Lower limb complications

NEW ENGLAND JOURNAL OF MEDICINE

Gabapentin/morphine combination therapy effective

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Gabapentin and opioids have been proposed as first-line therapies for the treatment of neuropathic pain (e.g. painful diabetic neuropathy [PDN] or post-herpetic neuralgia [PHN]).

2 This study investigated whether or not combination therapy with the mechanistically distinct analgesic agents gabapentin and morphine is synergistic; that is, whether or not it results in improved efficacy at low doses, with fewer adverse effects compared to single therapy.

3 This placebo-controlled, double-blind, four-period crossover study randomised 57 people with PDN or PHN to receive placebo (lorazepam), gabapentin, morphine or gabapentin and morphine in combination.

4 Measures of mean daily pain intensity (on a scale of 0–10, with higher numbers indicating more pain) at the maximal dose tolerated with each drug regimen were as follows: 5.72 (baseline); 4.49 (placebo); 4.15 (gabapentin); 3.70 (morphine); 3.06 (gabapentin/morphine combination therapy [$P<0.05$ versus placebo, gabapentin alone and morphine alone]).

5 The maximal tolerable doses of gabapentin and morphine in combination therapy were lower than each drug in isolation.

6 The main side effects of the drugs in combination were constipation, sedation and dry mouth.

Gilron I, Bailey JM, Tu D et al (2005) Morphine, gabapentin, or their combination for neuropathic pain. *New England Journal of Medicine* **352**: 1324–34

The 'Ring of Fire': exploring different painful neuropathy treatments

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In the words of the song, love, like painful neuropathy, is a burning thing. There is no treatment for incurable romantics and so many treatments for painful neuropathy that it is clear that no single therapy is significantly better than any other for all patients. Every trial has a large placebo effect and most drugs provide only partial relief of symptoms. Recently, there has been interest in combinations of gabapentin and opiate analgesia and, in pregabalin, the latest licensed therapy for neuropathic pain.

Gilron et al (see left) describe a small study of morphine and gabapentin, singly and in combination. They conclude that combination therapy reduces the doses of each that are required for treating painful symptoms but overall side effects are increased.

Freynhagen et al (see below) and Richter et al (see page 172) describe two studies from America on the use of pregabalin in patients with neuropathic pain. Between the two studies there were 684 patients. Of these around 87 % had diabetic painful neuropathy. Both studies demonstrated that 300 mg/day of pregabalin was effective in reducing neuropathic pain symptoms compared to placebo. Efficacy was increased by taking 600 mg/day, but the level of side effects also increased significantly at higher doses.

All drug companies compare their newest therapies against placebo. This is for obvious commercial reasons. Hopefully, one day soon we will have an altruistic group who can compare new therapies against the established best so that true evidence-based care can be practised.

As an aside, the other papers in this quarter's section concern revascularisation. Advocates of primary angioplasty are usually specialised centres with selected populations. It is difficult to perform placebo angioplasty and it may be hard to compare the results of these case series with local results on all comers.

PAIN

Effects of fixed-dose versus flexible-dose pregabalin regimens

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Common types of neuropathic pain include post-herpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN).

2 This 12-week, randomised, double-blind, multicentre, parallel-group, placebo-controlled trial examined the use of pregabalin in people with PHN or DPN.

3 Patients were randomised to receive either placebo (n=65) or one of two pregabalin regimens: a fixed-dose scheme (300 mg/day for 1 week, 600 mg/day for 11 weeks; n=132), or a flexible-dosing scheme (150, 300, 450 or 600 mg/day with weekly escalation based on individual patient tolerability and response; n=141).

4 The mean pain score was significantly reduced compared to placebo with both pregabalin dosing regimens (flexible schedule: $P=0.002$; fixed schedule: $P<0.001$).

5 Dizziness, peripheral oedema, weight gain and somnolence were the most frequent side effects observed in those people taking pregabalin.

6 These findings are consistent with previous studies demonstrating that pregabalin use in the treatment of chronic neuropathic pain in DPN or PHN is safe and efficacious.

