Eur J Clin Pharmacol (1994) 46: 517–522

European Journal of Clinical Pharmacology

The effectiveness of topically applied capsaicin

A meta-analysis

W. Y. Zhang, A. Li Wan Po

Pharmacoepidemiology Section, The Pharmacy Practice Research Group, The School of Pharmacy, The Queen's University of Belfast, Belfast, UK

Received: 20 October 1993 / Accepted in revised form: 22 March 1994

Abstract. To undertake a quantitative overview of trials of topical capsaicin for the treatment of diabetic neuropathy, osteoarthritis, post-herpetic neuralgia, and psoriasis.

A systematic search of the literature using both computerized and manual methods for identifying clinical trials of capsaicin. The trials identified were abstracted for response data, which then were analysed using established meta-analytic methods for both fixed and random effects modelling.

The odds ratio of the response rate of subjects receiving topical capsaicin relative to that of subjects on placebo was used as the main outcome measure. The difference in the response rate was used as the response variable under the random effects model. When dropouts were mentioned and unambiguous assignment could not be made, the analysis was made on the basis of intention to treat.

Capsaicin cream give more pain relief to patients with diabetic neuropathy than placebo did. The odds ratio (OR) and corresponding 95% confidence interval (95% CI) in favour of capsaicin cream were OR = 2.74 (95% CI = 1.73, 4.32). Using a random effect model the rate difference (RD) in favour of capsaicin cream was RD = 0.25 (95% CI = 0.15, 0.35).

Capsaicin cream was also better than placebo in providing pain relief in osteoarthritis: OR = 4.36 (95% CI = 2.77, 6.88) and RD = 0.29 (95% CI = 0.20, 0.37) and in psoriasis: OR = 2.80 (95% CI = 1.69, 4.62) and RD = 0.35 (95% CI = 0.14, 0.56). There was, however, evidence of heterogeneity in the individual RDs in psoriasis, and complete blinding was difficulty because of the initial discomfort associated with topical capsaicin.

In post-herpetic neuralgia the results were even less convincing.

Topical capsaicin appears to be effective in the management of a variety of painful clinical conditions affecting the skin. However, totally blind trials are difficult to conduct with this substance. Future trials will need to address this problem more rigorously if a definitive answer about the effectiveness of capsaicin is to be obtained.

Key words: Capsaicin, Diabetic neuropathy; pain relief, patients

Correspondence to: A. Li Wan Po, The School of Pharmacy, The Queen's University of Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK

Capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide) is the alkaloid which makes chillies hot. Chauca, the physician who accompanied Columbus on his second voyage to the West Indies, first referred to capsaicin in 1494 [1]. Early pharmacopoeias, including the British Pharmacopoeia, describe the use of capsaicin as a tonic and a carminative useful in dyspepsia.

Topical capsaicin was described as a counter-irritant in lumbago, neuralgia, and rheumatic disorders [2]. Official formulations included Emplastrum Capsici BPC, Unguentum Capsici BP, and Tinctura Capsici BP. Some of these formulations have lasted to this day and many compound proprietary topical analgesic preparations still contain capsicum extracts or capsaicin [3].

Recent interest has centred on the use of capsaicin as a topical analgesic for a variety of conditions characterized by pain not responsive to classical analgesics, including the opiates, paracetamol, and non-steroidal anti-inflammatory drugs. Interest in its mode of action has been heightened by the discovery that it depletes local sensory terminals of substance P, a hendecapeptide [4]. Substance P has also been implicated in the pathogenesis of a number of diseases, including arthritis, asthma, psoriasis, and inflammatory bowel disease [5–7].

This new insight into the mode of action of capsaicin has led to a number of clinical trials. In this report we provide a systematic quantitative meta-analysis of the results to date.

