Strategies for the Prevention of Postherpetic Neuralgia

(excluding herpes zoster vaccination)

Robert H. Dworkin, PhD

Professor of Anesthesiology, Neurology, Oncology, and Psychiatry

University of Rochester School of Medicine and Dentistry

Dorsal horn atrophy, dorsal root ganglion fibrosis, and loss of epidermal nerve fibers on the affected side in PHN

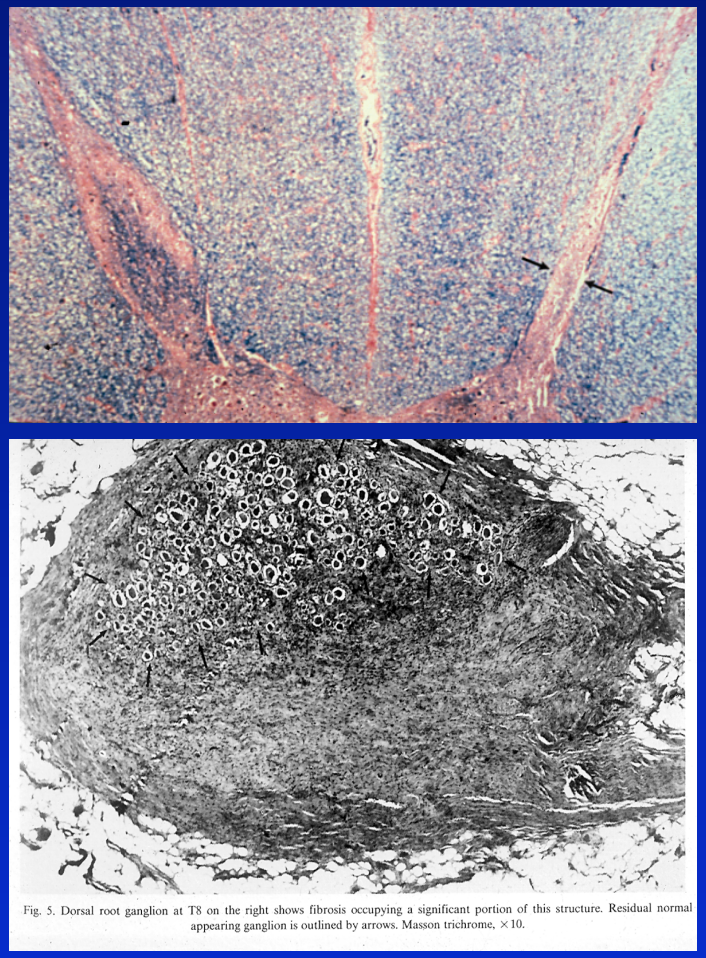
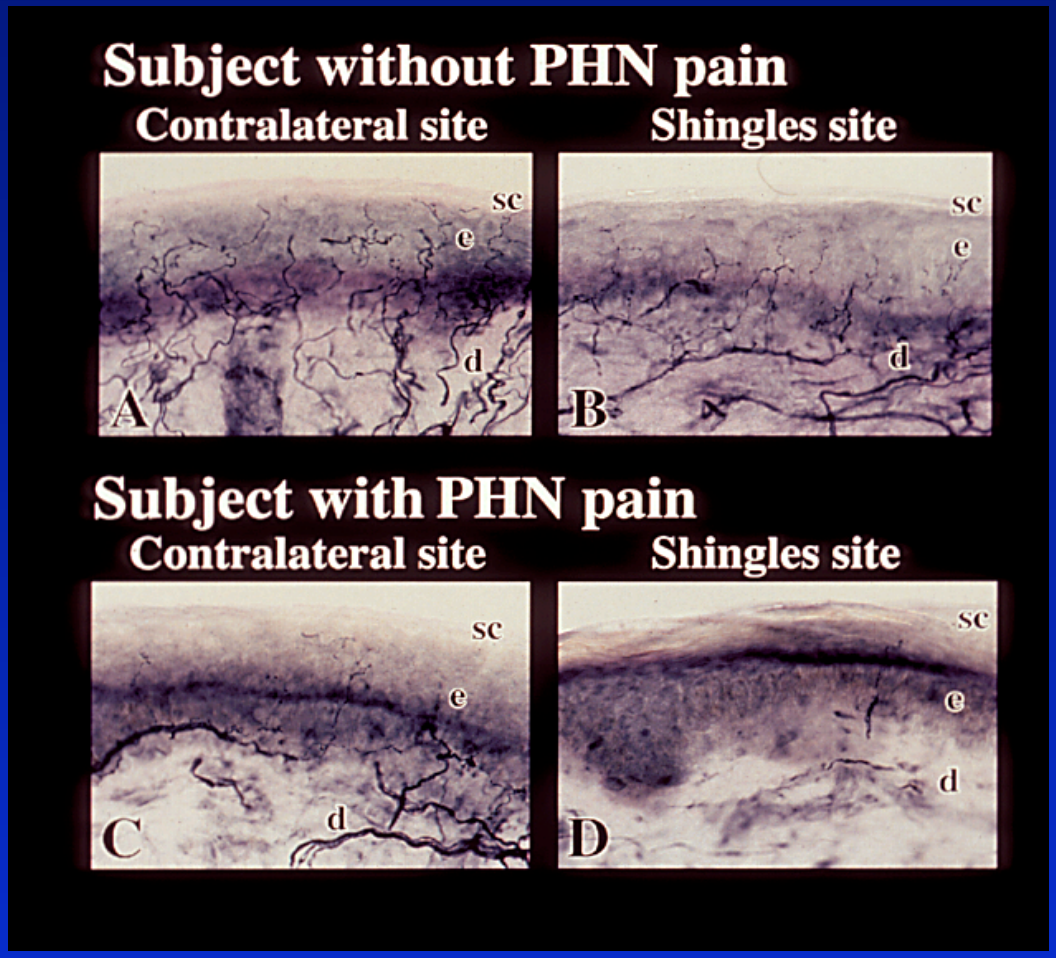


Fig. 5. Dorsal root ganglion at T8 on the right shows fibrosis occupying a significant portion of this structure. Residual normal appearing ganglion is outlined by arrows. Masson trichrome, ×10.

Watson CPN, et al.
Pain, 1988;34:129-138.



Oaklander AL, et al.
Annals of Neurology, 1998;44:789-795.

