Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial

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See Comment page 1218

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Summary

Background Drugs for neuropathic pain have incomplete efficacy and dose-limiting side-effects when given as monotherapy. We assessed the efficacy and tolerability of combined nortriptyline and gabapentin compared with each drug given alone.

Methods In this double-blind, double-dummy, crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia, and who had a daily pain score of at least 4 (scale 0–10), were enrolled and treated at one study site in Canada between Nov 5, 2004, and Dec 13, 2007. 56 patients were randomised in a 1:1:1 ratio with a balanced Latin square design to receive one of three sequences of daily oral gabapentin, nortriptyline, and their combination. In sequence, a different drug was given to each randomised group in three treatment periods. During each 6-week treatment period, drug doses were titrated towards maximum tolerated dose. The primary outcome was mean daily pain at maximum tolerated dose. Analysis was by intention to treat. This trial is registered, number ISRCTN73178636.

Findings 45 patients completed all three treatment periods; 47 patients completed at least two treatment periods and were analysed for the primary outcome. Mean daily pain (0–10; numerical rating scale) was 5·4 (95% CI 5·0 to 5·8) at baseline, and at maximum tolerated dose, pain was 3·2 (2·5 to 3·8) for gabapentin, 2·9 (2·4 to 3·4) for nortriptyline, and 2·3 (1·8 to 2·8) for combination treatment. Pain with combination treatment was significantly lower than with gabapentin (–0·9, 95% CI –1·4 to –0·3, p=0·001) or nortriptyline alone (–0·6, 95% CI –1·1 to –0·1, p=0·02). At maximum tolerated dose, the most common adverse event was dry mouth, which was significantly less frequent in patients on gabapentin than on nortriptyline (p<0·0001) or combination treatment (p<0·0001). No serious adverse events were recorded for any patients during the trial.

Interpretation Combined gabapentin and nortriptyline seems to be more efficacious than either drug given alone for neuropathic pain, therefore we recommend use of this combination in patients who show a partial response to either drug given alone and seek additional pain relief. Future trials should compare other combinations to their respective monotherapies for treatment of such pain.

Funding Canadian Institutes of Health Research.

Introduction

First described by the International Association for the Study of Pain in 1994 as pain ''initiated or caused by a primary lesion or dysfunction in the nervous system'',[1] neuropathic pain affects more than 2–3% of the general population,[2,3] and its precise definition continues to be reassessed.[4] Disorders causing neuropathic pain include cervical or lumbar radiculopathy, diabetic polyneuropathy, post-traumatic neuropathy, and postherpetic neuralgia. Neuropathic pain impairs patients' mood, quality of life, daily activities, and occupational performance, and generates health-care costs three times higher than in matched controls.[5] Such pain costs an estimated US$40 billion per year in the USA alone.[6]

Gabapentin and nortriptyline are two of several first-line drugs with the most favourable therapeutic profiles.[7,8] However, when given as monotherapy, the maximum tolerated doses of these drugs rarely reduce pain by more than 60% and provide relief in only 40–60% of patients because of incomplete efficacy and dose-limiting side-effects.[7,8] Combination of different drugs could provide additive or synergistic analgesia thus leading to increased efficacy or tolerability, or both. The merits of this strategy were shown in a previous trial in which combined morphine and gabapentin had superior analgesic efficacy to either drug given alone.[9]

Gabapentin is a 3-alkylated analogue of γ aminobutyric acid; it modulates α-2-δ calcium channel subunits, which are thought to be important in neuropathic pain.[10] Nortriptyline is a metabolite of amitriptyline with several putative pharmacological mechanisms including blockade of norepinephrine and serotonin uptake, blockade of sodium channels, and sympathetic blockade and antagonism of N-methyl-D-aspartate glutamate receptors.[11] A preclinical study in a nociceptive pain model suggests that synergistic interactions could occur between these two drug classes.[12]

