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A randomized controlled trial of gabapentin for chronic low back pain with and without a radiating component

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Abstract

Gabapentin is prescribed for analgesia in chronic low back pain, yet there are no controlled trials supporting this practice. This randomized, two-arm, 12-week, parallel group study compared gabapentin (forced titration up to 3600 mg daily) to inert placebo. The primary efficacy measure was change in pain intensity from baseline to the last week on treatment measured by the Descriptor Differential Scale; the secondary outcome was disability (Oswestry Disability Index). The intention-to-treat analysis comprised 108 randomized chronic back pain patients (daily pain for ≥ 6 months) whose pain did (43%) or did not radiate into the lower extremity. Random effects regression models which did not impute missing scores were used to analyze outcome data. Pain intensity decreased significantly over time ($p < .0001$) with subjects on gabapentin or placebo reporting reductions of about 30% from baseline, but did not differ significantly between groups ($p = .423$). The same results pertained for disability scores. In responder analyses of those who completed 12 weeks (N=72), the proportion reporting at least 30% or 50% reduction in pain

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intensity, or at least “Minimal Improvement” on the Physician Clinical Global Impression of Change did not differ significantly between groups. There were no significant differences in analgesia between participants with radiating (n = 46) and non-radiating (n = 62) pain either within or between treatment arms. There was no significant correlation between gabapentin plasma concentration and pain intensity. Gabapentin appears to be ineffective for analgesia in chronic low back pain with or without a radiating component.

1. Introduction

Chronic low back pain is a prevalent, disabling condition for which there are few effective interventions [6,10]. Antidepressants, non-steroidal anti-inflammatory agents, and opioids are often employed, but there are questions about their long-term efficacy or safety [6]. Gabapentin has some evidence of efficacy for fibromyalgia, a musculoskeletal pain syndrome [1], and is recommended as a first line treatment for neuropathic pain in many recent clinical practice guidelines, but the number-needed-to-treat is relatively high for these conditions [eg, 12,25,33]. Gabapentin is prescribed frequently for chronic back pain syndromes in both primary care and specialty pain clinics, particularly when there is a ‘radicular’ or neuropathic component with pain radiating into the upper or lower legs [6]. Although case reports, single dose, and open label studies suggest potential benefits [28,42], there are no randomized, placebo-controlled trials supporting its efficacy [29]. This is unfortunate since gabapentin differs structurally from other analgesics, and is thought to differ mechanistically by reducing stimulated release of transmitters by binding at calcium channel alpha$_2$ –delta proteins [38].

We conducted a 12-week, two-arm, randomized, double-blind, placebo-controlled trial to examine the efficacy of gabapentin in patients with chronic low back pain with or without leg pain. We attempted to address some of the methodological limitations of back pain analgesic studies in terms of biases in sampling and duration of the trial, and potential confounding by co-morbid pain and depression [24,40]. We recruited patients from primary care and community settings rather than pain specialty centers to enhance generalizability and guard against a bias toward enrolling treatment ‘failures.’ A 12-week design was used to guard against a trend toward analgesic efficacy associated with brief trials, and because this is the minimum to claim an indication for a chronic pain condition with most regulatory agencies [23]. Patients with mood disorders were excluded to limit potential effects of gabapentin on depressed or anxious mood independent of analgesia.

2. Methods

2.1. Protocol

The research protocol was approved by the Human Research Protections Programs of the Department of Veterans Affairs (VA) Healthcare System, San Diego, California, and the University of California, San Diego. Written informed consent was obtained before entry into the study. Participants were compensated for travel expenses, at $5 per study visit or up to $50 for completion of the 12-week trial, but there were no other financial incentives to participate. Individuals were recruited by posting of flyers at VA San Diego and University

of California, San Diego primary care clinics, and by announcements in metropolitan area newspapers. Potential enrollees were told they would be assigned by chance to an inert placebo ('sugar pill') or to a licensed medication customarily used to treat seizures. It was noted that the research was investigating if gabapentin might have pain-relieving properties because of possible effects on nervous system neurotransmitters involved in pain.

Inclusion criteria were: (1) ages 21 to 70; (2) nonspecific low back pain primarily in the lumbar region, present on a daily basis for the previous 6 months or longer, adjectivally described as of at least "mild" intensity (≥ 2 on a "0" to "10" Numeric Rating Scale and having an impact on two or more aspects of everyday life; (3) English-speaking, literate, able to understand the study and communicate with the study team; (4) presently not a candidate for back surgery (one prior back surgery permitted if it was > 5 years ago); (5) agreement to discontinue muscle relaxants, antidepressants, and opioids at least two weeks before eligibility assessment and throughout the study (NSAIDs were permitted); and (6) if female, not pregnant or lactating, and has a negative pregnancy test at screening.

Exclusions were: (1) A major coexisting medical illness (e.g., renal or hepatic disease, chronic obstructive pulmonary disease, cancer, or class III or IV organic heart disease) that might increase risks of gabapentin, or major surgical or non-surgical intervention for any disorder within the past 12 months, since rehabilitation from treatment may confound study outcomes; (2) significant coexisting orthopedic or pain problems or back pain due to other disorders (e.g., fibromyalgia, vertebral fracture, osteomyelitis, metastatic cancer, rheumatoid arthritis; spinal stenosis); (3) meeting DSM-IV criteria for alcohol or other substance use disorder (within the previous 12 months or with positive urine toxicology at eligibility assessment); or current major depression or dysthymia; or lifetime diagnosis of bipolar disorder, psychosis or cognitive impairment disorder (e.g. dementia); (4) history of multiple adverse drug reactions or known allergy to gabapentin; (5) use of psychotropics (e.g., antidepressants, anxiolytics), which would need to be continued during the study, or other drugs or agents (i.e., herbal preparations) which might interact with the study drug; (6) prior treatment with the study drug; (7) use of systemic corticosteroids or corticosteroid injections within 3 months of screening; or concurrent behavioral therapies, chiropractic treatment, or transcutaneous electrical nerve stimulation unit; (8) renal impairment (creatinine > 1.8mg/dL); (9) hepatic impairment (bilirubin > 1.5 × upper normal limit, or AST or ALT > 2 × upper normal limit); (10) hematologic abnormality (hemoglobin < 9.4 gm/dL; absolute WBC count < 3000/mm^3, platelets < 100,000; (11) pregnancy; (12) use of experimental drugs or participation in other clinical trials within 2 months of screening for eligibility. There was no revision of inclusion or exclusion criteria or other methods during the study.

After an individual was enrolled and randomized, research visits occurred weekly for Weeks 1–5, then at Weeks 7, 9, and 12. Visits consisted of monitoring of vital signs, completion of standardized questionnaires on pain, mood, function, and life quality, and an interview by the study physician to assess for adverse effects, adherence, and a clinical rating of change in overall impact of back pain.