Proportion of patients developing PHN: famciclovir vs. placebo

	Days following enrollment					
	30			60	90	
120	150	180				
Patients ≥ 18 yrs						
Famciclovir	41.3	38.2	27.9*		24.6*	
20.4*	15.0*					
Placebo	44.1	39.5	32.7	29.6	26.4	23.8
Patients ≥ 50 yrs						
Famciclovir	54.6	50.1	34.9*		28.8*	
25.8*	19.5*					
Placebo	67.9	61.1	49.2	45.8	42.2	40.3

Risk factors for PHN

1. Older age
2. More severe acute pain
3. Greater rash severity
7. Presence of a prodrome
8. Female sex
9. Trigeminal distribution
10. Greater sensory abnormalities in the affected dermatome
11. Generalized subclinical polyneuropathy
12. More pronounced immune responses
13. HIV infection, organ transplant, connective tissue disease
14. MRI brainstem and cervical cord abnormalities
15. Viremia
16. CSF interleukin 8 concentration (at rash healing)
17. HLA-A haplotype (*3303-B*4403-DRB1*1302)
18. Fever ≥ 38°C

Greater acute pain is a risk factor for PHN

1.	Riopelle et al.	1984	72
2.	Harding et al.	1987	71
3.	Dworkin et al.	1992	19
4.	Leijon et al.	1993	52
5.	Cioni et al.	1994	52
6.	Beutner et al.	1995	1141
7.	Bruxelle	1995	301
8.	McKendrick and Wood	1995	160
9.	Whitley et al.	1996	208
10.	Wood et al.	1996	316
11.	Dworkin et al.	1998	419
12.	Meister et al.	1998	635
13.	Söltz-Szöts et al.	1998	511
14.	Harrison et al. (AIDS)	1999	170
15.	Decroix et al.	2000	1897
16.	Haanpää et al.	2000	113
17.	Tyring et al.	2000	597
18.	Zaal et al.	2000	81
19.	Scott et al.	2003	165
20.	Jung et al.	2004	965
21.	Kotani et al.	2004	170

Whitley RJ, Shukla S, Crooks RJ. The identification of risk factors associated with persistent pain following herpes zoster. Journal of Infectious Diseases, 1998;178:S71–S75.

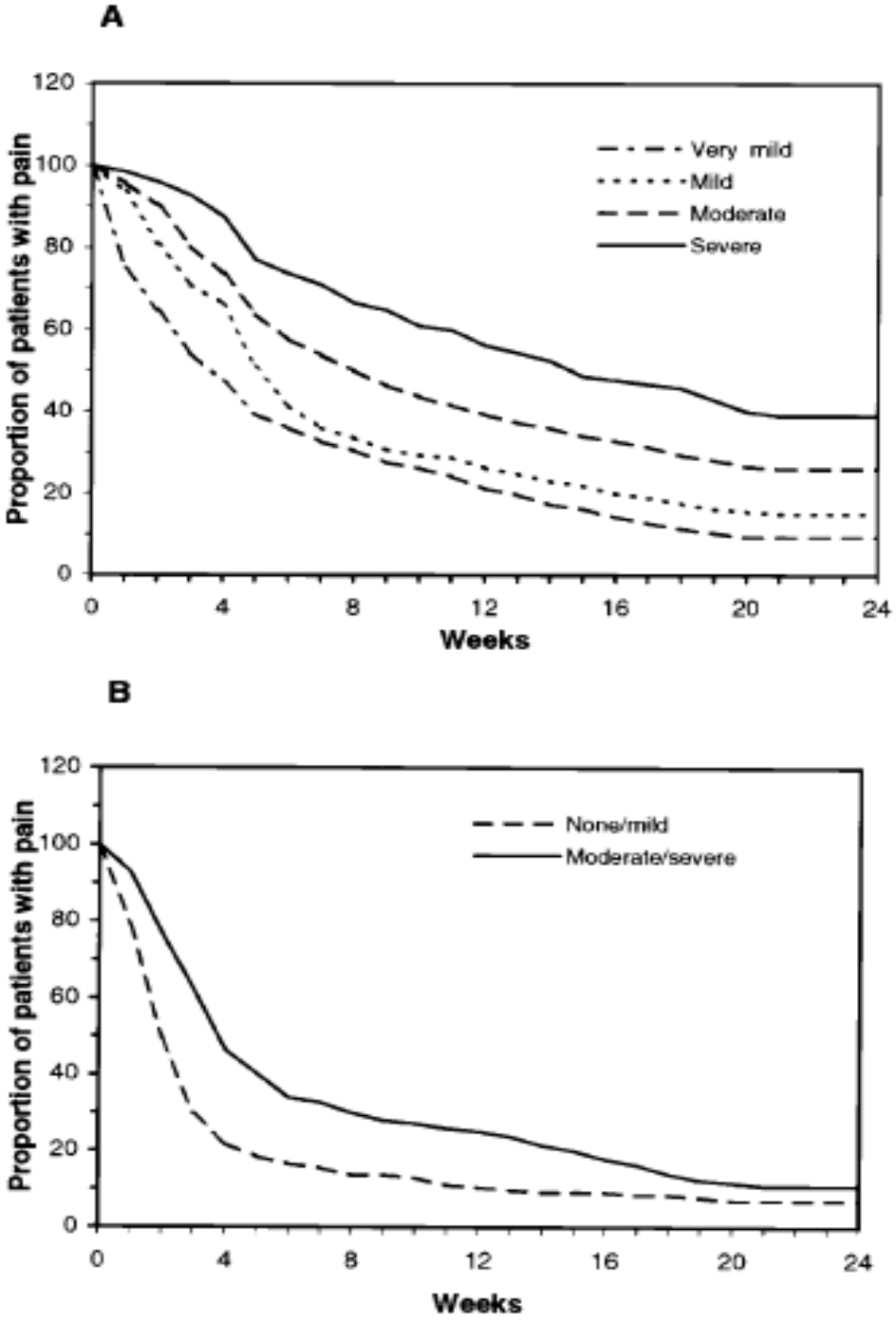


Figure 1. Duration of zoster-associated pain according to pain severity at presentation in trial 5 patients, who were ≥50 (A) or trial 4 patients who were <50 (B) years old. A, For very mild vs. severe pain, hazard ratio (HR) = 3.00 (confidence limit [CI] = 2.26–3.99; P = .0001); for mild vs. severe pain, HR = 2.23 (CI = 1.69–2.95; P = .0001); for moderate vs. severe pain, HR = 1.58 (CI = 1.21–2.06; P = .0007). B, For mild vs. severe pain, HR = 1.69 (CI = 1.34–2.13; P .0001).

If you come to a fork in the road, take it.

— Yogi Berra

Is severe acute pain a *modifiable* risk factor?

YES

Is severe acute pain a *causal* risk factor?

