Nevralgia Post Herpetica

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Herpes Zoster

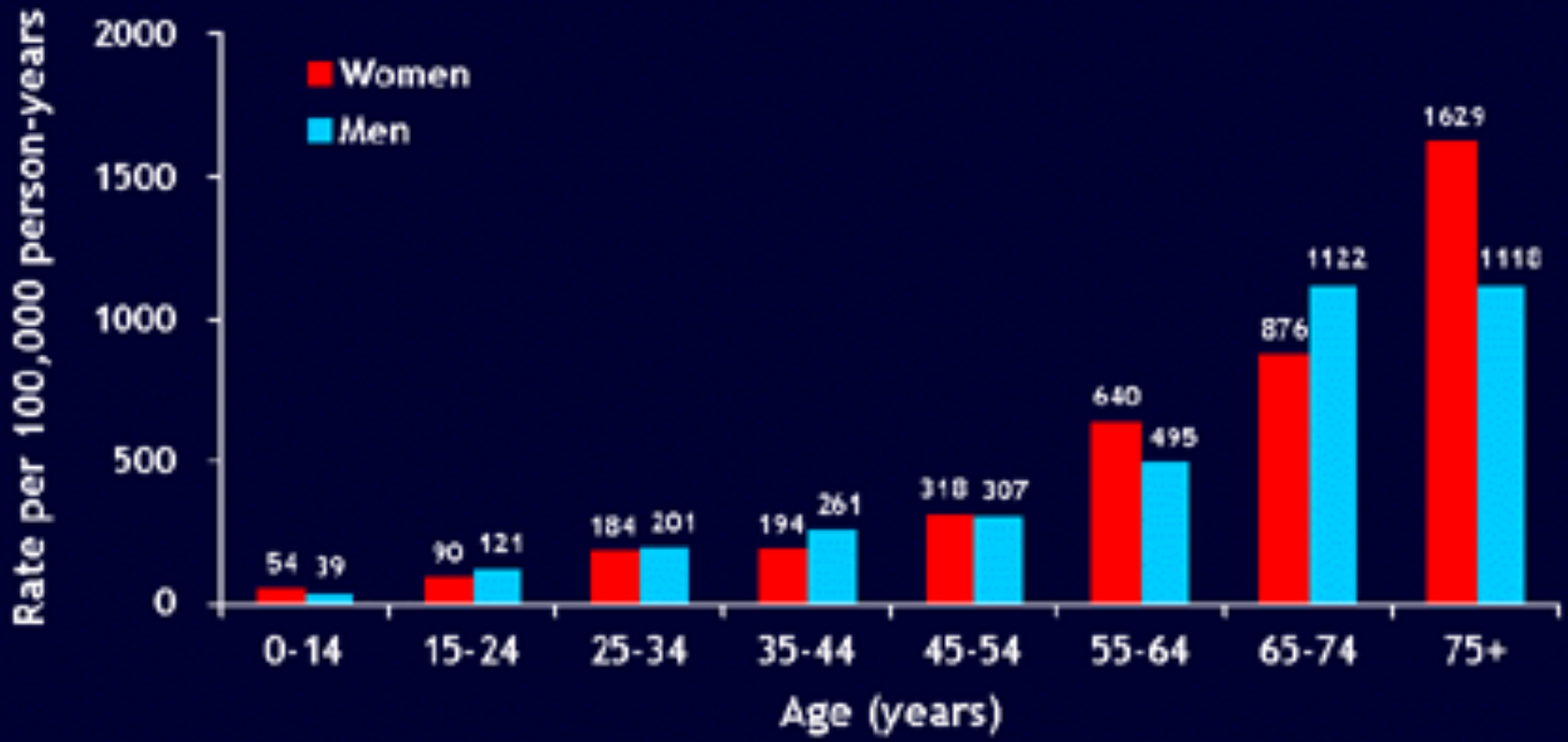
Manifestazione clinica dell'età matura ed avanzata

Incidenza media di HZ: 3.4/1000 paz/anno

oltre i 75 anni prevalenza 10 volte superiore a quella dei ventenni

bisogna sempre sospettare una immunodepressione o una malattia degenerativa

Incidence of Herpes Zoster Increases With Age



Donahue J et al. *Arch Intern Med* 1995;155:1605-1609.

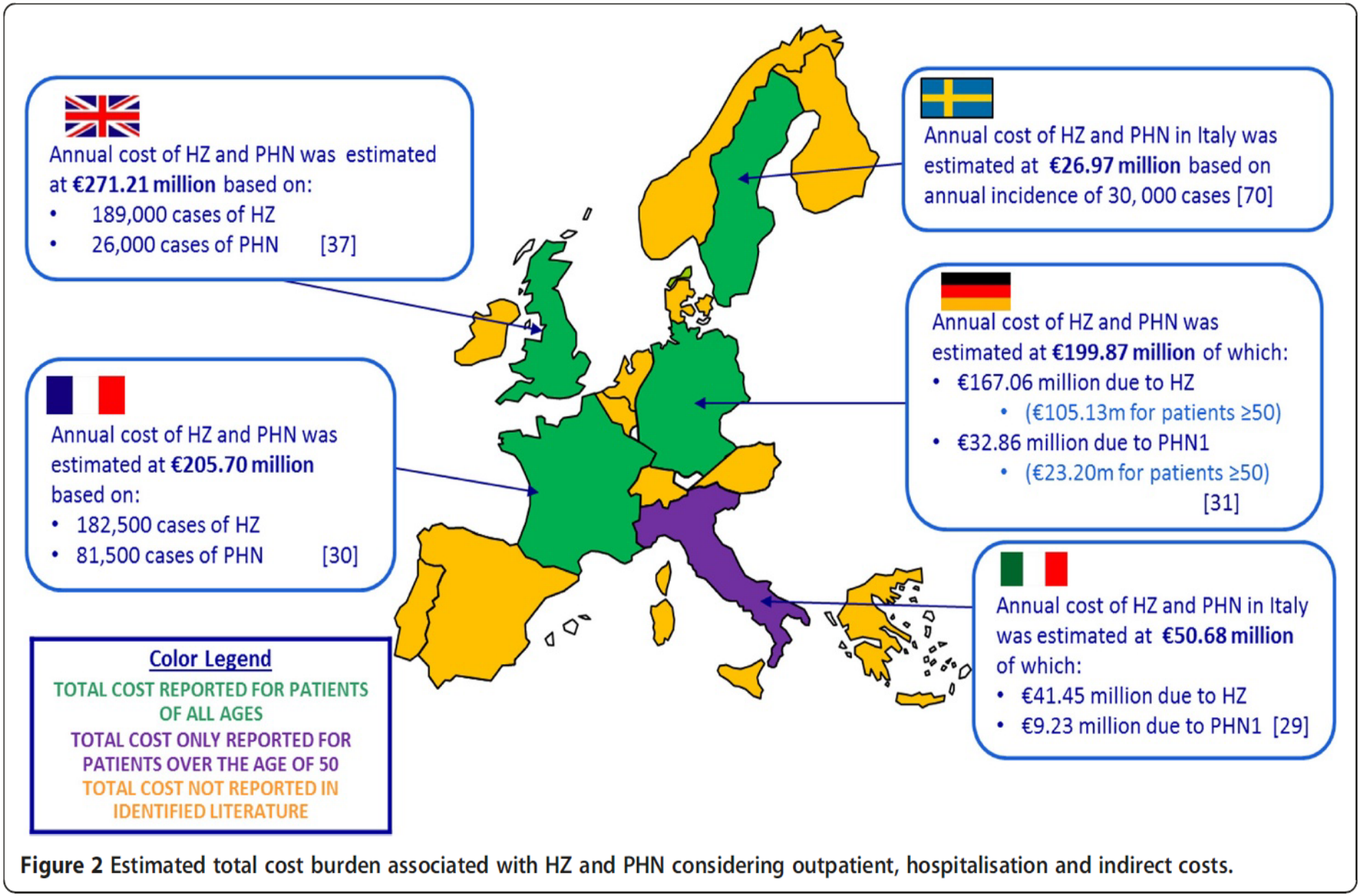
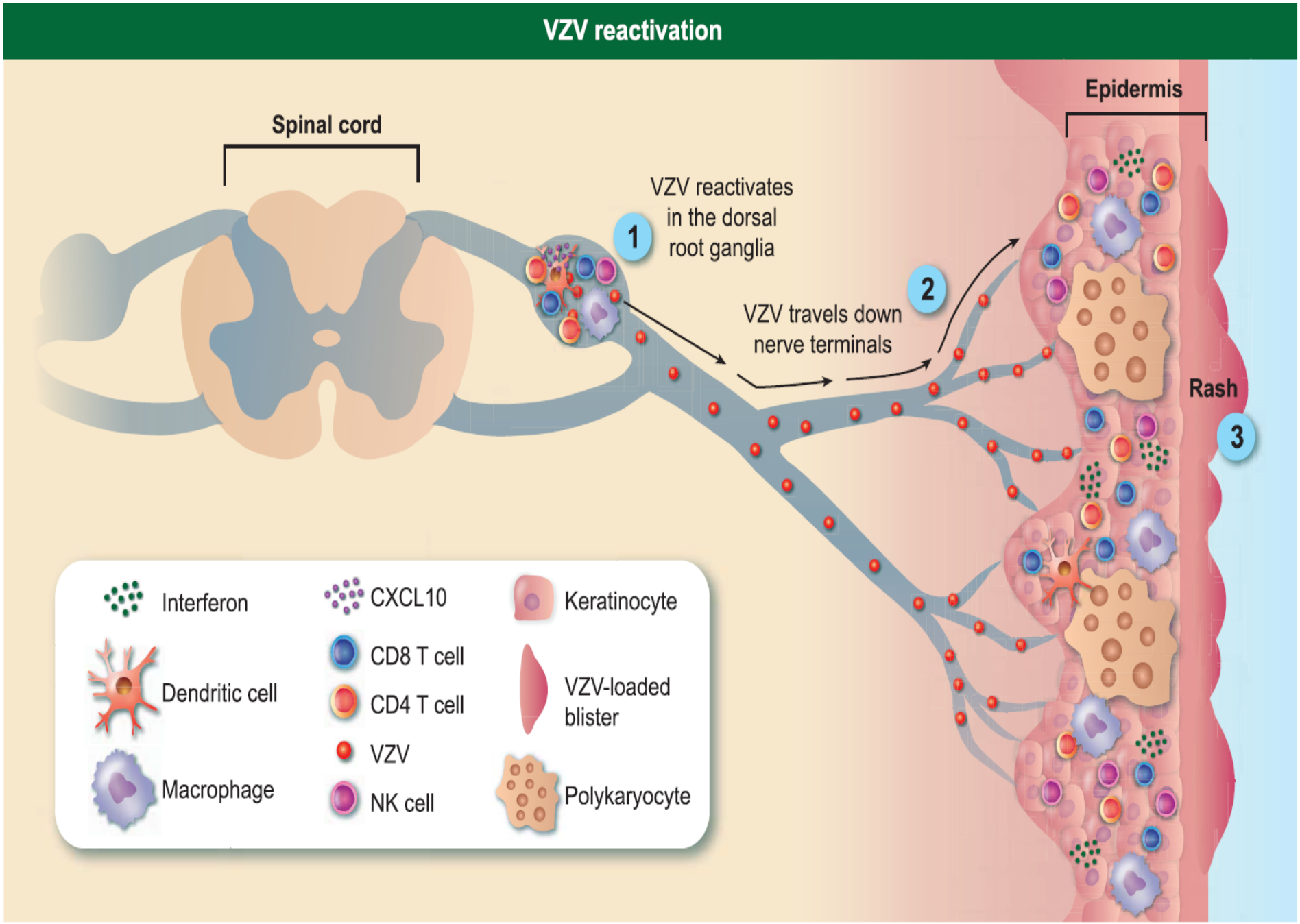


Figure 2 Estimated total cost burden associated with HZ and PHN considering outpatient, hospitalisation and indirect costs.