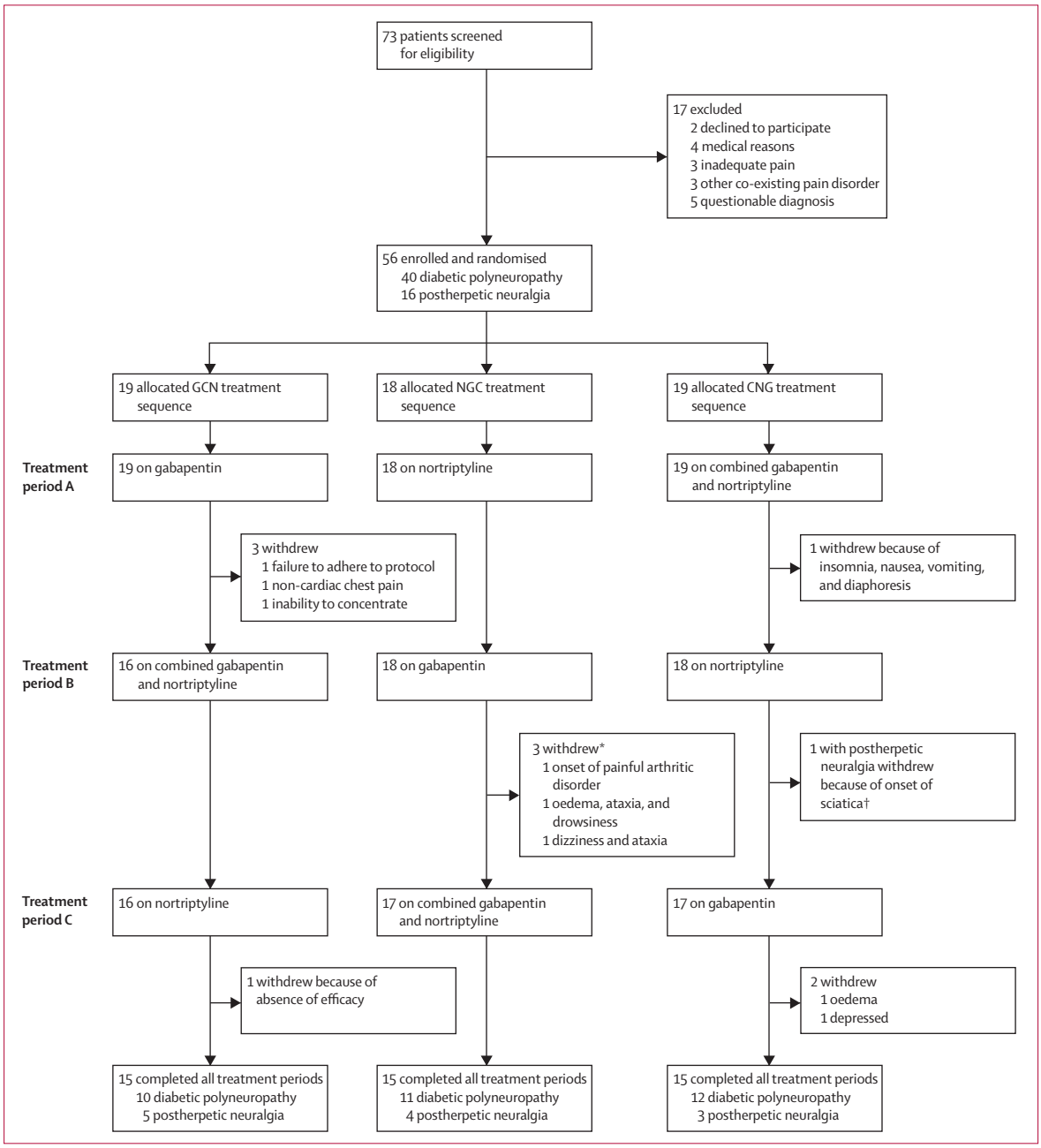

Figure 1: **Trial profile**
GCN=gabapentin, combined nortriptyline and gabapentin, and nortriptyline. NGC=nortriptyline, gabapentin, and combined nortriptyline and gabapentin. CNG=combined nortriptyline and gabapentin, nortriptyline, and gabapentin. *Two patients who withdrew during treatment period B went on to participate in treatment period C. †Patient completed the phase on maximum tolerated dose of nortriptyline before withdrawal and therefore was included in calculations for patients receiving nortriptyline.

We aimed to assess the efficacy of combined gabapentin and nortriptyline compared with monotherapy using either drug for patients with neuropathic pain. Although diabetic polyneuropathy and postherpetic neuralgia are aetiologically and pathologically distinct diagnostic entities, they are both associated with the type of neuropathic pain that has similar response to treatment with opioids, tricyclic antidepressants, and anticonvulsants (eg, gabapentin).[7,8] Thus, we have expanded the trial to include these two neuropathic disorders to broaden generalisability, as in previous trials.[9,13]

Methods

Participants

Patients were recruited for treatment in one study centre (university hospital research clinic) in Canada between

	Patients with diabetic polyneuropathy (n=40)	Patients with postherpetic neuralgia (n=16)
Age (years)	61 (53–69)	68 (65–73)
Sex		
Men	26 (65%)	9 (56%)
Women	14 (35%)	7 (44%)
Ethnic group*		
White	40 (100%)	16 (100%)
Duration of pain or time since herpes zoster onset (years)	5·2 (3·4)	2·8 (4·3)
Duration of diabetes (years)	5·8 (5·8)	NA
Site of postherpetic neuralgia		
Trigeminal	NA	3 (19%)
Cervical	NA	4 (25%)
Thoracic	NA	9 (56%)
Pain intensity (0–10; NRS)†	5·5 (1·5)	5·0 (1·3)
Allodynia	29 (73%)	12 (75%)
Concomitant drugs		
None	22 (55%)	6 (38%)
Opioids	8 (20%)	4 (25%)
Acetaminophen or NSAIDs	14 (35%)	6 (38%)
Previous drugs		
None	4 (10%)	0
Short-acting opioids as needed	11 (28%)	11 (69%)
Sustained-release opioids	3 (8%)	3 (19%)
Gabapentin or pregabalin	8 (20%)	7 (44%)
Tricyclic antidepressant	13 (33%)	5 (31%)
Carbamazepine or phenytoin	1 (3%)	4 (25%)

Data are median (IQR), number (%), or mean (SD). NA=not applicable. NRS=numerical rating scale. NSAID=non-steroidal anti-inflammatory drug. *Established from hospital registration data. †Measured on a scale with 0 indicating no pain, and 10 indicating the worst pain imaginable.

Table 1: **Demographic characteristics at baseline**

Nov 5, 2004, and Dec 13, 2007. Patients with diabetic polyneuropathy satisfied diagnostic criteria for diabetes mellitus,[14] and suffered from distal, symmetric, sensory diabetic polyneuropathy. Diabetic polyneuropathy was established by at least a moderate decrease in pinprick, temperature or vibration sense in both feet, or by bilaterally decreased or absent ankle jerk reflexes. Patients with postherpetic neuralgia had had an eruption of a herpes zoster rash, which was recorded by a clinician, 6 months or more before enrolment. After telephone screening, patients were invited to the clinic for recording of history, physical examination, detailed neurological examination, laboratory tests, and an electrocardiogram.

Eligible patients had daily pain (score ≥4 on a scale of 0–10) for at least 6 months directly preceding the start of the trial, aspartate aminotransferase and alanine aminotransferase concentration of 120% of the upper limit of normal or less, serum creatinine concentration of 150% of the upper limit of normal or less, and haemoglobin A1c concentration of less than 13%. Patients had sufficient cognitive function and language skills for telephone communication and completion of study questionnaires.

Exclusion criteria included patient history or laboratory results that suggested the presence of an inherited neuropathy or neuropathy attributable to other causes, such as hypothyroidism, vitamin B12 deficiency, connective tissue disease, amyloidosis, and toxic exposure. Other exclusions were any major organ system disease, cardiovascular autonomic neuropathy, baseline postural hypotension of more than 20 mm Hg, sedation or ataxia due to concomitant drugs or other cause, urinary symptoms attributable to benign prostatic hypertrophy in male participants, psychiatric or substance abuse disorder, hypersensitivity to any of the study drugs, or a coexisting disorder causing pain as severe as the neuropathic pain. Women of childbearing potential were required to receive a highly effective form of contraception.

Trial-related health care was provided free of charge and trial participants were reimbursed for trial-related travel expenses. No other compensation was offered to trial participants at any time during the study. All participants supplied written informed consent. This trial received institutional ethics approval from Queen's University, Kingston, ON, Canada.