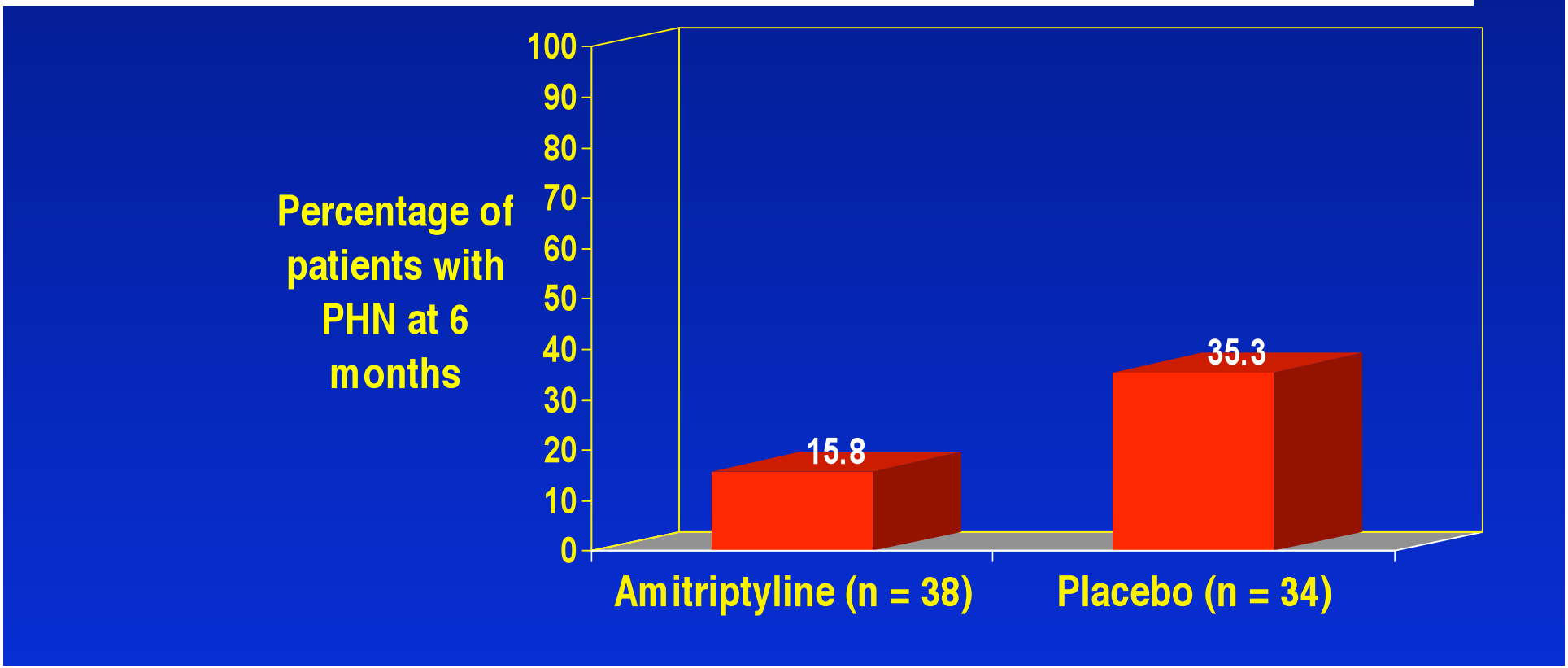
HAS BEEN A REASONABLE HYPOTHESIS,

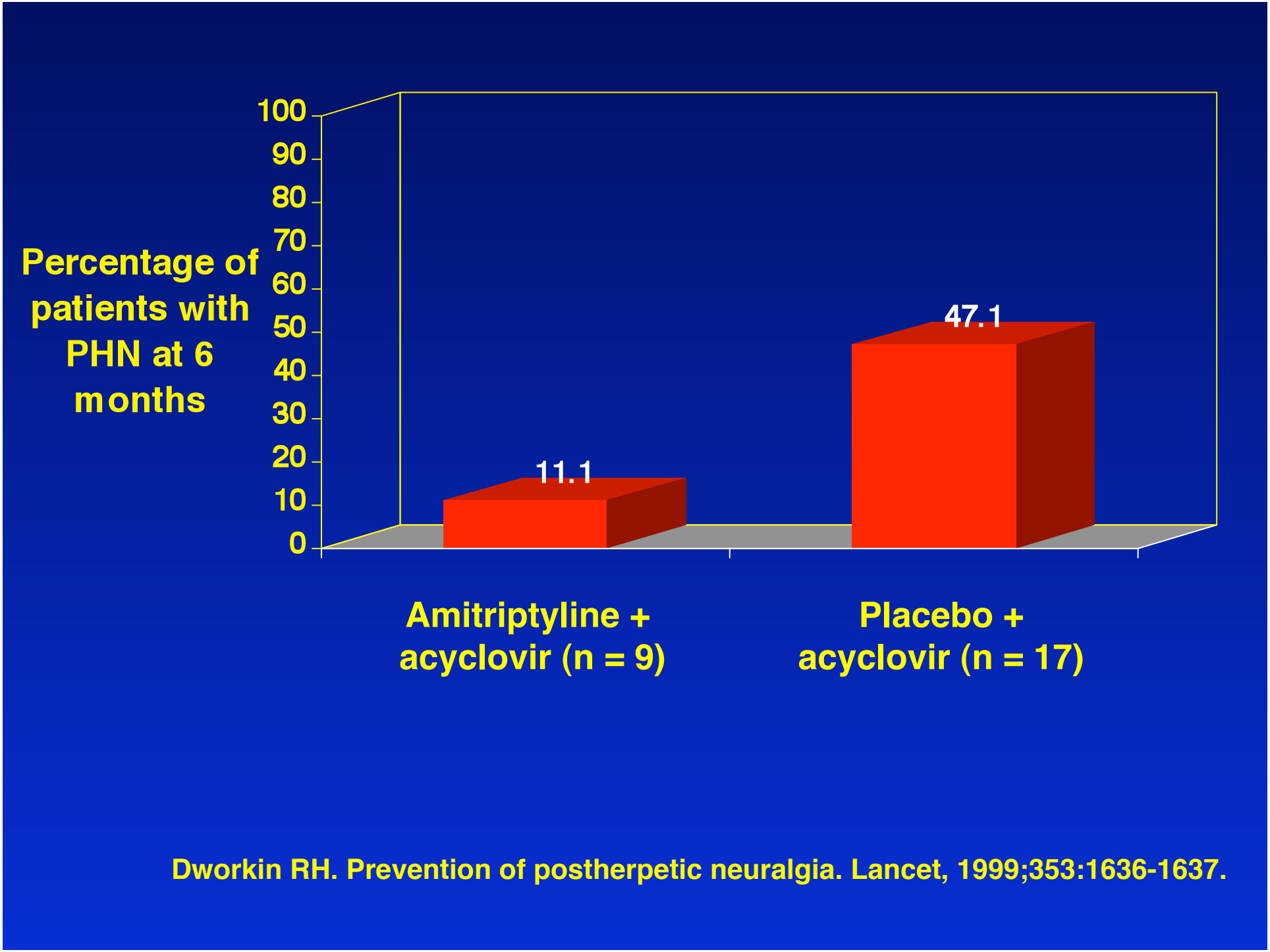
BUT MAYBE NOT…

Original Article

The Effects of Pre-Emptive Treatment of Postherpetic Neuralgia with Amitriptyline: A Randomized, Double-Blind, Placebo-Controlled Trial

