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N-OF-1 RANDOMIZED TRIALS TO ASSESS THE EFFICACY OF GABAPENTIN FOR CHRONIC NEUROPATHIC PAIN


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ABSTRACT

Objective: To compare the efficacy of gabapentin with placebo for neuropathic pain at the individual and population levels

Design: N-of-1 trial methodology with three double-blind, randomized, cross-over comparisons of gabapentin with placebo.

Setting: Specialist outpatient clinics at two Australian hospitals

Patients: Adults with chronic neuropathic pain.

Interventions: Following a dose finding period, participants underwent three comparisons of two week periods on gabapentin (600 mg to 1800 mg per day) and placebo. The dose-finding period was commenced by 112 patients, of whom 39 had no response so did not enrol, leaving 73 trial participants. Of these, 48 completed and seven partially completed their trials, and 18 withdrew.

Outcomes measures: VAS (0-10) of pain, sleep interference and functional limitation; frequency of adverse events and medication preference. The aggregate response was determined by weighting the response to each measure equally.

Results: Of the 55 participants who completed at least one cycle, the aggregate response to gabapentin was better than placebo in 16 (29%), of whom 15 continued gabapentin post-trial. No difference was shown in 38 (69%) and one (2%) showed a better response to placebo. Fifteen of these 39 continued gabapentin post-trial. Meta-analysis of the participants’ mean scores showed overall mean difference scores (standard deviation) for gabapentin by 0.8 (0.2) for pain, 0.6 (0.2) for sleep interference and 0.6 (0.2) for functional limitation.

Conclusions: The response rate and mean reduction in symptoms with gabapentin were small. Gabapentin prescribing post-trial was significantly influenced by the trial results.
Keywords: randomized controlled trials, cross-over trials, gabapentin, pain, neuralgia.
1. Introduction

Gabapentin is one of many options for the pharmacological treatment of neuropathic pain, a condition characterized by neuronal hyperexcitability in damaged areas of the nervous system. There is level one evidence for the effectiveness of gabapentin in diabetic neuropathy, post-herpetic neuralgia and other neuropathic pain conditions [1,2]. The number needed to treat (NNT) for diabetic neuropathy is 2.9 (CI 2.2-4.3), for post-herpetic neuralgia 3.9 (CI 3.0-5.7), and for chronic neuropathic pain of all types 4.3 (CI 3.5-5.7) [2]. While the results of randomized controlled trials (RCTs) and meta-analyses are useful in defining and predicting the mean clinical response to gabapentin at a population level, they comprise a wide range of responses by individuals, each of which is difficult to predict. Single patient or n-of-1 trials help to better define individual responses to treatment. N-of-1 trials are within-patient randomized, double-blind, cross-over comparisons, comparing a drug with a placebo (or another drug). They provide the most rigorous information available for any individual patient [3,4], and hence the potential to better target medication to responders. The results of series of n-of-1 trials can also be meta-analyzed to give an estimate of response at a population level [5]. In the treatment of neuropathic pain, although there is a case report of an n-of-1 trial of a spinal cord stimulator (6) we have been unable to find any publications describing the use of n-of-1 trials methodology for the use of gabapentin.

We conducted a series of n-of-1 trials comparing gabapentin with placebo in patients with chronic neuropathic pain in the hospital setting to test the efficacy of gabapentin in individuals and subsequently at a population level by meta-analysis of completed trials. We also documented the changes in prescribing of pain medications that occurred with n-of-1 trials, in the expectation that they would foster more appropriate, i.e. selective, use.
2. Methods

2.1 Trial Design

These n-of-1 trials were randomized, double-blind, cross-over comparisons of gabapentin and placebo within individual participants. N-of-1 trials were offered to 2 groups of patients who had shown a clinical response to gabapentin – those who had completed a 2-3 week dose finding period on gabapentin and those who were already on a maintenance dose of gabapentin. Each n-of-1 trial lasted 12 weeks and consisted of three cycles of gabapentin and placebo treatment pairs assigned in random order, with each treatment lasting two weeks. Only measurements taken in the second week were used to allow for wash-out since the effects of gabapentin wear off within two days as it has an elimination half-life of 5-7 hours (Figure 1). The choice of initial therapy was balanced in blocks of three to ensure that equivalent numbers started the study on either gabapentin or placebo. The participants, their doctors and the dispensing pharmacies were all blinded to the identity and order of all treatment periods.