Procedures

This randomised trial of three treatments—gabapentin, nortriptyline, and combined gabapentin and nortriptyline—had a three-period (A, B, and C) crossover design with 6 weeks per treatment period. As per a balanced Latin square crossover design, patients were randomised (double-blind) in a 1:1:1 ratio and allocated to one of three possible treatment sequences to be taken in treatment period A, B, and C, respectively: gabapentin, combined treatment, and nortriptyline (GCN); nortriptyline, gabapentin, and combined treatment (NGC); or combined treatment, nortriptyline, and gabapentin (CNG). A trial pharmacist prepared a concealed allocation schedule by computer randomisation of these three sequences, in blocks of three, to a consecutive number series; the pharmacist had no further participation in the trial. Patients were assigned in turn to the next consecutive number, and the corresponding series of study drugs was dispensed.

Drugs were given as yellow and orange capsules to maintain double-blinding. Capsules were identical in appearance for all treatments as per a double-dummy design. Yellow capsules were given twice daily and orange capsules were given three times daily. For each treatment, yellow and orange capsules contained, respectively, placebo and 400 mg gabapentin, 10 mg nortriptyline and placebo, or 10 mg nortriptyline and 400 mg gabapentin. Target daily dose ceilings were 3600 mg gabapentin and 100 mg nortriptyline, either singly or in combination.

Patients completed a diary at baseline with pain intensity ratings for 7 days after discontinuation of tricyclic antidepressants, or gabapentin or pregabalin,

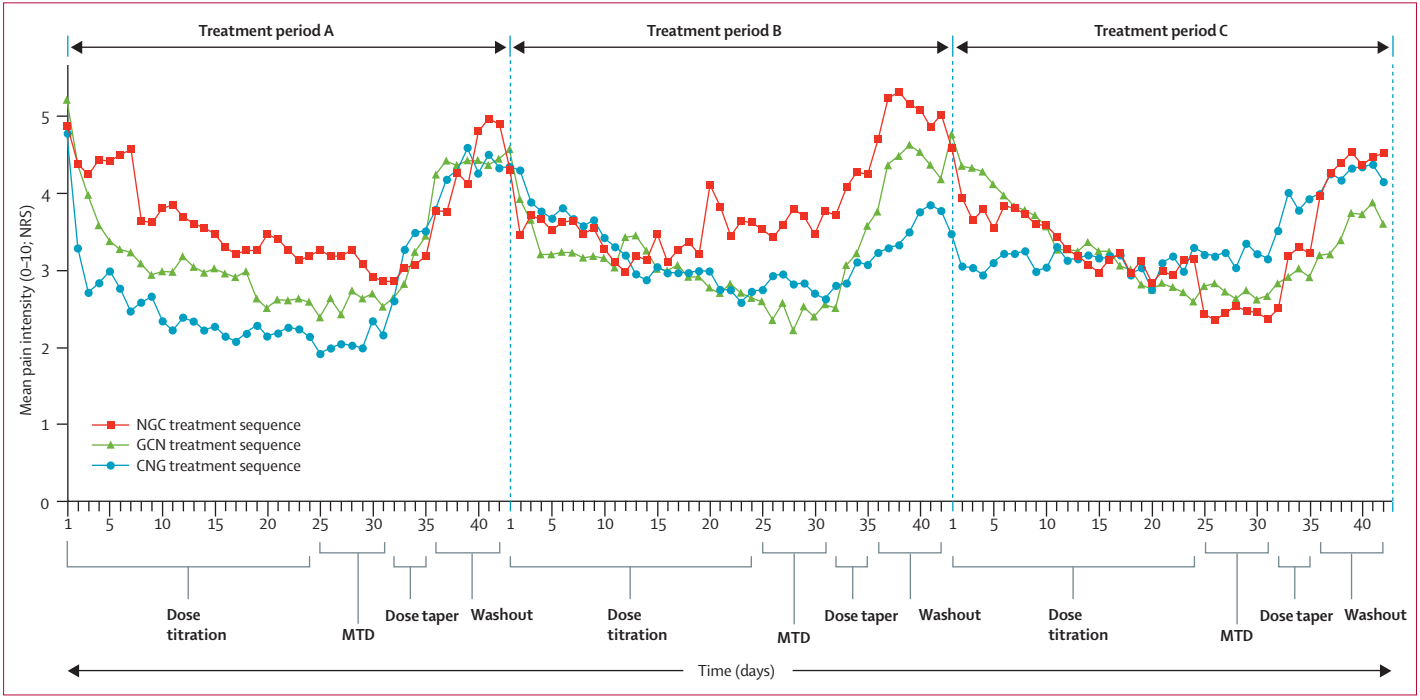

Figure 2: **Mean daily pain intensity**
Each treatment period contained phases of drug dose titration (24 days), maximum tolerated dose (MTD; 7 days), dose taper (4 days), and washout (7 days). NRS=numerical rating scale. NGC=nortriptyline, gabapentin, and combined nortriptyline and gabapentin. GCN=gabapentin, combined nortriptyline and gabapentin, and nortriptyline. CNG=combined nortriptyline and gabapentin, nortriptyline, and gabapentin.

or both before starting to take the study drug. Patients taking, and perceiving benefit from, sustained-release opioids, non-steroidal anti-inflammatory drugs, or paracetamol were allowed to continue these drugs at a steady dose for the entire study. However, procedural pain treatments (eg, nerve blocks or acupuncture) were forbidden. The dose-escalation schedule for each set of tablets was identical for every treatment period. During the first 24 days of each 6-week period, the dose was escalated towards a maximum tolerated dose or the target ceiling dose, whichever was reached first. Days 25–31 of each treatment period were classed as the patients' maximum tolerated dose for that treatment. Days 32–35 of each treatment period were classed as the dose taper phase, and days 36–42 were the drug washout phase.

