Postherpetic Neuralgia: from Vaccine to Symptomatic Treatment

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Declaration of interest

- Has lectured or served on advisory boards for Abbott, Astellas, Eli Lilly, Janssen-Cilag, Medtronic, MSD, Mundipharma, Orion, Pfizer and Sanofi-Pasteur

- Has participated in international congresses as a guest of Astellas and Pfizer

Contents

- Course of herpes zoster
- Prevention of postherpetic neuralgia
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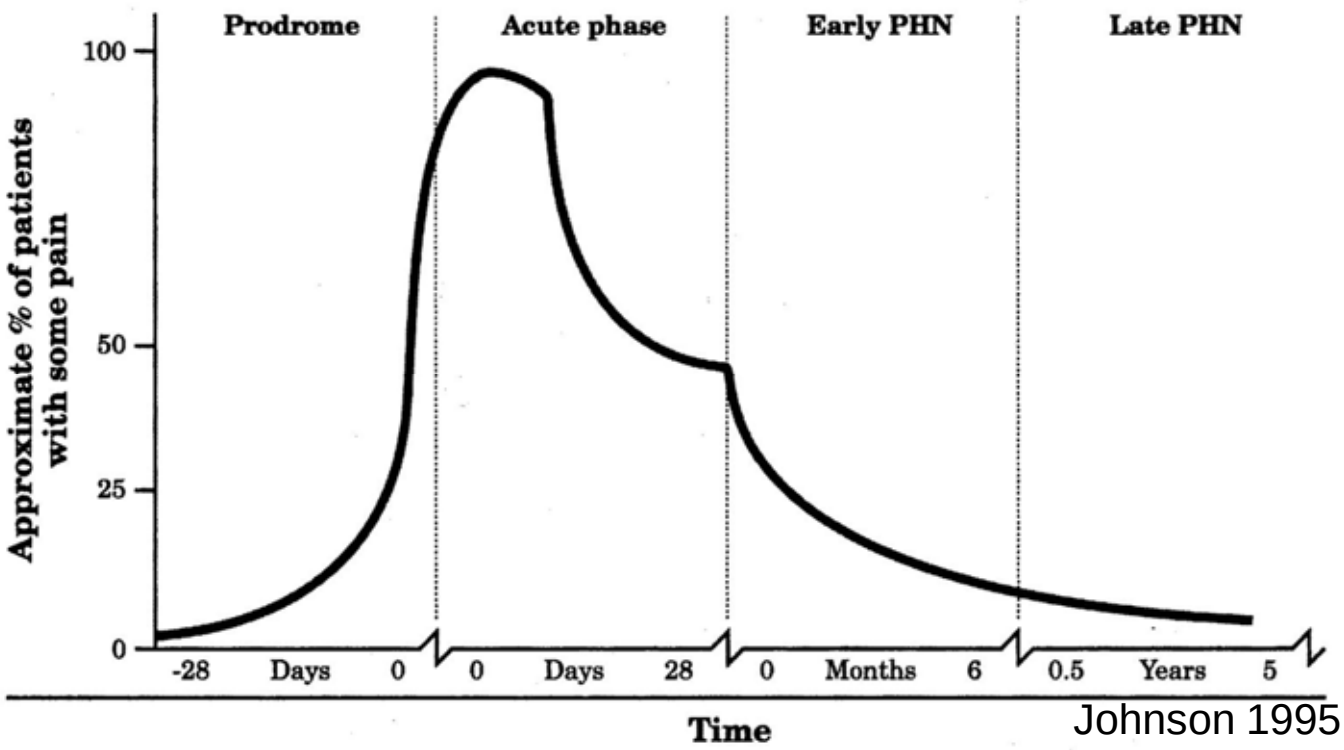
Herpes zoster

- Caused by reactivation of VZV
  - Risk factors: age ?¯ CMI ?¯
  - Protecting factors: contacts with varicella
- Incidence 3-4/1000 person years
  - ?¸ aged ?¸ immunocompromised ?¸ natural boosting ?¸
- Life-time prevalence 20-35% (50% for those ≥ 85 y)
- Usually painful but self-limiting
- PHN is the most common complication of HZ

Zoster-associated pain



Johnson 1995

Prodrome: ganglionitis, neuritis

Acute phase: neuritis, dermatitis

Risk factors for PHN: old age, severe pain, severe rash, ophthalmic zoster

Management of acute herpes zoster [1]

Antiviral treatment, if

- Age $\geq$ 50y
- Moderate/severe pain and/or rash
- Nontruncal involvement
- Immunocompromised patient
- Complicated course of the disease

Acute pain relief

- Analgesics (simple a. $\rightarrow$ mild opioids $\rightarrow$ strong opioids[2])
- Gabapentinoids / TCA / corticosteroids, if pain is not adequately relieved with analgesics

