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Treatment of Postherpetic Neuralgia

A Systematic Review of the Literature

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■ OBJECTIVES We wanted to determine whether any treatment had been shown to reduce pain or disability from postherpetic neuralgia (PHN), a common sequela of herpes zoster in elderly patients.

■ STUDY DESIGN We undertook a systematic review of English-language randomized controlled trials (RCTs) of treatments of PHN with evaluation periods longer than 24 hours.

■ DATA SOURCES We systematically searched MEDLINE, Current Contents, and the Cochrane Library. We also searched reference lists of identified trials and reviews and contacted content experts.

■ OUTCOMES MEASURED Two reviewers independently evaluated RCTs for methodologic quality and data extraction. Outcomes of primary focus were pain and quality of life.

■ RESULTS Twenty-seven RCTs met inclusion criteria and were reviewed. Six trials of tricyclic antidepressants found evidence for clinically meaningful effects over 6 weeks. All other treatments were evaluated in no more than 2 trials meeting our inclusion criteria. Topical capsaicin 0.075%, gabapentin, and controlled-release oxycodone were shown to be effective, but the clinically meaningful benefit is difficult to quantify. Intrathecal methylprednisolone and possibly bupivacaine sympathetic blocks are helpful in refractory cases. Other treatments evaluated, including topical lidocaine, had no evidence or inconsistent evidence of benefit.

■ CONCLUSIONS No single best treatment for PHN is known. Tricyclic antidepressants, topical capsaicin, gabapentin, and oxycodone are effective for alleviating PHN; however, long-term, clinically meaningful benefits are uncertain and side effects are common. Patients with PHN refractory to these therapies may benefit from intrathecal methylprednisolone. Little evidence is available regarding treatment of PHN of less than 6 months' duration.

■ KEY WORDS Postherpetic neuralgia [non-MeSH]; pain; zoster; therapy; systematic review [non-MeSH]. (*J Fam Pract 2002; 51:121-128*)

KEY POINTS FOR CLINICIANS

- Spontaneous resolution is common in patients whose postherpetic neuralgia (PHN) has lasted for less than 6 months; treatment decisions are largely empiric and not evidence based.
- For PHN of longer duration, treatments shown to be more effective than placebo include tricyclic antidepressants, topical capsaicin 0.075%, gabapentin, and controlled-release oxycodone. Benefits should be weighed against adverse effects and costs.
- Patients with PHN refractory to currently available and studied topical and oral agents should be considered for intrathecal steroid therapy.

Postherpetic neuralgia (PHN), the most common complication of herpes zoster, is much more prevalent among adults older than 50 years than in younger people.[1,2] The largest English-language prospective study of patients presenting with zoster suggests that the average family physician can expect to see 4 cases of zoster per year and 1 case of PHN lasting more than 3 months every 3 years.[3] Among placebo cohorts from randomized controlled trials (RCTs) of acute zoster treatment, the incidence