2.2 Intervention

Treatment with study drug or inert placebo commenced generally within 48 hours of baseline assessment. Consistent with most trials of gabapentin in chronic pain we used a forced titration design to achieve a target daily dose (3600 mg) or maximum tolerable dose, based on the argument that maximum dosing improves likelihood of therapeutic effect [3,30]. Participants received 300mg QD on Day 1, 300mg BID on Day 2, and 300mg TID on Days 3 through 7. In Week 2 gabapentin was escalated in 300mg increments to a target dose of 600 mg TID. In Week 3 the target was 800mg TID, and in Week 4 and thereafter the aim was to achieve 1200mg TID. Dose titration was controlled by the research pharmacist, taking into account safety and tolerability assessments by the blinded study physician. If an adverse effect was reported, and was not intolerable, the daily dose was decreased to one at which the participants had experienced no adverse effects. The mean daily dose of gabapentin at the end of Week 5 was 3,265mg (N = 43). Study drug and inert placebo were packaged in identical-appearing gelatin capsules. Placebo was directed to be taken on a schedule consistent with that of the study drug.

2.3 Measures

We followed recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials in chronic pain [IMMPACT, 39] by measuring pain intensity, mood, and everyday function as outcomes. These assessments were obtained by blinded research personnel in a testing session separate from the session with the blinded study physician. The primary outcome measure was pain intensity as determined by the Descriptor Differential Scale [17]. This measure was chosen over other (eg, numeric) rating scales because it is thought to have superior psychometric properties [17], and because of concerns that patients may apply idiosyncratic meanings to numeric rating scales [9]. The Descriptor Differential Scale (DDS) [17] contains 24 words that describe the intensity and unpleasantness of pain. Individuals rate their pain relative to these descriptors. Ratings are aggregated to provide a 0 to 20 point rating separately for pain magnitude and unpleasantness. The DDS demonstrates good internal consistency, reliability, objective correlation with experimentally induced pain, and sensitivity to detect analgesic intervention in clinical pain [11]. DDS verbal descriptors of pain intensity correspond to pain magnitude ratings over a wide range (e.g., DDS intensity 6–7 = very weak pain; 8 = mild pain; 9 = moderate pain; 10–11 = slightly intense pain; 12–13 = strong pain; ≥ 14 = intense to extreme pain) [11]. We also employed several supplemental measures of outcome. At baseline and 12-week exit patients were asked to rate pain intensity on a standard Numeric Rating Scale (0= “no pain,” 10 = “worst pain imaginable”). At exit patients were also asked to describe their pain as “improved,” “the same,” or “worse” and to rate the percentage of change from baseline. Another supplemental outcome was the physician-rated Clinical Global Impression, which asks the blinded study physician to rate clinical change since baseline on a 7-point scale (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). The physician rated overall change combining pain intensity and function [18].

The main secondary outcome of everyday functioning was assessed using the Oswestry Disability Index (ODI, Version 2.0) [14]. The Oswestry surveys 10 areas of daily life (ie, use

of analgesics, personal hygiene, lifting, walking, sitting, standing, sleeping, social life, traveling, and sex), with responses describing levels of performance on a 1 to 6 scale, where 1 = no interference due to pain, while 6 = complete interference. Scores range from 0 (best state of health) to 100 (worst). It is sensitive to change in mild-to-moderately affected samples [8].

Mood was assessed at baseline and exit, using the Beck Depression Inventory II (BDI-II) [4]. This is a standard index of self-reported mood. It consists of 21 sets of questions, each having four or five graded statements ordered to show increasing depression symptoms; total scores range from 0 to 63. Scores below 10 are considered to reflect minimal depression symptoms. The items of the Beck are clinically derived and have undergone extensive reliability and validation studies [4]. BDI II scores were used it to characterize the sample and clarify interpretation of results (e.g., relating analgesia and mood).

The assessment for qualification at study entry included review of medical records, a routine blood count and tests of hepatic, renal and thyroid function, urine toxicology for opioids and drugs of abuse, and a standardized orthopedic evaluation [41]. Orthopedic diagnoses were rendered by the study physician in consultation with the research orthopedic surgeon, by using all available information, including history, directed physical examination relevant to spine disease, and laboratory data, which usually included review of plain radiographs or magnetic resonance imaging. Because of the acknowledged limitations of an anatomic diagnosis in most chronic back pain, we primarily used a regional descriptive approach according to the Quebec Nomenclature on Activity-Related Spine Disorders [37]. Using this system back pain was described as: I = Pain without radiation; II = Pain with proximal (above knee) radiation; III = Pain with distal (below knee) radiation. Subjects with other Quebec Classifications (ie, IV = Pain and radiation above or below knee with neurologic signs; V = Presumptive compression of a spinal nerve root) were excluded based on their low frequency (< 5%) in primary care back pain. To examine if response differed according to pain location [24], patients were asked to estimate what proportion of pain could be attributed to each site (eg, 80% back, 20% leg). At each research visit a standardized questionnaire was used to record non-protocol medical or other treatments for back pain.

The study physician used the Structured Clinical Interview for DSM-IV [36] to examine for excluded psychiatric conditions (e.g., bipolar disorder, and major depression or a substance use disorder within the previous 12 months). To monitor for threats to internal validity and confounding by prescription or illicit drugs we obtained urine toxicology by dip stick (for ethanol, amphetamines, methylphenidate, barbiturates, benzodiazepines, cocaine and benzoylecgonine, methaqualone, phencyclidine, cannabis, opioids, and methadone) at baseline and at Weeks 3, 7, and 12 (LifeSign LLC, Skillman, New Jersey, USA).

Concentrations of gabapentin were determined from samples obtained at the Week 5 and 12 visits. Gabapentin in plasma was assayed by liquid chromatography-mass spectrometry. The dynamic range of the assay was 0.1–500ng/mL, and precision and accuracy within the dynamic range were ≤7.4% and ≤±3.2%, respectively. To maintain blinding all participants underwent venepuncture.

Because adverse effects are often not mentioned if left to spontaneous self-report, we employed the UKU Side Effect Rating Scale (Udvalg for Kliniske Undersoegelser: Committee for Clinical Investigations) a manualized, structured interview, administered by the study physician, which systematically inquires about 48 potential psychological, neurological, autonomic, sexual, dermatological and other symptoms [20]. The UKU records the presence and severity of the symptom (0 = none or doubtful; 1 = mild; 2 = moderate; 3 = severe) and the likelihood of causal relationship to the psychotropic medication (0 = improbable; 1 = possible; 2 = probable).