Ophthalmological consultation, if ophthalmic HZ

Care, psychosocial support, close follow-up

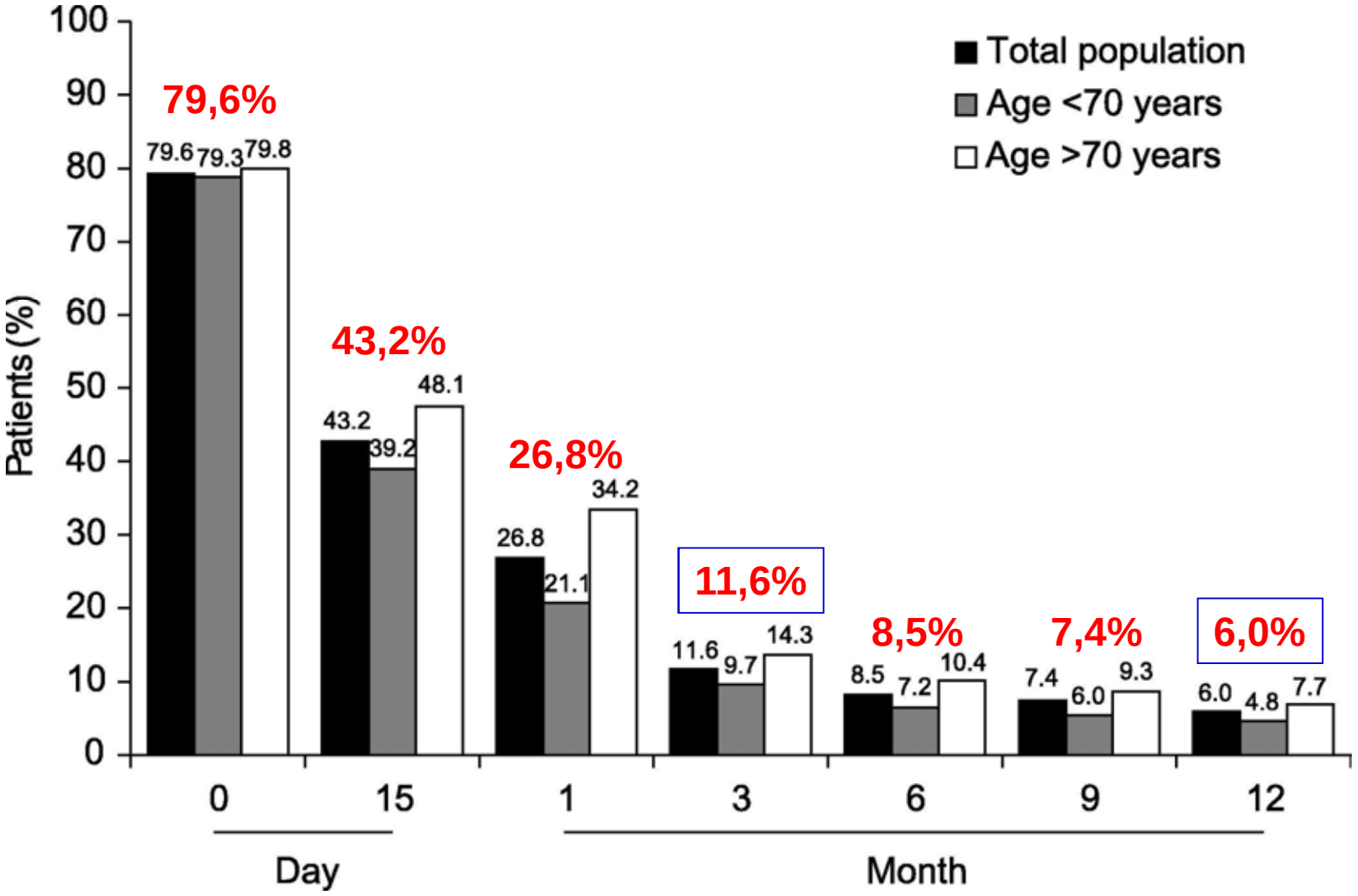
1. Dworkin et al. Clin Infect Dis 2007 2. Dworkin et al. Pain 2009

Patient perspective on HZ and its complications: An observational prospective study in patients aged over 50 y in general practice

- 12-month, longitudinal, prospective, multi-center observational study in France
- Patients aged ≥ 50 y with acute HZ presenting within 7 days of rash onset were included
- N = 1354 (76% completed the 12-month follow-up)
- Antivirals to 94%, analgesics to 83%
  (anticonvulsants to 9.7%, TCAs to 0.7%, other ADs to 0.4%)
- PHN (any pain at 3 months): 11,6%
  Early active treatment à better prognosis