A research nurse telephoned patients twice weekly to record and assess adverse events by open-ended questioning, and guide drug dose titration; the nurse was masked for the entire trial. With each dose increase, adverse events were rated by the patient (mild, moderate, or severe), and patients were asked if they could tolerate the present dose for another 2–3 days. If so, this dose was continued with the expectation that tolerance to side-effects would develop. If side-effects were intolerable or did not improve, or both, the dose was decreased to the previous dose-titration step until the next scheduled telephone call. At a subsequent telephone call, an increase to the dose at which side-effects were a problem was attempted. If the increased dose resulted in intolerable side-effects, at the next telephone call the dose was decreased back to the previous dose, which was then defined as the maximum tolerated dose. If adverse events or lack of efficacy necessitated withdrawal from the study treatment, patients were offered the opportunity to pursue the next drug treatment in sequence in the next treatment phase, after taper and washout of the treatment from which they withdrew.

Outcome measures were consistent with Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines,[15] and included measures of pain intensity, interference with function, mood, quality of life, and global pain relief. The primary outcome was pain intensity (0–10 on a numerical rating scale [NRS]), which was rated three times daily, and the mean was taken over 7 days at the maximum tolerated dose. Secondary outcomes were maximum tolerated dose of study drug, serum concentration of study drug, brief pain inventory,[16] patient-reported nocturnal pain (rated 0–10, for the preceding night during each telephone contact), short-form McGill pain questionnaire (SF-MPQ),[17] short-form 36-item general health survey (SF-36),[18] Beck depression inventory,[19] adverse events, serious adverse events, global pain relief (rated pain worse, no relief, slight relief, moderate relief, a lot of relief, or complete relief), results of blinding questionnaires completed by patients and the research nurse, and bodyweight.

	Baseline (n=56)	Gabapentin (n=46)	p value*	Nortriptyline (n=50)	p value*	Combined gabapentin and nortriptyline (n=50)
Daily pain intensity (0–10; NRS)†	5·4 (5·0–5·8)	3·2 (2·5–3·8)	0·001	2·9 (2·4–3·4)	0·02	2·3 (1·8–2·8)
Brief pain inventory (0–10; NRS)‡						
Worst pain in past 24 h	6·3 (0·3)	4·3 (0·4)	0·01	4·1 (0·3)	0·04	3·2 (0·3)
Least pain in past 24 h	3·1 (0·3)	2·6 (0·3)	0·01	2·1 (0·3)	0·32	1·8 (0·3)
Average pain	4·9 (0·2)	3·3 (0·3)	0·002	3·1 (0·2)	0·04	2·5 (0·2)
Pain at present time	3·9 (0·3)	2·7 (0·3)	..	2·8 (0·3)	..	2·1 (0·3)
Percentage pain relief on treatment	NA	48·1% (5·0)	0·007	45·7% (4·9)	0·002	63·4% (4·9)
Pain interference items (0–10; NRS)						
General activity	3·9 (0·4)	2·1 (0·3)	..	2·2 (0·3)	..	1·8 (0·3)
Mood	3·8 (0·3)	1·5 (0·3)§	0·51	2·1 (0·3)	0·01	1·3 (0·3)
Walking	3·9 (0·4)	2·2 (0·3)	..	2·0 (0·3)	..	2·1 (0·3)
Normal work	4·0 (0·4)	2·2 (0·3)	..	2·3 (0·3)	..	2·1 (0·3)
Social relations	2·8 (0·3)	1·4 (0·3)	..	1·4 (0·3)	..	1·1 (0·3)
Sleep	5·1 (0·4)	2·2 (0·3)	0·0003	2·3 (0·3)	<0·0001	1·0 (0·3)
Enjoyment of life	4·8 (0·4)	2·1 (0·3)	0·08	2·7 (0·3)	0·0005	1·5 (0·3)

Data are mean (95% CI), mean (SE), or percentage (rating on a scale of 0–10). For items rated on a scale of 0–10, increasing numbers indicate increasing pain and pain interference. NRS=numerical rating scale. NA=not applicable. *p values are for the difference between each drug treatment and the combined treatment group; where values are not shown, p values for the global test of treatment were not significant so no pairwise comparisons were done. †Measured for 7 days at baseline, and for 7 days at maximum tolerated dose. ‡Short form of inventory. §p=0·066 for the difference between gabapentin and nortriptyline.

Table 2: **Pain intensity at baseline and at maximum tolerated dose of treatment**

Statistical analysis

The preplanned main analysis compared pain scores for combination treatment versus monotherapy for patients on the maximum tolerated dose. On the basis of previous variance estimates and accounting for two pairwise comparisons (combination treatment *vs* gabapentin or nortriptyline), we calculated that 40 patients would provide an 80% probability of detecting a mean difference between treatments of about half of a clinically significant[20] amount of pain reduction (α=0·05, two-sided). Dropout rates in previous studies were about 10% per 4–6-week treatment period, therefore we anticipated that enrolment of 58 patients would yield 40 who completed the study.

Patients completing at least two study treatment periods (providing one pairwise comparison) were included in the efficacy analysis; analysis was by intention to treat. Patients receiving at least one dose of any study drug were included in analyses of adverse events. Mean pain intensity was calculated from patient diaries while patients were on the maximum tolerated dose. For inclusion, more than 50% of the scores had to be available; otherwise, the mean daily pain intensity was treated as missing. A linear mixed model[21] was formed with fixed effects of drug treatment, treatment sequence, treatment period, and the first-order carryover term, and the random effect as patient (nested in sequence); the model was first fitted with the pain intensity data. If the carryover effect was not significant, then a reduced model excluding the carryover term was refitted.

According to Jones and Kenward,[21] the extent of the carryover factor in the second and third treatment period was defined as treatment received in the first and second period, respectively; the extent of carryover in the first period was the same but an arbitrary treatment for all patients. The model was identifiable since treatment period was another factor in the model. The effect of carryover was first tested, and if it was not statistically significant, this term was dropped from the linear mixed model. The least-square mean (SD) estimated from the initial or reduced model was calculated for every drug treatment. For treatment effects, according to Fisher's least significant difference method for multiple comparisons,[22] the global difference between all the treatment groups was first tested in the model. Only when this test was significant, all three pairwise comparisons were made with the estimated contrast from the initial or reduced model. As a secondary analysis, change in pain during each treatment period was calculated as the difference between pain at treatment period baseline (mean of last 3 days of baseline before study start, or mean of last 3 days of washouts preceding periods B and C) and pain on treatment (mean of last 3 days on maximum tolerated dose). The percentage change in pain (change in pain/treatment period baseline) was analysed as per the above linear mixed model. Secondary continuous outcome measures were analysed in the same way with baseline scores included as an additional fixed effect in the model. Proportion data were analysed by Fisher's exact method.[23] All reported p values are two-sided. All analyses were done with SAS software (version 8.0).

