, with a maximum of 1200 mg methylcellulose per capsule. Participants will be informed that in each 4-week cycle, they will receive 2 weeks each of gabapentin and pregabalin, but kept unaware as to the order. Physicians will similarly remain blinded to the order of medications within each cycle.

Unblinding of the participant and treating doctor will occur at the end of the corresponding individual's N-of-1 trial. Unblinding will also be undertaken in the event of patient withdrawal from the trial.

3.3. Concomitant medications

Participants will be allowed to maintain other regular neuropathic pain medications at stable doses throughout the trial, including existing prescriptions of paracetamol, non-steroidal anti-inflammatory drugs, topical anaesthetic formulations, and opioid analgesia. The name, dose, and frequency of these interventions will be recorded at baseline. For the duration of the trial, participants will be discouraged from altering the dose of their existing medications, as well as commencing any new interventions for neuropathic pain. If these changes are unavoidable, they will be documented in the patient diary, with the patient possibly withdrawn from the study until stable.

Rescue analgesia in the form of paracetamol (to a maximum of 4 g daily) and ibuprofen (to a maximum of 1200 mg daily, in the absence of medical contraindications and unless previously prescribed a higher dose) will be permitted during the trial, and will similarly be recorded by name, dose and frequency. A sensitivity analysis will be undertaken with frequency of rescue analgesia use as a variable to evaluate whether there are any between-treatment differences, as well as to identify whether rescue analgesia use is a potential confounder of individual results.

3.4. Sample size

In accordance with a United Kingdom audit of pilot and feasibility studies [22,32,33], it is estimated that 30 completed trials will be sufficient to evaluate the acceptability and utility of N-of-1 trials in treating neuropathic pain. A previous neuropathic pain study in Port Kembla Hospital reported a 35% dropout rate, resulting in 48 completed trials [24]. The most common reason for withdrawal was increased pain while on placebo treatment. Given that this study has no placebo arm, we predict a reduced dropout rate of 25%, and will thus recruit a total of 40 patients.

While this study will also involve aggregate analysis of pregabalin versus gabapentin in neuropathic pain to look for trends in the data, this

is a pilot feasibility study and no formal power calculation was performed.

3.5. Safety evaluation

Prospective participants will have had previous exposure to gabapentin, as per the inclusion criteria. Given the similar safety profiles of gabapentin and pregabalin [2], novel adverse effects are expected to be rare. Participants will record adverse effects daily, and will be advised to immediately report any alarming or unexpected symptoms to their treating physician.

In accordance with the United States Food and Drug Administration, serious adverse events will be defined as those resulting in death, life-threatening illness, hospitalisation, disability, or permanent damage or dysfunction [34]. All serious adverse events will be reported to the principal investigator and appropriate measures will be taken. Subsequently, a decision will be made on a case-by-case basis on whether to continue the trial with appropriate precautions or withdraw.

3.6. Study withdrawal

Participants may be withdrawn from the study under the following conditions:

- Intolerable adverse effects or serious adverse events
- Clinical emergency
- Development of an exclusion criteria
- Non-compliance with study
- Loss to follow-up
- Patient or clinician request

The reason(s) for each withdrawal will be recorded. Valid data from completed cycles will still be used for individual and aggregate analysis.

3.7. Trial completion

After completing all three cycles, the results of the N-of-1 trial will be provided to the patient and treating doctor for review. Outcomes will be presented in the form of mean pain scores (with standard deviations) for gabapentin and pregabalin. Data will also be summarised graphically to facilitate patient and physician interpretation. The patient and doctor will subsequently evaluate which of the two medications is best suited to the patient's neuropathic pain.

4. Data collection

Demographic information on each participant will be collected at study entry. This will include age, sex, concomitant therapies, and the duration, intensity, and aetiology of the neuropathic pain.

Participants will be assigned diaries to complete daily self-reported measures. Additional measures will be collected at the ends of each treatment block, each cycle, and the trial itself. To minimize carryover effects, data from the first week of each block will be discarded from the analysis.

4.1. Primary outcome

Pain intensity will be measured through daily completion of a 100 mm Visual Analogue Scale (VAS), adapted from designs by McCormack et al. [35] and Hawker et al. [36]. Participants will be invited to make a mark on a horizontal line corresponding to the perceived intensity of their pain over the previous day. The left anchor will be "no pain", while the right anchor will be "worst pain one can imagine".