Bouhassira et al. Pain 2012;153:342-9

Prevalence of zoster-related pain over 12 months of follow-up



Bouhassira et al. Pain 2012;153:342-9

Natural history of pain following HZ

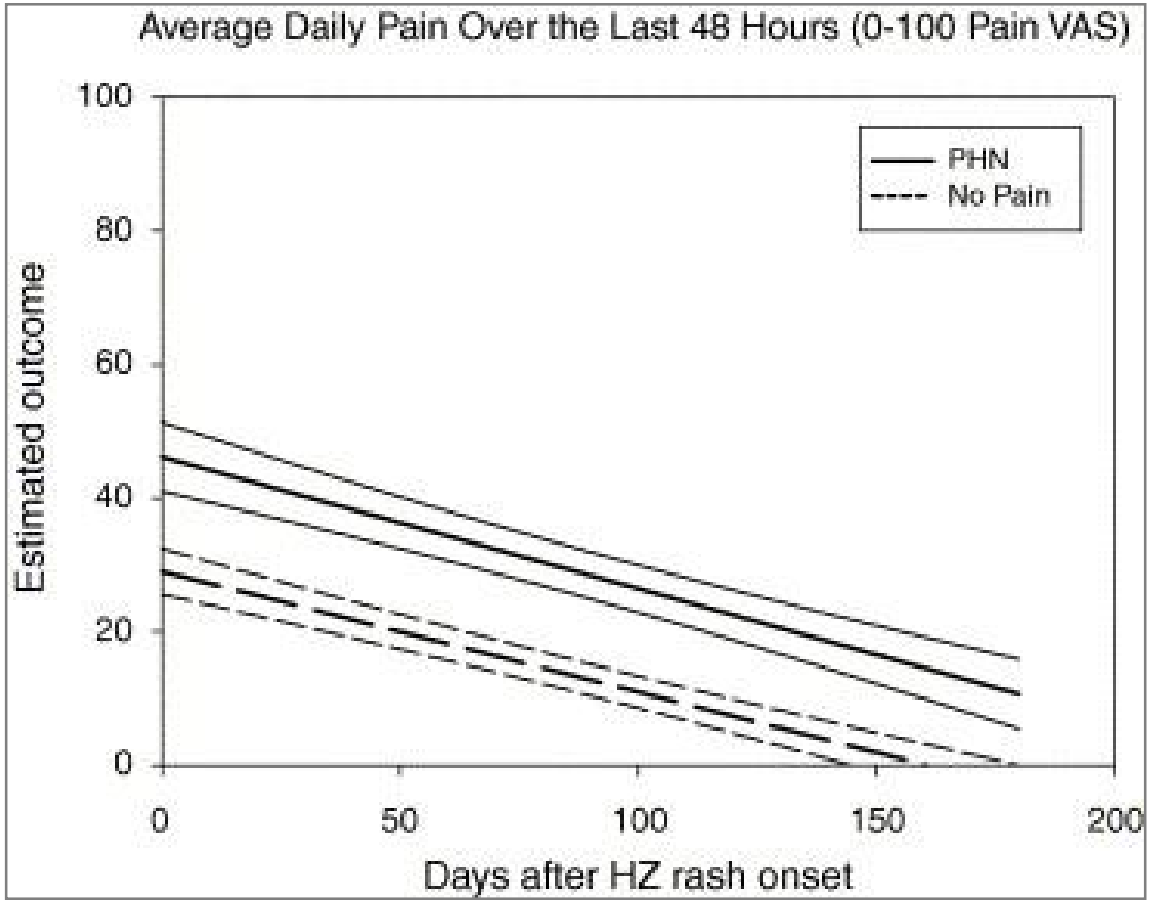
- Longitudinal observational study of 94 patient at elevated risk for developing PHN (age > 50 y, pain ≥ 20/100)
- Inclusion visit within 2-6 weeks after rash onset
- PHN: presence of pain
- Clinically meaningful PHN: pain ≥ 30/100
- At 3 months:

  PHN: 47 (**50 %**), clinically meaningful PHN: 3 (3%)
- At 6 months:

  PHN: 30 (**32%**). clinically meaningful pain: 2 (2%)
  - Median pain 11/100
- Conclusion: in general, prognosis is good

Thyregod et al. Pain 2007;128:148–156

Resolution of pain over the study follow-up



Estimates of average daily pain in 30 subjects with PHN at 6 months (solid line with 95% CI) and 64 subjects with no-pain at 6 months (dashed line with 95% CI).

Conclusion: the rate of recovery was the same in the PHN and no-pain groups.

Thyregod et al. Pain 2007;128:148–156

Natural history of herpes zoster: late follow-up

- Visit 5: N = 43, median **3.9 y** after HZ onset (14 with PHN6)
  - No recurrence of pain
  - Only 2 patients continued with PHN
- Visit 6: N = 10, median **7.7 y** after HZ onset
- Sensory function continued to normalize but was still abnormal in many patients, especially in those with PHN6
- Skin innervation was still abnormal at 7.7 years
- Conclusion: recovery of sensory function and anatomic reinnervation of the skin is not a requirement for pain resolution

Reda et al. Pain 2013;154:2227-2233

Medical treatment of PHN

- Level A evidence: TCAs, gabapentin, pregabalin, opioids, topical lidocaine, 8% capsaicin patch

BUT

- All drugs for postherpetic neuralgia
  - have a modest effect
  - at best, reduce pain by 50% in 50% of patients
  - have side effects
- There is need for prevention of PHN!