TABLE 1

RESULTS

Treatment vs Control	Treatment Duration	Efficacy Results	Adverse Effects
TOPICAL THERAPIES			
Lidocaine patch vs placebo[10]	3-4 weeks	No significant difference between groups in pain VAS improvement. Lidocaine > placebo in 0-5 pain relief scale (2.6 vs 2.1, P = .023).	Not reported clearly, but no significant differences. 1% vs 0 dropouts (because of skin irritation).
Lidocaine patch vs placebo[11]	2-14 days	Lidocaine > placebo in median time to withdrawal because of pain (> 14 days vs 3.8 days, P >.001). More preferred lidocaine (78% vs 10%, P < .001).	28% vs 34% (all skin reactions). 0 vs 6% dropouts.
Capsaicin 0.075% cream vs placebo[12]	6 weeks	Capsaicin > placebo on pain relief VAS (20.9% vs 5.8%). Capsaicin > placebo in improvement in functional capacity (NS).	61% vs 33% skin reactions (P< .05, NNH = 3). 24% vs 3% dropouts (NNH = 4) (mostly skin reactions).
Capsaicin 0.075% cream vs placebo[13]	6 weeks	Capsaicin > placebo in mean change in pain VAS (30% decrease vs 1% increase, P < .05). Capsaicin > placebo for 40% or greater pain relief (54% vs 6%, P < .02, NNT 2).	31% vs 13% skin reactions (NNH = 5). No dropouts (but 3 lost to follow-up).
Benzydamine cream vs placebo[14]	2 weeks	No differences between groups in pain measures or sleep scores. Patients favored vehicle more often than benzydamine.	17% vs 4% skin reactions (NNH = 7). 4% vs 0 dropouts (NNH = 25) (rash).
Benzydamine cream vs placebo[15]	2 weeks	Benzydamine > placebo for proportion reporting pain reduction (52% vs 38%, NS).	Not reported. 4% vs 2% dropouts (NNH = 50) (skin irritation).
ORAL THERAPIES			
Amitriptyline vs lorazepam vs placebo[16]	6 weeks	Amitriptyline > lorazepam or placebo for pain relief "complete" or "a lot" (39% vs 8% vs 8%, P < .001, NNT = 3). Lorazepam >placebo for 1-2 weeks but effect not maintained.	88% vs 98% vs 72% (NNH = 6 for amitriptyline). Amitriptyline adverse effect rate decreased to 62% in final 2 weeks. 5 vs 6 vs 3 dropouts.
Amitriptyline vs placebo[17]	3 weeks	Amitriptyline > placebo for good or excellent results (67% vs 4%, P < .001, NNT = 2). Amitriptyline > placebo in sleep score improvement (P<.001).	67% vs 54% (NNH = 8) (dry mouth, drowsiness, constipation). 4% vs 21% dropouts (appears related to amitriptyline withdrawal symptoms).
Amitriptyline vs Fluphenazine vs combination vs control[18]	8 weeks	Mean decrease in VAS score 29.3 for amitriptyline (P < .001), 12.2 for combination (P= .04), 11.5 for fluphenazine (P = .08), and 5.39 for control (NS).	Incidence not reported. Dry mouth more common with amitriptyline. Sleepiness more common with fluphenazine. One amitriptyline withdrawal because of sedation.
Amitriptyline vs nortriptyline[19]	5 weeks	Both drugs effective. No significant differences in efficacy (including sleep and disability measures).	97% vs 97% (dry mouth, constipation, dizziness). 30% vs 15% intolerable side effects (P = .05, NNH = 7).
Amitriptyline vs maprotiline[20]	5 weeks	Amitriptyline > maprotiline in VAS scales (P < .01). No significant differences in categorical scale of pain relief, sleep or disability ratings.	63% vs 88% (dry mouth, constipation, sedation, dizziness). 34% vs 47% dropouts.
Desipramine vs benztropine[21]	6 weeks	Desipramine > benztropine for pain relief "complete" or "a lot" (42% vs 5%, NNT = 3). Desipramine > benztropine for pain relief rated moderate or better (63% vs 11%, NNT = 2).	100% vs 79% (NNH = 4) (dry mouth, dizziness, constipation). 89% vs 42% side effects in final 2 weeks. 5 vs 3 dropouts.

(continued on next page)

of pain at 3 months has been reported as 17% to 60%; at 6 months, 5% to 39%.[4] There is limited evidence that therapies for acute zoster have an impact on PHN.[4]

This review addresses therapies to reduce pain or improve quality of life in patients with PHN. The condition has been variously defined in terms of timing (either following resolution of acute zoster [rash healing] or a defined time after onset of zoster), duration (any time after zoster or a minimum of 6 months after zoster), and type of pain (such as lancinating pain or allodynia [pain caused by a stimulus that does not nor-