2.4 Statistical Analysis

Study data were electronically entered into a database and analyses were performed using the Statistical Package for the Social Sciences program (SPSS-PC, Windows V10.0) and the R statistical software (The R Foundation for Statistical Computing, Version 2.15.1, 2012, Vienna, Austria). Descriptive analyses and group comparisons examined the baseline demographic and clinical characteristics of the gabapentin and placebo intervention groups. Two-sample Welch t-tests or Wilcoxon rank-sum tests were used to compare placebo and gabapentin groups on continuous and ordinal variables. Fisher's exact test was used to compare the two groups on gender and treatment emergent adverse effects. Since we specifically did not want to obscure any initial or side effect-based differences between the two groups, the critical alpha level was set at 0.05 for statistical significance, without an adjustment for multiple comparisons. All comparisons were two-tailed. The primary hypothesis was evaluated by an intent-to-treat analysis including all randomized participants who received one dose of study drug. For the primary analysis of analgesia a mean-matching variance-stabilizing transformation was applied to the DDS pain scores since these data were not normally distributed. DDS scores are a sum of answers to "more than or less than" type questions about pain intensity, and have a range from 0 to 20. The distribution for this type of variable is quasi-Binomial rather than Gaussian. The mean-matching variance-stabilizing transformation we applied is an order-preserving symmetrizing transformation for count data such as this, which allows use of a linear regression model rather than a more complicated Poisson regression model to address the primary question [5]. Transformed pain intensity scores were modeled as a function of time (week) and group (gabapentin treatment vs. placebo). Random (subject-specific) intercept and slopes were fitted to the data. Both weeks prior to the treatment/placebo administration (screening and week 1) were treated as time 0. The statement of the main model is as follows: $Z_{ij} = \alpha_i + \beta_i (t_j - 1) I [t_j > 1] + \gamma I [\text{Group} = \text{Treatment}] + \epsilon_{ij}$ where Z_{ij} is the transformed pain core for subject "i" at time "j". The main variable of interest in this regression analysis is the Treatment/Placebo group indicator. As a secondary analysis, the addition of several covariates to the model above was evaluated as well. Covariates included age, gender, days per week of back pain and proportion (i.e. %) of pain due to back (rather than leg). Covariates were modeled as fixed effects in additional mixed effects regression models. Because we used random effects regression models to analyze the DDS data we did not impute missing scores. In follow-up analyses we employed the same approach using DDS pain "unpleasantness" scores as the outcome.

The analysis of the secondary outcome used the same approach with Oswestry scores (untransformed) as the outcome. Additionally, we conducted exploratory analyses. It has

been recommended that chronic back pain randomized trials report “responder” analyses, based on participants who complete an efficacy phase and meet a “response” criterion, to gauge if treatment provides a “useful” level of pain relief with tolerable adverse effects [23]. In one responder analysis we used a chi-square test of proportions to compare the treatment groups on the simple percentages of patients attaining ≥30% and ≥50% decrease in DDS pain intensity. In another analysis we compared proportions of patients who rated themselves as “improved” by ≥ 30% and ≥ 50% in terms of reduced pain intensity (≥ 30% was N = 23 assigned gabapentin and 21 placebo; ≥ 50% was N = 16 assigned gabapentin and 13 assigned placebo). These cut-points were based on reports suggesting that they reflect patients’ perception of change of moderate to substantial clinical importance [13,15].. The same approach was used to assess the Physician’s Global Impression of Change, examining the proportion of completers who were rated as having at least “minimal” benefit (score ≥ 1). In a separate supplemental analysis of patients completing the study we used t-tests to compare baseline and exit Numeric Pain Rating (0–10) scores of pain intensity between groups.

Mood measured by the Beck Depression Inventory-II was compared between gabapentin and placebo groups at the start and end of the study. A mixed effects model, similar to the one used for the primary analysis was used to model the total score as a function of group and time.

We conducted a power analysis for the study based on moderate effect sizes (0.5 SD to 0.7SD) noted in prior reports comparing placebo and cyclic antidepressants as analgesics in back pain, and data that 4.4 DDS pain units is equal to 1 standard deviation [2]. We hypothesized that gabapentin would be superior to placebo (mean 1 > mean 2). With α =0.05 and sizes of 53 and 55 per group, standard power analyses [7] indicated power of 80% or greater to detect a difference across groups if the standardized effect size is comparable to our prior studies (0.55 SD). Moreover the power was 64% for population differences =0.45 SD. This corresponds to a decrease in DDS verbal descriptors from “moderate” to “mild” pain or “strong” to “moderate” pain [11]. This corresponds to a > 30% reduction in pain intensity, and would be clinically meaningful [15]. A similar approach was used to address effects on improving daily function as measured by the Oswestry. In our prior work nortriptyline improved function 0.5 SD compared to placebo. Using the same assumptions as above, standard power analyses (α = 0.05, N = 108) indicated power > 80% for the ANOVA to detect an overall difference.

2.5 Assignment

The VA San Diego Healthcare System Research Pharmacy conducted a one-to-one allocation to gabapentin or placebo using a stratified block computer-generated randomization scheme. To ensure equivalence between groups on presence of a radiating component of back pain the allocation system stratified for presence or absence of pain radiating into the leg (above or below the knee).

2.6 Masking

Gabapentin and placebo were prepared in identical-appearing gelatin capsules. They were directed to be taken on the same schedule of dose escalation during the titration and maintenance phases of the trial. The code for participant assignment was held by the research pharmacy until completion of data analysis. Participants and the blinded study physician were asked to guess treatment (gabapentin or placebo) after the first week on treatment and at the Week 12 exit visit [27]. The overall proportion of correct guesses by patients who received at least one week of treatment (N = 98 with data) was 51% (p = 0.920). Guessing by the physician was not significantly different from chance for the placebo group (45%, p = 0.575), but was significantly better than chance for the treatment group (78%, p < 0.0001) and because of the treatment group was significantly better overall (62%, p = 0.018). Since more informed guesses might result from study completers we also analyzed data on 72 individuals who completed the study (38 were assigned to gabapentin and 34 were assigned to placebo). Of individuals assigned gabapentin 22 of 38 guessed they were on the active study drug, and for those assigned placebo 16 of 34 guessed placebo treatment (53% overall proportion guessing correctly, chi square, p = 0.724). This suggests that participant masking was successful. Data on physician guesses for completers were obtained for all 38 individuals assigned to gabapentin and 33 of 34 persons assigned to placebo. Of 38 individuals assigned gabapentin the physician correctly guessed that 29 were on the active study drug, and of those assigned placebo 14 of 33 were guessed to be on the active study drug (61% overall proportion of correct guesses, chi square, p = 0. 097). Again the proportion of correct guesses for assignment to placebo was not significantly different from chance (p = 0.486), but physician guesses for active treatment were significant (p = . 002). This suggests that masking of physicians was only partly successful.

At the exit visit the blinded study physician presented the participant with a sealed envelope which was to be opened after leaving the research site. This envelope, prepared by the research pharmacist, contained a 2 week's supply of capsules labeled with treatment assignment (gabapentin or placebo). An enclosed letter provided instructions on how to continue on active study drug if desired, or to discontinue gabapentin by tapering over 2 weeks. The letter also mentioned that patients could request a trial of gabapentin from their personal physician if the assignment were to placebo. This procedure was explained verbally beforehand by the study physician.