VZV reactivation
Spinal cord
Epidermis
VZV reactivates in the dorsal root ganglia
1
VZV travels down nerve terminals
2
Rash
3
Interferon
CXCL10
Keratinocyte
Dendritic cell
CD8 T cell
CD4 T cell
VZV-loaded blister
VZV
Macrophage
NK cell
Polykaryocyte

Herpes Zoster

Immunità

Il VZV si mantiene latente nei DRG. La sua riattivazione determina l'HZ. La riattivazione è secondaria ad una riduzione della immunità cellulo mediata (CMI) specifica per il VZV pur in presenza di elevati livelli circolanti di Ab anti VZV. La riduzione della CMI si verifica in conseguenza dell'età, di immunodepressione ed immunosoppressione.

Herpes Zoster

Il virus, riattivato, si diffonde mono o plurimetamericamente

in senso periferico, verso la cute:
1 - 4 dermatomeri (manifestazioni acute cutanee)

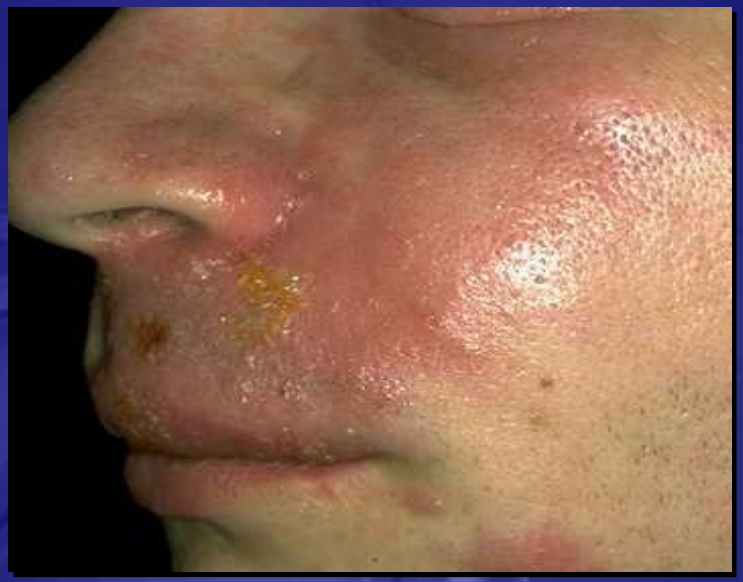
in senso centripeto, verso il midollo:
in genere colonizzando il corno posteriore omolaterale e, nelle forme più gravi, anche altre strutture midollari (leptomeningi, corna anteriori)

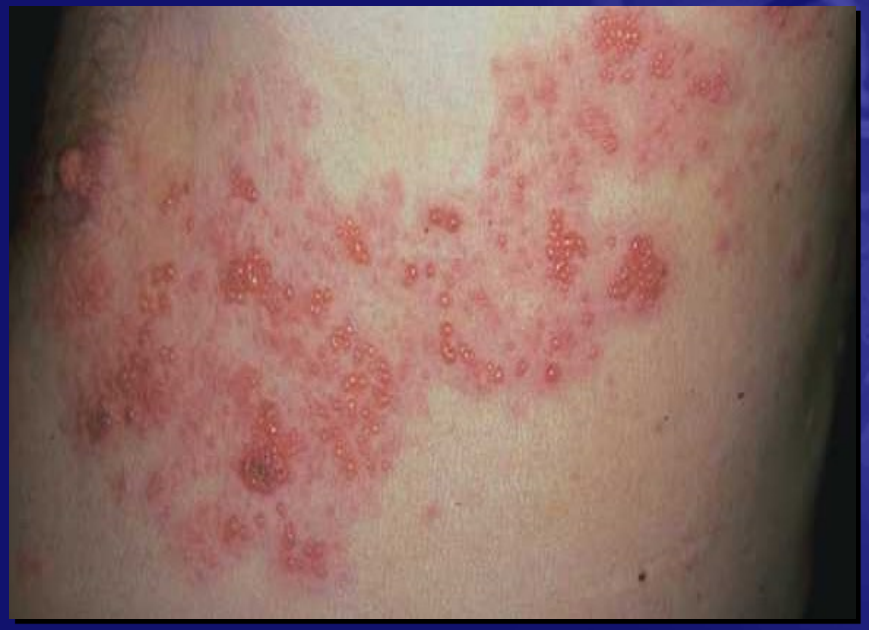
Coinvolgimento motorio più frequente di quanto atteso (bystander damage of motor axons)

Herpes Zoster

SEDE	%
CRANIALE	15*
CERVICALE	12
TORACICA	55
LOMBARE	14
SACRALE	3
GENERALIZZATO	1
TOTALE	100

* Prevalentemente Branca trigeminale oftalmica





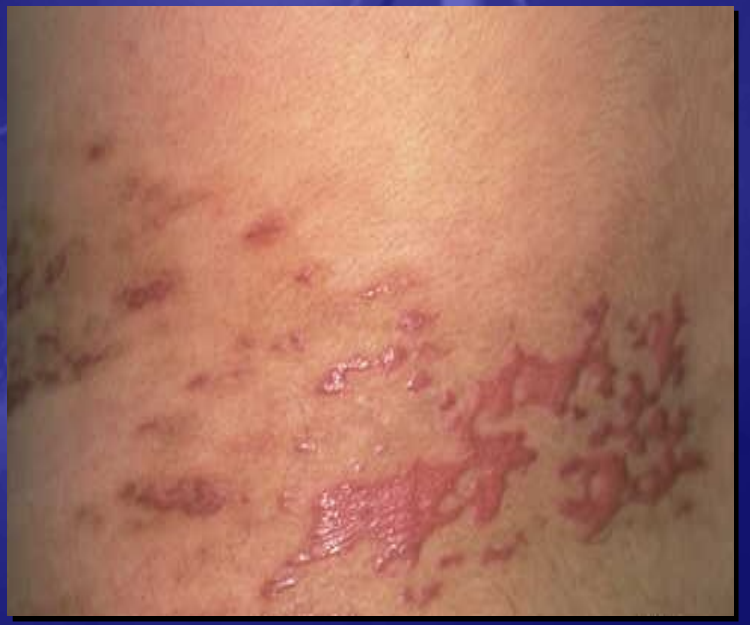
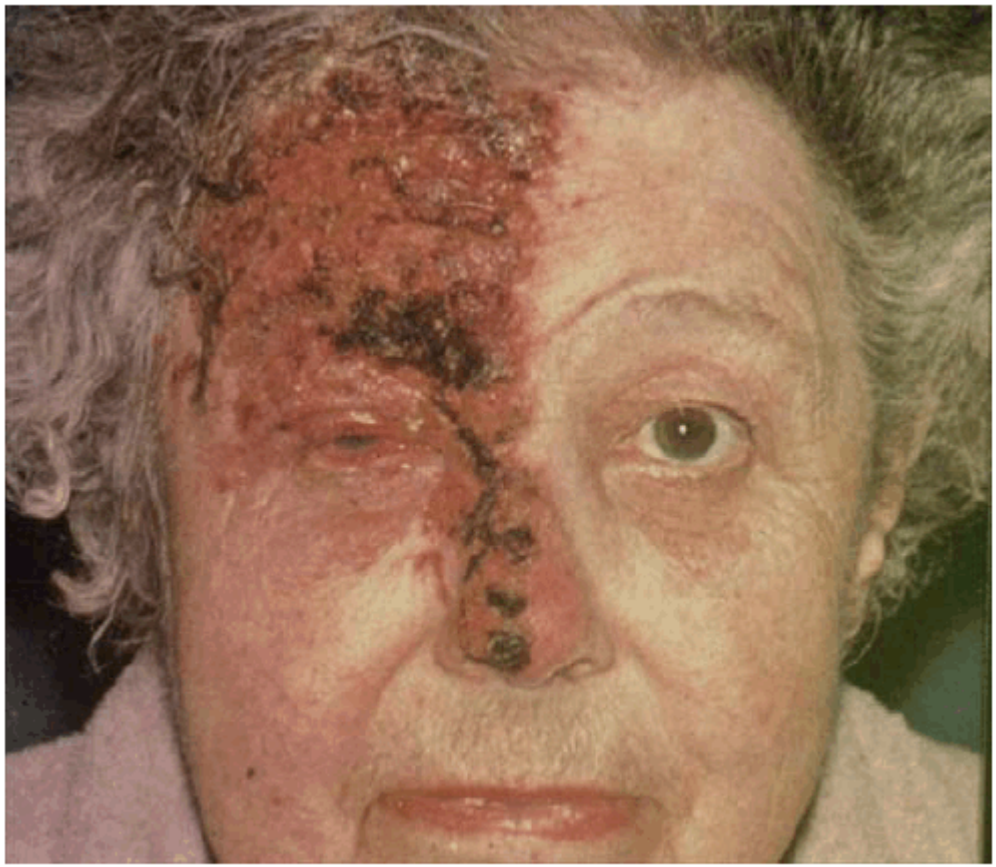


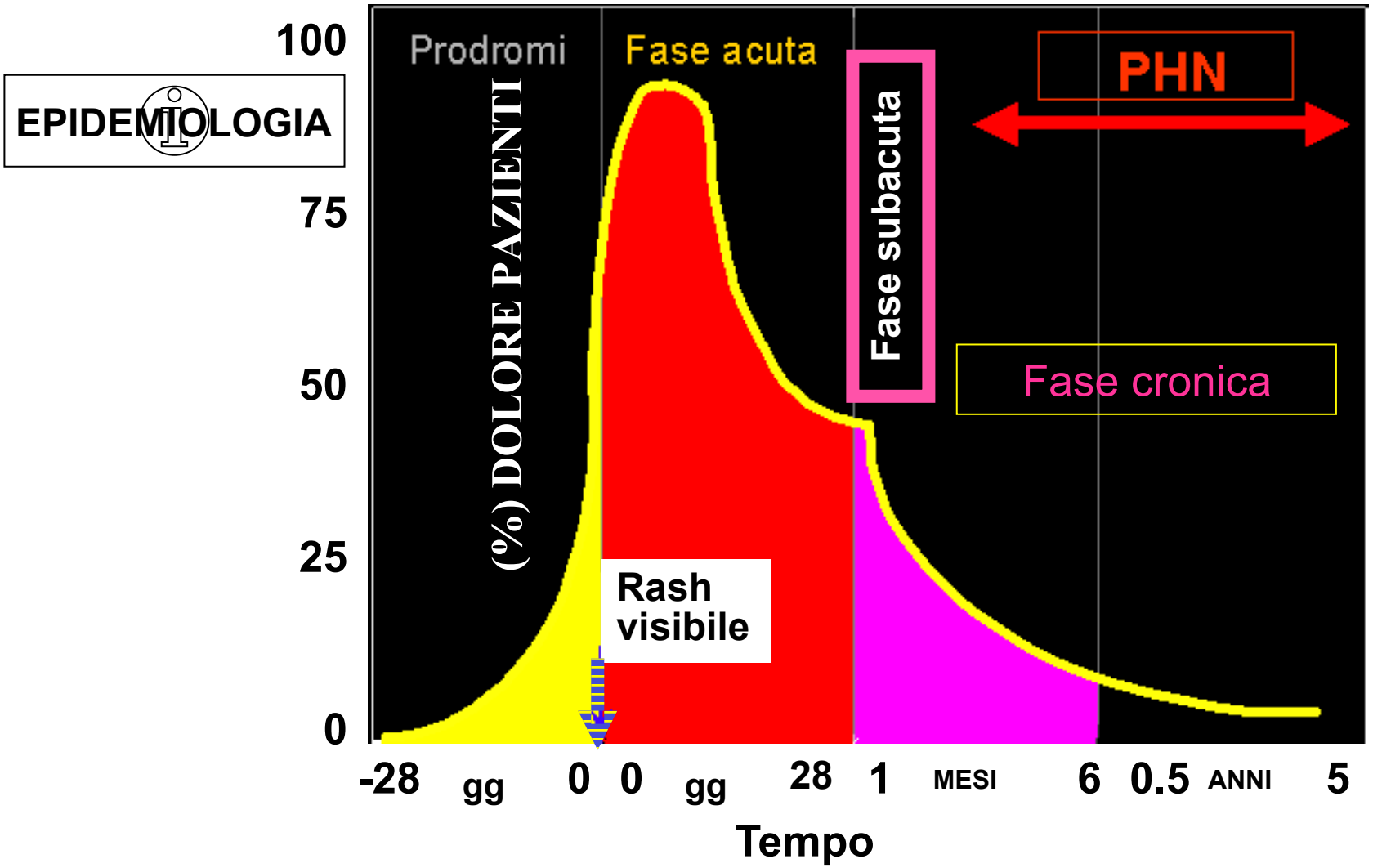
FIGURE 2. Case of herpes zoster ophthalmicus