Subjects and methods

Literature search

The English language medical literature (January 1980 to February 1994) was computer searched using the Institute of Scientific Information Database (BIDS). The key word in the title and abstract was

Table 1. Published clinical investigations of capsaicin

Disease	Study design		
	Double-blind placebo controlled trials Number [references]	Uncontrolled studies Number [references]	Case reports Number [references]
Diabetic neuropathy	4 [11–14]	–	1 [15]
Arthritis	3 [17–19]	–	–
Postherpetic neuralgia	2 [25, 26]	4 [27–30]	3 [31–33]
Psoriasis	4 [36–39]	–	–
Postmastectomy	1 [43]	2 [45–46]	–
Amputation stump pain	–	–	2 [47–48]

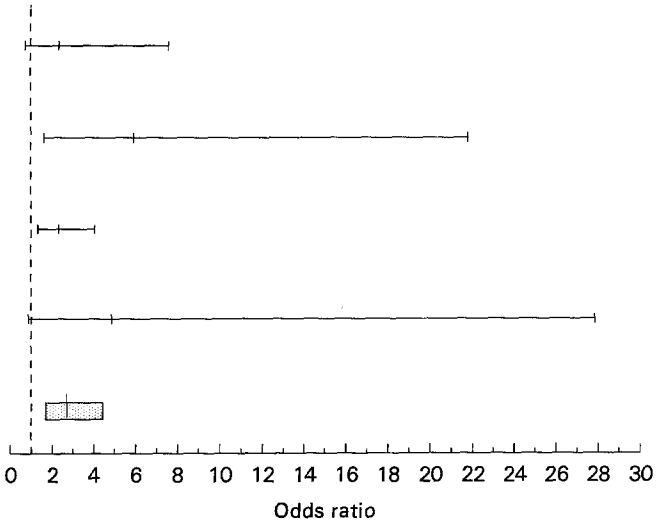

Fig. 1. Odds ratio and associated 95 % confidence interval in favour of improvement with capsaicin in diabetic neuropathy. Individual results: ——; pooled result: ▨

capsaicin without any qualifier. From the resulting list, any paper that suggested a clinical investigation was identified and a hard copy obtained. Reviews were also scanned to identify other possibly relevant references. When the hardcopies were received, any clinical investigation mentioned and not previously identified was retrieved. Medline was searched over the same period to identify any papers missed by the BIDS search. No attempt was made to retrieve full reports of unpublished studies from manufacturers or authors of abstracts.

Statistical analysis

Two approaches were used for pooling the data: the Mantel-Haenszel method [8] and the random effects model proposed by DerSimonian and Laird [9]. With the former, the odds ratio for the patients showing improvement in favour of capsaicin treatment was calculated for each trial, according to the method of Yusuf et al [10], before pooling. With the DerSimonian and Laird method, the response rate or risk difference in favour of the capsaicin treatment was the statistic of interest.

Inclusion and exclusion criteria

In order to be included in the statistical pooling of response, a trial had to be randomized, double-blind, and placebo-controlled. The number of subjects treated and showing improvement had to be described for both capsaicin and placebo treatments. Case reports, uncontrolled studies, and some abstracts in which the necessary data were not available were excluded, although the results were included in a semi-quantitative summary. The response used for pooling was the proportion of subjects showing improvement, from which we derived the odds ratio and response rate difference (or risk difference) in favour of capsaicin cream.

Results and discussion

Table 1 lists the number and types of clinical investigations of topical capsaicin identified by our searches. The features of the randomized placebo-controlled trials are shown in Table 2.

Capsaicin and diabetic neuropathy

Peripheral neuropathy is a well-known complication of diabetes mellitus, and in long-term diabetics (>25 y) as many as 50 % may be affected [16]. The associated pain correlates well with degeneration of small diameter type C unmyelinated and thinly myelinated (Aδ) nerve fibres. Large myelinated fibres may occasionally be involved. Current treatments are not very effective and the rationale for the use of capsaicin is its effects on the type C nociceptive afferent nerve fibres.

In diabetic neuropathy, capsaicin cream produced significantly higher response rates than placebo cream did in two of the trials [12, 13] but not in the other two [11, 14] (Table 3). Nevertheless, in all four trials the trend was in favour of capsaicin cream. This result was confirmed by pooling. The pooled odds ratio (Fig. 1) in favour of capsaicin cream was 2.74 (95 % CI 1.73, 4.32). The corresponding response rate difference (Table 4) was 0.25 (95 % CI 0.15, 0.35).