3. Results

3.1 Participant flow and follow-up

Figure 1 depicts the progress of volunteers through the trial. During the period of funding and performance of the study (January 1, 2004 to December 31, 2009) we conducted telephone screening of individuals who responded to announcements of the study. From these inquiries 310 individuals were identified as potentially eligible; of these 119 declined an invitation to be further interviewed and 191 possibly eligible individuals were evaluated in person. Of these 83 (43.5%) either declined participation or were disqualified for meeting one or more exclusion criteria. A total of 108 individuals were randomized (56.5% of those

evaluated in person): 55 were assigned to gabapentin and 53 to placebo; of those randomized 72 (71.3%) completed all 12 weeks on study.

Demographic and clinical characteristics of the randomized participants are presented in Table 1. There were no statistically significant differences between gabapentin and placebo groups in background demographics or clinical characteristics. There also were no statistically significant differences between those who were and were not randomized (N of 108 and 83, respectively) after assessment of eligibility in terms of age, education, gender, height, weight, duration or intensity of back pain, or of disability in everyday function.

In general the sample consisted of white, married men (about 10% were African-American, 9% Hispanic, 6% Asian, and 5% Other) in their mid-50s who were at least high school educated (about 2% reported less than a high school education, 54% high school or some college, 18% a college degree, 26% some post-college education). Back pain was of very longstanding duration and was present on an almost daily basis (an average of 6.7 [±.37] days per week). Mean DDS pain intensity scores indicated pain of “moderate” intensity, and ODI scores reflected mild to moderate adverse impact of back pain on everyday function. In terms of regional Quebec Classification, 54% (n = 58) reported back pain only (Classification I), 24% (n = 26) had back and lower extremity pain above the knee (Classification II), and 22% (n = 24) had back and lower extremity pain below the knee (Classification III). Mean (SD) pain intensity did not differ meaningfully across these classifications: Classification I = 8.98 (3.62); Classification II = 10.23 (4.86); Classification III = 9.38 (5.43) (Kruskal-Wallis p-value = 0.3684). As might be expected in sample with non-specific chronic low back pain few (n = 5; 5%) had a prior back surgery. At baseline a majority of individuals (n = 66; 61%) were taking NSAIDs for analgesia. As part of the enrollment process, any participants prescribed opioid analgesics were asked to discontinue these agents at least two weeks before baseline and to refrain from opioids during the study. No participant was taking muscle relaxants. About a third of participants (n = 34; 31%) were involved in some form of self-care for pain (e.g., exercise, meditation, heat/ice). There were no significant differences at entry between treatment arms with respect to current use of NSAIDs or other adjunctive therapies for chronic back pain. None of the urine toxicology samples obtained on study revealed opioids or drugs of abuse.

Of those who withdrew before completing 12 weeks, 19 were assigned to gabapentin and 17 to placebo. The major primary reason for attrition was similar in both groups and most often was for adverse effects or lack of efficacy; a sizeable proportion was lost to follow-up and no reason could be obtained for withdrawal (see Table 2). Baseline demographic and clinical characteristics (eg, pain duration, intensity, presence of radicular pain) of individuals who completed 12 weeks on study did not differ from the entire randomized sample (all P-values non-significant).

3.2 Analyses

The intent-to-treat analysis, consisting of all individuals who were randomized and received one dose of study drug, revealed that pain intensity decreased significantly over time for all participants ($p < .0001$) with subjects on gabapentin or placebo reporting pain reductions of about 30% from baseline. On the primary outcome measure of DDS pain intensity there

were no significant differences between treatment groups (p = .423). Similarly there were no significant differences between groups with regard to change in pain unpleasantness (p = .523). There was no effect of age or gender on these outcomes. Figure 2 illustrates the specific results for pain intensity. The same pattern of significance was observed in an additional mixed model, with Oswestry score as the secondary outcome (eg, p = .804). Only time was a significant factor (there was significant improvement with time). We also conducted an exploratory analysis using only those who completed 12 weeks on study (N=72). In one analysis we used the 0–10 Numeric Rating Scale of pain intensity, as assessed at screening and exit. There were no significant differences in pain intensity scores between gabapentin and placebo groups either at the start or at the end of study (5.8 vs. 5.7, p = 0.759 and 3.5 vs. 4.1, p=0.234, respectively). Scores were significantly lower at exit relative to baseline (p < 0.0001) for both groups, but the reduction was not significantly different between groups (2.2 vs. 1.6, p=0.253). This agrees with the primary result of pain reduction over time overall, but no difference between treatment and placebo groups. The responder analyses limited the sample to study completers. The proportions of patients with either a ≥ 30% or a ≥50% decrease in DDS pain intensity did not differ significantly by group (36% vs 36%, p = 1, and 26% vs. 29%, p = 0.924, respectively). The proportions of patients at exit who estimated their pain had “improved” by ≥ 30% and by ≥50% also did not differ significantly by group (43% vs 38%, p = 0.722, and 23% vs. 20%, p = 0.920, respectively). Likewise the proportion of individuals who were rated by the study physician as having at least “Minimal Improvement” (score ≥ 1) on the Physician Clinical Global Impression of Change did not differ significantly between groups (gabapentin = 14 of 38, 36.8%; placebo = 11 of 33, 33.3%; p=0.95; one participant was missing a rating).

Because the potential for interventions to be effective might vary according to the presence of leg pain [24], participants were grouped according to presence of pain confined to the low back (Quebec I), or pain with a radiating component (Quebec II or III). Reduction in pain intensity was similar between participants with radiating (n = 46) and non-radiating (n = 62) pain both within and between treatment arms (all mixed model analysis p-values not significant).

We assessed for a relationship of gabapentin concentration to pain intensity. Week 5 concentrations of gabapentin were obtained on 39 of 55 individuals assigned study drug, and at Week 12 on 34 of 38 who completed the study. At beginning of Week 5 mean plasma concentrations were 6.8 ± 3.7 (median 6.1), and for study completers the mean Week 12 exit serum concentration of gabapentin was 9.6 ± 7.1 ug/ml (median 8.9 ug/ml). There was no significant correlation between gabapentin plasma concentration and pain intensity at beginning of Week 5 (rho = 0.09, p=0.585) and at exit Week 12 (rho = 0.21, p=0.232).

Mood was measured at baseline and exit. By design none of the participants met criteria for major depression, which is consistent with the low mean scores for the Beck Depression Inventory II (see Table 1) for both groups. There were no significant differences in mood scores between gabapentin and placebo groups either at the start or at the end of study (p = 0.719 and 0.519, respectively), however, scores were significantly lower at exit relative to baseline (p = 0.0007). There was no significant correlation between change in mood and pain intensity.

3.3 Adverse drug effects

Most participants (49 of 55 on gabapentin and 35 of 53 on placebo) experienced treatment emergent adverse effects determined as “possibly” or “probably” attributable to study drug by the UKU physician rating during the trial (see Table 3). Six adverse effects were significantly ($p < .05$) more likely to be experienced by individuals assigned to gabapentin (fatigue, dry mouth, difficulties with mental concentration, memory, or visual accommodation, and loss of balance), but in general the frequency of specific adverse effects was comparable between treatments. No participants reported suicidal ideation.