Attal et al. EJN 2006;13:1153-69
Hempenstall et al. PLoS Medicine 2005;2:e164
Mou et al. Pain 2013;1632-1639

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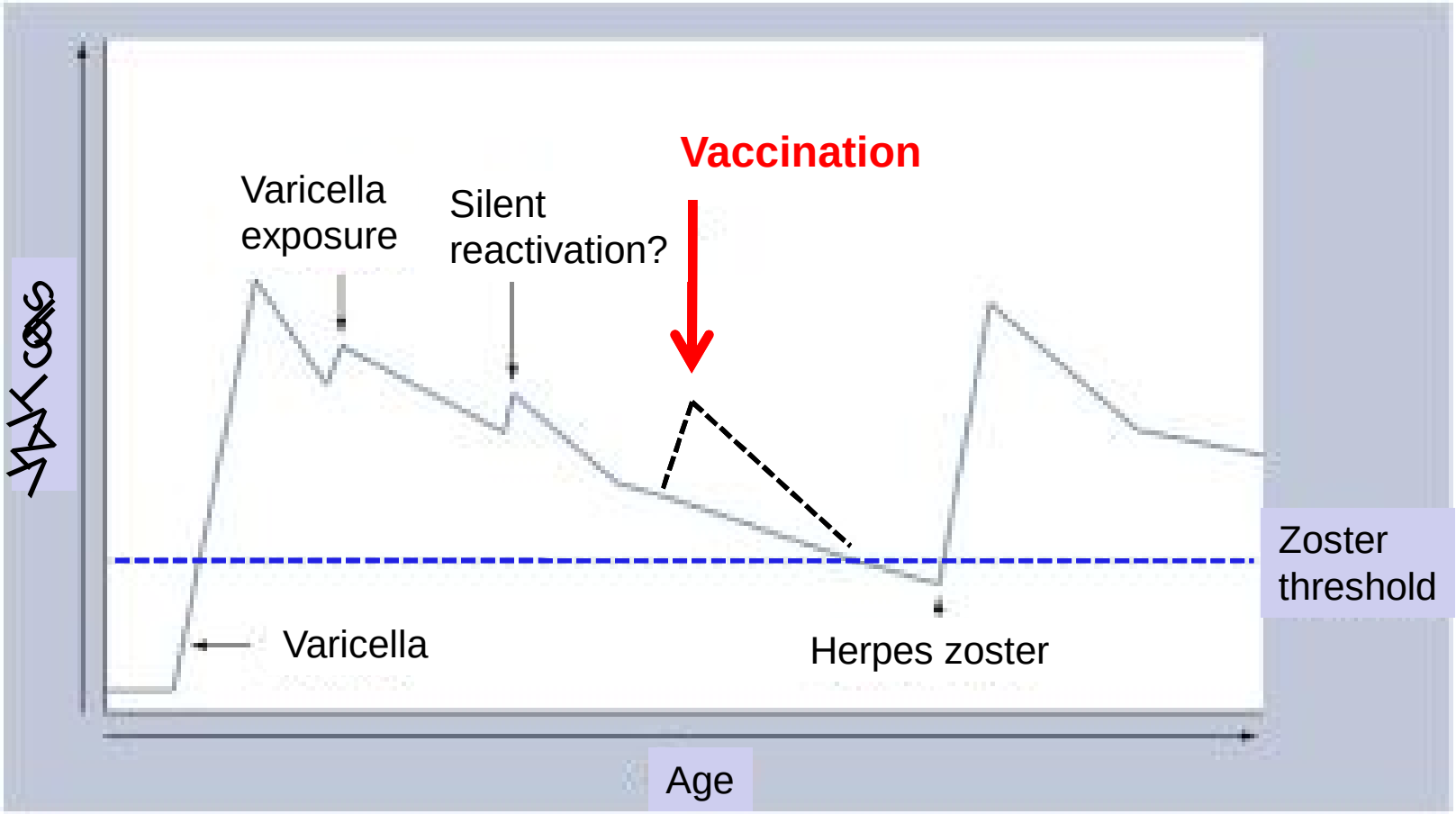
Options to prevent PHN

- Vaccination of children against varicella
- Optimal treatment of HZ
- Vaccination of elderly adults against HZ