This trial is registered, number ISRCTN73178636.

	Baseline (n=56)	Gabapentin (n=46)	p value*	Nortriptyline (n=50)	p value*	Combined gabapentin and nortriptyline (n=50)
SF-MPQ						
Sensory score	14·5 (0·1)	6·7 (0·8)	..	7·4 (0·8)	..	5·3 (0·8)
Affective score	4·3 (0·1)	1·6 (0·3)	..	2·0 (0·3)	..	1·4 (0·3)
Total score	18·8 (0·2)	8·3 (1·0)	..	9·4 (1·0)	..	6·7 (1·0)
Visual analogue scale (0–10 cm)	4·3 (0·4)	2·4 (0·3)	..	2·5 (0·3)	..	2·0 (0·3)
Present pain intensity score (0–3)	2·0 (0·2)	1·5 (0·2)	..	1·6 (0·1)	..	1·3 (0·1)
SF-36 domains						
Physical functioning	57·1 (3·8)	61·6 (2·6)	..	61·7 (2·5)	..	64·3 (2·5)
Role-physical	39·7 (5·2)	54·1 (4·7)	..	52·7 (4·6)	..	55·6 (4·6)
Bodily pain	39·8 (2·2)	54·6 (2·6)	..	54·8 (2·5)	..	59·5 (2·5)
General health	57·4 (3·2)	58·7 (2·4)	..	62·6 (2·4)	..	61·7 (2·4)
Vitality	47·4 (2·7)	58·5 (2·7)†	0·8	49·3 (2·6)	<0·0001	59·2 (2·6)
Social functioning	66·1 (3·2)	83·1 (3·3)	..	77·7 (3·2)	..	78·5 (3·2)
Role-emotional	60·1 (5·4)	75·8 (5·4)	..	67·1 (5·3)	..	69·5 (5·3)
Mental health	69·6 (2·1)	78·8 (2·2)	..	75·8 (2·1)	..	77·5 (2·1)
SF-36 total score	56·8 (2·1)	65·4 (1·8)	..	63·1 (1·8)	..	66·3 (1·8)
Beck depression inventory score	8·3 (0·7)	5·8 (0·5)‡	0·5	6·8 (0·5)	0·01	5·4 (0·5)

Data are mean (SE). Higher SF-MPQ scores indicate more pain, higher SF-36 scores indicate better quality of life, and higher Beck depression inventory scores indicate more depression. *p values are for the difference between each drug treatment and the combined treatment group; where values are not shown, p values for the global test of treatment were not significant so no pairwise comparisons were done. †p<0·0001 for the difference between gabapentin and nortriptyline. ‡p=0·075 for the difference between gabapentin and nortriptyline.

Table 3: **Short-form McGill pain questionnaire (SF-MPQ), short-form 36-item general health survey (SF-36), and Beck depression inventory (BDI) scores**

Role of the funding source

Peer reviewers from the Canadian Institutes of Health Research commented on early versions of the trial protocol and, as such, affected the study design. The sponsor of the study did not participate in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Of 73 patients screened for eligibility, almost a quarter were excluded. 56 patients with either diabetic polyneuropathy (71%) or postherpetic neuralgia (29%) were enrolled and randomised. 47 (84%) patients completed at least two treatment periods and were included in efficacy analyses; 11 patients withdrew from at least one treatment period, and therefore 45 (80%) completed all treatment periods. Table 1 shows the demographic characteristics of patients at baseline. Allodynia was recorded in about three-quarters of patients which, in the case of the diabetic polyneuropathy group, was somewhat higher than was reported in previous studies.[9,24]

Figure 2 shows the primary outcome of mean daily pain intensity throughout the trial for each treatment sequence group. No significant effects of treatment sequence, treatment period, or carryover were recorded in the main analysis, but effects of drug treatment were statistically significant (p=0·0043). Pain intensity at baseline and maximum tolerated dose is shown in table 2; pain with combination treatment was significantly lower than with gabapentin (–0·9, 95% CI –1·4 to –0·3) or nortriptyline alone (–0·6, 95% CI –1·1 to –0·1). For patients with diabetic polyneuropathy, pain with combination treatment (2·2, 95% CI 1·5–2·8) was significantly lower than with nortriptyline (2·9, 2·3–3·6, p=0·018) or gabapentin alone (3·1, 2·4–3·7, p=0·009). For patients with postherpetic neuralgia, pain with combination treatment (2·5, 1·4–3·6) was lower than with nortriptyline (2·9, 1·7–4·0) or gabapentin alone (3·4, 2·2–4·5), but the overall effect of drug treatment was not significant (p=0·054), possibly because of small sample size. Analysis of mean percentage change in pain intensity for all patients indicated greater pain reduction with combination treatment (52·8% [SE 4·6]) than with nortriptyline (38·8% [4·6], p=0·01) or gabapentin alone (31·1% [4·6], p=0·0002).

In analysis of secondary outcomes, mean maximum tolerated dose of gabapentin was 2433 mg (SE 106) as monotherapy versus 2180 mg (108) in combination (p=0·0009). For nortriptyline, maximum tolerated dose was 61·6 mg (3·6) as monotherapy versus 50·1 mg (3·5) in combination (p=0·0006). At maximum tolerated dose, mean serum drug concentration of gabapentin was 9·57 mg/L (SE 0·53) as monotherapy versus 9·42 mg/L (0·72) in combination, and nortriptyline was 0·047 mg/L