Most adverse effects were rated as being of “mild” or “moderate” severity. For gabapentin 6 of 55 experienced “no” adverse effects; 19 of 55 experienced “mild” adverse effects; 21 of 55 reported adverse effects of “moderate” intensity, and 9 of 55 experienced at least one “marked” adverse effect. For placebo 18 of 53 reported no adverse effects, 18 experienced at most a “mild” adverse effect, 12 reported at most a “moderate” intensity adverse effect, and 5 noted at least one “marked” adverse effect. A higher proportion of subjects in the gabapentin group experienced at least one adverse event than in the placebo group (89% vs. 66%, Fisher’s exact p=0.008), and a higher proportion of subjects in the gabapentin group experienced at least one moderate to marked adverse event than in the placebo group (55% vs. 32%, Fisher’s exact $p = 0.03$).

4. Discussion

4.1. Main findings

This randomized Phase II clinical trial in chronic non-specific low back pain did not detect analgesic effects for gabapentin compared to placebo. Adverse effects were higher than expected, given that gabapentin is often considered to have a benign side effect profile. Because of evidence that gabapentin is efficacious for neuropathic pain syndromes we also examined whether back pain with a radiating component into the legs was differentially responsive. Again there was no support for gabapentin analgesia. The secondary outcome of disability in everyday function due to back pain also indicated no difference between gabapentin and placebo. Reasons for this lack of effect are not clear, but may be related to the etiopathogenesis of back pain, to characteristics of our back pain sample, to dosing or plasma concentration, or to methodological limitations of the research.

The etiopathogenesis of chronic low back pain syndromes is not clear, and it is likely a heterogeneous phenomenon, with both neuropathic and somatic components. Several large-scale randomized trials suggest gabapentin is analgesic in neuropathic pain states [4,30,32,34], and is associated with improved life quality and functioning [4]. Pregabalin, an analogue of gabapentin with arguably the same mechanism of action, is reported to be analgesic for fibromyalgia, a condition of widespread musculoskeletal or soft tissue pain [25,31]. To the extent that aspects of chronic back pain might reflect either neuropathic [16] or musculoskeletal components, one might have expected an analgesic effect in the present study. An effect of dosing on our negative results is possible. We used forced-titration to maximum tolerable dose, a design that can be criticized for failing to detect possible lower concentration “therapeutic windows” [21]. Nevertheless this forced titration approach is

methodologically consistent with most of the chronic pain literature, and the daily doses of gabapentin (and pregabalin equivalents) employed in successful trials in neuropathic pain and fibromyalgia were in the same range as used in our study. Our negative results are consistent with a prior low dose trial (1,200 mg daily) [22]. Although there is no agreed upon plasma concentration for analgesia, and concentrations are not reported in studies of neuropathic pain and fibromyalgia [eg.12], our obtained values were in line with expectations based on prescribed daily doses, and provide a validity check on the experimental manipulation. The study featured a four-week dose escalation phase and eight weeks on treatment. Based on previous data on time to onset of efficacy in trials of anticonvulsants in neuropathic pain, and antidepressants in chronic back pain, this treatment duration is likely to have been adequate to observe onset of a therapeutic effect [eg. 12,35]. At the same time we acknowledge that one must be cautious in concluding gabapentin is ineffective: there was a large placebo effect, and carefully controlled trials may not reflect real life clinical experience [24].

4.2. Study limitations

Our study has important limitations which impact the generalizability of the results. The sample size is small, and on average pain intensity was in the mild-to-moderate range, making it possible that a “basement” effect precluded detection of an overall therapeutic effect.. Attrition was high. On the other hand, our sample size was adequate to detect a clinically meaningful effect, and attrition was similar to that reported historically for other recent clinical trials in chronic back pain (eg, 25–30%, see [35]. Pain radiating into the lower extremities may be a proxy, but we did not use a standardized instrument to ascertain specifically for neuropathic pain, which has been reported to affect one-third of chronic back patients [16]. Our sample is not likely to be purely neuropathic, and our design and power estimates did not address this issue. Short-term studies suggest gabapentin may be efficacious in rigorously defined lumbar root pain (sciatica) [44], a treatment-resistant and disabling subset of the chronic back pain population [19]. One open label study concluded that compared to usual care, gabapentin reduced pain intensity and improved walking distance in lumbar spinal stenosis, a condition associated with neurologic intermittent claudication, manifest as symptoms of leg pain, numbness, and cramping precipitated by standing or walking [43]. In any event he inclusion of non-radiating and radiating pain in the same trial may have underpowered an ability to detect efficacy if only one form were responsive. Furthermore we did not assess pain intensity at rest and upon movement, and we therefore may have missed differential effects. Other limitations are that we did not explore effects on sleep, or of co-prescribed opioids. Current formulations of gabapentin allow for single night-time dosing, may impact sleep, and might exert beneficial effects indirectly through these effects. Gabapentin might be effective when combined with opioids [26]. The generalizability of our results is limited by our exclusion of patients receiving opioid analgesics.

4.3. Perspective

Effective and safe pharmacotherapy of chronic low back pain remains elusive. Some antidepressants may be efficacious (e.g., duloxetine) but there are questions about other agents in this class. The longer term effectiveness of NSAIDs and opioids is not established.

They have known safety hazards. In hopes of identifying an alternative, the present study assessed the efficacy of a compound with a novel mechanism of action in a sample not confounded by opioids or benzodiazepines. Such approaches are reasonable but limited by the lack of a clearer definition of chronic back pain phenotypes and mechanisms.

4.4. Conclusion

The calcium channel alpha$_2$ –delta ligand gabapentin, which is analgesic in selected neuropathic pain conditions and perhaps widespread pain disorders (fibromyalgia), was expected to be effective in chronic back pain, given its overlap with both neuropathic and diffuse musculoskeletal pain syndromes. Results did not support its use in a general low back pain sample with and without a pain radiating to the legs. Future studies, with larger sample sizes in chronic back pain specifically selected for neurologic syndromes (e.g., sciatica) may be able to define a therapeutic role for gabapentin.

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Conflict of interest statement

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Bibliography

1. Arnold LM, Goldenberg DL, Standord SB. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheumatism. 2007; 56:1336–1344. http://onlinelibrary.wiley.com/doi/10.1002/art.22457/epdf. [PubMed: 17393438]
2. Atkinson JH, Slater MA, Wahlgren DR, Williams RA, Zisook S, Pruitt SD, Epping-Jordan JE, Patterson TL, Grant I, Abramson I, Garfin SR. Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. Pain. 1999; 83:137–145. http://www.ncbi.nlm.nih.gov/pubmed/10534584. [PubMed: 10534584]
3. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998; 280:1831–1836. http://jama.jamanetwork.com/article.aspx?articleid=188227. [PubMed: 9846777]
4. Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.