In addition to the double-blind trials, in one case report capsaicin was described as being effective against pain due to diabetic neuropathy [15].

Capsaicin and osteoarthritis

Substance P has recently been implicated in the pathogenesis and modulation of inflammation and pain in arthritis [20–23]. Since local application of capsaicin to the peripheral sensory endings in the skin results in depletion of substance P from the whole neurone, both peripherally and centrally [24], its use in relieving the pain of arthritis has been suggested.

Table 2. Features of randomised placebo-controlled trials of topical capsaicin

Trial	Ref.	Design and duration	Outline of demographics				Capsaicin formulation	Number with clinical improvement		Method of assessment
			Age (y)	M/F	Type of disease	Exclusions		Capsaicin	placebo	
1	[11]	DB-P[a], 4 weeks	18–85	–	Diabetes I and II, neuropathy	–	0.075 % cream, qid	17/24	11/22	PE[b]
2	[12]	DB-P, 8 weeks	18–92	19/35	Diabetes I and II, neuropathy	FBG[c] ≥ 10 mmol/l, other skin disorders	0.075 % cream, qid	17/19	11/22	PE
3	[13]	DB-P, 8 weeks	18–85	139/138	Diabetes I and II, neuropathy	FBG ≥ 9.99 mmol/l, other skin disorders	0.075 % cream, qid	65/91	57/111	PE
4	[14]	DB-P, 8 weeks	18–85	11/11	Diabetes I and II, neuropathy	FBG ≥ 10 mmol/l, other skin disorders	0.075 % cream, qid	6/10	2/10	PE
5	[17]	DB-P, 4 weeks	31–82	25/45	Primary osteoarthritis	Other skin disorders	0.025 % cream, qid	24/34	15/30	PE
6	[18]	DB-P, 4 weeks	65 (±2)	5/9	Primary osteoarthritis	Other skin disorders	0.075 % cream, qid	57/135	13/132	AT[d]
7	[19]	DB-P, 4 weeks	–	–	Primary osteoarthritis	–	0.025 % cream, qid	6/23	2/28	AT
8	[25]	DB-P, 6 weeks	54–90	20/12	Postherpetic neuralgia	–	0.075 % cream, tid or qid	4/16	1/16	PE
9	[26]	DB-P, 4 weeks	–	–	Postherpetic neuralgia	–	0.025 % cream, qid	[h]	[h]	[h]
10	[36]	DB-P, 6 weeks	25–85	23/21	Psoriasis	–	0.025 % cream, qid	23/34	15/34	Itching, scaling erythema[e]
11	[37]	Open[f], 8 weeks	32	7/3	Psoriasis	–	0.025 % cream, qid	7/10	0/10	Itching, scaling erythema
12	[38]	DB-P, 6 weeks	–	–	Psoriasis	–	0.025 % cream, qid	8/10	3/10	Itching, scaling erythema
13	[39]	DB-P, 6 weeks	13–73	107/90	Psoriasis	–	0.025 % cream, qid	40/61	37/76	Itching, scaling erythema
14	[44]	DB-P, 6 weeks	36–78	–	Postmastectomy pain	Other skin disorders	0.075 % cream, qid	5/13	1/10	Global ratings[g]

[a] Double-blind, vehicle-controlled, parallel trial
[b] PE: Physician's global evaluation, scored pain relief as completely gone 3, much better 2, better 1, no change 0, worse –1, much worse –2. Clinical improvement = completely gone, much better or better
[c] FBG: fasting blood glucose
[d] AT: Articular tenderness, estimated using a standardized dolorimiter (McCarty DJ et al. (1965) A dolorimeter for quantification of articular tenderness. Arthr Rheum 8: 551–559)
[e] Psoriasis was rated as to degree of change in itching, scaling and erythema, as well as to overall appearence. Clinical improvement = much better or better rating of overall apperence
[f] Psoriasis plaques on one side of the body were treated with capsaicin. Psoriasis lessions on another side of the body were treated with placebo
[g] Global ratings took into account pain, pain relief, disabling side-effect and level of satisfaction. Clinical improvement = excellent or good rating
[h] Only abstract available. Not included in analysis