Rationale for vaccination against HZ



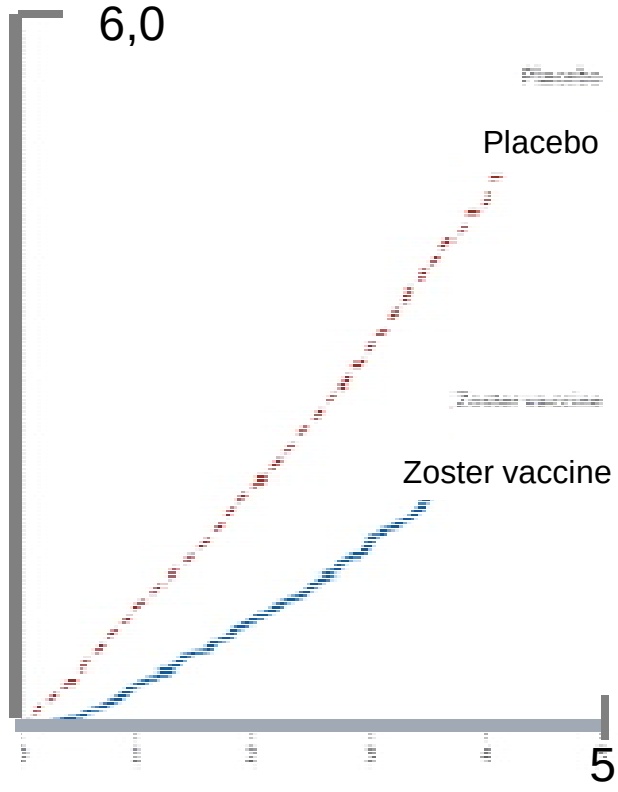
Vaccination against HZ: the Shingles Prevention Study

- Phase III multicenter double-blinded randomized placebo-controlled study compared zoster vaccine (live attenuated VZV-vaccine) to placebo in immunocompetent elderly people
- 38 546 participants (age $\geq$ 60 y), of whom 95% completed the study
- Median follow-up 3.1 years
- Primary endpoint: BOI due to HZ
- Secondary endpoints: incidence of HZ and PHN

Oxman et al. NEJM 2005;353;2271-84

Efficacy of Zostavax®

- BOI due to HZ ? 61.1%
- Incidence of HZ ? 51.3%
- Incidence of PHN ? 66.5%



Zostavax® is licensed:
- against HZ for people aged ≥ 60 y in the USA
- against HZ and PHN for people aged ≥ 50 y in Europe

Oxman et al. NEJM 2005;353;2271-84

Zostavax® vaccination in practice

- Single s.c. injection in the upper arm
- Concomitant administration[1]
  - with Pneumovax® à Zostavax® efficacy ê
    Four-week interval between the two vaccines
  - with influenza vaccine à no decrease of effect
- Not for immunocompromised
  - ACIP*: Administration of 20 mg/day of prednisone for >2 weeks: no live-attenuated vaccines for at least 3 months after discontinuation of therapy)2

1 McIntyre et al. 46th Ann Meeting of Inf Dis Society of America (Oct 2008)
2 Morb Mort Weekly Rep 2006;55(RR55):1-48.
* Advisory Committee of Immunization Practices

Safety of Zostavax®

- Mild adverse events (Injection-site reactions)
  - Erythema (35.8% vs. 7.0%)
  - Pain or tenderness (34.5% vs. 8.5%)
  - Swelling 26.2% vs. 4.5%)
- No difference in SAEs between vaccine and placebo in the global analysis
- In safety sub-study relative risk for SAEs was 2.19 (P= .04) in age-group ≥ 80 y

Oxman et al. NEJM 2005;353;2271-84. Simberkoff et al. Ann Intern Med 2010;52:545-54
Fried. J Am Ger Soc 2010;58:1799-1800

HZ vaccination efficacy according to age at vaccination

	Incidence of HZ			Burden of illness*			Incidence of PHN		
	Vaccine	Placebo	VE (95% CI)	Vaccine	Placebo	VE (95% CI)	Vaccine	Placebo	VE (95% CI)
Age									
50–59 y	1.99	6.60	70 (54–81)	0.13	0.49	73 (53–85)	NA	NA	NA
60–69 y	3.90	10.79	64 (56–71)	1.50	4.33	66 (52–76)	0.26	0.74	66 (20–87)
≥ 70 y	7.18	11.50	38 (28–52)	3.47	7.78	55 (40–67)	0.71	2.13	67 (43–81)

The Shingles Prevention Study: N = 38546 (age > 60 years)[1]
Further study: N = 22439 (age 50-59 years)[2]

The vaccine efficacy at preventing HZ and BOI ?ý with age.

Decline of vaccine efficacy after 5 years.[3]

1. Oxman et al. NEJM 2005;352:2271-84 2.Schmader et al. Clin Infect Dis 2012;54:922-8
3. Schmader et al. Clin Infect Dis 2012;55:1320-8

Efficacy of zoster vaccine in older?