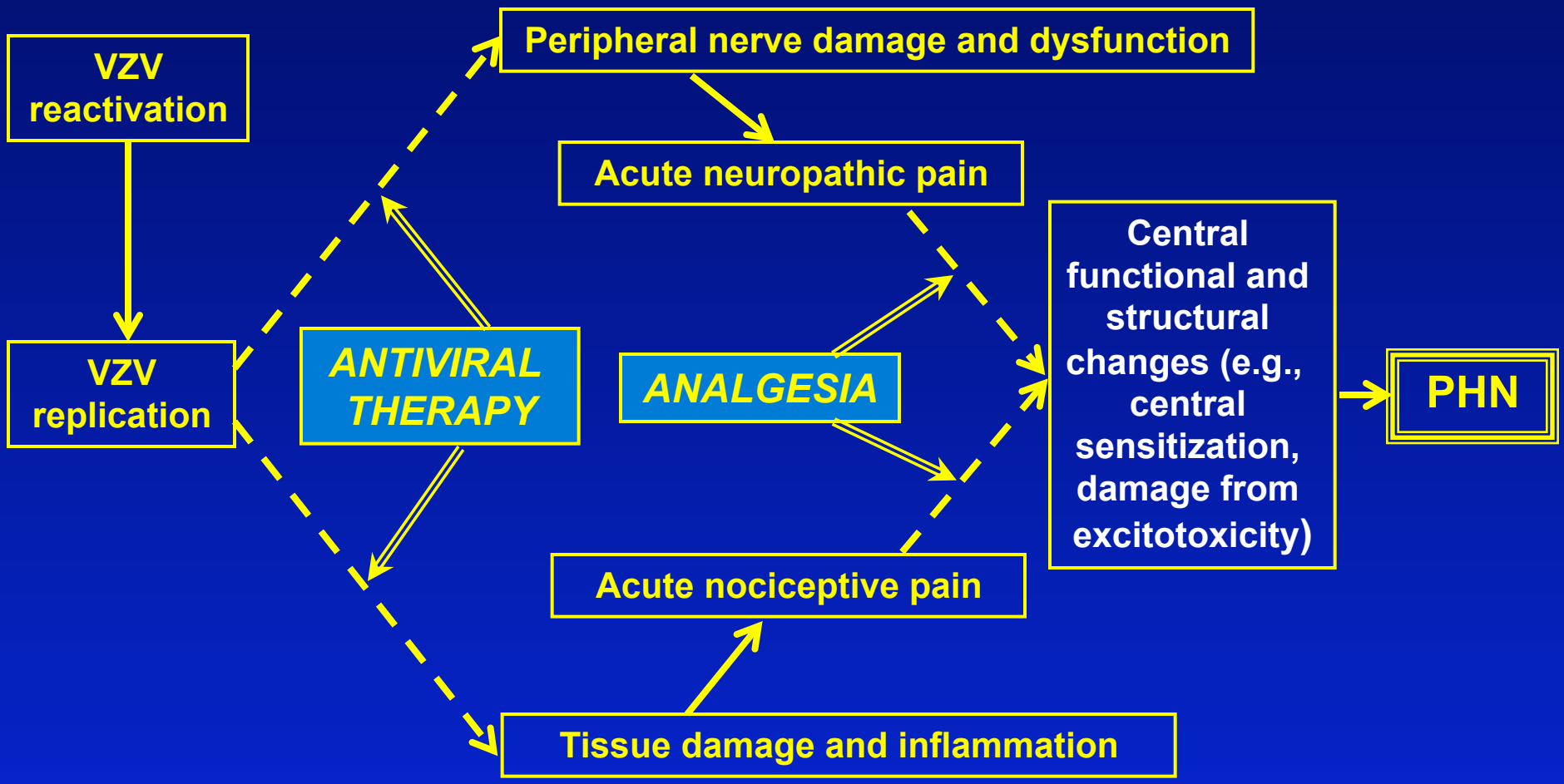
David Bowsher, MD, PhD, FRCPEd, FRCPath
Pain Research Institute, Walton Hospital, Liverpool, United Kingdom





Dworkin RH. Prevention of postherpetic neuralgia. Lancet, 1999;353:1636-1637.