Photo/MN Oxman, University of California, San Diego

Zoster-Associated Pain

EPIDEMIOLOGIA



PHN: FATTORI DI RISCHIO

Età,

Eruzione cutanea

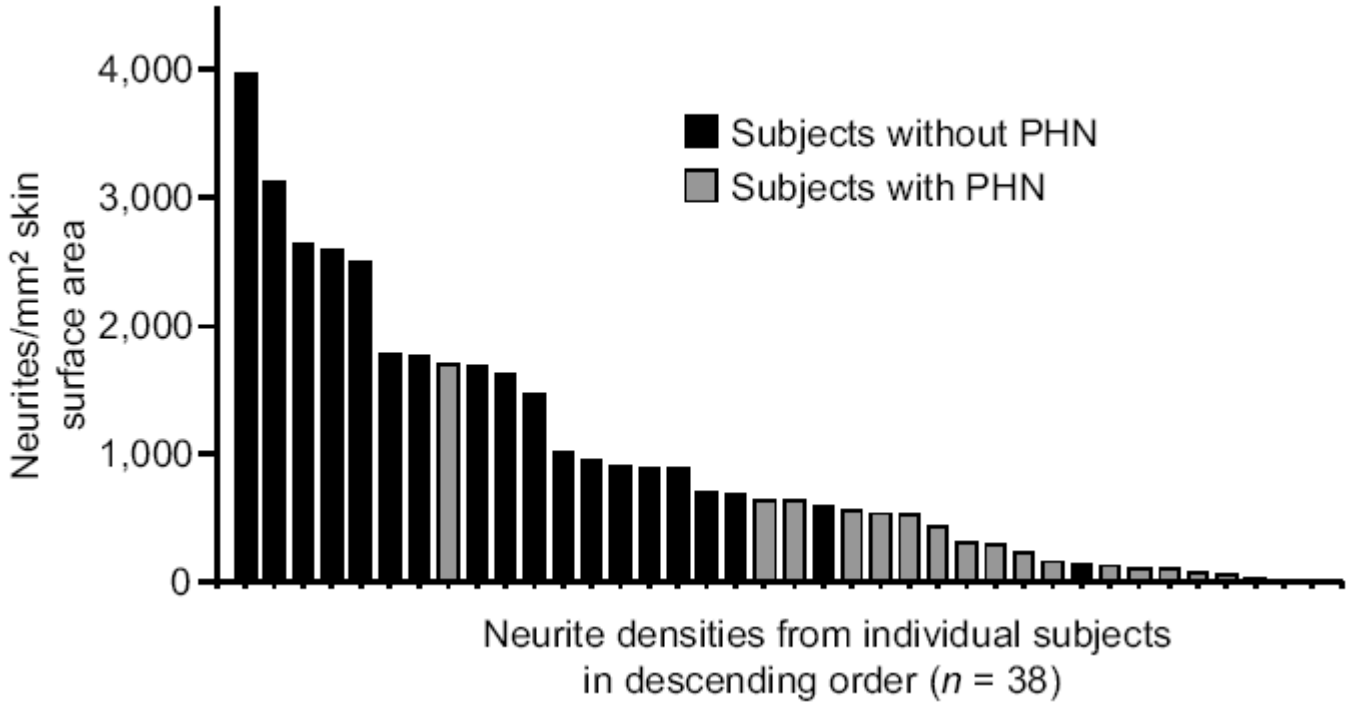
Prodomi con dolore

Febbre

Intensità dolore in fase acuta

Razza bianca

Stress emotivi e traumatici



La soglia stimata per l'insorgenza di PHN è 650 fibre /mmq di superficie cutanea. Anche la presenza di atrofia delle corna posteriori del midollo è caratteristica dei paz con PHN rispetto ai paz con HZ ma senza PHN (infezione diretta del midollo o degenerazione trans-sinaptica). *Neurobiol Dis 1998;209–227*

La PHN si considera cronica quando il dolore persiste per 4 mesi o più dall'esordio del rash, e, negli studi clinici, la PHN è abitualmente definita come un dolore che persiste per almeno 3-6 mesi.

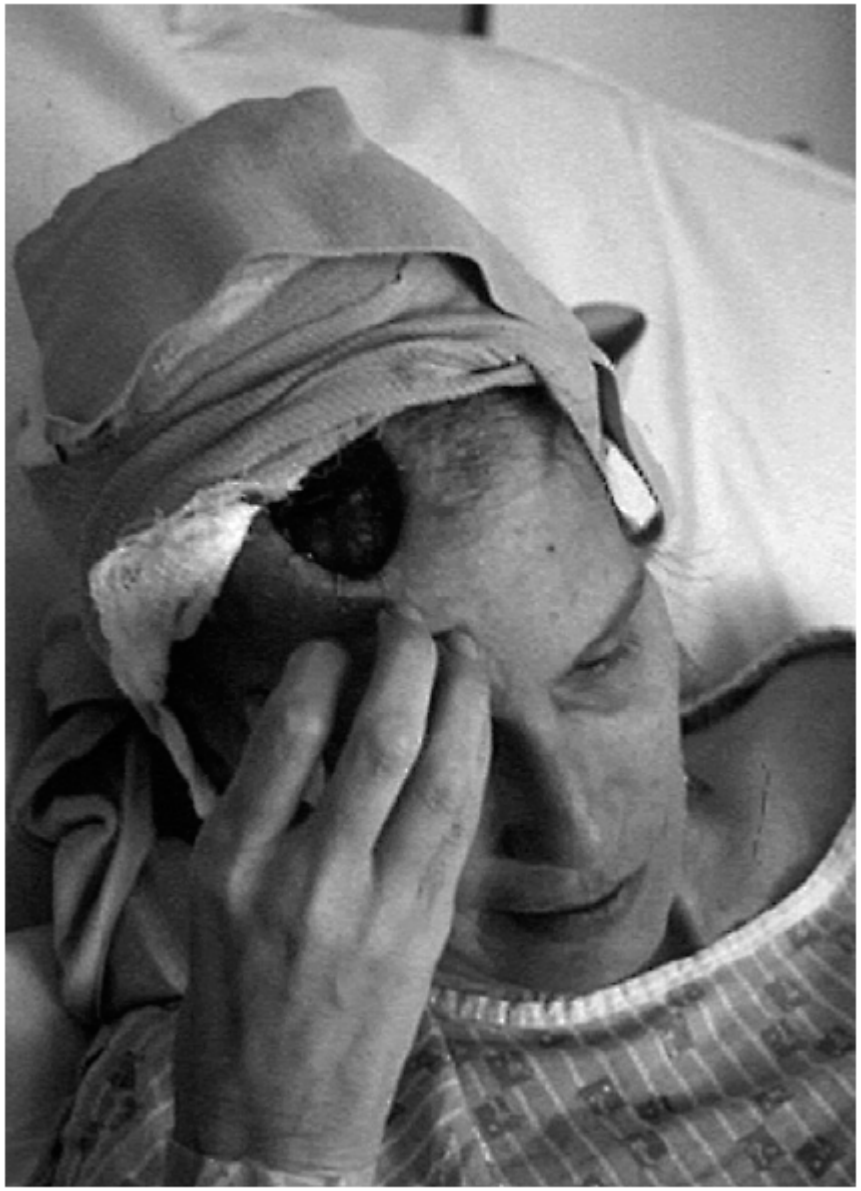
J Pain Symptom Manage 2004;28:396–411.

Nevralgia post herpetica

La maggior parte dei pazienti che rispondono a questi criteri di definizione della PHN descrivono la presenza di un'associazione di 1) dolore continuo di tipo urente o incessante, 2) dolori intermittenti pungenti, 3) alterazione della soglia sensoriale con conseguenti disturbi sensoriali, comprese le parestesie, e 4) dolore provocato da stimoli meccanici o termici altrimenti innocui (allodinia).

Alcuni pazienti con PHN avvertono una perdita profonda della sensibilità nelle zone a maggior dolore (anestesia dolorosa o dolore da deafferentazione).

J Pain Symptom Manage 2004;28:396–411.



Conseguenza del prurito e dell’anestesia

Prevenzione della neuropatia post herpetica

Nessun trattamento ha dimostrato di prevenire in modo completo la neuropatia post-herpetica, ma alcuni trattamenti possono abbreviare la durata o ridurre la severità dei sintomi.

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Médecine et maladies infectieuses 42 (2012) 53–58

Médecine et maladies infectieuses

General review

Effectiveness of antiviral treatment on acute phase of herpes zoster and development of post herpetic neuralgia: Review of international publications

Efficacité des traitements antiviraux sur la douleur de la phase éruptive du zona et sur la survenue de douleurs post-zostériennes chez des sujets immunocompétents: revue de publications internationales

J. Bruxelle [a,*], S. Pinchinat [b]

[a] *Fondation ophtalmologique A.-de-Rothschild, centre d'évaluation et de traitement de la douleur, 25, rue Manin, 75019 Paris, France*
[b] *BIOSTATEM, parc d'activité Via-Domitia, 205, avenue des Gardians, 34160 Castries, France*

Received 4 May 2011; accepted 3 November 2011
Available online 12 December 2011

Table 2
Patients 50 years of age or older reporting post-herpetic neuralgia, in randomized controlled trials with antiviral treatment.
Patients, âgés de 50 ans ou plus, présentant des douleurs post-zostériennes (DPZ) dans le cadre d'essais cliniques randomisés (ECR) évaluant les antiviraux.

	Acyclovir versus placebo (%)	Valacyclovir versus acyclovir (%)	Valacyclovir versus famcyclovir (%)	Famcyclovir versus placebo (%)
Dose	800 mg 5 times/day, for 7 to 10 days	1000 mg 3 times/day, for 7 days	1000 mg 3 times/day 7 days compared to 500 mg times/day, for 7 days	500 mg 3 times/day, for 7 days
PHN at 3 months	25 versus 54*	31 versus 38[a]	32 versus 34***	34.9 versus 49.2*
PHN at 6 months	15 versus 35*	19.9 versus 25.7**	19 versus 19	19.5 versus 40.3*

According to Johnson et al. [1].
* $P < 0.05$; ** $P = 0.08$; *** $P = 0.84$.
[a] Glaxo Wellcome (RJ Crooks), personal communication.