TABLE 1 *(continued)*

RESULTS			
Treatment vs Control	**Treatment Duration***	**Efficacy Results**	**Adverse Effects**
Gabapentin vs placebo[22]	8 weeks	All measures, including quality of life and sleep, favored gabapentin. Gabapentin > placebo for pain much or moderately improved (43.2% vs 12.1%, NNT = 3.2). Gabapentin > placebo for "no pain" at final week (16% vs 8.8%, NNT = 13.9).	55% vs 28% (NNH = 3) (somnolence, dizziness, ataxia). 19% vs 12% (NNH = 15) or 13% vs 10% (NNH = 26) dropouts (reporting inconsistent).
Oxycodone controlled-release vs placebo[23]	4 weeks	Oxycodone > placebo in 1-5 pain relief scale (2.9 vs 1.9) and lower disability scores. No significant differences between groups in pain intensity. More preferred oxycodone (67% vs 11%, *P* = .001, NNT = 2).	76% vs 49% (NNH = 3) (constipation, nausea, sedation). 5 vs 3 dropouts.
Tramadol vs clomipramine with or without levomepromazine[24]	6 weeks	No significant differences between groups in pain intensity. Tramadol > control for pain relief satisfactory or better (90% vs 55%). Tramadol > control for pain relief good or excellent (60% vs 45%).	77% vs 83% (dry mouth and constipation with tramadol). 41% vs 39% dropouts.
Dextromethorphan vs placebo[25]	6 weeks	No significant differences between groups.	100% vs 3% (NNH = 1) (sedation, dizziness, lightheadedness). 22% vs 0 dropouts (NNH = 4).
Memantine vs placebo[26]	5 weeks (7 weeks)	No significant differences between groups.	83% vs 67% (NS) (dizziness, headache, nausea). 25% vs 8% dropouts (NNH = 6).
Acyclovir vs placebo[27]	12 weeks (6 months)	Acyclovir associated with higher pain rating than placebo at some time points. No difference in proportion with clinical improvement (40% vs 40%).	Not reported.
OTHER THERAPIES			
Vincristine iontophoresis vs saline iontophoresis[28]	4 weeks (90 days)	Vincristine < saline for pain relief at 4 weeks (36% vs 56%, NS). Vincristine < saline for pain relief at 90 days (27% vs 33%, NS).	Not explicitly reported. "Most patients complained of a burning sensation at the negative electrode."
Vincristine in DMSO iontophoresis vs saline iontophoresis[29]	4 weeks (6 weeks)	Vincristine > saline for "improved" at 4 weeks (90% vs 10%, NNT = 1) and 6 weeks (60% vs 0, NNT = 2). Most treated patients had "improvement" but none were "cured."	"Most patients were prescribed a mild steroid cream to reduce irritation." "Several burns were seen" but "they were painless." One vincristine death in patient with heart disease.
Acupuncture vs mock TENS[31]	6 weeks (14 weeks)	7 patients in each group were "better" after treatment. No significant differences between treatments.	Not reported. "Auricular acupuncture is a painful and unpleasant experience." 43% vs 9% dropouts.
Acupuncture vs TENS[32]	6 weeks (6 months)	Acupuncture > TENS for pain improvement during treatment (50% vs 7.7%).	All but 1 acupuncture patient dropped out after treatment because of inadequate pain relief.
Intrathecal methylprednisolone plus lidocaine vs intrathecal lidocaine alone vs no treatment[33]	4 weeks (2 years)	92% vs 7% vs 3% had pain relief > 50% at 2 years (*P* < .001, NNT = 1). Similar results in analgesic use.	Not reported formally, but "no clinical complications were observed."
Intrathecal methylprednisolone vs epidural methylprednisolone[34]	4 weeks (24 weeks)	Intrathecal > epidural for global pain relief > 50% at 4 weeks (92% vs 25%, *P* < .01, NNT = 2) and 24 weeks (92% vs 17%, *P* < .01, NNT = 2).	Not reported formally, but "no clinical complications were observed."
Mixture of gangliosides (Cronassial) vs placebo SQ[35]	8 weeks	Mean pain scores and mean sleep scores improved with Cronassial but not placebo.	50% vs 0 (NNH = 2) (injection site pain). 25% vs 0 dropouts (NNH = 4).
Bupivacaine sympathetic blocks vs lidocaine IV[36]	2-3 weeks (1 year)	Bupivacaine had lower pain VAS than lidocaine at 3 months (24 vs 57, *P* < .0001) and 1 year (16 vs 44, *P* < .003). Similar results in global score, including pain, sleep, analgesic use, and incapacity.	"No complications," but side effects not reported.