2.2 Participants and ethics approval

Participants came from specialist outpatient pain clinics in two Australian public hospitals, one in Port Kembla and the other in Brisbane. A few patients commenced as inpatients with follow-up as outpatients. Ethics approval was obtained from the relevant respective hospital and university ethics committees.

Participants had to be willing to leave unchanged their usual medications, and their physical treatment and/or use of physical aids (all of which must have been used for the preceding 3 months). Informed consent was obtained from all participants.

2.3 Eligibility criteria

Any adult patient with a clinical diagnosis of chronic neuropathic pain was eligible for inclusion in the study. Neuropathic pain was defined as pain initiated or caused by a primary lesion or dysfunction in the
nervous system [7]. Specific conditions included phantom limb pain, post-stroke pain, post-herpetic neuralgia, diabetic neuropathy and complex regional pain syndrome. Pain had to be of at least 3 months duration and of sufficient severity to warrant consideration of long-term gabapentin use. Patients were not admitted to the study if any of the following criteria were present: previous sensitivity to gabapentin, patients with a history of seizure; pregnancy; creatinine clearance <30 mls/min; certain H2 antagonists and pregabalin therapy; and episodic pain, for example, trigeminal neuralgia.

2.4 Medication

The open-label dose finding period was 2-3 weeks. To follow usual clinical practice, patients were titrated to a maximum of 1,800 mg / day (600 mg 3 times daily), depending on response and adverse effects. This maximum dose was determined by the previous prescribing patterns for gabapentin at the respective hospitals. If there was no reduction in symptoms during the dose-finding period, the patient was not offered a trial. Patients who were already on gabapentin did not require a dose-finding period and were continued on their current doses. In the gabapentin periods of the n-of-1 trial, the gabapentin was commenced at 300 mg twice daily on day 1, and increased by 300mg per day until the dose established in the dose-finding period was reached, either 600mg, 900mg, 1200mg or 1800mg per day.

The placebo capsules, manufactured by Arrow Pharmaceuticals, were identical to the corresponding active medication. Twelve weeks medication kits of gabapentin and placebo capsules for each participant were prepared by a community pharmacy in four-week lots, with two weeks of gabapentin and two weeks of placebo, the order allocated by a computer generated randomization schedule generated by the University of Queensland n-of-1 trials service. Each 12 week kit was numbered and sent to the hospital pharmacies for dispensing in order of application by enrolling participants. After the n-of-1 trial, the participant was provided with gabapentin for two weeks while awaiting their results.
Many participants were also on stable doses of paracetamol, tricyclic antidepressants, non-steroidal anti-inflammatory drugs or opioids. Breakthrough/escape medication most commonly involved the addition of oral opioids. If debilitating pain was not controlled during a particular two-week period, this could be truncated and the next two-week treatment period commenced.

2.5 Data collection and analysis

Descriptive information collected on each participant at entry included age, sex, duration and severity of chronic pain, degree of sleep interference, previous therapy, type of neuropathic pain, areas affected, and concomitant pain therapy. Throughout the trial cycles, the primary outcome was pain and secondary outcomes were sleep interference, functional limitation, adverse events and medication preference. Specifically these were recorded by participants in diaries as:

- a daily estimation of pain in the marker area on a visual analog scale marked 0 to 10 (adapted from Daut et al [8] and Bellamy et al[9]) as the primary outcome measure.
- a daily estimation of sleep interference on a visual analog scales marked 0 to 10.
- a fortnightly Patient Specific Function Scale adapted from Stratford et al [10]. Participants rated, on a 0 to 10 visual analogue scale, the degree to which up to five of their activities of daily living were limited by pain.
- a fortnightly check-list of symptoms that could be adverse events, along with severity ratings.
- a fortnightly global assessment of their medication preference comparing the their medication from the preceding fortnight with that from the fortnight before this.

Participants also recorded daily their use of analgesics or therapies other than the trial medications. Unused pill counts were used to monitored compliance.
After 12 weeks all questionnaires were sent to the University of Queensland n-of-1 trial centre for analysis. We averaged daily pain and sleep interference scores over the second week of each treatment period, discarding data from the first week to avoid carry-over effects. Using method advocated by Zucker and colleagues [5] we calculated mean (SD) differences in pain, sleep interference and functional limitation scores between treatments for each of the three cycles and from these calculated the overall mean difference for the three cycles using hierarchical Bayesian random effects models. Like Zucker and colleagues [5], we assumed that the mean differences are normally distributed, and used their standard non-informative prior and hyperprior distributions. Calculations using Markov chain Monte Carlo simulations were undertaken in WinBUGS version 1.4.1 (http://www.mrc-bsu.cam.ac.uk/bugs). Simulations of size N=10,000 were run after a burn in-period of 5,000 iterations and convergence in the final samples was checked using visual plots of simulation histories.