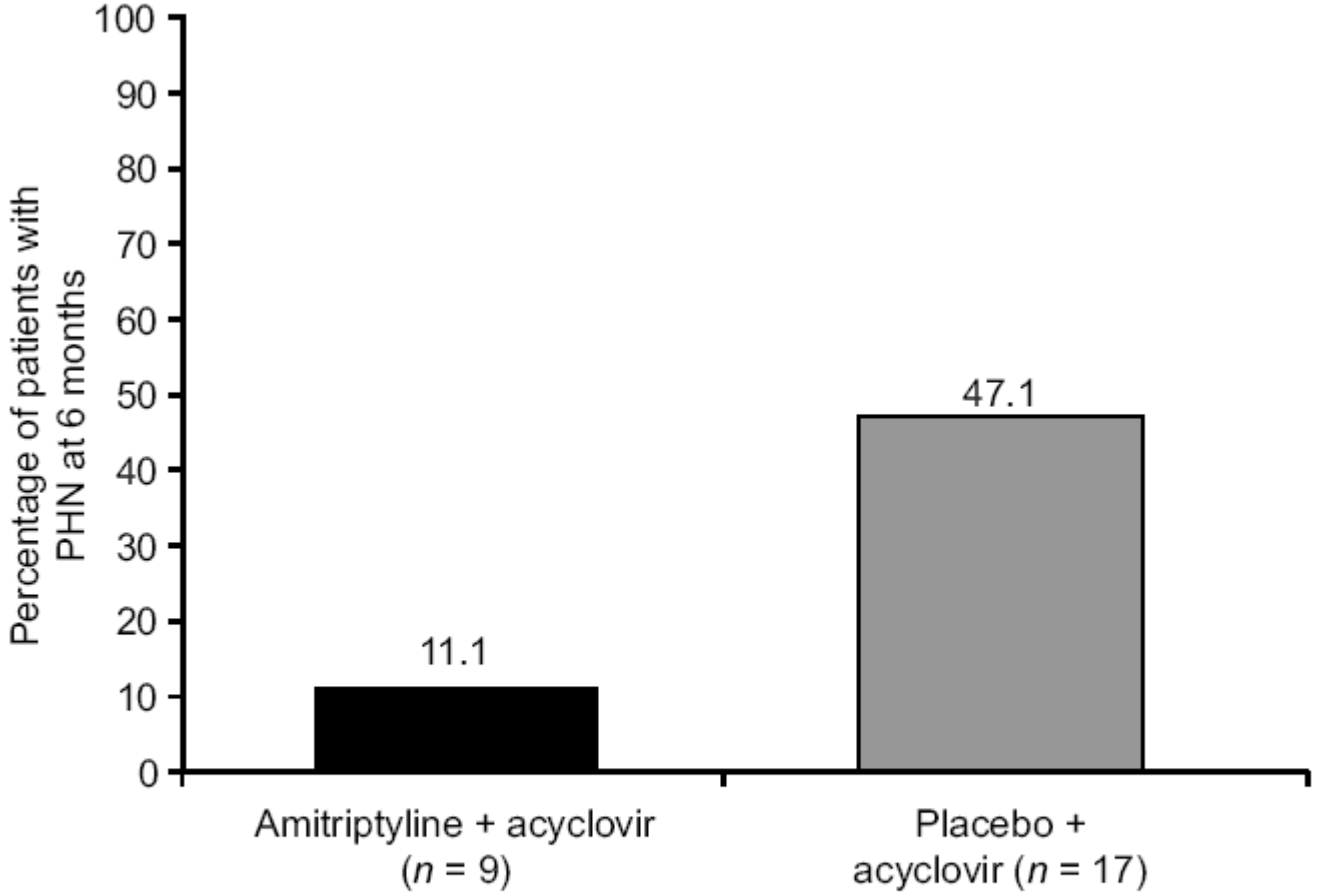


Fig. 5. Combination of antivirals with tricyclic antidepressants reduces the incidence of PHN at 6 months.[53] Reprinted from The Lancet Volume 353. Dworkin RH. Prevention of postherpetic neuralgia. Pages 1636–7, © 1999, with permission from Elsevier.

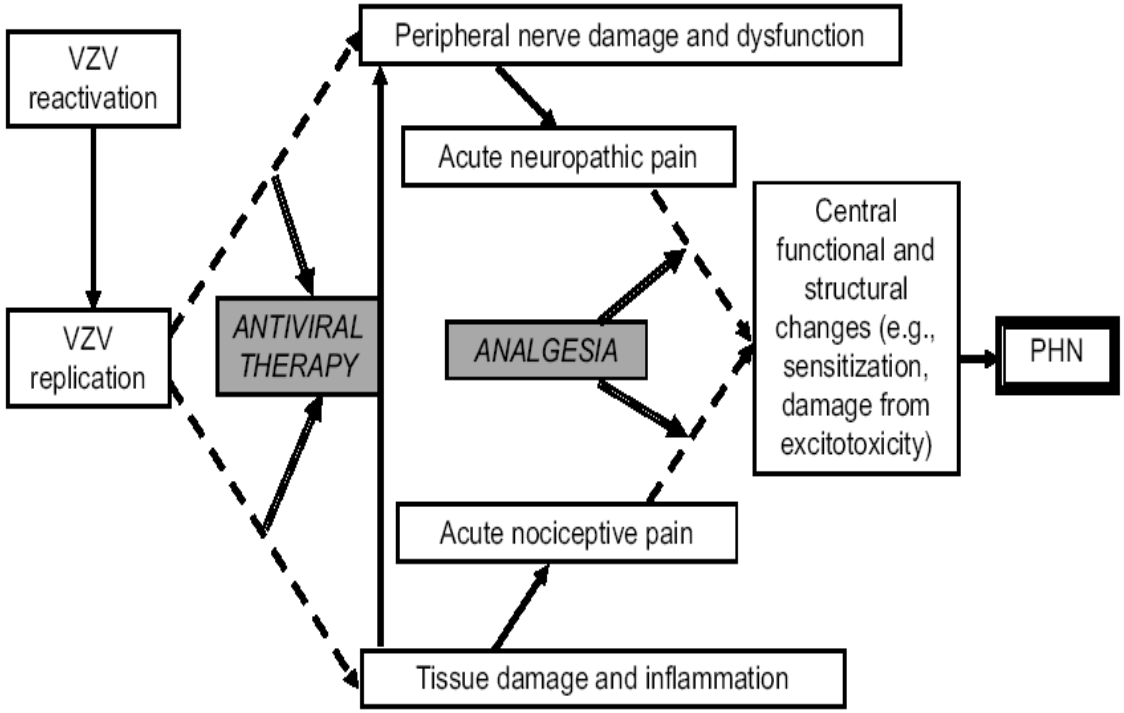
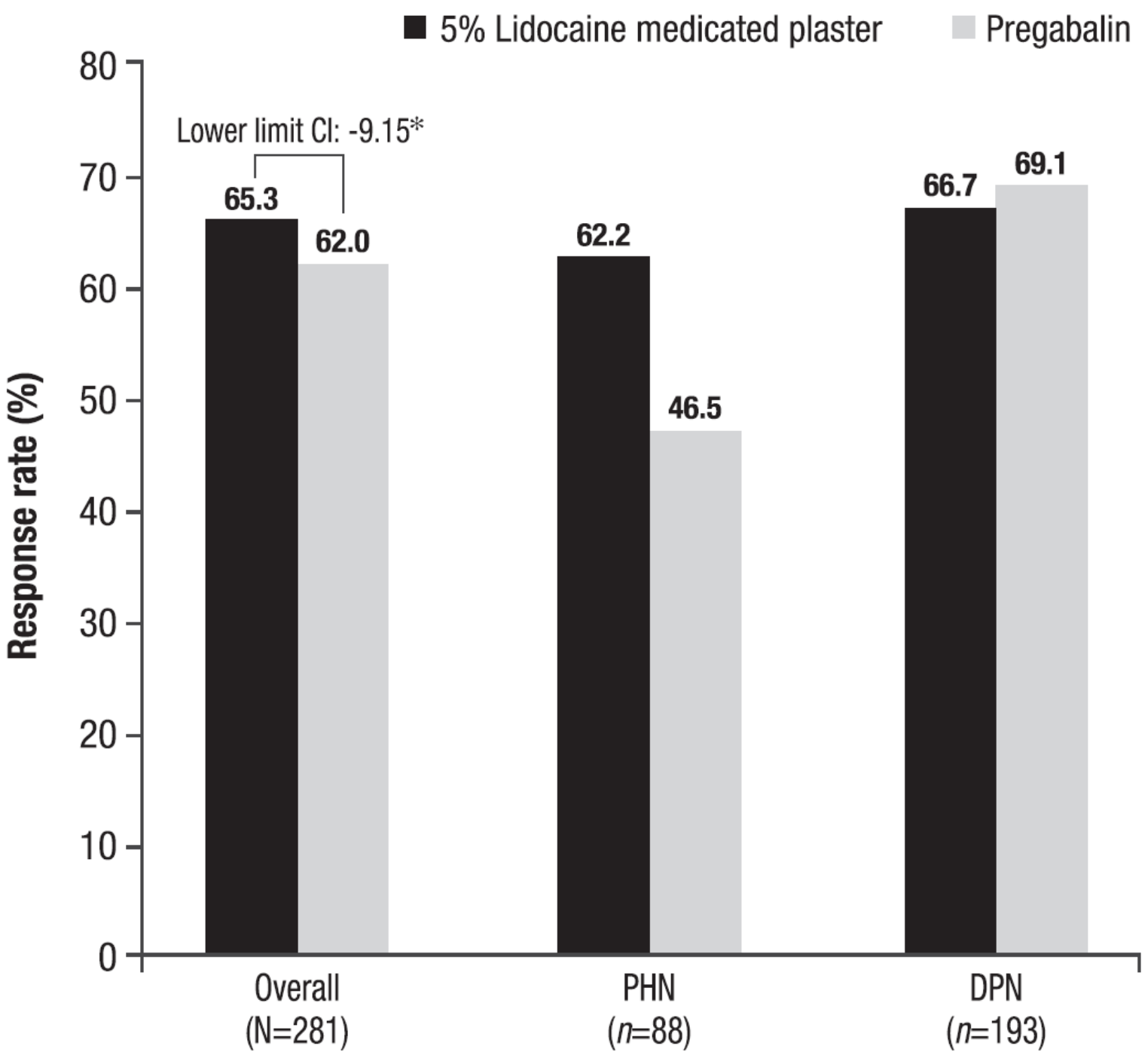
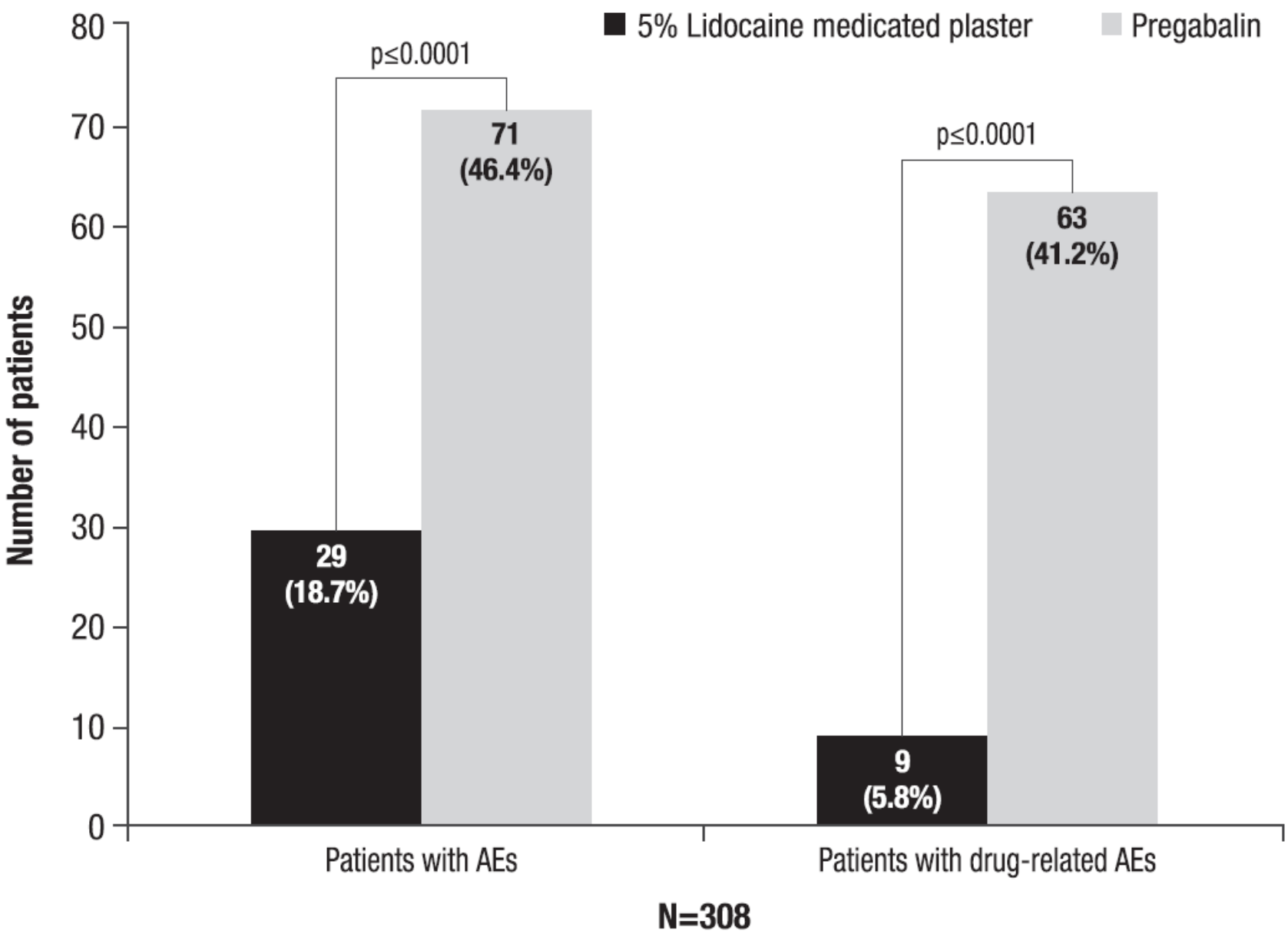
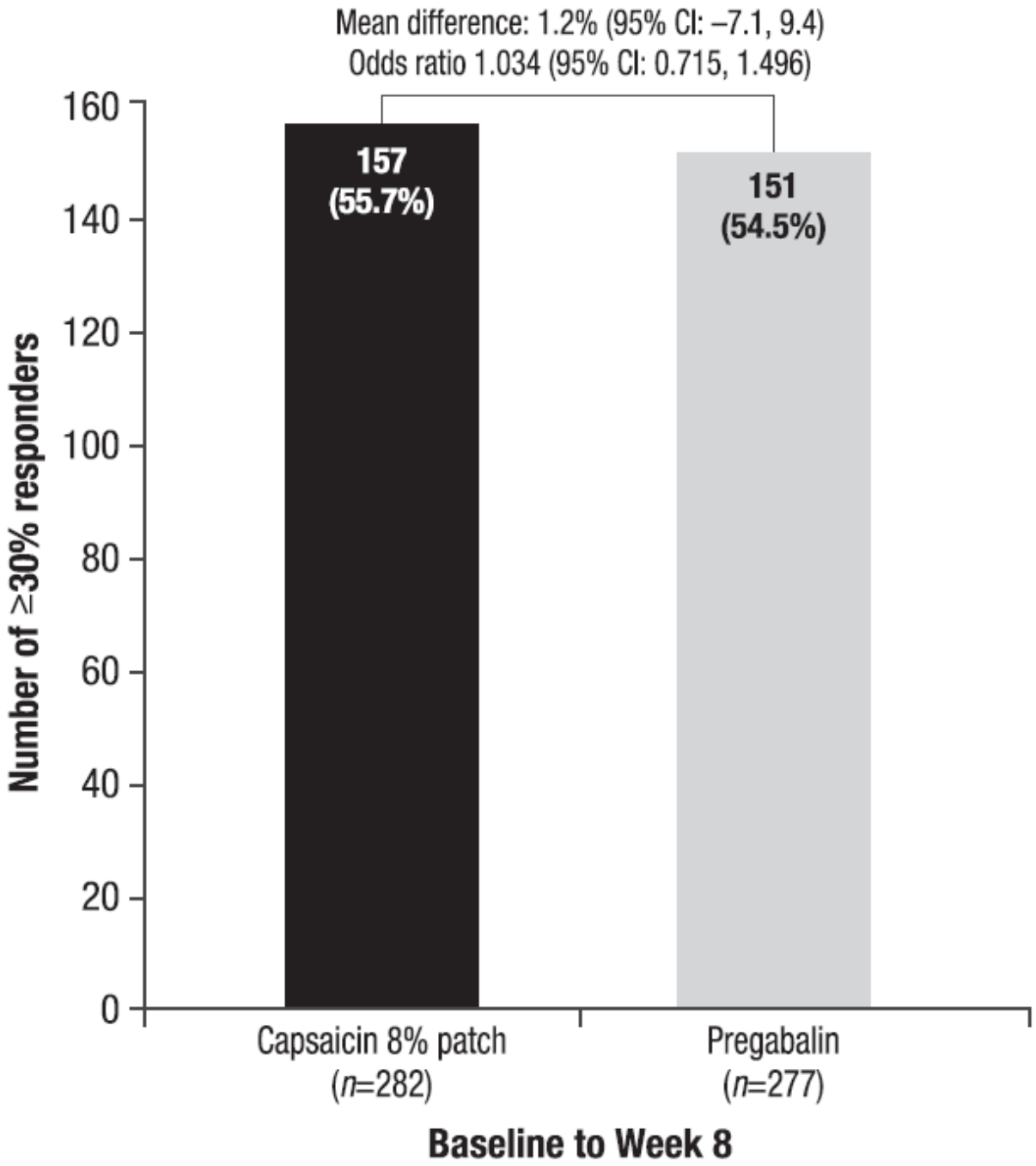