	During dose titration			At maximum tolerated dose		
	Gabapentin (n=54)	Nortriptyline (n=52)	Combined gabapentin and nortriptyline (n=52)	Gabapentin (n=46)	Nortriptyline (n=50)	Combined gabapentin and nortriptyline (n=50)
Dry mouth	11 (20%)	29 (56%)*	27 (52%)†	8 (17%)	29 (58%)‡	30 (60%)§
Fatigue	7 (13%)	9 (17%)	6 (12%)	2 (4%)	6 (12%)	4 (8%)
Somnolence	9 (17%)	8 (15%)	9 (17%)	1 (2%)	1 (2%)	4 (8%)
Insomnia	3 (6%)	9 (17%)	6 (12%)	0	2 (4%)	2 (4%)
Dizziness	7 (13%)	6 (12%)	6 (12%)	4 (9%)	2 (4%)	4 (8%)
Headache	7 (13%)	5 (10%)	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Constipation	4 (7%)	6 (12%)	5 (10%)	1 (2%)	1 (2%)	1 (2%)
Ataxia	5 (9%)	1 (2%)	5 (10%)	3 (7%)	1 (2%)	5 (10%)
Feeling intoxicated	6 (11%)	1 (2%)	4 (8%)	1 (2%)	0	2 (4%)
Inability to concentrate	6 (11%)	0¶	3 (6%)	2 (4%)	0	2 (4%)
High blood sugar‖	4 (7%)	3 (6%)	4 (8%)	5 (11%)	2 (4%)	3 (6%)
Oedema	5 (9%)	2 (4%)	3 (6%)	4 (9%)	2 (4%)	4 (8%)
Abdominal cramping	5 (9%)	3 (6%)	3 (6%)	0	0	1 (2%)
Urinary retention	2 (4%)	4 (8%)	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Emotional lability	1 (2%)	4 (8%)	1 (2%)	1 (2%)	3 (6%)	0
Difficulty swallowing	0	1 (2%)	0	0	3 (6%)	1 (2%)
Pruritus	0	3 (6%)	0	1 (2%)	1 (2%)	0
Excessive sweating	1 (2%)	3 (6%)	0	2 (4%)	1 (2%)	0
Weight gain	3 (6%)	1 (2%)	3 (6%)	1 (2%)	1 (2%)	0
Blurry vision	3 (6%)	0	0	1 (2%)	0	1 (2%)

Data are number (%). *p=0·0003 for difference between nortriptyline and gabapentin. †p=0·001 for difference between combination treatment and gabapentin. ‡p<0·0001 for difference between nortriptyline and gabapentin. §p<0·0001 for difference between combination treatment and gabapentin. ¶p=0·03 for difference between nortriptyline and gabapentin. ‖Reported by patient home blood glucose monitoring.

Table 4: **Treatment-emergent adverse events in 5% of patients or more**

(0·005) as monotherapy versus 0·045 mg/L (0·005) in combination, but effect of drug treatment was not significant (p=0·37 for difference between combination treatment and gabapentn; p=0·11 for difference between combination treatment and nortriptyline).

Brief pain inventory scores for worst pain and average pain were significantly lower with combination treatment than with gabapentin or nortriptyline alone, and pain relief with combination treatment was significantly higher (table 2). Brief pain inventory scores also indicated that sleep interference was significantly lower with combination treatment than with gabapentin or nortriptyline alone. For mood and enjoyment of life, combination treatment had significantly lower interference than nortriptyline alone. Interference with mood was lower for gabapentin than nortriptyline, but the difference was not significant (table 2). Nocturnal pain at maximum tolerated dose was lower with combination treatment (1·4 [SE 0·4]) than with gabapentin (2·2 [0·4]) or nortriptyline alone (2·0 [0·4]), but the overall effect of drug treatment was not significant (p=0·13).

SF-MPQ results indicated that combination treatment had a reduced sensory effect and total pain score (p=0·08 and p=0·07, respectively, for overall effect of drug treatment) compared with gabapentin or nortriptyline alone (table 3). Significantly higher vitality was recorded for combination treatment and gabapentin alone than for nortriptyline alone in SF-36; moreover, SF-36 total score showed weak evidence that combination treatment was better than monotherapy (p=0·057 for overall effect of drug treatment). Combination treatment was also associated with a significantly lower Beck depression inventory score than nortriptyline alone; gabapentin also had a lower score than nortriptyline, but the difference was not significant (table 3).

Table 4 describes adverse events reported by patients during drug dose titration and at maximum tolerated dose. During dose titration, moderate or severe dry mouth was significantly more frequent with nortriptyline or combination treatment than with gabapentin, whereas inability to concentrate was significantly less frequent with nortriptyline than with gabapentin. At maximum tolerated dose, moderate or severe dry mouth was significantly more frequent with nortriptyline or combination treatment than with gabapentin. No other significant differences in adverse events were recorded. No serious adverse events were recorded for any patients during the trial.

Of the patients who completed a given treatment period and reported at least moderate pain relief at maximum tolerated dose, 65% (30/46) were on gabapentin, 76% (38/50) were on nortriptyline, and 84% (42/50) were on combination treatment, with no

significant differences between these treatments. According to blinding questionnaire responses, correct guesses by patients with respect to their treatment assignment were achieved by 10 (21%) patients on gabapentin, 18 (35%) on nortriptyline, and 15 (29%) on combination treatment. The research nurse correctly guessed patients' treatment assignments for 28 (58%) patients on gabapentin, 24 (47%) on nortriptyline, and 25 (48%) on combination treatment. Mean bodyweight for all participants at baseline was 91·7 kg (SE 2·9), and at maximum tolerated dose, mean bodyweight with nortriptyline (92·5 kg [0·4]) was significantly lower than with gabapentin (93·8 kg [0·5], p=0·01) or combination treatment (93·5 kg [0·4], p=0·04).

Discussion

This trial shows that combination of an antidepressant and an anticonvulsant drug seems to be superior to monotherapy for neuropathic pain. We have shown that treatment with combined gabapentin and nortriptyline results in lower mean daily pain intensity than does monotherapy with either drug. Combination treatment also results in increased percentage change in pain, and reduced pain intensity and increased pain relief according to the brief pain inventory. At maximum tolerated dose, frequency of adverse events was similar across all treatment groups, except for increased dry mouth with combination treatment and nortriptyline compared with gabapentin. Although significant differences in pain intensity between combination treatment and monotherapy were moderate, these differences are within the same range of magnitude as those reported in our previous trial comparing combination of morphine and gabapentin with monotherapy.[9]

Combined gabapentin and nortriptyline resulted in clinically significant improvement in sleep interference, a major complication of neuropathic pain.[25] Since combination treatment improved both pain and sleep more than monotherapy, the weak evidence that quality of life was improved (according to SF-36 total scores) is notable. Combination treatment reduced pain more than monotherapy in both subgroups of diabetic polyneuropathy and postherpetic neuralgia, although the reduction was not significant for postherpetic neuralgia. Reduction in both subgroups suggests that the interaction of the drugs—each of which as monotherapy have similar efficacy for diabetic neuropathy and postherpetic neuralgia—was favourable in both these disorders. Our trial used common antidepressant and anticonvulsant drugs for the treatment of common disorders associated with neuropathic pain, but these results might not be generalisable to all combinations of antidepressants and anticonvulsants, or to all neuropathic pain disorders.