*Follow-up duration listed in parentheses if separate from treatment duration.
DMSO denotes dimethylsulfoxide; IV, intravenous; NNH, number needed to harm; NNT, number needed to treat; NS, not significant, used for *P* values > .1; SQ, subcutaneous; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale reported as 100-mm scale.

mally provoke pain]).[5,6] PHN may include a spectrum of presentations, from brief intermittent mild pain that resolves spontaneously to chronic persistent disabling pain recalcitrant to multiple therapies. To avoid missing potentially relevant findings, we defined PHN broadly as any pain after cutaneous healing of zoster.

METHODS
Search Strategy
Medline (1966 to present) was searched on October 19, 2000. The search combined the terms "post-herpetic or postherpetic" and "neuralgia or neuropathy

or pain" and publication type "clinical trial (including phases I to IV) or controlled clinical trial or randomized controlled trial." The Cochrane Controlled Trials Registry 2000, Issue 3, was searched with the same terms. Current Contents was searched to identify more recent references. We also identified trials through article reference lists (from included trials and 40 reviews), contact of authors and content experts, and the Food and Drug Administration (FDA) Web site.

Selection Criteria

Inclusion criteria for this review were RCTs that enrolled patients with PHN (history of zoster, pain in the dermatomal distribution of the zoster rash, and pain persisting or occurring after resolution of the zoster rash), addressed relevant end points (pain resolution, pain severity, effect on quality of life), and had full reports available in English. Since responses to initial therapy may change over time, we included only trials with evaluation periods lasting more than 24 hours.

The authors independently evaluated trials meeting these inclusion criteria for quality and independently extracted data. Quality was evaluated using the Jadad scale,[7] which addresses selected criteria (randomization technique, allocation concealment, blinding, accounting of dropouts) and rates methodologic quality on a 5-point scale, with 5 representing the highest score. Differences were resolved through discussion. Trials scoring only 1 point were excluded except for 2 instances noted in our discussion.

RESULTS

Searching identified 186 potential trials, of which 92 were excluded as irrelevant on the basis of titles and abstracts alone. Of the 94 citations reviewed in greater detail, 64 were excluded for the following reasons: not describing a trial (10), not describing a trial of treatment for PHN (10), describing an uncontrolled trial (7), no randomization (7), evaluation period limited to 24 hours or less (13), duplicate publication (4), language other than English (7), not providing results specifically for patients with PHN (3), and available only in abstract form (3). One unpublished trial of mexiletine was identified through a review by Hanania and Brietstein; Dr Hanania informed us, however, that this trial had been stopped early because the treatment group had experienced serious side effects. One controlled trial was excluded because correspondence with the investigator did not confirm that it had been randomized. One trial was excluded because it included only 6 patients with PHN. (A list of excluded studies is available in Table

W1 at http://www.jfponline.com/.)

Of the remaining 27 trials reviewed for methodologic quality, most (16) received a Jadad score of 4. The 2 authors had substantial agreement on quality ratings ($\kappa = 0.75$). Table W2 (available online at http://www.jfponline.com) provides details of treatment regimens, quality ratings, ages of subjects, and duration of PHN. One trial with a Jadad score of 1 was excluded.[8] Most subjects were elderly and had had PHN for longer than 6 months.

Topical Therapies

Topical therapies evaluated were lidocaine, capsaicin, and benzydamine (Table 1). Lidocaine patch therapy is the only agent with a specific FDA indication for PHN. We found few trials supporting the FDA approval. The only published RCT of relatively unselected patients with PHN (n = 35) showed significant benefit versus placebo but was excluded because evaluation sessions had been limited to 12 hours.[9] We reviewed a report of an unpublished RCT comparing lidocaine patch with vehicle placebo used in the application for FDA approval.[10] This trial found a large, statistically significant reduction in pain scores with placebo throughout the 3- to 4-week trial. This trial found a similar statistically significant reduction in pain scores with lidocaine patch and no significant difference comparing lidocaine patch with placebo.