Fig. 6. A hypothesized model for attenuating nerve damage and acute pain during HZ and thereby preventing the development of PHN. This model proposes that combined antiviral and analgesic treatment in patients with HZ might decrease the risk of developing PHN by both inhibiting viral replication and reducing the acute afferent barrage of nociceptive and neuropathic pain.[54] Reprinted with permission from Dworkin RH, Perkins FM, Nagasako EM. Prospects for the prevention of postherpetic neuralgia in herpes zoster patients. *Clin J Pain* 2000;**16**(2 Suppl):S90–100.


5% Lidocaine medicated plaster
Pregabalin
Response rate (%)
80
70
60
50
40
30
20
10
0
Lower limit CI: -9.15*
65.3
62.0
62.2
46.5
66.7
69.1
Overall
(N=281)
PHN
(n=88)
DPN
(n=193)


5% Lidocaine medicated plaster
Pregabalin
Number of patients
80
70
60
50
40
30
20
10
0
p≤0.0001
71
(46.4%)
29
(18.7%)
p≤0.0001
63
(41.2%)
9
(5.8%)
Patients with AEs
Patients with drug-related AEs
N=308


Mean difference: 1.2% (95% CI: –7.1, 9.4)
Odds ratio 1.034 (95% CI: 0.715, 1.496)
160
140
120
100
80
60
40
20
0
Number of ≥30% responders
157
(55.7%)
151
(54.5%)
Capsaicin 8% patch
(n=282)
Pregabalin
(n=277)
Baseline to Week 8

PHN
Raccomandazioni e Linee Guida 1

European Journal of Neurology 2010, **17:** 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
PHN	Capsaicin 8% patch** Gabapentin Gabapentin ER** Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCA[b]	Capsaicin cream Valproate*		Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids

Raccomandazioni e Linee Guida 2

Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update

Robert H. Dworkin, PhD; Alec B. O'Connor, MD; Joseph Audette, MD; Ralf Baron, Dr Med; Geoffrey K. Gourlay, PhD; Maija L. Haanpää, MD, PhD; Joel L. Kent, MD; Elliot J. Krane, MD; Alyssa A. LeBel, MD; Robert M. Levy, MD, PhD; Sean C. Mackey, MD, PhD; John Mayer, DC, PhD; Christine Miaskowski, RN, PhD; Srinivasa N. Raja, MD; Andrew S. C. Rice, MB, MD, FRCA; Kenneth E. Schmader, MD; Brett Stacey, MD; Steven Stanos, DO; Rolf-Detlef Treede, Dr Med; Dennis C. Turk, PhD; Gary A. Walco, PhD; and Christopher D. Wells, MB

Mayo Clin Proc. 2010;85(3)(suppl):S3-S14

TABLE 1. **Stepwise Pharmacological Management of Neuropathic Pain**

Initiate therapy for the disease causing NP, if applicable
Initiate symptom treatment with one or more of the following:
- A secondary-amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel α_2-δ ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP, topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies

TABLE 7. APIs Reported in Topical Compounded Medications Used in Pain Management According to an Internet Survey[102]

Local anesthetics	NSAIDs
Lidocaine 2%, 4%, 5%	Diclofenac
Prilocaine	Ketoprofen 4%, 5%, 10%
Bupivacaine	Aspirin
Tetracaine	Flurbiprofen 5%
Corticosteroids	Ibuprofen 2%
Dexamethasone 0.15%	Piroxicam 0.5%, 2%
Hydrocortisone 10%	Anticonvulsants
Antidepressants	Carbamazapine 2%
Amitriptyline 2%	Gabapentin 6%
Nortriptyline	Others
Doxepin	Baclofen 5%
Opioids	Orphenadrine
Fentanyl	Lecithin
Hydromorphone	Capsaicin 0.025%, 0.05%
Morphine	Cyclobenzaprine 0.5%, 1%, 2%
Sufentanil	Clonidine 0.2%
Loperamide	Diphenhydramine 1%
NMDA receptor	Nifedipine
Antagonists	Guanethidine 1%, 2%
Ketamine 5%, 10%, 15%, 20%	Guaifenesin
Dextromethorphan	Haloperidol
Amantadine	

API indicates active pharmaceutical ingredient; NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug.

Farmaci ad azione topica

Qutenza (Capsaicina 8%)

- Una applicazione ogni 3 mesi (ottima compliance)
- NNT 12 (ma negli studi il gruppo di controllo è capsaicina 0.04%)
- Nessun caso oltre il 30% di efficacia
- Effetti collaterali locali importanti
- 50% dei pazienti è “non responder”
- Effetti a lungo termine? (recente chiusura di studio di safety)

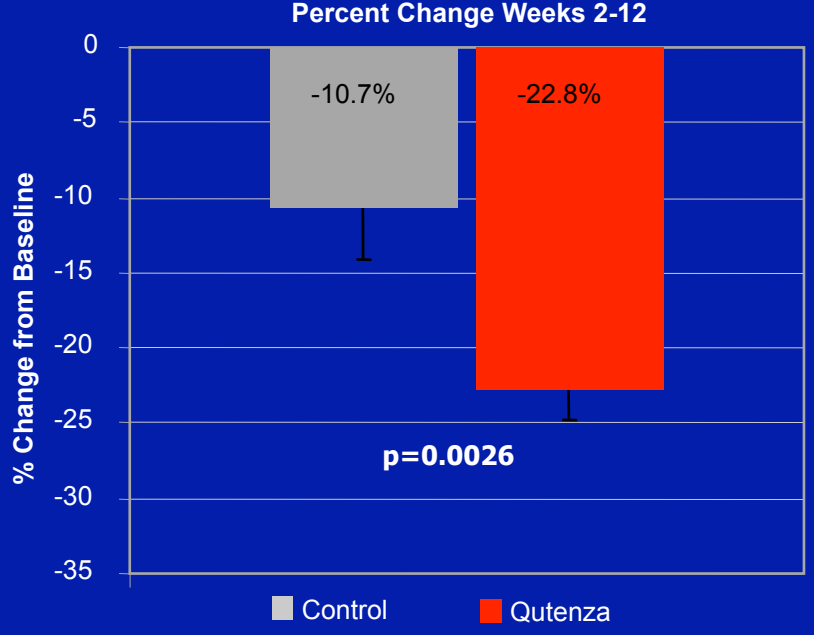
Versatis (Lidocaina 5%)