Preventing PHN by attenuating nerve damage and acute pain in herpes zoster



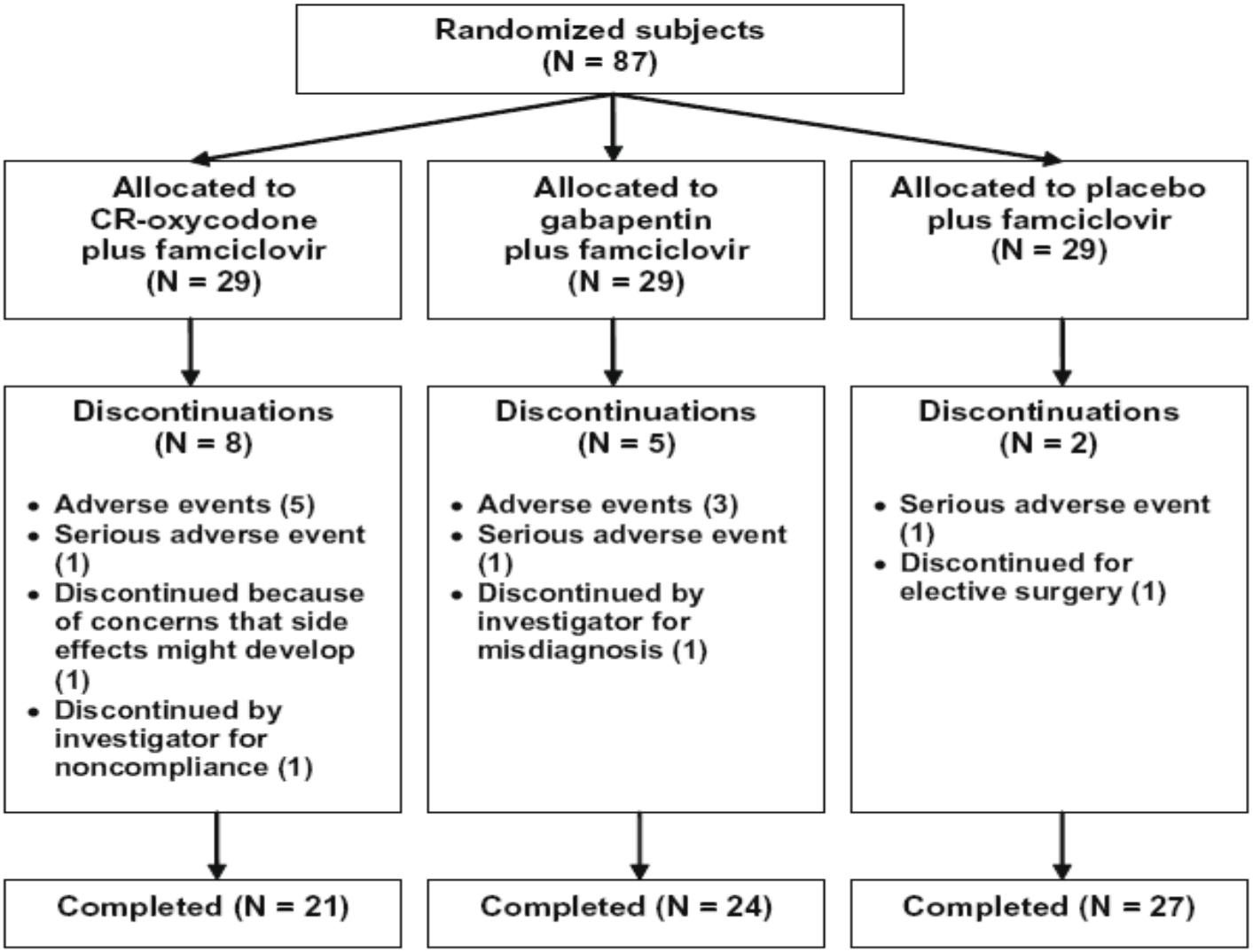
VZV = varicella-zoster virus

Dworkin RH, et al. Clinical Journal of Pain, 2000;16:S90-S100.

A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster

Robert H. Dworkin [a,*], Richard L. Barbano [b], Stephen K. Tyring [c], Robert F. Betts [d], Michael P. McDermott [e], Janet Pennella-Vaughan [f], Gary J. Bennett [g], Erhan Berber [h], John W. Gnann [i], Carrie Irvine [j], Cornelia Kamp [b], Karl Kieburtz [b], Mitchell B. Max [k], Kenneth E. Schmader [l]

Pain, 2009;142:209-217



	mean	≥ 30% response		LS difference*	
CR-oxycodone vs. placebo					
days 1-8	-1.26	.01		55 vs. 28%	.03
days 1-14	-1.22	.02		79 vs. 45%	.01
days 1-28	-.78	.14		86 vs. 76%	.32
Gabapentin vs. placebo					
days 1-8	-.75	.13		34 vs. 28%	.57
days 1-14	-.44	.37		55 vs. 45%	.43
days 1-28	.00	>.99		62 vs. 76%	.26

*Least squares mean difference between groups in mean daily diary worst pain. Intention-to-treat analysis with last observation carried forward in patients with at least one post-randomization diary.

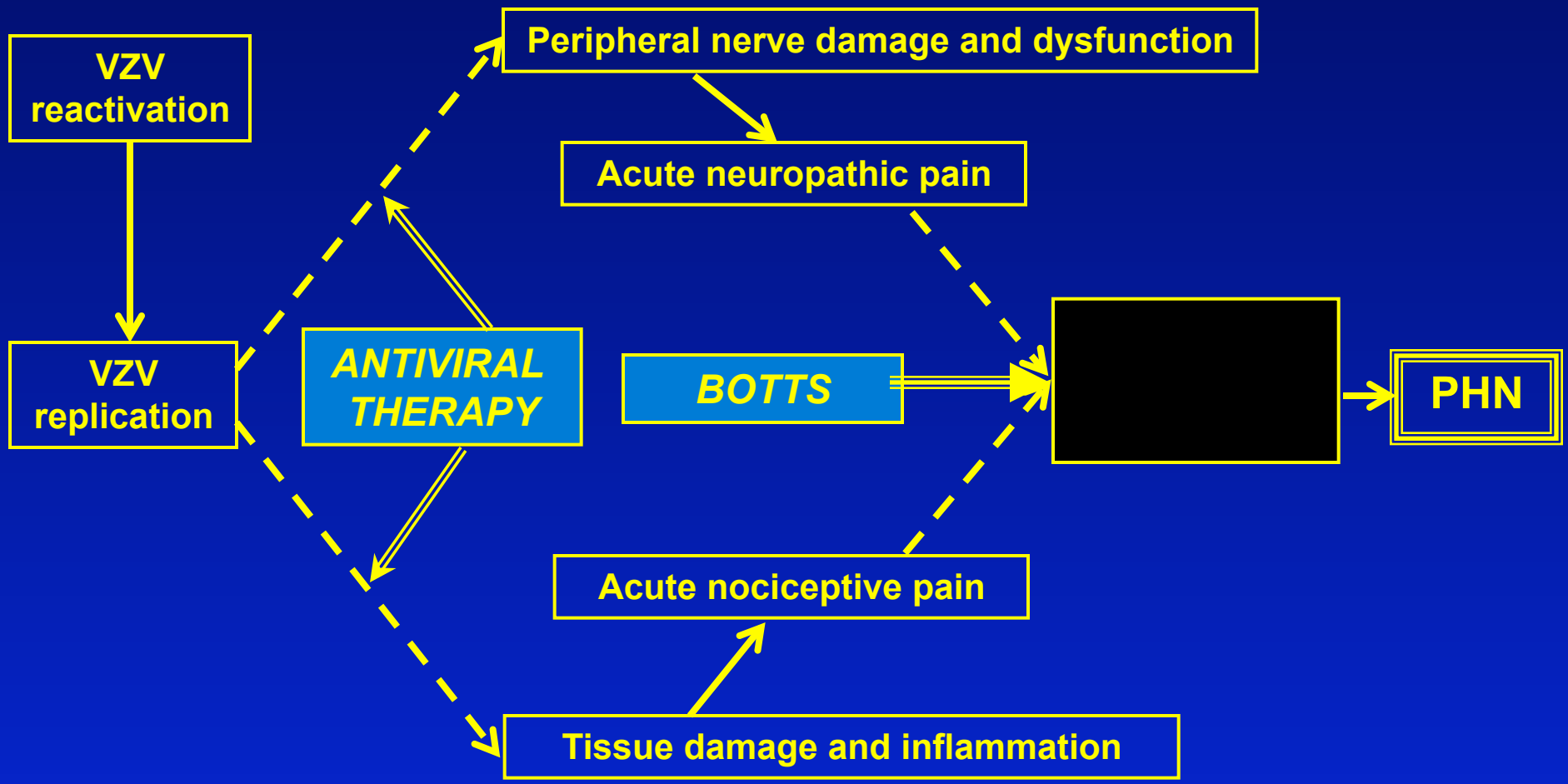
Table 2. Corticosteroid and analgesic medications that can be considered for treatment of patients with herpes zoster