5. Brown LD, Cai T, Zhou H. Nonparametric regression in exponential families. Annals Statistics. 2010; 38:2005–2046.
6. Chou R, Huffman LH. American Pain Society. American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Annals of Internal Medicine. 2007; 147:505–514. http://annals.org/article.aspx?articleid=736857. [PubMed: 17909211]
7. Cohen, J. Statistical Power Analyses for the Behavioral Sciences. New York: Academic Press; 1977. (Rev Ed)
8. Davidson M, Keating JL. A comparison of five low back disability questionnaires: reliability and responsiveness. Physical Therapy. 2002; 82:8–24. http://ptjournal.apta.org/content/82/1/8.long. [PubMed: 11784274]
9. de C Williams AC, Davies HTO, Chadury Y. Simple pain rating scales hide complex idiosyncratic meanings. Pain. 2000; 85:457–463. http://www.ncbi.nlm.nih.gov/pubmed/?term=Simple+pain+rating+scales+hide+complex+idiosyncratic+meanings. [PubMed: 10781919]
10. Deyo RA, Weinstein JN. Low back pain. New Engl J Med. 2001; 344:363–370. [PubMed: 11172169]
11. Doctor JN, Slater MA, Atkinson JH. The Descriptor Differential Scale of pain intensity: an evaluation of item and scale properties. Pain. 1995; 61:251–260. http://www.ncbi.nlm.nih.gov/pubmed/?term=The+Descriptor+Differential+Scale+of+pain+intensity%3A+an+evaluation+of+item+and+scale+properties. [PubMed: 7659435]
12. Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2003; 60:1274–1283. http://www.ncbi.nlm.nih.gov/pubmed?term=Pregabalin%5BTitle%5D%20AND%20treatment%5BTitle%5D%20AND%20postherpetic%5BTitle%5D%20AND%20neuralgia%5BTitle%5D%20AND%20randomized%5BTitle%5D%20AND%20placebo-controlled%5BTitle%5D%20AND%20trial%5BTitle%5D. [PubMed: 12707429]
13. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008; 9:105–121. [PubMed: 18055266]
14. Fairbank JCT, Pynsent PB. The Oswestry Disability Index. Spine. 2000; 25:2940–2953. http://www.jpain.org/article/S1526-5900(07)00899-1/abstract. [PubMed: 11074683]
15. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001; 94:149–158. http://www.ncbi.nlm.nih.gov/pubmed/?term=Clinical+importance+of+changes+in+chronic+pain+intensity+measured+on+an+11-point+numerical+pain+rating+scale. [PubMed: 11690728]
16. Fishbain DA, Cole B, Lewis JE, Gao J. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review. Pain Medicine. 2014; 15:4–15. http://onlinelibrary.wiley.com/doi/10.1111/pme.12229/abstract. [PubMed: 24118776]
17. Gracely RH, Kwilosz DM. The Descriptor Differential Scale: applying psychophysical principles to clinical pain assessment. Pain. 1988; 35:279–288. http://www.ncbi.nlm.nih.gov/pubmed/?term=The+Descriptor+Differential+Scale%3A+applying+psychophysical+principles+to+clinical+pain+assessment. [PubMed: 3226757]
18. Guy, W. Clinical global impression, ECDEU Assessment Manual for Psychopharmacology. Washington, D.C.: US Government Printing Office; 1976.
19. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline, and their combination vs. placebo in patients with chronic lumbar root pain. Pain. 2007; 130:60–75. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1974876/.

20. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross sectional study of side effects in neuroleptic-treated patients. Acta Psychiat Scand. 1987; 334:7–96. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.1987.tb10566.x/abstract.
21. Max, MB. Antidepressants as Analgesics. In: Fields, HL.; Liebeskind, JC., editors. Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues. Seattle: IASP Press; 1994. p. 229-246.
22. McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain? A randomized, double-blind, placebo-controlled study. The Pain Clinic. 2001; 13:103–107. http://www.maneyonline.com/doi/abs/10.1163/156856901753420945.
23. Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. Ann Rheum Dis. 2010; 69:374–379. http://ard.bmj.com/content/69/2/374.long. [PubMed: 19364730]
24. Moore RA, Straube S, Derry S, McQuay HJ. Topical review: chronic low back pain analgesic studies - a methodological minefield. Pain. 2010; 149:431–434. http://www.ncbi.nlm.nih.gov/pubmed/?term=Topical+review%3A+chronic+low+back+pain+analgesic+studies+-+a+methodological+minefield. [PubMed: 20304558]
25. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews. 2014 Apr 27.4:CD007938. [PubMed: 24771480]
26. Morlion B. Chronic low back pain: pharmacological, interventional and surgical strategies. Nature Reviews. Neurology. 2013; 9:462–473. http://www.ncbi.nlm.nih.gov/pubmed/?term=Chronic+low+back+pain%3A+pharmacological%2C+interventional+and+surgical+strategies. [PubMed: 23817349]
27. Moscucci M, Byrne L, Weintraub M, Cox C. Blinding, unblinding, and the placebo effect: an analysis of patients' guesses of treatment assignment in a double-blind clinical trial. Clin Pharmacol Ther. 1987; 41:259–265. http://www.ncbi.nlm.nih.gov/pubmed/?term=Blinding%2C+unblinding%2C+and+the+placebo+effect%3A+an+analysis+of+patients'+guesses+of+treatment+assignment+in+a+double-blind+clinical+trial. [PubMed: 3816016]
28. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, Singh U, Singh PK. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar discectomy: a randomized, double blind, placebo-controlled study. J Neurosurg Anesthesiol. 2005; 17:65–68. http://www.ncbi.nlm.nih.gov/pubmed/?term=Evaluation+of+the+optimal+preemptive+dose+of+gabapentin+for+postoperative+pain+relief+after+lumbar+discectomy%3A+a+randomized%2C+double+blind%2C+placebo-controlled+study. [PubMed: 15840990]
29. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, McLachian AJ, Koes B. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. BMJ. 2012; 344:e479–e512. http://www.bmj.com/content/bmj/344/bmj.e497.full.pdf.
30. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomized, double blind, placebo controlled study. Pain. 2001; 94:215–224. http://www.ncbi.nlm.nih.gov/pubmed/11690735. [PubMed: 11690735]
31. Roskell NS, Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. Pain Practice. 2011; 11:516–527. http://www.ncbi.nlm.nih.gov/pubmed/21199320. [PubMed: 21199320]
32. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA. 1998; 280:1837–1842. http://jama.jamanetwork.com/article.aspx?articleid=188226. [PubMed: 9846778]
33. Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double blind, placebo-controlled trial. Pain. 2002; 99:557–566. http://www.ncbi.nlm.nih.gov/pubmed/12406532. [PubMed: 12406532]
34. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology. 2000; 55:915–720. http://www.ncbi.nlm.nih.gov/pubmed/11061244. [PubMed: 11061244]