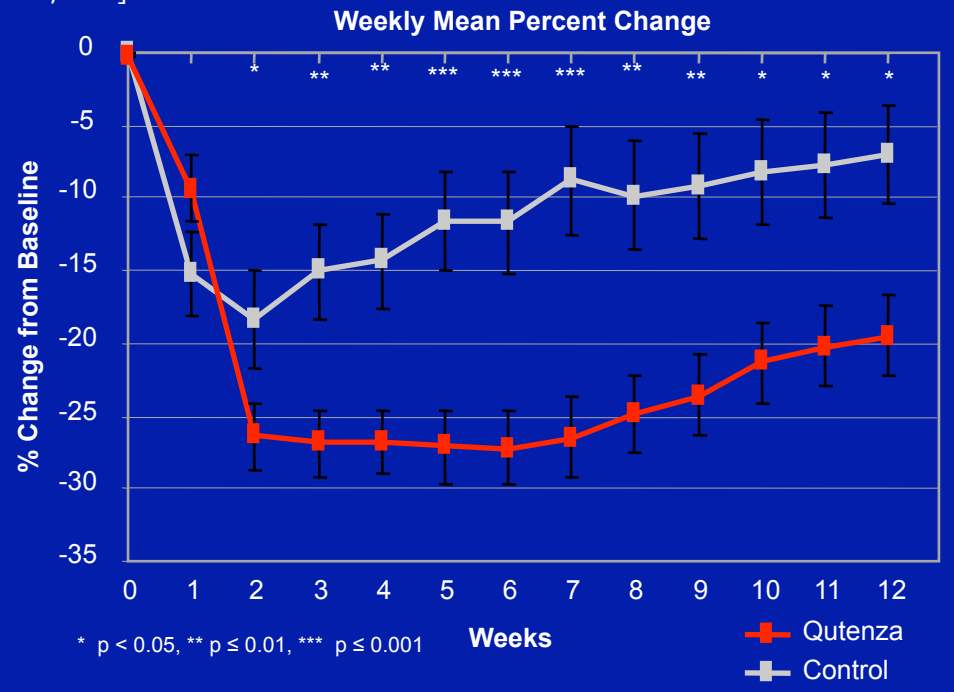
- Blocca i canali del sodio voltaggio dipendenti
- Ben tollerata
- Efficace solo su neuropatie focali
- Efficace soprattutto sulla allodinia

Changes in PHN Pain Following Qutenza™ Treatment

Percent (%) Change from Baseline

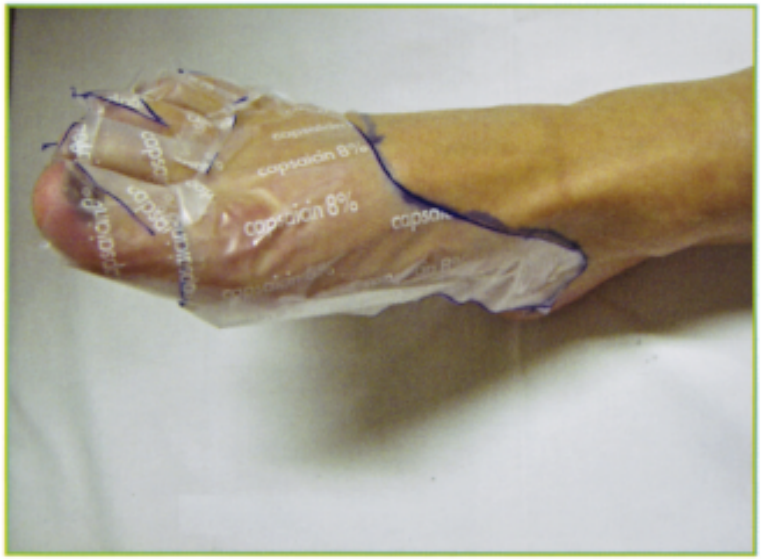
30-, 60- and 90-minute application
All Qutenza vs. All Control
[mean, SEM]

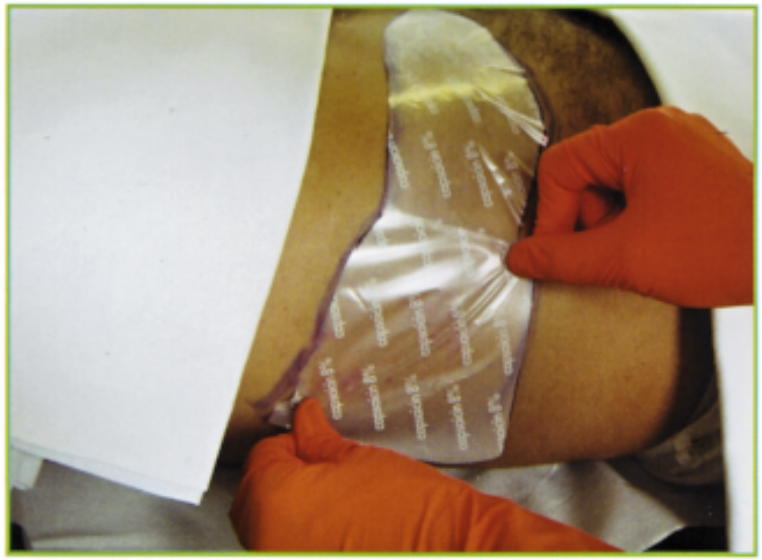




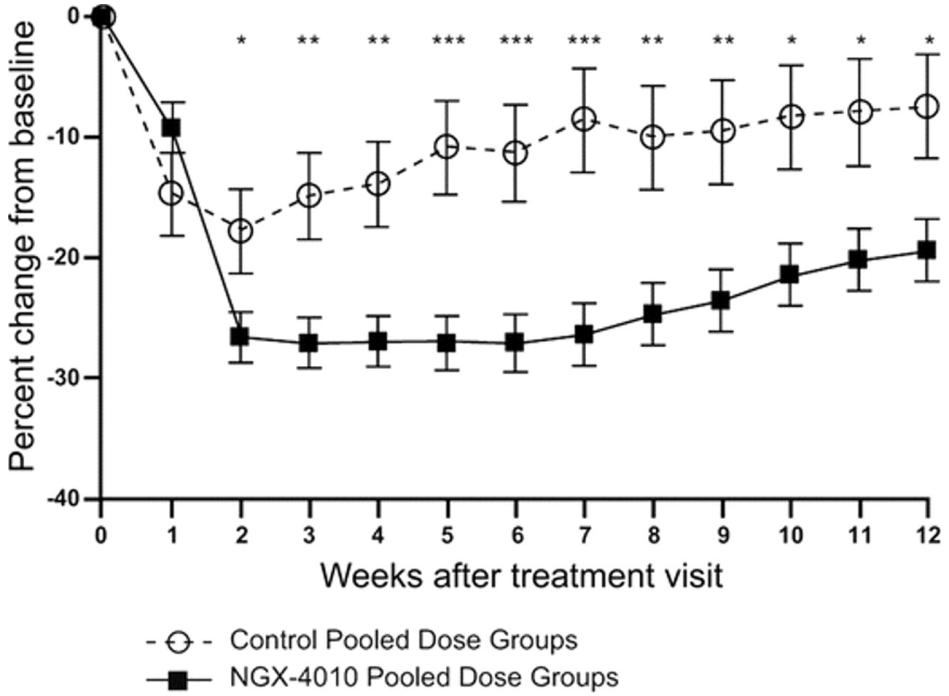
Simpson DM , et al. Neurology 2008; 70:2305-13

Capsaicin 8%





PHN



Treatment-Emergent Adverse Events with Capsaicin 8% Patch Compared with Pregabalin in ELEVATE Study[15]

TEAE	Capsaicin 8% patch, $n = 282$	Pregabalin, $n = 277$
Overall n (%)	173 (61.3)	151 (54.5)
Application site pain	67 (23.8)	0 (0.0)
Erythema	59 (20.9)	1 (0.4)
Burning sensation	44 (15.6)	0 (0.0)
Application site erythema	25 (8.9)	0 (0.0)
Pain	15 (5.3)	2 (0.7)
Headache	3 (1.1)	26 (9.4)
Abdominal pain upper	2 (0.7)	8 (2.9)
Nausea	1 (0.4)	30 (10.8)
Asthenia	1 (0.4)	9 (3.2)
Dizziness	0 (0.0)	51 (18.4)
Somnolence	0 (0.0)	43 (15.5)
Weight increased	0 (0.0)	17 (6.1)
Vertigo	0 (0.0)	14 (5.1)
Dry mouth	0 (0.0)	13 (4.7)
Fatigue	0 (0.0)	12 (4.3)
Peripheral edema	0 (0.0)	11 (4.0)
Disturbances in attention	0 (0.0)	8 (2.9)
Diarrhea	0 (0.0)	7 (2.5)
Days free from drug-related TEAE, %	90.5	70.4

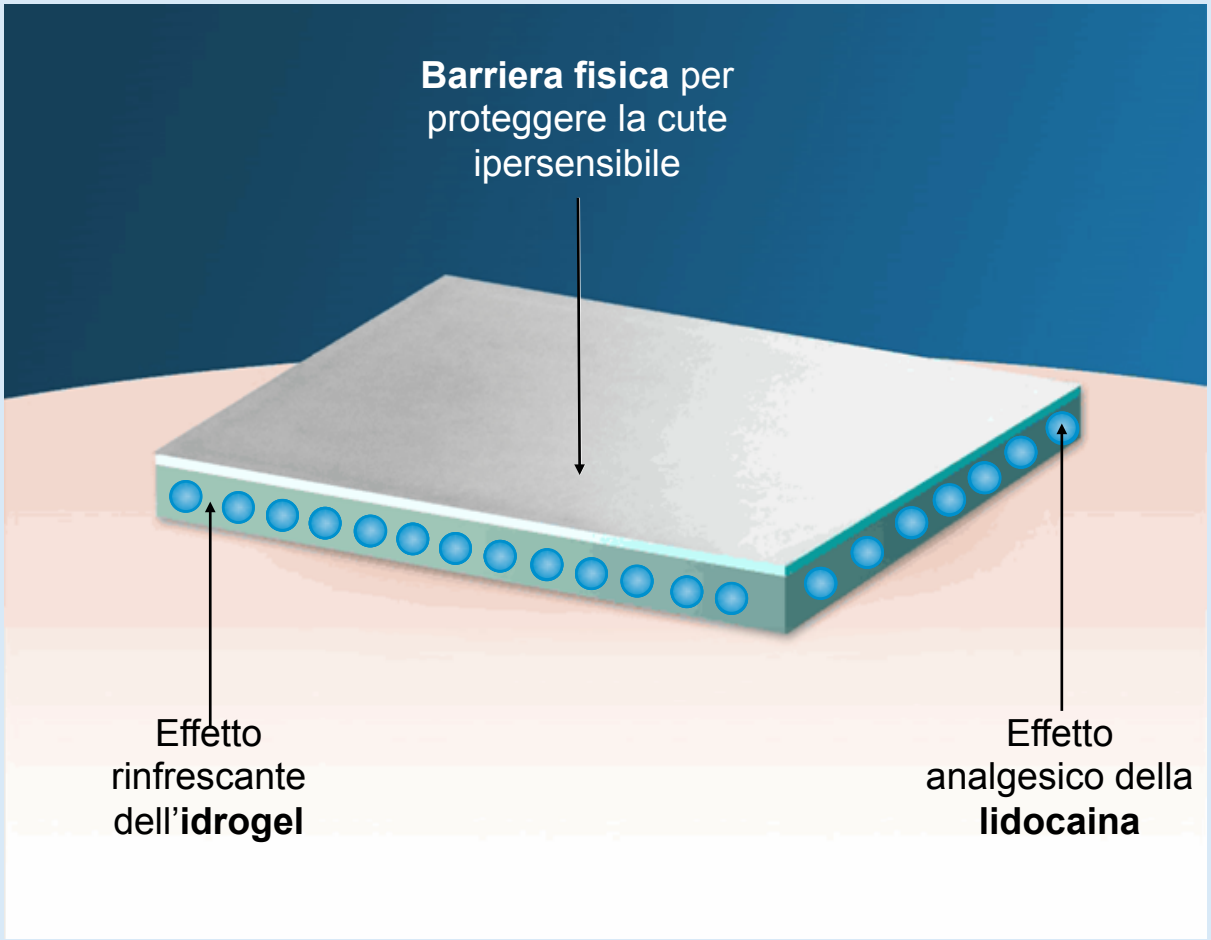
TEAE = treatment-emergent adverse event.