Table 3. Summary of results of individual clinical trials using Mantel-Haenszel (M-H) and DerSimonian and Laird's (D-L) methods

		M-H method				D-L method		
		OR	lnOR	SE(lnOR)	Z	RD	SE(RD)	Z
Diabetic neuropathy	Trial 1[11]	2.36	0.86	0.60	1.43	0.21	0.14	1.47
	Trial 2[12]	5.92	1.78	0.66	2.67*	0.39	0.13	3.09**
	Trial 3[13]	2.31	0.84	0.29	2.89**	0.20	0.07	2.99**
	Trial 4[14]	4.87	1.58	0.89	1.78	0.40	0.20	2.00*
Osteoarthritis	Trial 1[17]	2.34	0.85	0.51	1.67	0.21	0.12	1.71
	Trial 2[18]	5.29	1.67	0.28	6.00**	0.32	0.05	6.50**
	Trial 3[19]	4.07	1.40	0.77	1.83	0.19	0.10	1.83
Postherpetic neuralgia	At 2 weeks[25]	3.37	1.22	0.70	1.74	0.31	0.17	1.82
	At 6 weeks[25]	5.48	1.70	0.70	2.43*	0.44	0.16	2.75**
Psoriasis	Trial 1[36]	2.56	0.94	0.48	1.94	0.24	0.12	2.03*
	Trial 2[37]	13.80	2.63	0.87	3.03**	0.63	0.15	4.14**
	Trial 3[38]	6.82	1.92	0.87	2.19*	0.50	0.19	2.60**
	Trial 4[39]	1.98	0.68	0.35	1.97*	0.17	0.08	2.02*

* Statistically significant $P < 0.05$; ** Highly statistically significant $P < 0.01$
OR, Odds ratio in favour improvement with capsaicin cream; RD, rate difference in favour of improvement with capsaicin cream

Table 4. Summary of pooled results using Mantel-Haenszel (M-H) and DerSimonian and Laird's (D-L) methods

	M-H method					D-L method			
	OR	lnOR	SE(lnOR)	Z	X_h^2	RD	SE(RD)	Z	X_h^2
Diabetic neuropathy	2.74	1.01	0.23	4.31**	2.19	0.25	0.05	4.71**	2.47
Osteoarthritis	4.36	1.47	0.23	6.39**	1.98	0.29	0.04	6.83**	1.89
Psoriasis	2.80	1.03	0.26	4.02**	5.48	0.35	0.11	3.21**	8.57*

* Statistically significant $P < 0.05$; ** Highly statistically significant $P < 0.01$
X_h^2, Chi square statistic for heterogeneity

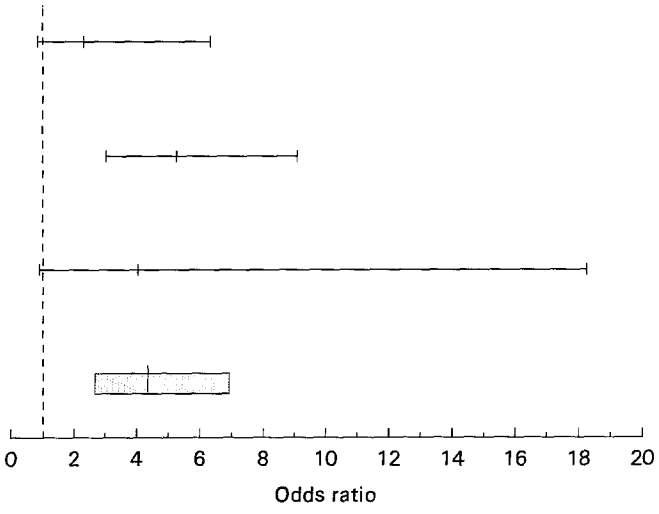

Fig. 2. Odds ratio and associated 95% confidence interval in favour of improvement with capsaicin in osteoarthritis. Individual results: —; pooled result: ▭