Freynhagen R, Strojek K, Griesing T et al (2005) Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial. *Pain* **115**: 254–63

'Pregabalin (600 mg/day) is safe and efficacious in the treatment of painful diabetic neuropathy'

THE JOURNAL OF PAIN

Pregabalin safe and efficacious in relief of painful neuropathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study was a 6-week, randomised, placebo-controlled, double-blind, multicentre study examining the effectiveness of pregabalin in treating painful diabetic neuropathy (PDN).

2 Participants (n=246) with PDN were randomised to receive pregabalin (150 or 600 mg/day) or placebo.

3 Mean pain scores, measured at the end of the trial, were lower in patients taking 600 mg/day pregabalin (4.3 versus 5.6 for placebo; *P*=0.0002).

4 The 150 mg/day dose of pregabalin was essentially no different to placebo.

5 Pregabalin (600 mg/day) is safe and efficacious in the treatment of PDN.

Richter RW, Portenoy R, Sharma U et al (2005) Relief of painful diabetic peripheral neuropathy with pregabalin: A randomized, placebo-controlled trial. *The Journal of Pain* **6**: 253–60

'Pre-operative medical optimisation may enhance the prospects of patients undergoing myocardial injury as a result of surgery for critical limb ischaemia'

EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY

Peri-operative myocardial injury and lower limb ischaemia

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The major causes of mortality and morbidity in people undergoing vascular surgery are cardiovascular complications. Over 50 % of deaths are caused by myocardial infarction.

2 This study examined markers of peri-operative myocardial injury (MI; including cardiac troponin I [cTnI], creatine kinase [CK]: CK-myocardial band [CK-MB] ratio and ECG changes) in people operated on for critical lower limb ischaemia.

3 cTnI, CK:CK-MB and ECG were performed pre- and peri-operatively (on days 1, 2 and 3) on 29 patients. Thirty-eight per cent of patients exhibited MI, as measured by elevated cTnI.

4 Pre-operative medical optimisation may enhance the prospects of patients undergoing MI.

Hobbs SD, Yapanis M, Burns PJ (2005) Peri-operative myocardial injury in patients undergoing surgery for critical limb ischaemia. *European Journal of Vascular and Endovascular Surgery* **29**: 301–4

EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY

Assessing peripheral angioplasty as first choice for ischaemia

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 This prospective study aimed to assess the effectiveness of percutaneous transluminal angioplasty (PTA) as a first-choice revascularisation technique in people with diabetes hospitalised for critical limb ischaemia from 1999–2003.

2 Out of 993 patients who successfully underwent PTA, there were 17 major amputations, one death and 33 non-fatal complications. Clinical restenosis was observed in 87 patients. The mean follow-up period was 26±15 months.

3 The authors concluded that PTA is feasible as a first-choice revascularisation technique. Furthermore, it is safe and efficacious for limb salvage in people with diabetes.

Faglia E, Dalla Paola L, Clerici G et al (2005) Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischaemia. *European Journal of Vascular and Endovascular Surgery* **29**: 620–7

JOURNAL OF VASCULAR SURGERY

PTA: 10-year effectiveness in treating ischaemia

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 In recent years, the use of percutaneous transluminal angioplasty (PTA) as a primary revascularisation technique in people with critical limb ischaemia (CLI) has increased.

2 This study aimed to assess the safety, efficacy and long-term effects of using PTA to treat CLI, taking into account limb salvage and continued clinical improvement.

3 PTA was used to treat 111 patients (138 limbs) over the period August 1993–March 2004. The mean follow-up period was 14.7 months (ranging from 1–75 months).

4 There was a technical success rate of 96 % and an initial clinical success rate of 93 %. Within 30 days of the operation, the overall procedure-related complication rate (includes death, acute renal failure and limb loss) was <1 %. The limb salvage rate after 5 years was 89.1 % ± 4.0 % standard error.

5 However, the primary patency rate was low (31 % at 5 years). The authors suggest that this might reflect the CLI population characteristics in the study (e.g. 24 % of patients were older than 80 years; 58 % had diabetes).

6 The authors concluded that PTA is an efficacious, feasible and safe procedure for treating CLI.

Kudo T, Chandra FA, Ahn SS (2005) The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischaemia: A 10-year experience. *Journal of Vascular Surgery* **41**: 423–35