Lidocaina cerotto 5%
Tecnologia

- Formulazione farmaceutica: Cerotto idrogel, autoadesivo
- Principio attivo: **Lidocaina**
- Dimensioni: 10 cm x 14 cm
- Dosaggio per cerotto: 5% (50 mg/grammo di base adesiva)
- Dose di carico totale: 700 mg a cerotto

- Schema di applicazione: **12 ore on/off** con un sollievo dal dolore per 24 ore
- Da uno ad un massimo di tre cerotti applicati contemporaneamente

Lidocaina cerotto 5%
Meccanismo d'azione



Lidocaina cerotto 5% vs pregabalin

Efficacia e sicurezza di Lidocaina cerotto 5% in comparazione con pregabalin nel trattamento della nevralgia posterpetica e della polineuropatia diabetica dolorosa

Disegno:

Multicentrico europeo, randomizzato, con fase di confronto e associazione, Lidocaina cerotto 5% vs pregabalin

Obiettivo primario:

Valutare l'efficacia e la sicurezza di Lidocaina cerotto 5% verso pregabalin in pazienti affetti da nevralgia post-erpetica **(PHN)** e polineuropatia diabetica **(DPN)**

Popolazione:

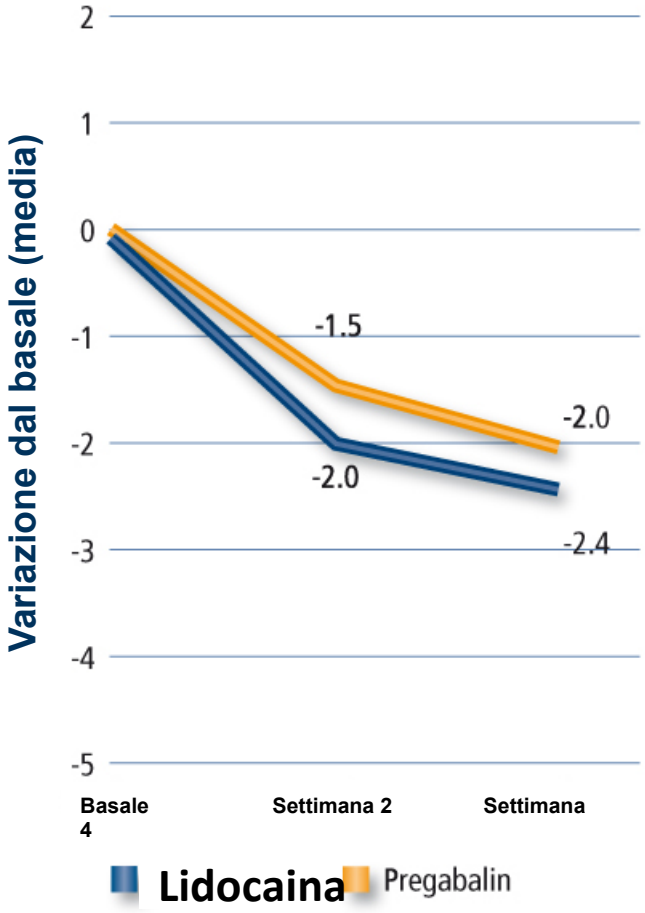
281pazienti, 88 con PHN e 193 con DPN

Baron R et al. Curr Med Res Opin 25(7): 1663-1676, 2009;
Baron R et al. Curr Med Res Opin 25(7): 1677-1687, 2009;
Rehm S et al. Curr Med Res Opin 26(7): 1607-1619, 2010

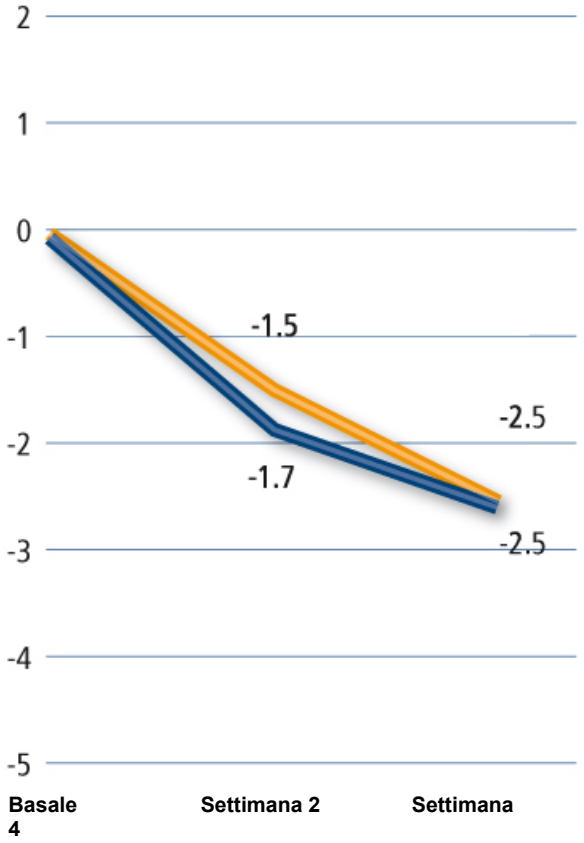
Lidocaina cerotto 5% *vs* pregabalin
Fase di confronto: efficacia

NRS-3: variazione rispetto al basale

PHN (PP)



DPN, (PP)



Lidocaina Pregabalin

Baron R et al. Curr Med Res Opin 25(7): 1663-1676, 2009;

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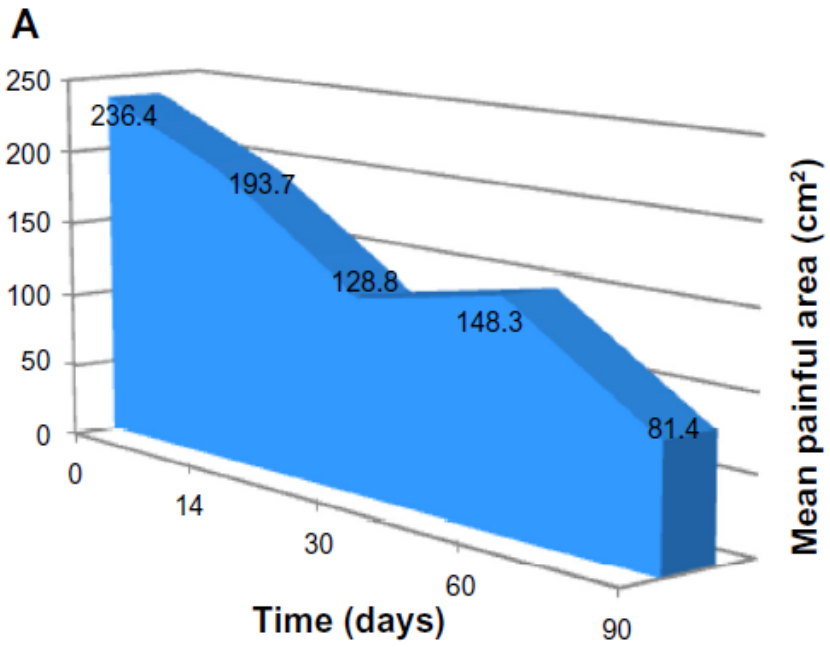
CASE SERIES

Reduction of painful area as new possible therapeutic target in post-herpetic neuropathic pain treated with 5% lidocaine medicated plaster: a case series

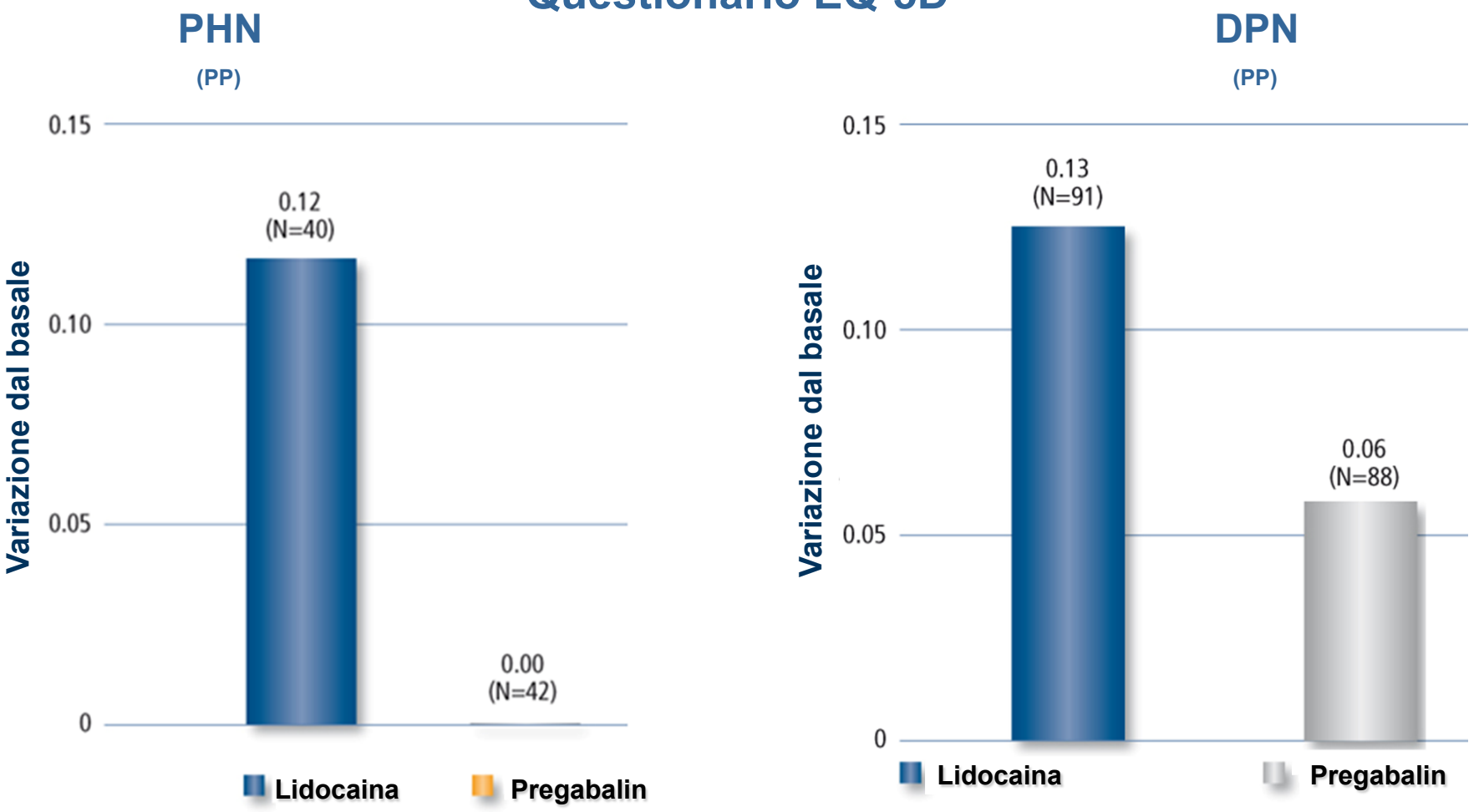


Roberto Casale[1,2]
Maria Di Matteo[3,7]
Cristina E Minella[4,7]
Guido Fanelli[5,7]
Massimo Allegri[4,6,7]