Three findings in the unpublished trial were used to support arguments for efficacy: (1) a statistically significant difference in the pain relief score at the final visit; (2) differences in allodynia (based on investigators' sensory skin testing, described as stroking the maximally painful area with a foam brush and recording the pain scale rating) at the beginning of the trial; and (3) a greater increase in pain scores among lidocaine subjects upon trial conclusion (ie, after stopping study medication). The clinical relevance of these 3 findings is unclear.

The FDA declined to approve lidocaine patch therapy on the basis of these 2 studies and required an additional trial to demonstrate benefit. An "enriched enrollment study" involved subjects who had used lidocaine patch for at least 1 month and received at least moderate relief but had pain without the patch.[11] Lidocaine patch was clearly effective in this highly selected cohort.

Capsaicin 0.075% cream was effective in 2 trials of patients with severe refractory PHN.[12,13] The benefit appeared modest in the larger trial (pain was eliminated or nearly eliminated in less than 20% of capsaicin patients) and greater in the smaller trial. Blinding had limited efficacy because of the stinging effect of capsaicin.

Benzydamine cream, an antiprostaglandin, was not effective in a 2-week crossover trial.[14] The cream showed a nonsignificant trend for pain reduction in an earlier 2-week crossover trial.[15]

Oral Therapies

Oral therapies evaluated were tricyclic antidepressants, gabapentin, oxycodone, tramadol, dextromethorphan, memantine, acyclovir, lorazepam, and fluphenazine (Table 1).

Tricyclic antidepressants have been shown to be effective in multiple small short-term crossover trials. Amitriptyline was highly effective in 2 placebo-controlled trials.[16,17] In 1 of these trials, amitriptyline was more effective than lorazepam.[16] In another trial, amitriptyline was more effective than fluphenazine (a phenothiazine) and glycopyrrolate placebo.[18] Nortriptyline was as effective as amitriptyline in a comparison trial,[19] while maprotiline was not.[20] Desipramine was highly effective in a trial using benztropine as an "active placebo" in that the anticholinergic properties of benztropine were used to match the side effects of desipramine.[21] In all these studies, the analgesic effects of tricyclic antidepressants appeared independent of antidepressant effects. No randomized trial data were collected to assess the use of antidepressants for longer than 8 weeks.

Gabapentin, an anticonvulsant, was effective in a single large placebo-controlled trial.[22] The number needed to treat (NNT) was 3.2 for the outcome of moderate or better pain relief and 13.9 for the outcome of no pain during the eighth week of treatment. The proportion of patients whose pain was much improved or who had no pain was not reported.

Controlled-release oxycodone was effective in a crossover trial in which 45% of patients had previously used opioids.[23] Tramadol may be effective but was not compared against placebo.[24] High-dose dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist, was not shown to be effective for PHN in a small crossover trial.[25] Memantine, another NMDA antagonist, was also ineffective.[26] Acyclovir did not show any greater efficacy than placebo in a small trial.[27] Lorazepam and fluphenazine did not show statistically significant benefit in comparison with placebo in the amitriptyline trials.[16,18]

Other Therapies

Other therapies evaluated were vincristine iontophoresis, acupuncture, intrathecal methylprednisolone, and subcutaneous administration of a mixture of gangliosides (Table 1).