Medication	Beginning dosage	Titration	Maximum dosage	Most common adverse effects
1. Opioids	5 mg every 4 h as needed; dosage can be converted to long-acting opioid analgesic combined with short-acting medication continued as needed	Increase by 5 mg 4 times daily every 2 days as tolerated	No maximum dosage with careful titration; consider evaluation by a pain specialist at dosages >120 mg daily	Nausea/vomiting, constipation, sedation, dizziness
or				
Tramadol	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 2 days as tolerated	400 mg daily (100 mg 4 times daily); for patients >75 years of age, 300 mg daily in divided doses	Nausea/vomiting, constipation, sedation, dizziness, seizures, postural hypotension
2. Gabapentin	0 mg at bedtime or 100–300 mg 3 times daily	Increase by 100–300 mg 3 times daily every 2 days as tolerated	3600 mg daily (1200 mg 3 times daily); reduce if renal function is impaired	Sedation, dizziness, peripheral edema
or				
Pregabalin	75 mg at bedtime or 75 mg twice daily	Increase by 75 mg twice daily every 3 days as tolerated	600 mg daily (300 mg twice daily); reduce if renal function is impaired	Sedation, dizziness, peripheral edema
3. TCAs	25 mg at bedtime	Increase by 25 mg daily every 2–3 days as tolerated	150 mg daily	Sedation, dry mouth, blurred vision, weight gain, urinary retention[c]
{Oral corticosteroids}	daily for 7 days	After 60 mg daily for 7 days, decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days, and then discontinue	60 mg daily	Gastrointestinal distress, nausea, changes in mood, edema

[a] Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 5 mg twice daily for oxycodone); dosages given are for short-acting formulations.
[b] Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 10 mg at bedtime for tricyclic antidepressants).
[c] Consider a screening electrocardiogram for patients ≥40 years of age.

Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al.
Clinical Infectious Diseases, 2007;44(suppl 1):S1-S26.

Preventing PHN by attenuating nerve damage and targeting the TS in zoster



VZV = varicella-zoster virus

Dworkin RH, et al. Clinical Journal of Pain, 2000;16:S90-S100.

BOTTS (blockers of the transition state)

1. Glial cell modulators (PPF, AV-411)
2. GCH1 inhibitors
3. Pain sensitivity
4. Catastophizing
5. Expectations

Shingles Trial of Oral Medication to Prevent Postherpetic Neuralgia (STOMP-PHN)

- Morphine or matching placebo for 28 days in herpes zoster patients all treated with famciclovir beginning within 5 days of rash onset.
- Primary endpoint: incidence of PHN defined as presence of any pain in the affected dermatome 120 days after rash onset.
- 95% power to detect a reduction in the incidence of PHN from 25% in the placebo group to 12.5% in the morphine group (80% power to detect a reduction of 25% to 15%).
- Requires 250 patients per group, inflated to 300 patients per group to account for the anticipated 16% withdrawal rate.
- Total sample size = 600 patients.

Shingles Trial of Oral Medication to Prevent Postherpetic Neuralgia (STOMP-PHN)

- Morphine or matching placebo for 28 days in herpes zoster patients all treated with famciclovir beginning within 5 days of rash onset.
- Primary endpoint: incidence of PHN defined as presence of ***any pain*** in the affected dermatome 120 days after rash onset.
- 95% power to detect a reduction in the incidence of PHN from 25% in the placebo group to 12.5% in the morphine group (80% power to detect a reduction of 25% to 15%).
- Requires 250 patients per group, inflated to 300 patients per group to account for the anticipated 16% withdrawal rate.
- Total sample size = 600 patients.

Primary endpoints for PHN prevention RCTs:

1. Any pain 4 (or 6) months after rash onset.
2. Pain intensity (e.g., 0-10 scale) 4 (or 6) months after rash onset.
3. Clinically significant pain (e.g., ≥ 3/10) 4 (or 6) months after rash onset.
4. Time to resolution of any zoster-associated pain (ZAP).
5. Time to resolution of clinically significant ZAP.
6. Area under a pain intensity-by-duration curve.
7. Area under a "truncated" pain intensity-by-duration curve (e.g., Oxman burden of illness).

Pain 107 (2004) 202–206

PAIN

www.elsevier.com/locate/pain

Topical review

Interventions to prevent postherpetic neuralgia: cutaneous and percutaneous techniques

Wim Opstelten[a,*], Albert J.M. van Wijck[b], Robert J. Stolker[c]

1. Topical local anesthetics
2. Subcutaneous local anesthetics and corticosteroids
3. Sympathetic blocks
4. Epidural blocks
5. Other invasive interventions

"As most studies were uncontrolled and often of limited size, we cannot conclude that the interventions resulted in a lower incidence of PHN than could be expected from the natural course of pain in HZ.

Moreover, differences in endpoints, PHN definition, and inclusion and exclusion criteria make the results of the studies almost impossible to compare."

—Opstelten, van Wijck, Stolker, 2004

Optimum Pain Relief With Continuous Epidural Infusion of Local Anesthetics Shortens the Duration of Zoster-Associated Pain

(*Clin J Pain* 2004;20:302–308)

Haruhiko Manabe, MD, Kenjiro Dan, MD,†‡ Kazuhiko Hirata, MD,† Koichiro Hori, MD,† Shinjiro Shono, MD,† Shinichiro Tateshi, MD,* Hiroyuki Ishino, MD,* and Kazuo Higa, MD†*