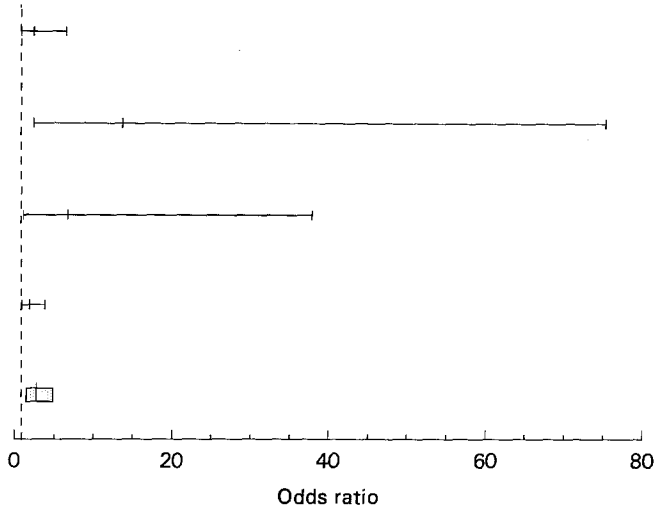

Fig. 3. Odds ratio and associated 95% confidence interval in favour of improvement with capsaicin in psoriasis. Individual results: —; pooled result: ▭

Only three randomized placebo-controlled trials [17–19] in osteoarthritis were eligible for pooling. The results in all three trials were in favour of capsaicin cream, although the usual statistical significance level ($P = 0.05$) was not reached in two of the trials. The pooled results (Fig. 2) supported the usefulness of capsaicin cream in this condition: odds ratio 4.36 (95% CI 2.77, 6.88). The corresponding response rate difference (Table 4) was 0.29 (95% CI 0.20, 0.37).

In two of the three randomized placebo-controlled trials in osteoarthritis, rheumatoid arthritis was also investigated. One reported positive [17] the other negative results [18] with capsaicin cream. However, the sample sizes were too small to make meaningful comparisons. In one trial [18] only five subjects were studied.

Capsaicin and post-herpetic neuralgia

The pathogenesis of post-herpetic neuralgia is still poorly understood and treatment is still largely unsatisfactory [34]. The pain associated with post-herpetic neuralgia is often referred to as neurogenic pain, since (unlike nociceptive pain) specific nerve endings within damaged tissues are not stimulated to initiate impulses following the classical pain pathways. Instead, impulses are generated as a result of neural dysfunction, and the pain is typically unresponsive to conventional analgesics, including opiates [35]. The usual explanation put forward for capsaicin-induced analgesia in post-herpetic neuralgia is interference with the biosynthesis of neurotransmitters, notably substance P. The latter is produced by the same nociceptive type C sensory neurons.

The majority of published reports on the clinical effectiveness of capsaicin cream in post-herpetic neuralgia are uncontrolled studies [27–30] or case reports [31–33]. Of the two double-blind, placebo-controlled studies [25, 26], data were available from only one. The reported results were in favour of capsaicin cream at six weeks (OR = 5.48; 95% CI 1.39, 21.59 and RD = 0.44; 95% CI 0.13, 0.75) but not at two weeks (OR = 3.37; 95% CI 0.86, 13.36 and RD = 0.31; 95% CI −0.02, 0.64) (Table 3).

Capsaicin and psoriasis

The rationale for the use of capsaicin in psoriasis is that substance P concentrations have been shown to be increased in psoriasis plaques and to fall with resolution of the condition [40]. Therefore, inhibition of release of substance P from cutaneous sensory neurones should relieve the itch and inflammation attributed to this neurotransmitter. However, conflicting data have been reported by other authors [41].

All four trials eligible for pooling [36–39] suggested that capsaicin cream was useful in psoriasis (Table 3 and Fig. 3). There was improvement in the severity of itch, scaling, and erythema. The pooled results confirmed this (OR = 2.80; 95% CI 1.69, 4.62 and RD = 0.35; 95% CI 0.14, 0.56). However, interpretation of the results should be cautious, since the chi-square statistic suggested that there was heterogeneity in the response rates (Table 4).

Capsaicin and post-mastectomy pain

The post-mastectomy pain syndrome is thought to be due to injury to the intercostobrachial nerve [42–43], although other factors may be involved. The rationale for the use of capsaicin is unclear, except that the pain is not classical and is generally unresponsive to the usual analgesics. In the only placebo-controlled trial, 0.075% capsaicin cream was significantly better in controlling jabbing and providing overall pain relief. However, the authors reported that the double-blind design was compromised by the burning sensation induced by capsaicin [44].