Iontophoresis is a process whereby topical medications are applied via electricity. Vincristine iontophoresis was no more effective than saline iontophoresis in one small trial.[28] Vincristine and dimethylsulfoxide iontophoresis was effective at reducing but not eliminating pain in another small trial.[29] Dimethylsulfoxide may have an independent analgesic effect.[30]

Acupuncture was no more effective than mock transcutaneous electrical nerve stimulation (TENS) in 1 trial,[31] while a smaller trial suggested a short-term effect.[32]

Intrathecal methylprednisolone acetate plus lidocaine was highly effective for achieving good or excellent results (pain relief > 50%) in patients with longstanding PHN refractory to multiple conventional therapies.[33] All patients whose response to methylprednisolone was poor (8%) had had PHN for more than 5 years. The intrathecal route appears more effective than the epidural route of administration.[34]

A mixture of gangliosides given by subcutaneous injection was more effective than placebo, but poor tolerability and derivation from bovine brain tissue severely limit its acceptability.[35]

Sympathetic blocks using bupivacaine were more effective than intravenous lidocaine infusions in 1 trial,[36] but results were not reported in a fashion that conveys the proportion of patients who improved significantly.

DISCUSSION

Effective Therapies

The therapy for which evidence for efficacy is best is tricyclic antidepressants. Three placebo-controlled RCTs demonstrated that only 2 to 3 patients with PHN need to be treated to achieve 1 good or excellent result (NNT = 2-3). Since none of these studies lasted longer than 8 weeks, the long-term efficacy of antidepressants for the treatment of PHN is unknown. Follow-up of 10 patients who did well in 1 antidepressant trial found that only 2 patients were still doing well at 2 years.[19]

Other therapies shown to be effective in 1 or 2 trials are topical capsaicin 0.075%, gabapentin, and controlled-release oxycodone. For these studies, it is difficult to determine the number needed to treat for "meaningful" clinical benefit, although gabapentin demonstrated superiority to placebo in numerous quality-of-life measures.

For patients with severe PHN refractory to other treatments, 2 trials support benefit from intrathecal methylprednisolone and 1 trial suggests benefit from bupivacaine sympathetic blocks. Cost data for selected therapies are presented in Table 2.

Therapies Not Proved Effective

Therapies of uncertain benefit that have not been adequately studied in randomized controlled trials include lidocaine patch, benzydamine cream, tra-

COSTS OF SELECTED DRUG THERAPIES

Medication	Typical Dosing	Amount for 30 days	AWP* (Generic)	Local Pharmacy Charge† (Generic)
Amitriptyline (Elavil)	75 mg nightly[17]	Ninety 25-mg tablets	$42.35 ($9.86 to $31.95)	$35.72 ($11.62)
		Thirty 75-mg tablets	$34.38 ($7.41 to $26.00)	$42.78 ($10.98)
Nortriptyline (Pamelor)	75 mg nightly[19]	Ninety 25-mg tablets	$125.99 ($30.86)	$133.46 ($26.78)
		Thirty 75-mg tablets	$120.64 ($64.94)	$128.72 ($18.84)
Capsaicin 0.075% (Zostrix)	Apply 4 times daily	Two 60-g tubes	$32.40 ($23.98)	$27.46 ($11.94)
Gabapentin (Neurontin)	1,200 mg 3 times daily	#180 600-mg tablets	$381.83	$369.62
Oxycodone (OxyContin)	20 mg every 12 hours	Sixty 20-mg tablets	$142.67	$150.78
Lidocaine patch (Lidoderm)	Up to three 700-mg patches for up to 12 hours per day	Ninety 700-mg patches	$394.14	$388.72

*AWP denotes average wholesale price, AmeriSource ECHO Retail Price Program, version 3.1q, (c) 1991-2000, March 5, 2001.
† Includes pharmacy dispensing fee from local (Columbia, Mo.) branch of national pharmacy chain for 30 days, March 5, 2001.

madol, and vincristine (and/or dimethylsulfoxide) iontophoresis.

Therapies unlikely to be beneficial based on single trials include lorazepam, fluphenazine, dextromethorphan, memantine, acyclovir, and acupuncture. Most of the negative trials did not report power; therefore, potential benefits of these treatments cannot be excluded.

Safety and Tolerability

The rates of adverse effects are high in all effective oral and topical therapies (Table 1). This situation is of special concern in elderly patients who have comorbid conditions and are taking multiple medications. Two tricyclic antidepressant trials[16,21] report a decreased incidence of side effects over time. The researchers emphasize the importance of starting at the lowest available dose with oral therapies and titrating slowly as indicated and tolerated.