- For those aged ≥ 80 y the vaccine was no more effective than placebo in preventing HZ or PHN[1-3]
- Improved efficacy in the elderly[4]
  a) Higher titer Oka vaccine
  b) Inactivated or subunit vaccines

1. http://www.fda.gov/ohrms/dockets/ac/cber05.html#VaccinesandRelatedBiological
2. http://www.merck.com/product/usa/pi_circulars/z/zostavax_pi2.pdf,
3. Fried. J Am Ger Soc 2010;58:1799-1800 , 4. http://globalvf.org/

Cost-effectiveness of Zostavax®

- US[1]: price ? 160 $, insurance coverage varies
- UK[2]: cost-effective, best in age group 60-69 y
  - Cost of QALY ? £ 13 000
- Canada[3]: cost-effective in ≥ 60 y
  - Cost of QALY ? $ Can 42 000
- Belgium[4]: cost-effective in ≥ 60 y
  - Cost of QALY ? € 7 000
- Netherlands[5]: possibly cost-effective in ≥ 60 y
  - Cost of QALY ? € 20 000

1. Adams et al Am J Health Syst Pharm 2010;67:724-7
2. Moore et al. 2010 http://www.resource-allocation-com/content/8/1/7
3. Najafzadeh et al. Pharmacoeconomics 2009;27:991-1004
4. Annemans et al. J Med Econ 2010;13:537-51
5. van Lier et al. BMC Healt Services Research 2010;10:237

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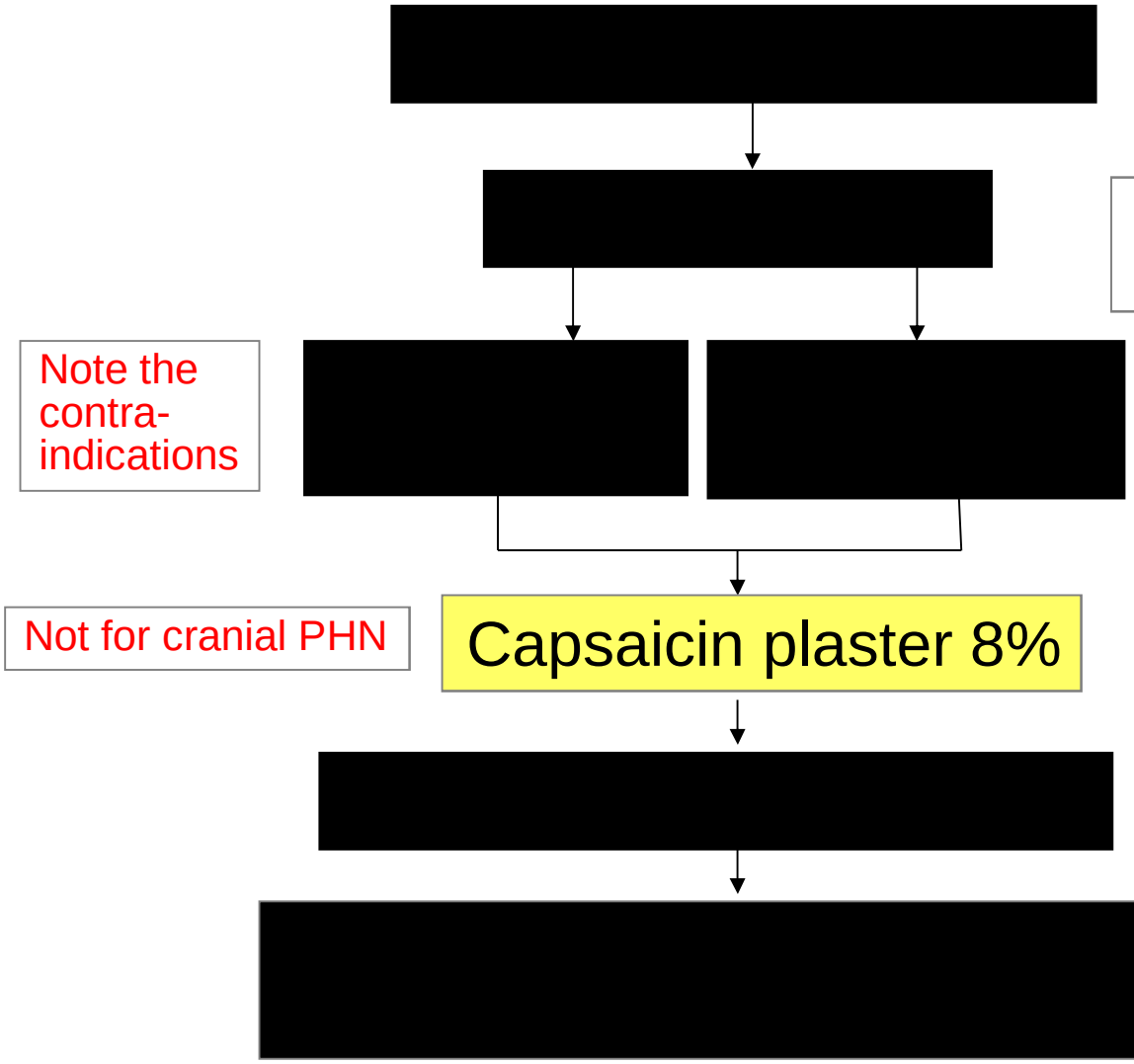
Treatment of PHN: monotherapy or rational combinations

EBM:



Note the contra-indications

Not for cranial PHN

Capsaicin plaster 8%

Also worth trying:

TNS, psychological methods[1]

Topical lidocain can be combined with any systemic drug.