Conclusion

Capsaicin cream appears to be a useful addition to the range of topical analgesic and antipruritic medications available. It appears to be effective in easing the pain associated with diabetic neuropathy and osteoarthritis, and some of the symptoms of psoriasis. In post-herpetic neuralgia the evidence is less convincing. Some potentially interesting applications are in post-mastectomy and stump pain.

It may be that much of capsaicin's effectiveness is attributable to placebo effects, since true blinding is difficult because of its irritant effects after application to the skin. Therefore until results from more extensive and well-controlled clinical trials become available, the verdict on topical capsaicin's effectiveness must remain open. However, given the intractable nature of the conditions being treated and the poor performance of other treatments, many clinicians will feel justified in using topical capsaicin on the strength of the available evidence.

References

1. Bernstein JE (1987) Capsaicin in the treatment of dermatologic disease. Cutis 39: 352–353
2. Council of Pharmaceutical Society of Great Britain (1952) Martindale – The Extra Pharmacopoeia 23 rd edn, vol 1. Pharmaceutical Press, London, pp 324
3. Li Wan Po A (1990) Non prescription drugs, 2 nd edn. Blackwell, Oxford
4. Virus RM, Gebhart GF (1979) Pharmacologic actions of capsaicin: apparent involvement of substance P and serotonin. Life Sci 25: 1273–1284
5. Vaught JL (1988) Substance P antagonists and analgesia: a review of the hypothesis. Life Sci 43: 1419–1431
6. Payan P (1989) Neuropeptides and inflammation. The role of substance P. Ann Rev Med 40: 341–352
7. Nicoll RA, Schenker C, Leeman SE (1980) Substance P as a transmitter candidate. Ann Rev Neurosci 3: 227–268
8. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22: 719–748
9. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Contr Clin Trials 7: 177–188
10. Yusuf S, Peto R, Lewis J, Collins R, Sleight P (1985) Beta-blockade during and after myocardial infarction: an overview of the randomised trials. Prog Cardiovasc Dis 27: 335–371
11. Chad DA, Aronin N, Lundstrom R, McKeon P, Ross D, Molitch M, Schipper HM, Stall G, Dyess E, Tarsy D (1990) Does capsaicin relieve the pain of diabetic neuropathy. Pain 42: 387–388
12. Scheffler NM, Sheitel PL, Lipton MN (1991) Treatment of painful diabetic neuropathy with capsaicin 0.075%. J Am Pediatr Med Assoc 31: 288–293
13. The Capsaicin Study Group (1991) Treatment of painful diabetic neuropathy with topical capsaicin – a multicentre, double-blind, vehicle-control study. Arch Intern Med 151: 2225–2229
14. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ (1992) Topical capsaicin in painful diabetic neuropathy – controlled study with long-term follow-up. Diab Care 15: 8–14
15. Ross DR, Varipapa RJ (1989) Treatment of painful diabetic neuropathy with topical capsaicin. New Engl J Med 321: 474–475
16. Pirart J (1978) Diabetic mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diab Care 1: 168–88, 252–263
17. Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, Albert D, Renold F (1991) Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 13: 383–393