35. Skljarevski V, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, Iyengar S, Atkinson JH, Backonja M. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine. 2010; 35:E578–E585. http://www.ncbi.nlm.nih.gov/pubmed/20461028. [PubMed: 20461028]
36. Spitzer, RL.; Williams, JB.; Gibbon, M.; First, MB. Structured Clinical Interview for DSM-IV. Washington DC: American Psychiatric Association; 1996.
37. Spitzer WO, LeBlanc FE, Dupuis M. Scientific approach to the assessment and management of activity-related spinal disorder. Spine. 1987; 15:120–123.
38. Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin—Calcium channel α_2-δ [$Ca_V\alpha_2$-δ] ligands. Pain. 2009; 142:13–16. http://www.ncbi.nlm.nih.gov/pubmed/?term=Mechanisms+of+analgesia+by+gabapentin+and+pregabalin—Calcium+channel+α2-δ+%5BCavα2-δ%5D+ligands. [PubMed: 19128880]
39. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003; 106:337–345. http://www.ncbi.nlm.nih.gov/pubmed/14659516. [PubMed: 14659516]
40. Turner JA, Denny MC. Do antidepressant medications relieve chronic low back pain? J Fam Pract. 1993; 37:545–553. http://www.ncbi.nlm.nih.gov/pubmed/?term=Do+antidepressant+medications+relieve+chronic+low+back+pain%3F. [PubMed: 8245805]
41. Waddell G, Main CJ. Assessment of severity in low back disorders. Spine. 1984; 9:204–208. http://www.ncbi.nlm.nih.gov/pubmed/6233713. [PubMed: 6233713]
42. Wu YT, Lai MH, Lu SC, Chang ST. Beneficial response to gabapentin portraying with interval change of brain SPECT imaging in a case with failed back surgery syndrome. Journal of Clinical Pharmacy and Therapeutics. 2011; 36:525–528. http://www.ncbi.nlm.nih.gov/pubmed/?term=Beneficial+response+to+gabapentin+portraying+with+interval+change+of+brain+SPECT+imaging+in+a+case+with+failed+back+surgery+syndrome. [PubMed: 21729117]
43. Yaksi A, Ozgonenel L, Ozgonenel B. The efficiency of gabapentin therapy in patients with lumbar spinal stenosis. Spine. 2007; 32:939–942. http://www.ncbi.nlm.nih.gov/pubmed/?term=The+efficiency+of+gabapentin+therapy+in+patients+with+lumbar+spinal+stenosis. [PubMed: 17450066]
44. Yildirim K, Sisecioglu M, Karatay S, Erdal A, Levent A, Ugur M, Senel K. The effectiveness of gabapentin in patients with chronic radiculopathy. Pain Clinic. 2003; 15:213–218. http://pesquisa.bvsalud.org/ses/resource/pt/CN-00474479.

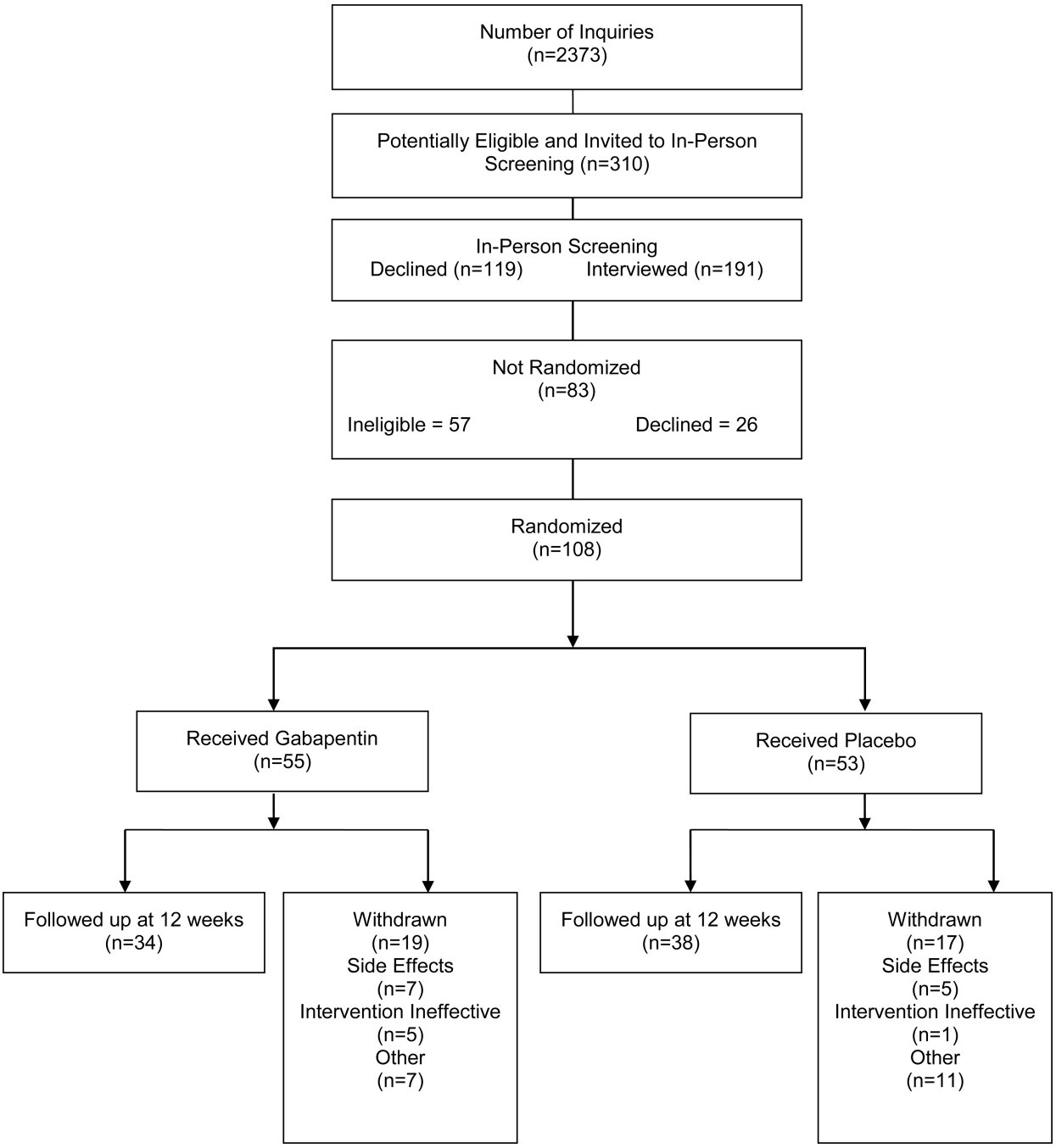

Figure 1.
Flow of participants in the trial of gabapentin for chronic low back pain with or without a radiating component