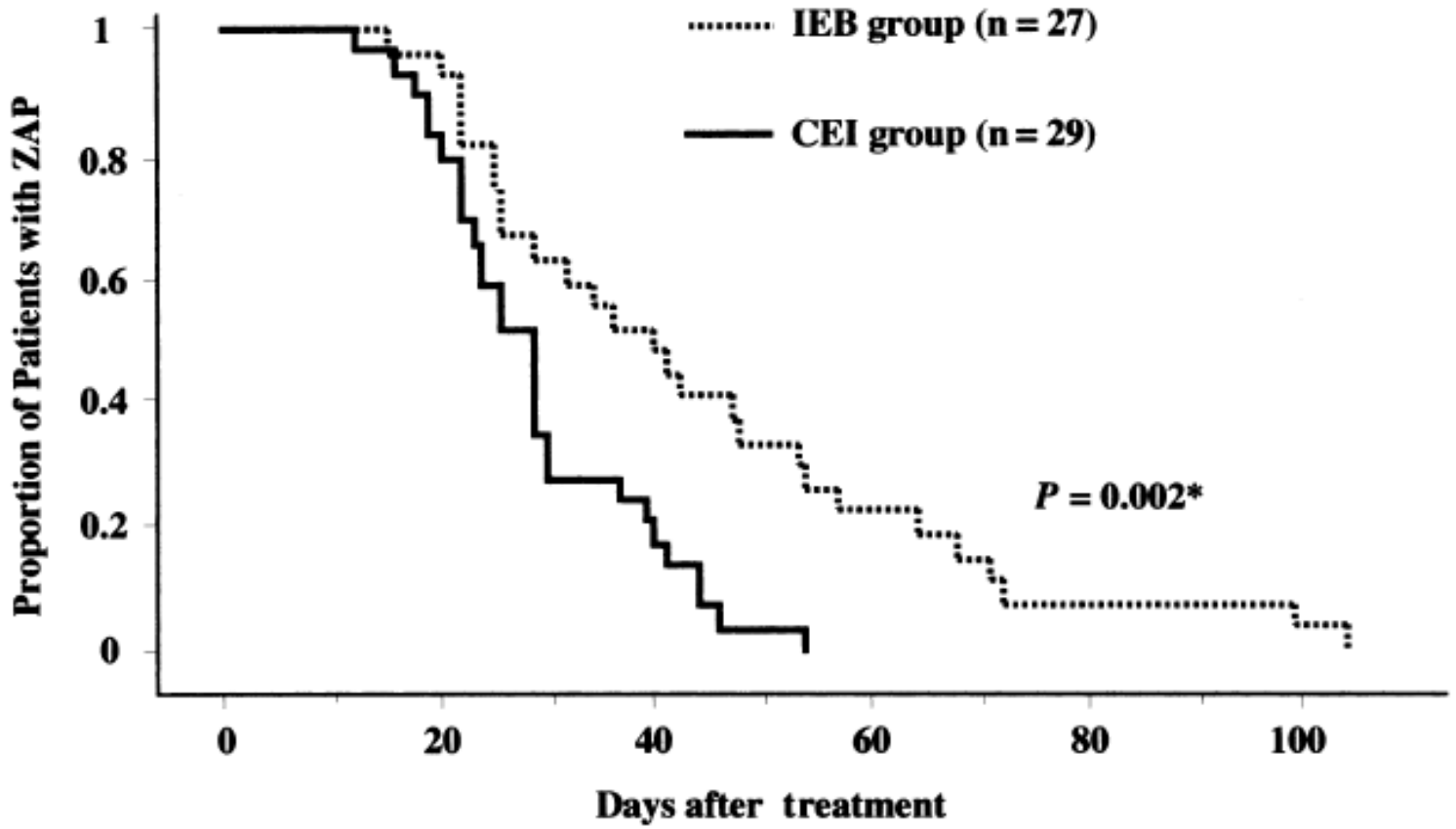
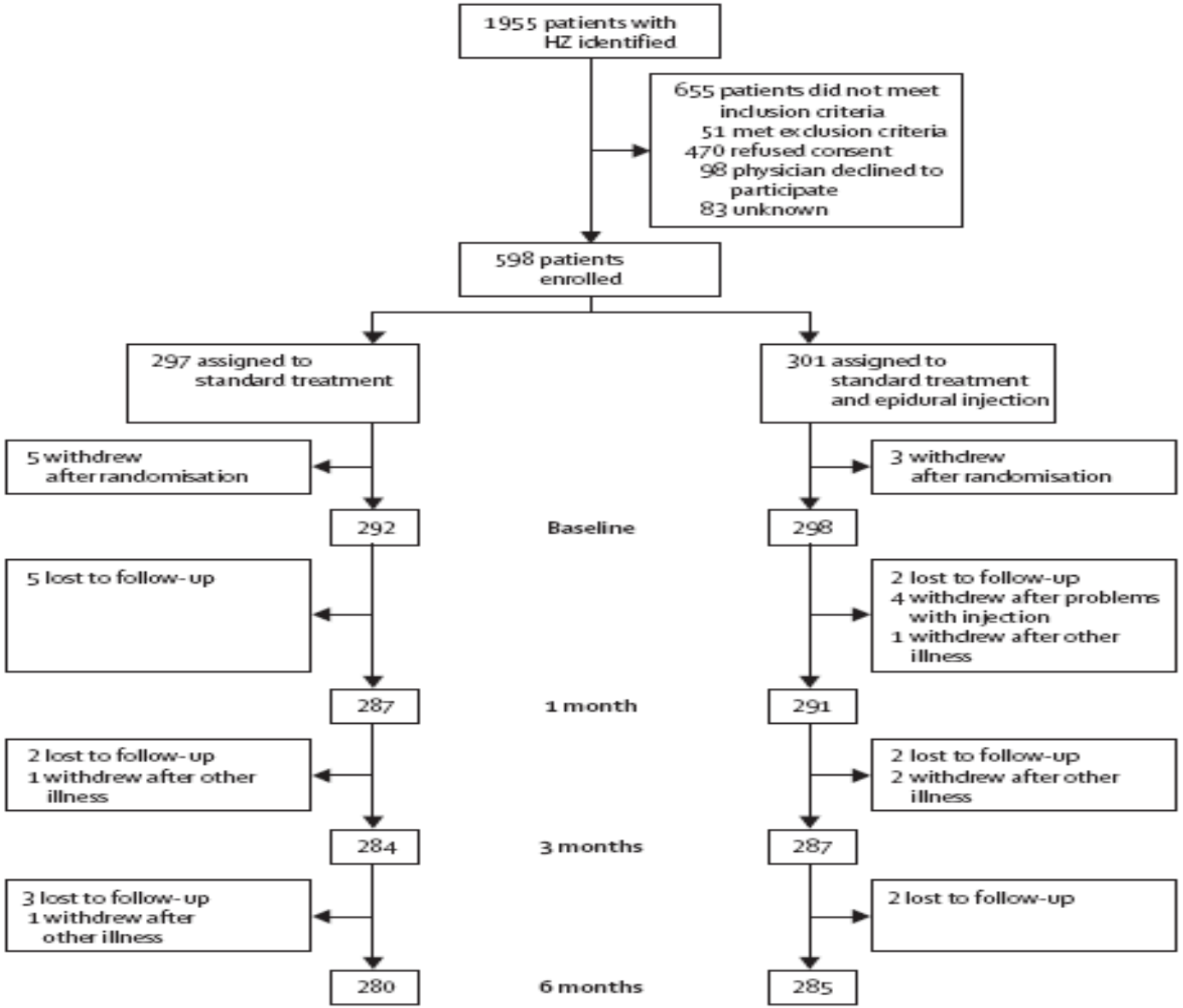


FIGURE 1. Time to resolution of zoster-associated pain for all patients. ZAP, zoster-associated pain; CEI, Continuous Epidural Infusion; IEB, Intermittent Epidural Boluses. *Comparison of effects between 2 groups, using the log-rank test.