As a method of quantifying pain, the Visual Analogue Scale is internally consistent and highly responsive to change [36]. In accordance with previous pain studies [37–41], the minimal clinically

important difference – that is, the minimum effect required to justify a change in treatment – will be defined as a >30% reduction on the VAS.

4.2. Secondary outcomes

4.2.1. Daily

1. Sleep interference due to pain, using a 100 mm VAS.
2. Adverse effects including category, frequency and severity. Adverse effects will additionally be recorded by the treating physician on the Case Report Form.
3. Patient satisfaction, measured with the Patient Global Assessment of Treatment Satisfaction Scale (adapted from Dworkin et al. [42]). Participants will rate on a 5-point categorical scale how satisfied they were with their treatment that day.

4.3. At the end of each treatment block

4. Functional limitation, measured via the Patient-Specific Function Scale (adapted from Stratford et al. [43]). Using a 100 mm VAS, participants will estimate the degree to which their pain interferes with five selected activities of daily living.
5. Mental state, measured via the Depression Anxiety Stress Scale 21 (adapted from Henry and Crawford [44]). Participants will complete a 21-item questionnaire designed to evaluate the severity of depression and anxiety-associated symptoms.

4.4. At the end of each cycle

6. Blinded medication preference; participants will be asked whether they preferred the first or second block in the preceding cycle.

4.5. At the end of the trial

7. Final medication preference; after reviewing the results of their trial, participants will be asked whether they preferred pregabalin or gabapentin overall. Participants will additionally be asked to rate five factors (pain, sleep, adverse effects, functional limitation, mental state) in order of how much they influenced this decision.
8. Satisfaction with the presentation of results, using a multi-item questionnaire.
9. Satisfaction with the overall trial, using a multi-item questionnaire. Participants and doctors will also be asked to describe their experience and provide feedback on the N-of-1 trial process.

4.6. Feasibility outcomes

The feasibility of this N-of-1 trial process will be assessed according to the following criteria:

1. Proportion of screened patients deemed to be eligible.
2. Proportion of eligible patients able to be recruited.
3. Proportion of study participants completing the full trial.
4. Patient compliance with the study, as measured via 1) diary completion rates and 2) unused medication counts.
5. Patients' and clinicians' opinions, feedback, and ideas regarding the N-of-1 trial process, including logistics, ease of comprehension, and overall satisfaction.

5. Data analysis

For all participants included in the analysis set, observations collected in the second week of each treatment period will be considered for analysis. Given the 6-h half-life of both gabapentin and pregabalin [11,50], this will permit sufficient wash-out and elimination of carry-over effects between treatment periods. All statistical analyses will

be conducted within the R-package.

5.1. Individual n-of-1 trials

For each n-of-1 trial, participant data for each outcome will be plotted by treatment period and cycle, and summaries for each treatment and cycle appropriate for each data type will be provided. Observations across the three cycles will be compared via Student's t-test (parametric), Wilcoxon signed-rank test (non-parametric), or chi-squared test (categorical) depending on the nature of the outcome. For this study, statistical significance of each hypothesis test will be set at $P < 0.05$, with Bonferroni correction applied for multiple secondary outcomes.

Missing data will be evaluated for each participant, and examined for patterns of missingness. A maximum of 2 days of missing data per treatment cycle is considered acceptable, representing at least 5 out of 7 days of viable data for analysis. No imputation will be conducted for missing data. Missing data exceeding 2 days in duration will result in exclusion of the treatment cycle from the individual and aggregate analysis.

The character and frequency of adverse effects will be individually tabulated for each patient, along with a record of any serious adverse events.

5.1.1. Aggregate analysis

An aggregated N-of-1 analysis will be conducted within a Bayesian hierarchical modelling framework. This is to account for within and between participant variability of the response. Such a model will be developed for each outcome, and unadjusted estimates of the treatment effect will be reported [23,45]. An adjusted estimate of the treatment effect will also be reported where the inclusion of particular covariates will be determined via an appropriate information criterion [46].