Lidocaina cerotto 5% *vs* pregabalin

Fase di confronto: qualità della vita

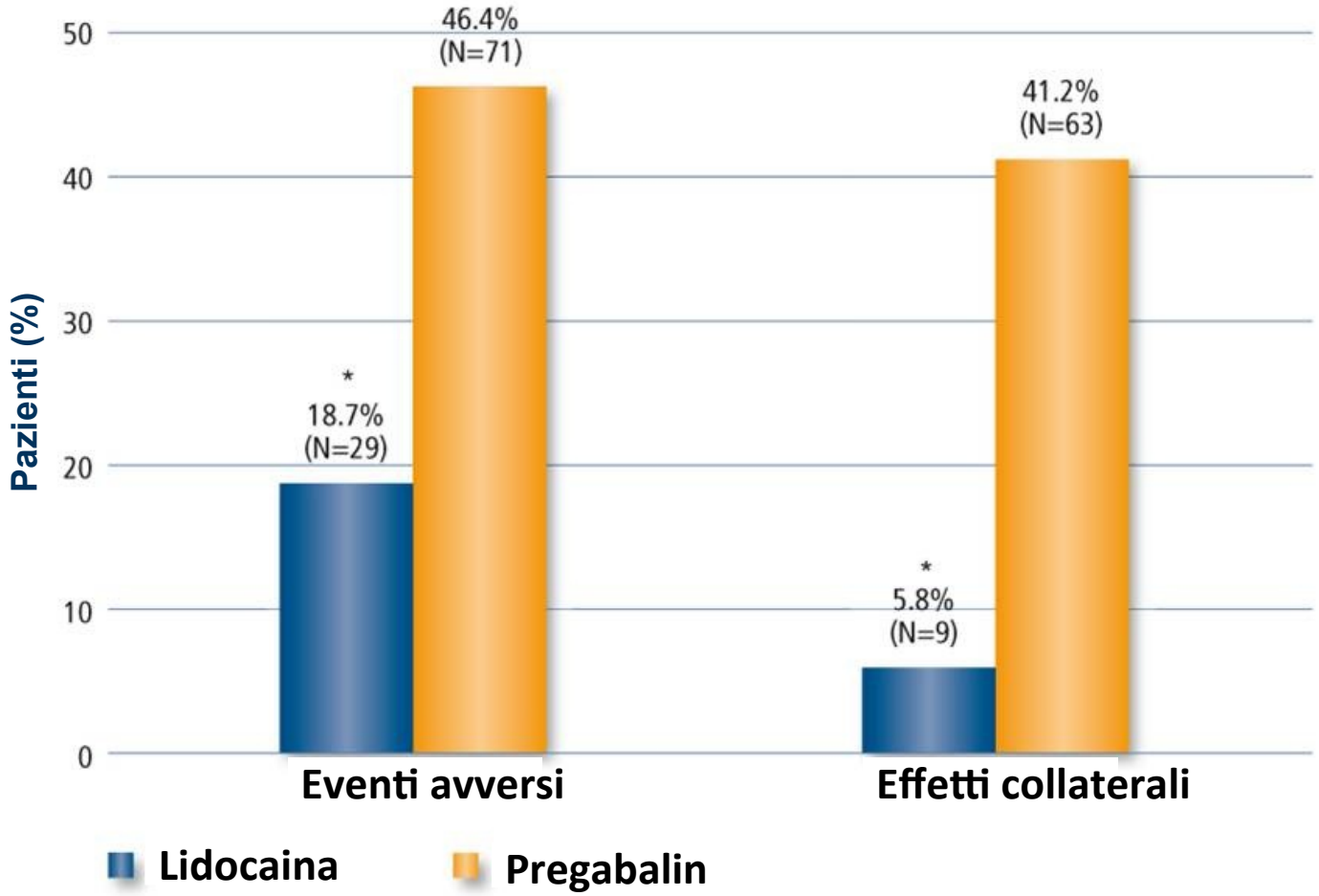
Questionario EQ-5D



Baron R et al. Curr Med Res Opin 25(7): 1663-1676, 2009;

Lidocaina cerotto 5% *vs* pregabalin
Fase di confronto: tollerabilità

Eventi avversi ed effetti collaterali



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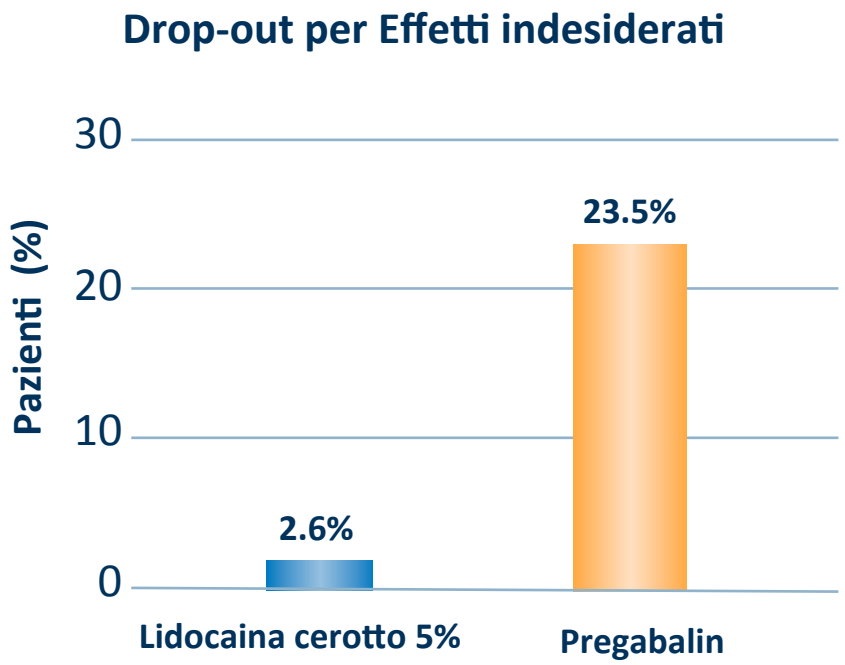
Lidocaina cerotto 5% *vs* pregabalin
Fase di confronto: tollerabilità

EFFETTI INDESIDERATI (ADR)	Lidocaina cerotto 5% N=155	Pregabalin N=153
N° ADR	16	161
PT con ADR (%)	5.8	41.2
PT con ADR più comuni (%)		
Vertigine/capogiro	-	19.6
Affaticamento	-	8.5
Sonnolenza	-	5.2
Reazione al sito di applicazione (eritema, parestesia, rush)	1.3	-



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The Varicella Zoster Vaccine

- Study design
  - Randomized, double-blinded, placebo-controlled
  - Large 38,546 subjects 60 years of age or older
  - Cases of herpes zoster were diagnosed by both clinical and laboratory criteria
  - Pain and discomfort measured repeatedly
  - More than 95% of subjects completed 3.12 year median surveillance

End Point 1

- Burden of Illness (BOI) due to Herpes Zoster
  - BOI Defined as

    "Incidence, severity and duration of associated pain and discomfort"

End Point 2

- Incidence of postherpetic neuralgia (PHN)

Diagnosis

- Clinically “suspected cases of herpes zoster”
  - Unilateral rash with no alternative diagnosis
- Confirmed/not confirmed by PCR, culture or clinical diagnosis by 5 physician evaluation committee

Incidence

- 957 confirmed cases of zoster
- 642 among placebo recipients
- 315 among vaccine recipients

Reduced incidence of herpes zoster by 51.3%

($P<0.001$)

Endpoint 1 – Burden Of Illness

- Zoster Brief Pain Inventory area under curve against time for 182 days after rash occurs
- Subjects with poorer initial health status experienced worse BOI
- **Zoster vaccine reduced BOI by 61.1% (P<0.001)**

End point 2 - PHN

- Neuropathic pain syndrome persisting after the dermatomal rash has healed
  - Frequency and severity of PHN increases with increasing age

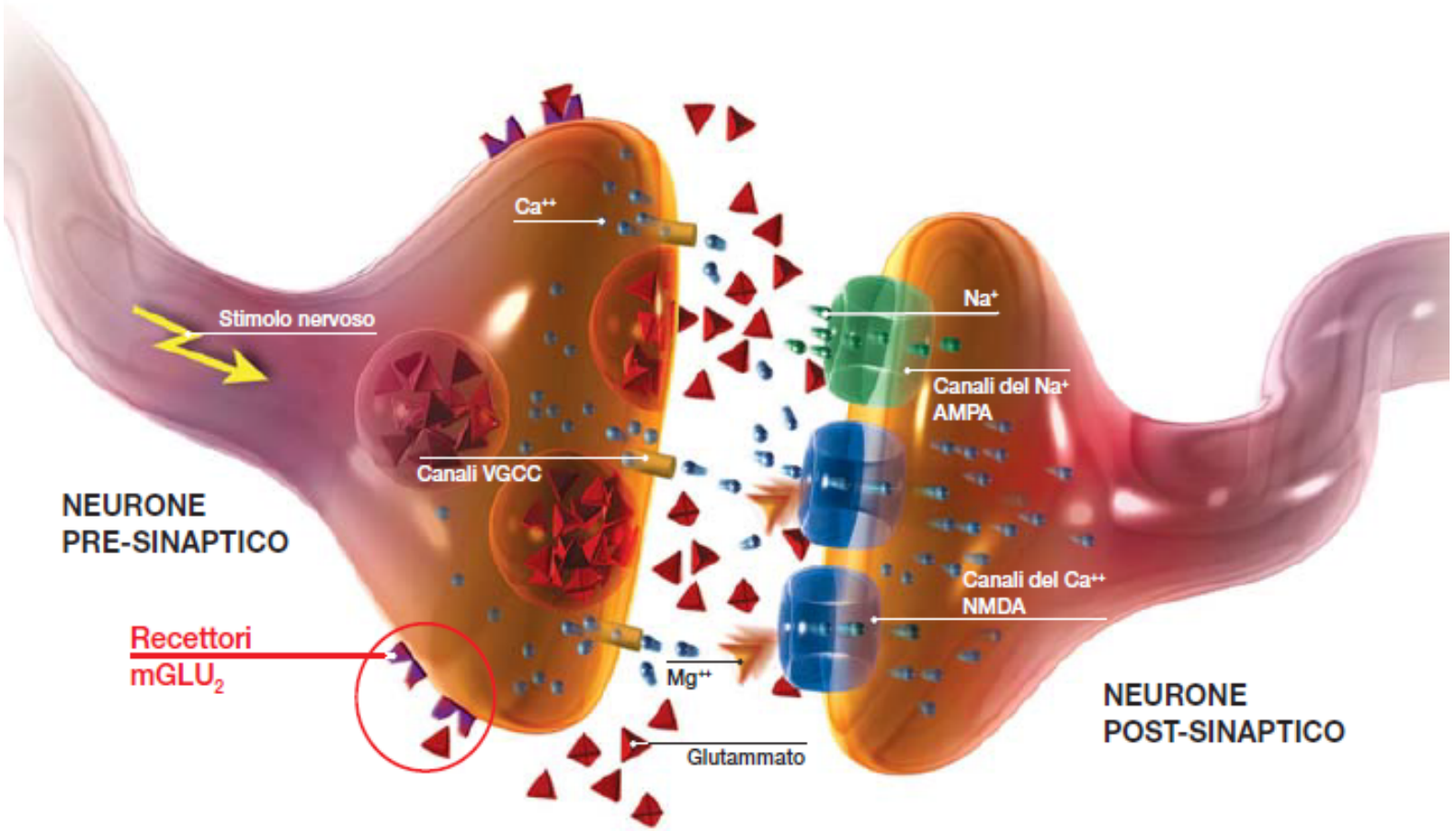
PHN incidence was reduced by 66.5% (P<0.001)

Result Summary

- Immunized individuals greater than 60 developed herpes zoster half as often
- Immunized individuals experience 60% less pain, severity and duration
- Immunized individuals develop PHN 1/3 as frequently and have milder cases

Adverse Effects

- 42 days following vaccine
  - 7 confirmed cases of HZ in immunized patient and 24 in the placebo group
  - Site reaction was greater in the immunized group (pain, pruritis, swelling)
  - Severe events
    - Immunized – 1 case of AE asthma, 1 case PMR
    - Placebo – 1 case anaphalactoid reaction (ate peanuts), 1case PMR, 1 case Goodpasture Syndrome



Grazie dell'attenzione