We designed the trial as double-blind but blinding questionnaire responses from the research nurse were correct more often than might be expected by chance, which suggests the possibility of partial unmasking of the nurse, perhaps because of clinical observations. However, we do not believe that this unmasking would have been substantial enough to affect the course of patients' treatment, particularly since patients maintained a high degree of masking.

The trial was designed to use simultaneous combination treatment as opposed to sequential treatment, which is more often used in clinical practice.[26] Sequential combination treatment restricts exposure of patients to more than one drug if they report incomplete relief with the first drug tried, but it might lead to suboptimum dose ratios for combination treatment if both drugs have common overlapping side-effects. For example, titration of the first drug to maximum tolerated dose might lead to substantial sedation, thus restricting the attainable dose of a second sedating drug so that the dose-ratio is imbalanced in favour of the first drug. Therefore, if optimum analgesic interaction requires balanced ratio of the two drugs, simultaneous dose titration of these drugs might be preferable.

In view of the inadequate efficacy and tolerability of drugs for neuropathic pain,[7,8] researchers continue efforts to identify new treatments.[27] However, neuropathic pain is transmitted via several complex pathways, and new monotherapies might fail to provide improvements.[28] Combination of drugs to enhance efficacy and tolerability is a recognised strategy for disorders such as asthma,[29] hypertension,[30] and cancer.[31] However, the insufficient evidence base for combination treatment in neuropathic pain has meant that potentially useful combinations have not been recognised, whereas futile or even harmful combinations continue to be used. For example, use of combined amitriptyline and fluphenazine has been shown to provide inferior efficacy and greater sedation than amitriptyline alone.[32] Furthermore, for patients with lumbar radiculopathy, no significant analgesia was reported with morphine or nortriptyline as monotherapy, and combination treatment failed to show efficacy.[33] Thus, although this trial and a previous trial of combined morphine and gabapentin[9] have shown positive results with combination treatment, not all combinations are beneficial.

We used a fixed-time method in this trial, whereby drug doses were titrated towards the maximum limit of tolerability, and found that maximum tolerated doses of nortriptyline and gabapentin were significantly lower as combination treatment than as monotherapy, which suggests at least some additivity of adverse events from drug combination. However, superior efficacy was achieved with combination treatment at reduced doses without increased frequency of adverse events, suggesting that additivity for analgesia was higher than for adverse events. Unlike complex preclinical interaction studies with isobolographic analyses,[34] the methods used in our trial cannot distinguish between additive versus synergistic effects since only the maximum tolerated dose was assessed rather than several different drug

doses. However, we can infer that the overall therapeutic profile favours combined treatment with nortriptyline and gabapentin. By contrast with differences in maximum tolerated dose, differences in serum drug concentrations of gabapentin and nortriptyline between combination and monotherapy were not significant, which could be due to increased pharmacokinetic variability and the small magnitude of differences.

Combination treatment was superior to nortriptyline, but not gabapentin, for improvements in mood interference and Beck depression inventory scores; improvements on gabapentin were higher than on nortriptyline although the difference was not significant. The result seems puzzling since an antidepressant would be expected to improve mood more than an anticonvulsant would, but depressed patients were excluded from our study, and nortriptyline doses were well below those used to treat depression.[11] The possibility that treatment-related mood changes are a secondary effect of pain improvement fails to explain these results since lower pain scores were recorded for nortriptyline than gabapentin. Of previous chronic pain trials comparing gabapentin with a tricyclic antidepressant, the only one which included mood outcome measures reported no difference between treatments.[35] Notably, Beck depression inventory and mood interference scores from the brief pain inventory in our previous trial with combined morphine and gabapentin also showed reduced mood interference with gabapentin, despite lower pain scores with morphine.[9] These findings suggest that gabapentin has a mild mood elevating effect independent of analgesia, which is an effect also reported in patients with epilepsy.[36] Therefore, combination of gabapentin with nortriptyline can improve mood compared with nortriptyline alone.

As might be expected in a real-world pragmatic trial, a subset of patients (27–32%) were receiving a tricyclic antidepressant, or gabapentin or pregabalin at some point before enrolment. This subgroup was heterogeneous with respect to drug taken, simultaneous receipt of both antidepressant and anticonvulsant drug classes before the start of the study, method of dose titration (done by their physician before the trial), magnitude of response to the drug, and timing of discontinuation before start of the trial. However, previous experience with these drug classes could have affected treatment response during the trial, thus introducing an element of partial enrichment.

The design of our trial includes a direct head-to-head comparison of each monotherapy. This provides important additional information since the merits of different treatments are generally compared with the use of numbers needed to treat which have several limitations.[8] In this respect, in addition to mood differences mentioned previously, we noted that the efficacy of nortriptyline and gabapentin were statistically similar with respect to pain, dry mouth occurred significantly more frequently with nortriptyline, and weight gain was greater with gabapentin. Overall, these findings are consistent with those reported in previous trials comparing a tricyclic antidepressant to gabapentin.[24,35,37]

In view of the potential benefits and drawbacks of any given drug combination, continued research is needed to develop the evidence base for rational combination treatment in neuropathic pain and other neuropathic disorders. Furthermore, no data are available to guide the choice of sequential versus simultaneous combination treatment and innovative trial designs are needed to address this issue. Although development of more effective and better tolerated monotherapies is much anticipated, our findings suggest that drug combinations represent the most effective strategy for many patients with neuropathic pain. On the basis of our results, we recommend combined gabapentin and nortriptyline for patients who have a partial response to either drug alone and seek additional pain relief.