The Bayesian method employed allows for individual assessment and group meta-analysis. The group meta-analysis could include data from all completed cycles, including from participants who completed less than three cycles. Assuming a minimum detectable difference of 1.0 for pain scores [11] and sleep interference scores [12], we defined a definite response as an adjusted mean absolute difference ≥1.0 less than the comparator, a probable response as a difference of ≥0.5 but <1.0 less than the comparator, and all other responses as no difference. Assuming a minimum detectable difference in functional limitation scores of 2.0 [13], we defined a definite response as an adjusted mean absolute difference ≥2.0 less than the comparator, a probable response as a difference of ≤1.0 but <2.0 and all other responses as no difference. As in Yelland et al [14], we defined fewer adverse events or a preference for one medication as a definite response if they occurred in all 3 cycles, a probable response if they occurred in 2 cycles and no response if they occurred in 0 or 1 cycles.
Our summary measure was an aggregate response score composed from an equally weighted combination of the five measures, each scored from -2 for a definite response to placebo to +2 for a definite response to gabapentin. This gave an aggregate score between -10 to 10. The absolute value of this score defined the response status with $\geq 6$ was considered a ‘definite response’, $\geq 3$ but $< 6$ a ‘probable response’, and $< 3$ was a ‘non-response’.

A report was then sent to the referring doctor. After looking at the symptoms recorded, the doctor and participant decided together whether gabapentin was of greater benefit than placebo. After the n-of-1 trial, participants were interviewed by telephone about subsequent management decisions.

3. Results

3.1 Recruitment and retention

Recruitment commenced in April 2004 and concluded in January 2006 due to reporting deadlines and funding constraints. One hundred and twelve patients commenced the dose-finding period; thirty-nine did not enrol in the trial due to a perceived lack of response to gabapentin (17), adverse events (12) or other reasons (10) (Figure 1). Seventy-three participants commenced n-of-1 trials. Fifty-five participants (75%) completed at least one cycle allowing a partial analysis. Forty-eight participants (65%) completed three cycles. Two of these were participants who repeated their trials after disputing the negative results of their first trial. In both second trials they showed a definite response to gabapentin and this response was used as their definitive result.
Twenty-five participants (35%) withdrew during the trial period; reasons included: excessive pain (8), side effects (6), unknown (6), inconvenience of trial (2), pain during placebo periods (2) and upcoming surgery (1).

### 3.2 Treatment effects

The demographic and clinical characteristics of participants commencing trials appear in Table 1. Mean difference and standard deviation for pain, sleep interference and functional limitation scores between gabapentin and placebo over each cycle are given in Table 2. Scores associated with gabapentin were lower than scores associated with placebo over all pain, sleep interference and functional limitation measurements for each cycle, and mean differences ranged from 0.37-0.98. Amongst the 55 participants who completed at least one cycle, the aggregate response of the five outcomes showed a definite response to gabapentin in 8 (15%), and a probable response in 8 (15%), giving a total of 16 positive responders (29%) (Table 3). There was no response to gabapentin in 38 (69%) and a probable response to placebo in one (2%). The response rate for participants on 1800 mg per day was significantly higher than for those taking less than 1800 mg per day (48% vs 19%, $\chi^2=5.3$, df=1, p=0.02). Response rates for individual outcomes of pain, sleep interference and adverse events resembled the aggregate response rates closely but differed somewhat for functional limitation where there were no definite responders and for medication preference where there were 11 definite responders.

Hierarchical Bayesian meta-analysis of the mean scores of participants completing at least one cycle showed lower overall mean difference scores (standard deviation) for gabapentin by 0.8 (0.2) for pain, 0.6 (0.2) for sleep interference and 0.6 (0.2) for functional limitation.
There were many changes in pain medications from before to after the trial. Of the 55 participants completing trials, 27 (49%) were prescribed gabapentin after their trial. Of the 15 taking gabapentin before their trial, eight (53%) continued gabapentin afterwards. Of the 40 not taking gabapentin before their trial, 23 (58%) were prescribed gabapentin afterwards.

The prescribing decisions about gabapentin immediately after the trial were consistent with the trial result in 33 (60%), inconsistent in 17 (31%) and unknown in five (9%). Gabapentin was continued in 15 (94%) of the 16 responders in comparison with 15 (38%) of the 39 non-responders ($\chi^2=14.0$, df=1, p<0.001).