For each model, weakly informative prior information will be considered such that conclusions will be predominately data-driven. After a burn-in period of 5000 observations, 10000 Markov Chain Monte Carlo simulations will be performed for each outcome variable using the probabilistic programming language Stan (version 2.27) [47]. Adjustments to this will be considered should the need arise. For all parameters of interest, posterior means along with 95% credible intervals will be reported. Evidence of a difference between treatments will be assessed via the posterior probability that the estimated effect is greater or less than 0, as appropriate. Any posterior probability that is less than 0.05 (or greater than 0.95) will be deemed as significant.

Aggregated missing data will be investigated to identify whether there is a difference in missing data frequency between pregabalin versus gabapentin.

5.2. Subgroup analysis

As multiple dose levels were featured in this study, a subgroup analysis of doses will also be considered if sample sizes permit. This will entail developing an augmented treatment variable, and following the above approaches for an aggregated analysis.

5.3. Individual analysis based on aggregated model

Individual analyses will also be conducted based on the fitted aggregated model. This will include assessing how variable the treatment effect is between participants, and reporting individual treatment effects and the proportion of these that are significant based on the aggregated model. The posterior mean of these estimates along with 95% credible interval will be reported.

5.4. Sensitivity analysis

A sensitivity analysis with respect to the choice of priors will be undertaken to evaluate the impact of more informative and vaguer priors. If the results are found to be sensitive to such a choice, a review of the selected priors for the analysis will be undertaken.

6. Discussion

Pregabalin and gabapentin are antiepileptics that demonstrate modest efficacy in relieving neuropathic pain [6,9–11,48]. Individual treatment responses in neuropathic pain differ significantly, and there is little head-to-head trial evidence on these two medications [10,11,13]. This study aims to explore the potential of N-of-1 trials in comparing pregabalin and gabapentin for individual cases of neuropathic pain.

There are several elements of this study that are particularly well suited to N-of-1 trials. Neuropathic pain is a chronic and relatively stable condition, and associated with significant morbidity and cost [49]. Therefore, trials have the potential to provide significant and long-term utility. Both pregabalin and gabapentin are fast-acting drugs, with short biological half-lives of approximately 6 h [11,50]. This rapid onset and offset of action reduces interference between the two treatment arms, and is thus well-suited to a multiple crossover design. In addition to overcoming inter-patient variability, N-of-1 trials also offer a significant advantage over informal open label trials in eliminating biases and preconceptions that may interfere with successful drug selection [51].

Attrition rates in N-of-1 trial studies are usually higher than those of randomised controlled trials [18,24]. This has been attributed to the long duration and greater complexity of multiple-medication crossover studies [52]. Patient withdrawal is a significant contributor to the complexity, cost, and duration of research studies, and further leads to attrition bias [53]. In a similar N-of-1 trial series comparing gabapentin with placebo, Yelland et al. reported a 35% withdrawal rate, with the most common reason being increased pain during placebo cycles [24]. Design strategies adopted to mitigate attrition in this study include: explicit instructions and labels [53]; rescue analgesia [24]; regular follow-up telephone calls [54]; and the absence of a placebo treatment arm [24].

In addition to evaluating the viability of N-of-1 trials in this clinical scenario, this trial will also contribute to the pool of comparative data on pregabalin and gabapentin in neuropathic pain. This data may be valuable in meta-analyses, as well as for power and sample size estimates for future studies.

One limitation of this study design is the inclusion of patients with a diverse range of aetiologies. Various types of neuropathic pain may respond differentially to pharmacological treatment [10]. Other studies have avoided this constraint by targeting specific classes of neuropathic pain: for example, diabetic neuropathy [29] or trigeminal neuralgia [48]. Nonetheless, as N-of-1 trials primarily aim to characterise individual treatment responses, inter-patient variability should not greatly impact the efficacy and feasibility of this study.

Trial status

Recruitment for this trial has not yet commenced.

Declaration of competing interest

Guy Bashford has received research and educational grants from Pfizer. Pfizer had no role in the design of this study, and will have no role in data collection, data analysis, and preparation of any resultant manuscript. Jane Nikles has a commercial interest in N-of-1 Hub Pty Ltd consultancy company. Veronica Murdoch, Samuel Tan, and James McGree, have no interests to declare.

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