Contributors

All authors participated in protocol development, and IG and RRH selected mood and quality-of-life measures. IG and JMB ran the trial and collected data. IG, DT, and RRH participated in data analysis; and IG, DT, RRH, ACJ, and RLH participated in data interpretation. All authors participated in writing of the report.

Conflicts of interest

IG has received honoraria for consulting or being a member of an advisory board, or both for Pfizer. RLH has received research grant support from Pfizer. All other authors declare that they have no conflicts of interest.

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recommend discontinuation of hormone-replacement therapy once lung cancer is diagnosed. Because the optimum safe duration of hormone-replacement therapy in terms of lung-cancer survival is unclear, such therapy should probably be avoided in women at a high risk of developing lung cancer, especially those with a history of smoking. These results, along with the findings showing no protection against coronary heart disease,[12] seriously question whether hormone-replacement therapy has any role in medicine today. It is difficult to presume that the benefits of routine use of such therapy for menopausal symptoms outweigh the increased risks of mortality, especially in the absence of improvement in the quality of life. Recent data on hormone-replacement therapy should reaffirm the importance of doing randomised trials even to test longstanding views that are based on lesser degrees of evidence.

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Neuropathic pain treatment: a further step forward

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Neuropathic pain—defined as pain resulting from lesions or diseases of the sensory transmission pathways in the peripheral or central nervous system—is characterised by pain and sensory abnormalities in body areas that have lost their normal sensory innervation. Neuropathic pains, irrespective of their many causes, share common symptoms and signs, which indicate both loss of input and development of hypersensitivity in the painful region. These pains need accurate identification and specific treatments.

In *The Lancet* today, Ian Gilron and colleagues[1] report the results of a randomised crossover trial of oral treatment with a tricyclic antidepressant (nortriptyline), an anticonvulsant (gabapentin), and their combination at maximum tolerated doses. Participants had chronic pain associated with two types of neuropathic pain: postherpetic neuralgia and painful diabetic neuropathy.[1] The results show that pain intensity and pain-related sleep disturbance are lower with combined treatment than with each drug alone. For interference of pain with mood, combined treatment was superior to nortriptyline but not to gabapentin given alone. The combination treatment seems not to be superior to each drug alone for pain interference with a quality-of-life measure.

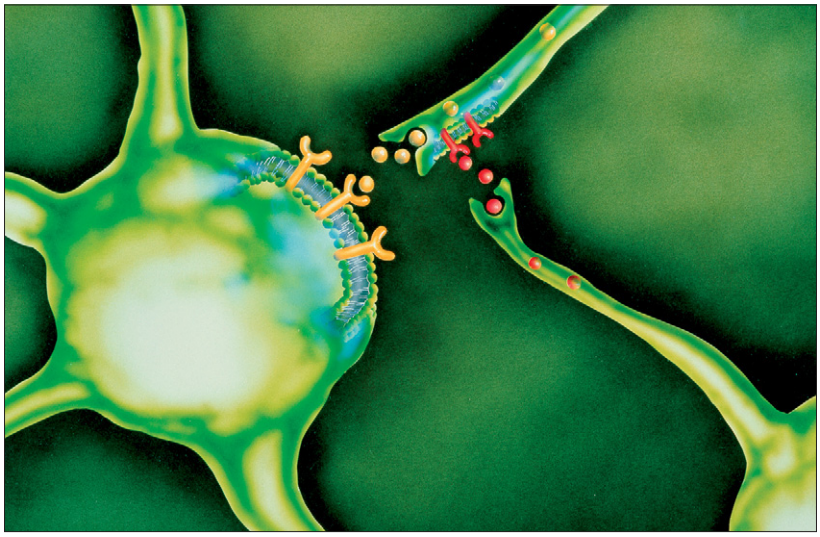
This study is most welcome because improved treatment for patients with chronic types of pain is urgently needed. A meta-analysis has shown that less than two-thirds of patients with chronic pain obtain sufficient pain relief with available drugs.[2] Today's study, however, does not tell the clinician whether a pain-relieving effect of each drug alone is needed to

achieve effect with the combination. In clinical practice, sequential treatment is most common, but in Gilron and colleagues' study, drugs in combination were given simultaneously.

The dynamic and plastic nature of the pain system suggests participation of several mechanisms in generation and maintenance of chronic pain. In neuropathic pain, the pain-signalling system is distorted and the plastic changes become increasingly complex. Hence a multifaceted treatment of these pains is a reasonable approach, but surprisingly few attempts have been made to address this issue.[3-5] Tricyclic antidepressants have several mechanisms of action, such as blockade of monoamine transporters, cholinergic receptors, N-methyl-D-aspartate (NMDA) receptors, and sodium channels.[6] Gabapentin presumably exerts its action by binding to a subunit in calcium ion-channels, and thereby reduces neurotransmitter release—eg, excitatory aminoacids from presynaptic neurons. Combination of the actions of tricyclic antidepressants and gabapentin adds an additional facet to pain modulation.[7] Gilron and colleagues' idea to use two classical antihyperalgesics is, therefore, a logical step forward.

Generally, available drugs lack molecular specificity and simply act as antihyperalgesics. Development of drugs that target specific parts of somatosensory processing is now underway,[8] and these drugs could be used for early treatment before neuroplastic changes have gone too far.[9] However, once a chronic pain state has been developed with associated biological, psychological, and social contributions to the pain, so one or even two drugs that target a specific mechanism are unlikely to cure the patient.

Gilron and colleagues' trial benefits from being an investigator-initiated study of two commonly used drugs for neuropathic pain. This type of study is unfortunately rare because most drug studies are based on large sample sizes from many sites, and financed by drug companies. To keep to a minimum the number of participants and costs, a crossover design had to be used. As the investigators acknowledge, previous experience with the drug classes in a subgroup of patients could introduce a risk of unmasking and enrichment. The study is also unusual because no placebo group was included, but it did not aim to show that nortriptyline and gabapentin are efficacious when given alone: many trials have shown this.[2,10] However, the extent to which use of only active drugs might have affected the patients' expectation of an effect, and thereby outcome, is unclear. The trial did not establish superiority of nortriptyline versus gabapentin, and only slight differences were reported in side-effect profiles, which supports the recommendation that both drug classes be used as first-line treatments.



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