18. McCarthy GM, McCarty DL (1992) Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. J Rheumatol 19: 604–607
19. Schinitzer TJ, Morton C, Coker S, Flynn P (1992) Effectiveness of reduced applications of topical capsaicin (0.025 %) in osteoarthritis. Arthritis and Rheumatism 35: S132
20. Harris ED (1990) Rheumatoid arthritis: pathophysiology and implications for therapy. New Engl J Med 322: 1277–1289
21. Lotz M, Carson DA, Vaughan JH (1987) Substance P activation of rheumatoid synoviocytes: neural pathogenesis of arthritis. Science 235: 893–895
22. Levine JD, Clark R, Devor M, Helms C, Moskowitz MA, Basbaum AI (1984) Intraneuronal substance P contributes to the severity of experimental arthritis. Science 226: 547–549
23. Badlamente MA, Cherney SA (1989) Periosteal and vascular innervation of the human patella in degenerative joints disease. Sem Arthr Rheum 18: 61–66
24. Fitzgerald M (1983) Capsaicin and sensory neurons – a review. Pain 15: 109–130
25. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Milliken LE (1989) Topical capsaicin treatment of chronic postherpetic neuralgia. J Am Acad Dermatol 21: 265–270
26. Drake HF, Harris AJ, Gamester RE, Justins D (1990) Randomised double-blind study of topical capsaicin for treatment of postherpetic neuralgia. Pain 5 [Suppl]: S58
27. Watson CPN, Evans RJ, Watt VR (1988) Postherpetic neuralgia and topical capsaicin. Can J Neurol Sci 15: 197
28. Peikert A, Hentrich M, Ochs G (1991) Topical 0.025 % capsaicin in chronic postherpetic neuralgia: efficacy, predictors of response and long-term course. J Neurol 238: 452–456
29. Bernstein JE, Bickers DR, Dahl MV, Roshal JY (1987) Treatment of chronic postherpetic neuralgia with topical capsaicin – a preliminary study. J Am Acad Dermatol 17: 93–96
30. Fusco BM, Alessandri M (1992) Analgesic effect of capsaicin in idiopathic trigeminal neuralgia. Anesth Analg 74: 375–377
31. Hawk RJ, Millikan LE (1988) Treatment of oral postherpetic neuralgia with topical capsaicin. Int J Dermatol 27 (5): 336
32. Bucci FA, Gabriels CF, Krohel GB (1988) Successful treatment of postherpetic neuralgia with capsaicin. Am J Ophthalmol 106: 758–759
33. Don PC (1988) Topical capsaicin for treatment of neuralgia associated with Herpes zoster infection. J Am Acad Dermatol 18: 135
34. Jolleys JV (1989) Treatment of shingles and postherpetic neuralgia. Br Med J 298: 1537–1538
35. Arner A, Meyerson BA (1988) Lack of analgesic effect of opiods on neuropathic and idiopathic forms of pain. Pain 33: 11–23
36. Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk HH (1986) Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad Dermatol 15: 504–507
37. Kurkcuoglu N, Alaybeyi F (1990) Topical capsaicin for psoriasis. Br J Dermatol 123: 549–550
38. Berberian B, Bernstein JE, Dodd WA, Ellis CN, Rumsfield J, Sulica VI (1990) Double-blind evaluation of capsaicin cream in pruritis psoriasis. Clin Res 38: 664 A
39. Ellis CN, Berberian B, Sulien VI, Dodd WA, Jarratt MT, Katz HI, Prawer S, Krueger G, Rex IH Jr, Wolf JE (1993) A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol 29: 438–442
40. Naukkarinen A, Nickoloff BJ, Faber EM (1989) Quantification of cutaneous sensory nerves and their substance P content in psoriasis. J Invest Dermatol 92: 126–129
41. Anand P, Springall DR, Blank MA, Sellu D, Polack JM, Bloom SR (1992) Neuropeptides in skin disease: increased VIP in eczema and psoriasis but not axillary hyperhidrosis. Br J Dermatol 124: 547–549
42. Granek I, Ashikari P, Foley KM (1984) The postmastectomy pain syndrome: clinical and anatomical correlations. Proc ASCO 3: 122
43. Assa J (1974) The intercostobrachial nerve in radical mastectomy. J Surg Oncol 6: 123–26
44. Watson CPN, Evans RJ (1992) The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain 51: 375–379
45. Watson CPN, Evans RJ, Watt UR (1989) The post-mastactomy pain syndrome and the effect of topical capsaicin. Pain 38: 177–186
46. Dini D, Bertelli G, Gozza A, Forno GG (1993) Treatment of the post-mastactomy pain syndrome with topical capsaicin. Pain 54: 223–226
47. Rayner HC, Atkins RC, Westerman RA (1989) Relief of local stump pain by capsaicin cream. Lancet II: 1276–1277
48. Weintraub M, Golik A, Rubio A (1990) Capsaicin for treatment of post-traumatic amputation stump pain. Lancet 336: 1003–1004