If PGL is not tolerated, GBP can be tried and vice versa.

Combination of GBP/PGL and AD is also possible.

If PGL/GBP fail and TCAs are contraindicated, consider SNRIs (DLX/VFX).

SCS can be considered[4]. (←age, cognitive function)

1. Daniel et al. EJP 2008. 2.Gilron et al. NEJM 2005. 3. Hanna et al. EJP 2008. 4. Harke et al. Anesth Analg 2002.

Dosing of drugs for PHN

Drug	Starting dose	Target dose
Topical lidocaine	5% cream: 3 times a day Patch: for 12h every day	5% cream: 3 times a day Max. 3 patches at the same time
Tricyclic antidepressants	10-25 mg at bedtime	20-150 mg (in 1-3 doses)
Gabapentin	300 mg at bedtime	3600 mg/day (in 3 doses)
Pregabalin	75 mg at bedtime	600 mg/day (in 2-3 doses)
Capsaicin patch	Patch for 30-60 min every 3 month	Max. 4 patches/session
Tramadol	50 mg/day	300-400 mg/day (in 2-3 doses)
Morphine (slow-release)	10-20 mg b.i.d.	160 mg/day (in 2 doses)
Oxycodone (slow-release)	10 mg b.i.d.	120 mg/day (in 2 doses)

Treatment with capsaicin patch

Define the treatment area

Local anesthetic cream

Treatment with capsaicin patch

Put the patch

Confirm adhesion

Treatment with capsaicin patch

Remove

Clean

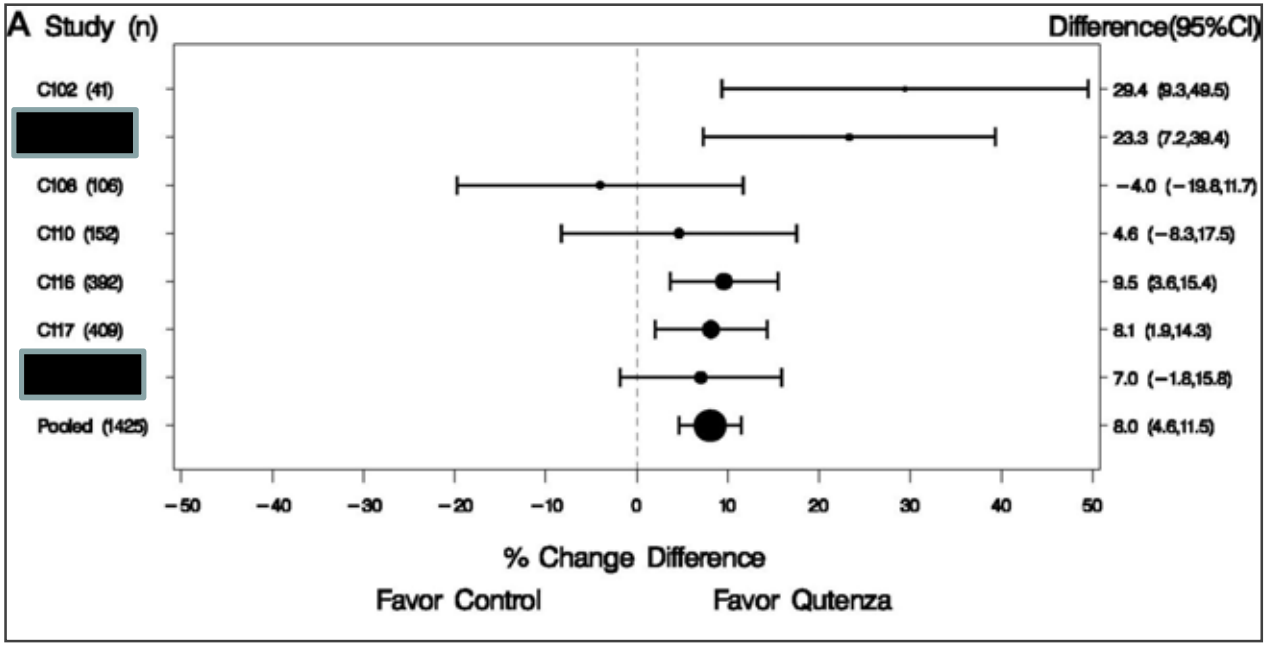
PAIN® 154 (2013) 1632–1639

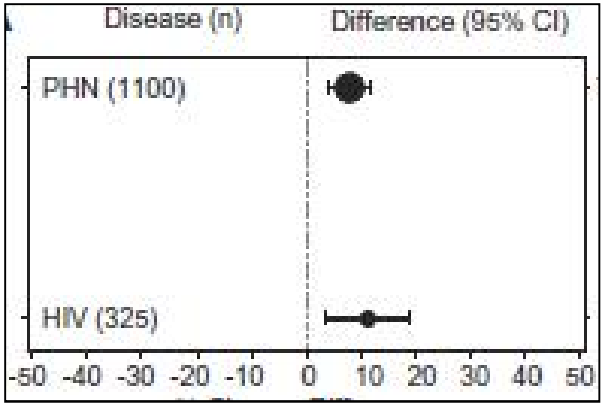
PAIN®

www.elsevier.com/locate/pain

Efficacy of Qutenza® (capsaicin) 8% patch for neuropathic pain: A meta-analysis of the Qutenza Clinical Trials Database