4. Discussion

In the present study, we used an n-of-1 trial to identify responders and target prescribing. In this cohort, only 29% of participants showed a positive response to gabapentin. Although the n-of-1 trial design does not allow a calculation of the ‘number needed to treat’, it is possible to calculate the ‘number needed to trial’ to find one positive responder as four. This number is surprisingly high given that the use of a dose-finding period for new patients and the inclusion of patients already taking gabapentin may have increased the response rate by excluding many patients with adverse events or no subjective response. In contrast, the ceiling dose of 1800 mg, compared with 3600 mg in other studies, may have reduced response rates, as there is evidence from this and another study of reduced effectiveness in trials using lower dosages [1].

The ability to generalize the results of this series of trials to the broader population of patients with neuropathic pain is limited by participant selection methods, the limited ceiling dose and the withdrawal rate. The population included patients with a clinical diagnosis of chronic neuropathic pain from a variety of causes.
For pain and sleep interference scores, the observed mean differences for each cycle were similar to the mean adjusted differences in the meta-analysis of all cycles, but were considerably less than those reported in other randomized controlled trials of gabapentin [15,16]. This is likely due to issues of external validity or generalizability, with n-of-1 patients more likely to arise from a more diverse population pool (e.g. more likely to have multiple co-morbidities) than those eligible for the RCTs.

The withdrawal rate of 35% was high, but this is fairly typical of n-of-1 trials [3,17,18] and indeed typical of many conventional randomized controlled trials [19]. The shift in response status from negative to positive in the two participants who repeated trials suggests either problems with the reproducibility of the method or the possibility of unblinding by the participants determined to show a positive result to support continuation of their gabapentin.

Neuropathic pain is among the most severe and difficult to manage of all chronic pains. Management involves a multifaceted approach including the use of various medicines, physiotherapy and behavioural modification. These were left unchanged in the present study, with only gabapentin or placebo as the introduced variables. This approach improves the generalizability of our results to clinical practice compared with neuropathic pain RCTs in which the experimental agent is used as monotherapy.

Although gabapentin has become established as a treatment for neuropathic pain, it is a relatively expensive medication. It cannot be generally subsidized in Australia for neuropathic pain without data from comparative head-to-head studies to show better value than cheaper alternatives. In the Australian health system it is only subsdized for pain in hospital-based outpatient clinics and not in general practice, resulting in much of the cost burden for gabapentin falling on the hospital sector. To target
long-term prescribing for a chronic condition such as neuropathic pain, this n-of-1 study provided high-level evidence to inform decisions about prescribing in the hospital sector. Almost every responder to gabapentin was continued on this medication following their trial. However 38% of non-responders were continued on gabapentin, suggesting that there were other factors influencing decisions to prescribe gabapentin. Some of these may have been the different weightings doctors and participants placed on each outcome compared with the aggregate response which was based on an equal weighting of five outcomes. Further qualitative investigation is required to understand the factors influencing prescribing for chronic neuropathic pain.
Contributors

Michael Yelland took overall responsibility for the study design and conduct, contributed to data analysis and preparation of the paper.

Chris Poulos, Peter Pillans, Guy Bashford and Jo Sturtevant contributed to the study design and conduct, contributed to data analysis and preparation of the paper.

Jane Nikles and Chris Del Mar obtained the original grant, contributed to the study design and conduct, contributed to data analysis and preparation of the paper.

Norma Vine coordinated the study, contributed to data collection and data analysis and had input into the paper.

Phillip Schluter provided statistical advice, set up the Bayesian analysis and had input into writing the paper.

Robyn Brown contributed to the study design, and data collection and analysis.

Meng Tan, Jonathan Chan and Fraser Mackenzie contributed to the study conduct and data collection analysis.

GUARANTOR: Michael Yelland
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References


Tables and Figures

Table 1. Demographic and clinical characteristics of completers/partial-completers and total commencers of the gabapentin n-of-1 trials.

Table 2. Mean difference and standard deviation (SD) for pain, sleep interference and functional limitations between gabapentin and placebo over each cycle (n=55). A positive mean difference signifies a lower (more favourable) score for gabapentin than for placebo whereas a negative mean difference signifies a lower (more favourable) score for placebo than for gabapentin.

Table 3. Response status in participants completing at least one cycle for each of the five outcomes and the aggregate response weighting all available outcomes equally (n=55).