No clinical complications were observed in the intrathecal steroid trials; specific side effects were not reported.

Lidocaine patch therapy has been promoted as causing clinically insignificant serum levels, no systemic side effects, and no drug–drug interactions.[11] However, the largest lidocaine patch RCT was too small to rule out significant but uncommon risks such as ventricular arrhythmia.[10] One death that could potentially be attributed to lidocaine absorption occurred in a patient with diffuse vascular disease who was on chronic hemodialysis for renal failure. Blood lidocaine levels were not obtained because venous access was poor.

Limitations

Variations in outcomes limit comparative conclusions. Sindrup and Jensen[37] reviewed treatments for neuropathic pain and presented data based on a suc-

cessful outcome defined as 50% reduction in pain scores, 50% pain relief, or categorical ratings of excellent, good, or moderate pain relief. Most studies used visual analog scales, but it is not clear that a 50% reduction in these measures is equivalent to clinically meaningful benefits at all levels of pain. We attempted to determine NNT data based on clearly meaningful outcomes such as "excellent or good," "complete," or "marked" pain relief as distinct from "moderate" or "some," but found these data unavailable in most reports. Quality-of-life measures, such as sleep and disability ratings, may be more important than measures of pain, but were reported in only one third of the trials.

We may have failed to include relevant trials. We identified 7 potentially relevant non–English language studies. Five had no abstracts available.[38-42] One single-blind trial reported reduced pain scores with topical prostaglandin E1 dissolved in Vaseline.[43] One trial compared iontophoresis with lidocaine and iontophoresis with 3 different calcium channel blockers in 10 patients. The authors found that all 4 treatments reduced pain, but had not included a placebo control group.[44] We also contacted 15 content experts to identify reports of unpublished trials; none of the 6 responses received identified such reports.

The evidence base for treatment of PHN is limited. Among the RCTs reviewed, 78% enrolled 50 or fewer patients. Because most of the subjects had PHN lasting longer than 1 year, our conclusions may not apply to patients with PHN of shorter duration. The latter group represents the majority of subjects with PHN presenting to primary care physicians.

We used the Jadad scale[7] as an attempt to quantitatively assess the methodologic quality of the studies we reviewed. In general, explicit validity checklists with summary scores have not consistently been shown to provide more reliable assessments of valid-

ity than qualitative assessments.[45-47] The Jadad scale is the first validity checklist that has some rigorous evidence supporting its use,[7,48] although its inter-rater reliability has been questioned.[49] We found the Jadad scale had an inherent bias against therapies that could not be adequately double-blinded. Thus 2 trials with a score of 1 were included.[29,36] In 1 trial of vincristine iontophoresis, the authors described the trial as single-blinded and provided ample explanation of why double-blinding was not achieved.[29] In 1 trial of sympathetic blocks, the treatment studied included an invasive procedure; therefore, there was no apparent way for the procedure itself to be double-blinded.[36]

The Jadad scale does not account for some threats to validity of included studies. We encountered numerous methodologic flaws, such as lack of intention to treat analysis in parallel trials (11) and lack of washout periods in crossover trials (4). Further limitations to interpretation of selected study results included potentially significant baseline differences between groups (8), small numbers, and short study durations. A list of the studies with these specific methodologic concerns is available in Table W3 at http://www.jfponline.com/.

CONCLUSIONS

For patients with PHN lasting less than 6 months, spontaneous resolution is common and treatment decisions are largely empiric and not evidence based. For PHN of longer duration, treatments shown to be more effective than placebo include tricyclic antidepressants, topical capsaicin 0.075%, gabapentin, and controlled-release oxycodone. These treatments all have adverse effects or costs that need to be considered on an individual basis. Lidocaine patch therapy may be safer for most patients but may be no more effective than placebo and is not suitable for patients with trigeminal PHN. Patients with PHN refractory to the currently available and studied topical and oral agents should be considered for intrathecal steroid therapy.

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