The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial

Albert J M van Wijck, Wim Opstelten, Karel G M Moons, Gerrit A van Essen, Robert J Stolker, Cornelis J Kalkman, Theo J M Verheij



Lancet 2006; 367: 219–24

See Comment page 186

Pain Clinic, Department of Anaesthesiology,

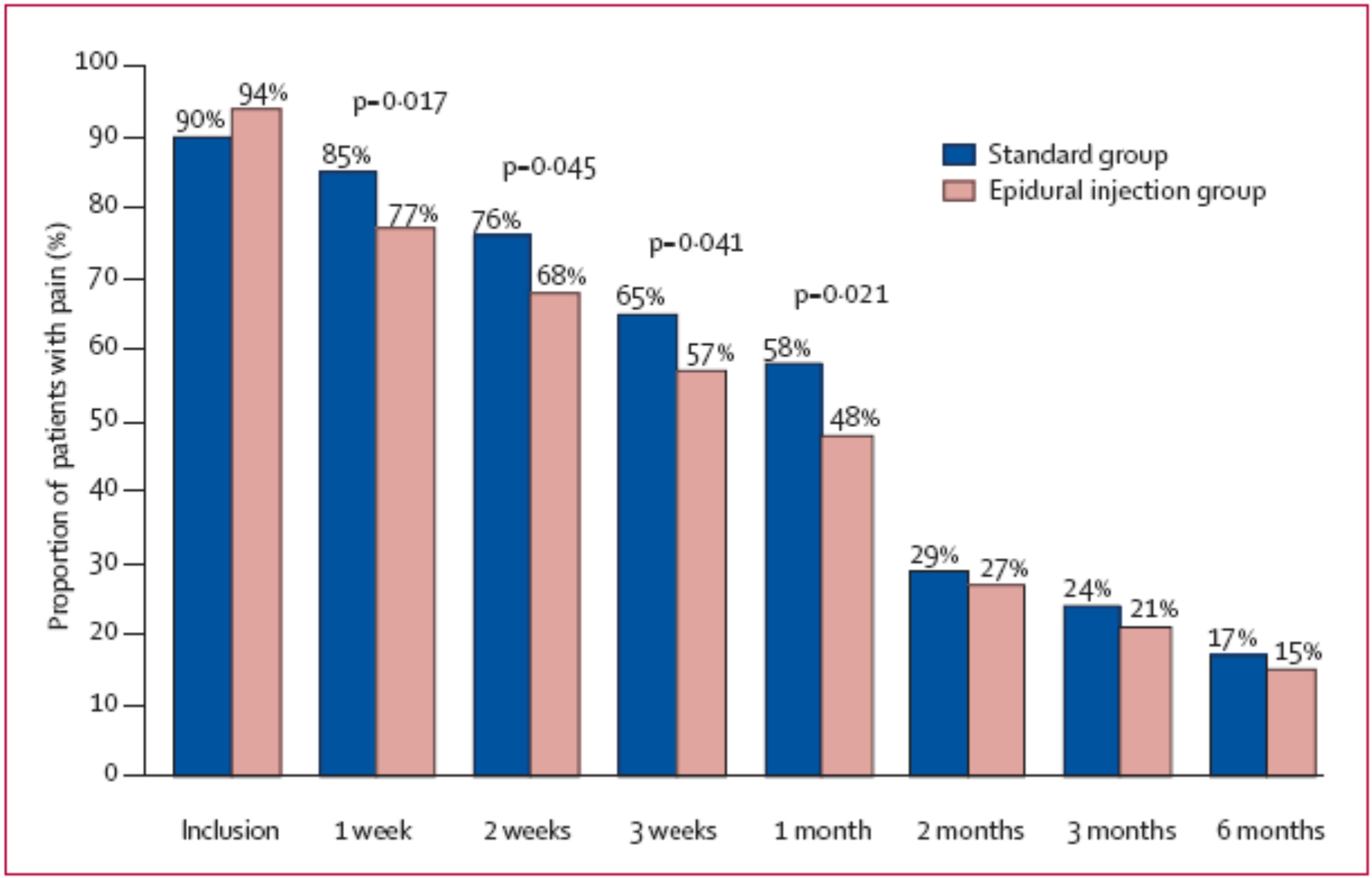


Figure 2: Proportion of patients with pain over time

van Wijck AJM, et al. Lancet, 2006;367:219-224.

Table 4. Logistic Regression Models for Presence of Postherpetic Neuralgia (n = 102)

Variable	Coefficient	Standard Error	P	Odds Ratio*	95% Confidence Interval
Initial model					
Zoster duration	−0.03	0.04	.554	0.98	0.90-1.06
Age	0.04	0.02	.115	1.04	0.99-1.08
Immune status	0.94	0.94	.320	1.39	0.05-3.20
Prodrome	0.72	0.61	.234	2.05	0.62-6.72
Physical health	0.15	0.07	.044	1.16	1.01-1.34
Acute pain intensity	0.24	0.13	.057	1.27	0.99-1.63
Measures of physical, role, social, and emotional functioning added to initial model					
Zoster duration	−0.03	0.05	.550	0.97	0.88-1.07
Age	0.06	0.03	.016	1.07	1.01-1.12
Immune status	0.52	1.09	.632	1.59	0.07-5.04
Prodrome	0.80	0.72	.273	2.21	0.54-9.15
Physical health	0.10	0.09	.237	1.11	0.93-1.32
Acute pain intensity	−0.05	0.16	.774	0.95	0.69-1.32
Role functioning	0.85	0.28	.003	2.34	1.34-4.08
Personality disorder symptoms	0.09	0.04	.021	1.09	1.01-1.18

*Odds ratios are adjusted for other terms included in the model, and odds ratios for continuous variables reflect the multiplicative increase in odds for PHN for every one point change in the variable.

Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Psychosocial risk factors for postherpetic neuralgia: a prospective study of patients with herpes zoster. Journal of Pain, 2005;6:782-790.