Figure 1. Flowchart of participants in n-of-1 trials of gabapentin versus placebo.
Table 1: Demographic and clinical characteristics of completers/partial-completers and total commencers of the gabapentin n-of-1 trials.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Completers/partial completers (n = 55)</th>
<th>Non-completers (n = 18)</th>
<th>Total (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years - mean (min, max)</td>
<td>57.8 (24, 94)</td>
<td>56.9 (31, 88)</td>
<td>57.6 (24, 94)</td>
</tr>
<tr>
<td>Duration of pain (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>4 (7%)</td>
<td>5 (28%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>2-5</td>
<td>28 (51%)</td>
<td>6 (33%)</td>
<td>34 (47%)</td>
</tr>
<tr>
<td>6-10</td>
<td>8 (15%)</td>
<td>1 (6%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>11 (20%)</td>
<td>3 (17%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (7%)</td>
<td>3 (17%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (33%)</td>
<td>12 (66%)</td>
<td>30 (41%)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (67%)</td>
<td>6 (34%)</td>
<td>43 (59%)</td>
</tr>
<tr>
<td>Pre-trial main regular medication</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>9 (16%)</td>
<td>2 (11%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4 (7%)</td>
<td>2 (11%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Opioids</td>
<td>10 (18%)</td>
<td>4 (22%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>5 (9%)</td>
<td>1 (6%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>6 (11%)</td>
<td>5 (28%)</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>Paracetamol plus codeine</td>
<td>8 (15%)</td>
<td>1 (6%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Other /unknown</td>
<td>2 (4%)</td>
<td>3 (17%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>No drug</td>
<td>7 (13%)</td>
<td>0 (0%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Daily gabapentin dose during trial (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>6 (10%)</td>
<td>1 (6%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>900</td>
<td>13 (24%)</td>
<td>7 (39%)</td>
<td>20 (27%)</td>
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<tr>
<td>1200</td>
<td>12 (22%)</td>
<td>4 (22%)</td>
<td>16 (22%)</td>
</tr>
<tr>
<td>1800</td>
<td>23 (42%)</td>
<td>6 (33%)</td>
<td>29 (40%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
Table 2. Mean difference and standard deviation (SD) for pain, sleep interference and functional limitation scores between gabapentin and placebo over each cycle (n=55). A positive mean difference signifies a lower (more favourable) score for gabapentin than for placebo whereas a negative mean difference signifies a lower (more favourable) score for placebo than for gabapentin.

<table>
<thead>
<tr>
<th>Scores</th>
<th>Cycle 1 mean diff. (SD)</th>
<th>Cycle 2 mean diff. (SD)</th>
<th>Cycle 3 mean diff. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0.61 (1.83)</td>
<td>0.60 (2.31)</td>
<td>0.84 (2.36)</td>
</tr>
<tr>
<td>Sleep interference</td>
<td>0.54 (1.70)</td>
<td>0.53 (2.07)</td>
<td>0.37 (2.43)</td>
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<tr>
<td>Functional limitation</td>
<td>0.64 (2.55)</td>
<td>0.41 (2.13)</td>
<td>0.98 (2.39)</td>
</tr>
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</table>
Table 3. Response status in participants completing at least one cycle for each of the five outcomes and the aggregate response weighting all available outcomes equally (n =55).

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin</th>
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<th>Placebo</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Definitely</td>
<td>Probably</td>
<td>No</td>
<td>Definitely</td>
</tr>
<tr>
<td>Pain scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely better</td>
<td>10</td>
<td>10</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Probably better</td>
<td>10</td>
<td>8</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>No difference</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Functional limitation scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely better</td>
<td>11</td>
<td>5</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Probably better</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregate response</td>
<td>8</td>
<td>8</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6</td>
<td>7</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Preferred medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregate response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Flowchart of participants in n-of-1 trials of gabapentin versus placebo

Patients with chronic neuropathic pain entering dose-finding period (n=112)

Enrolments in n-of-1 trial (n=73)

Completed 3 cycles (n=48)

Completed 1 or 2 cycles (n=7)

Insufficient data for analysis (n=18)

Non-enrolment (n=39)
  Lack of response (n=17)
  Adverse events (n=12)
  Other reasons (n=10)

Withdrawals (n=25)
  Excessive pain (n=8)
  Adverse events (n=6)
  Pain in placebo periods (n=2)
  Trial inconvenient (n=2)
  Surgery imminent (n=1)

Results to doctor and participant (n=55)