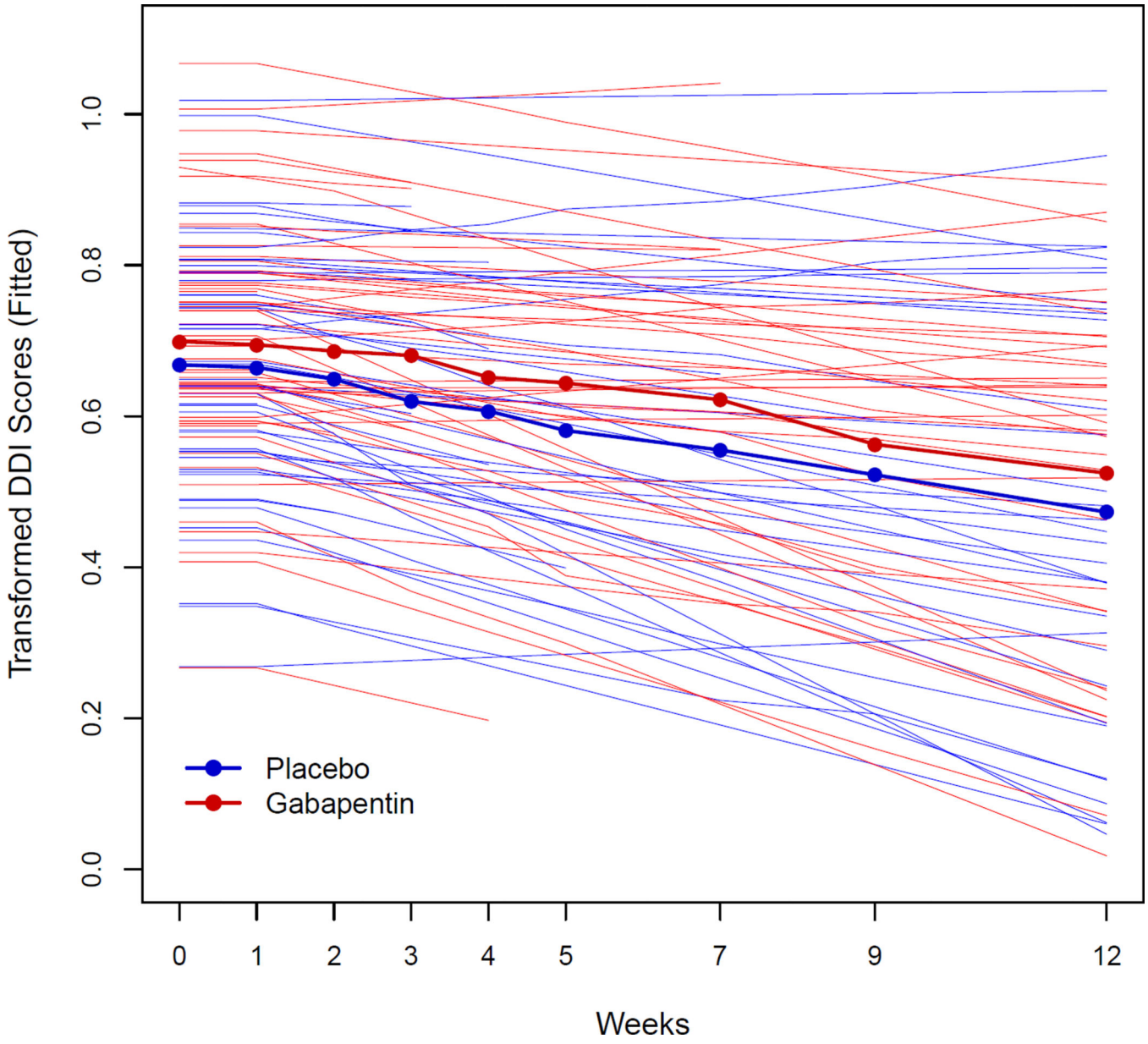

Figure 2.
Change in pain intensity measured by the Descriptor Differential Scale over the 12 weeks of the trial for gabapentin and placebo

Table 1

Demographics and Clinical Characteristics of Participants with Degenerative Disease of the Spine (N = 108)

Characteristic	Placebo	Gabapentin
Age mean + SD, years	54.62 + 11.38	57.58 + 8.84
Gender, no. (%) male	40 (75.5)	43 (81.1)
Education mean + SD, years	15.55 + 2.91	15.66 + 2.65
Marital Status, no. (%) married	24 (45.3)	28 (52.8)
Ethnicity, no. (%) Caucasian	38 (71.7)	38 (71.7)
Annual family income, $, median category	35,000 – 49,999	42,500 – 57,500
Pain duration, mean + SD, years	17.79 + 12.80	17.16 + 15.12
Previous back surgery, no. (%)	4 (7.7)	1 (1.9)
Radicular pain, no. (%)	22 (42.3)	24 (44.4)
NSAIDs, no. (%)	30 (56.6)	36 (65.4)
Antidepressants, no. (%)	1 (1.9)	2 (3.6)

Table 2

Primary Reason for Participant Withdrawal from Protocol

	Placebo (N = 17)	**Gabapentin (N = 19)**
Primary reasons for withdrawal	N	N
Adverse Effects		
Concentration difficulties	0	3
Dizziness	1	2
Loss of balance	0	1
Rash	0	1
Urinary disturbance	3	0
Tension/inner unrest	1	0
Drug not effective	1	5
Lost interest/unspecified	5	5
Medical exclusion	1	1
Time demands	2	1
Conflict with work	2	0
Protocol violation	1	0

Table 3

Treatment Emergent Adverse Effects (No., %) Attributed to Gabapentin or Placebo for Participants in the Intent-to-Treat analysis (N = 108)

Adverse Effect Placebo	Placebo (N = 53)		Gabapentin (N = 55)		Fisher's P
Asthenia/lassitude/fatigue	15	28.3	27	49.1	0.031
Orthostatic dizziness	14	26.4	24	43.6	0.071
Decreased salivation	10	18.9	22	40.0	0.020
Concentration difficulties	6	11.3	21	38.2	0.001
Increased sleep	11	20.8	21	38.2	0.058
Accommodation disturbance	3	5.7	19	34.5	0.0002
Loss of balance	2	3.8	18	32.7	0.0001
Failing memory	1	1.9	9	16.4	0.016
Constipation	9	17.0	7	12.7	0.595
Nausea/vomiting	8	15.1	7	12.7	0.785
Polyuria/polydipsia	6	11.3	7	12.7	1.000
Reduced sleep	10	18.9	7	12.7	0.435
Diarrhea	7	13.2	6	10.9	0.773
Erectile dysfunction	2	3.8	6	10.9	0.271
Weight gain	1	1.9	6	10.9	0.113
Decreased sexual desire	2	3.8	5	9.1	0.438
Increased dreaming	5	9.4	5	9.1	1.000
Tensions	1	1.9	5	9.1	0.206
Tension headache	2	3.8	3	5.5	1.000
Micturition disturbance	4	7.5	2	3.6	0.433
Paresthesia	3	5.7	2	3.6	0.676