Joy Mou [a], Florence Paillard [b], Barry Turnbull [c], Jeremiah Trudeau [a], Malcolm Stoker [d], Nathaniel P. Katz [a,*]





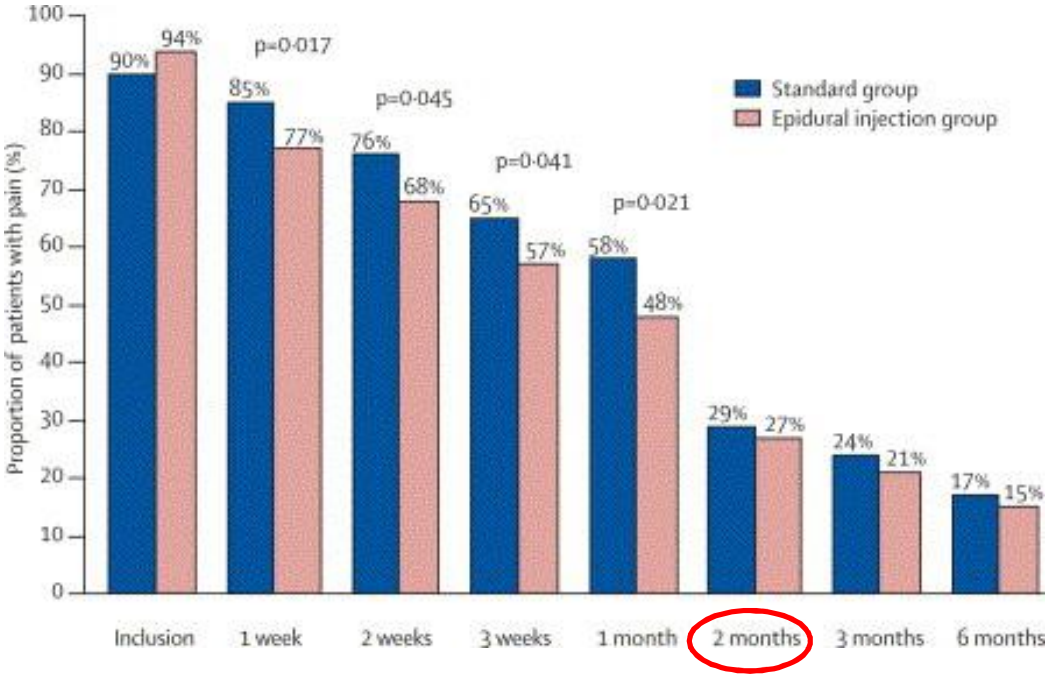
(left) Efficacy baseline vs weeks 2-12
(up) Efficacy in PHN and HIV-AN

1120 patients with PHN (5 studies), 338 patients with HIV-AN (2 studies).

Qutenza^{R} is effective for the treatment of PHN and HIV-AN.

Invasive treatments for HZ and PHN?

- Epidural methylprednisolone and bupivacaine a single shot relieves acute pain but does not prevent PHN[1]
- Use of sympathetic nerve blocks in PHN should be avoided[2]
- Intrathecal methylprednisolone: one RCT with excellent results[3], but another study was cancelled due to poor efficacy[4]; NOT recommended
- SCS: one small study (N=28), encouraging results[5]



1. van Wijk et al. Lancet 2006;367:219-224
2. Dworkin et al. Pain 2013 (e-pub)
3. Kotani et al. NEJM 2000;343:1514-9.
4. Rijsdijk et al. EJP 2013;17:714-23.
5. Harke et al. Anesth Analg 2002;94:694–700.

Any other hints for daily practice?

- Dynamic allodynia can be alleviated with tight clothing
- Very severe HZ pain: consider oral corticosteroid (only with antiviral!)
  - Safe, relieves acute pain, does not prevent PHN[1]
- Ophthalmic PHN: lidocaine eye drops (4 %) attenuate pain (RCT, N=24)[2]
  - The effect persisted median 36 hours

1. Han et al. Cochrane Database Syst. Rev. 2013 Mar;28:3:CD005582
2. Kanai et al. Anesth Analg 2010;110:1457-60

Conclusions

- HZ is a common, usually painful but self-limiting condition
- Early active treatment of HZ is recommended
- PHN is of limited duration and severity in most cases, but chronic intractable PHN is still possible
- Pharmacotherapy of PHN has modest effectiveness
- Zoster vaccine is clinically effective, but cost-effectiveness is dependent on the duration of the effect of vaccine
- New therapies are welcome

Thanks for your attention!