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Treatment of complex regional pain syndrome type I

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Reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome type I (CRPS I), is a disabling neuropathic pain syndrome. Controversy exists about the effectiveness of therapeutic interventions for the management of RSD/CRPS I. In order to ascertain appropriate therapies we conducted a review of existing randomized controlled trials of therapies for this disabling disease. Eligible trials were identified from the Cochrane, Pubmed, Embase and MEDLINE databases from 1966 through June 2000, from references in retrieved reports and from references in review articles. Twenty-six studies concerning treatment modalities were identified. Eighteen studies were randomized placebo-controlled trials and eight studies were randomized active-controlled trials. Three independent investigators reviewed articles for inclusion criteria using a 15-item checklist. Seventeen of the trials were of high quality according to the 15-item criteria. There was limited evidence for the effectiveness of these interventions because of the heterogeneity of treatment modalities. The search for trials concerning prevention of RSD/CRPS I resulted in two eligible studies. Both were of high quality and dealt with different interventions. There is limited evidence for their preventive effect. © 2002 European Federation of Chapters of the International Association for the Study of Pain

KEYWORDS: complex regional pain syndrome type I, reflex sympathetic dystrophy, randomized controlled trials, treatment, review.

INTRODUCTION

Complex regional pain syndrome (CRPS) types I and II are neuropathic pain syndromes accompanied by sudomotor and vasomotor disturbances. CRPS I, which corresponds to the common image of reflex sympathetic dystrophy (RSD) is defined as a painful, disabling syndrome (Merskey and Bogduck, 1994). The Consensus Conference of the International Association for Study of Pain defined CRPS I as a post-traumatic syndrome that presents with spontaneous pain that is not related to the territory of a single nerve and is disproportionate to the inciting event (Merskey and Bogduck, 1994; Schurmann *et al.*, 1999). The diagnostic criteria include (a) pain, allodynia, or hyperalgesia, (b) evidence at some time of oedema, vasomotor and sudomotor change in the pain region and (c) no other conditions that would otherwise account for the degree of pain and dysfunction. CRPS II is a pain syndrome that starts after a nerve injury and is not necessarily limited to the distribution of the injured nerve (Baron, 2000; Woolf and Mannion, 1999). The diagnostic criteria are the same as those of CRPS I. CRPS is differentiated from other neuropathic pain syndromes by the existence of oedema, vasomotor and sudomotor disturbances. Some authors previously used a positive response on sympathetic blockade and diffuse or patchy osteopenia as an important diagnostic criterion for RSD (Davidoff *et al.*,

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1989; Kozin *et al.*, 1981; Schwartzman and McLellan, 1987). In CRPS I the role of sympathetic block in diagnosis has been minimized. Consequently, each category under the term CRPS could be divided into patients responsive and unresponsive to sympathetic blocks (Stanton-Hicks *et al.*, 1995).

Currently practised treatments of RSD/CRPS I include radical scavengers (Zuurmond *et al.*, 1996), regional intravenous sympathetic blocks (Jadad *et al.*, 1995) and neuromodulation (Kemler *et al.*, 2000). Kingery *et al.* (Kingery, 1997) reviewed existing trials for RSD/CRPS management in 1997 and demonstrated that there is limited support for the effectiveness of topical dimethylsulphoxide (DMSO), epidural clonidine, intravenous regional blocks and intranasal calcitonine. Jadad *et al.* (1995) showed that there is no evidence for the efficacy of regional intravenous sympathetic (RIS) blockade. We conducted a systematic review of published trials for the treatment and prevention of this disease with an emphasis on randomized controlled trials (RCTs).

MATERIAL AND METHODS

Selection of studies

A computer-assisted search of the Cochrane, Pubmed, Embase and MEDLINE databases from 1966 through June 2000 was conducted using the keywords 'complex regional pain syndrome type I', 'reflex sympathetic dystrophy' in combination with 'trial' or 'randomized trials' or 'random allocation' or 'prospective studies' or 'double/single blind' and 'prevention'. Additional reports were identified from reference lists in retrieved reports and in review articles. In 1994 the term CRPS was introduced (Merskey and Bogduck, 1994; Schurmann *et al.*, 1999). Because of the differences in diagnostic criteria between RSD and currently used CRPS I, studies about RSD and CRPS I were reviewed separately.

Two investigators independently reviewed all identified trials to determine whether a study should be included. Studies were included if they were double- or single-blinded RCTs with patients suffering from RSD or CRPS I using pain intensity as the main outcome measure. Only studies from the Dutch, German and English literature were included. We excluded non-randomized studies. Case reports and clinical observations were also excluded.

Methodological quality of the studies

Trials concerning treatment effectiveness were scored using a 15-item check list (de Vet *et al.*, 1997) (Table 1), which included selection and restriction of the study group, treatment allocation, study size, prognostic comparability, drop-outs, interventions, extra treatments, blinding procedure, outcome measurements, follow-up period, side-effects and analysis and presentation of data. Each criterion was weighted, resulting in a maximum score of 100 for each study. The essence of a good clinical trial is the (statistical) comparability of the different treatment groups. Thus allocation procedure and drop-out rates are key elements in controlled trials. Therefore, these criteria received the highest possible scores in the check list. Three independent investigators (T. Forouzanfar and W. E. J. Weber reviewed the placebo-controlled studies; T. Forouzanfar and A. J. A. Köke reviewed active-controlled studies) assessed the methodological quality of the trials. Disagreements were resolved by consensus between the two investigators. If no agreement could be reached a third investigator was consulted. The assessment resulted in a hierarchical list in which higher scores indicate studies with a higher methodological quality. Trials dealing with prevention of RSD or CRPS I were scored using the same methodology.

Outcome of the studies

We considered a study to be positive if the pain intensity was significantly reduced by the therapeutic intervention described when compared with placebo or a control group. A study was classified as 'negative' if no difference in pain was achieved by the intervention when compared with the placebo. If the therapeutic intervention under

TABLE 1. Methodological 15-item criteria score.

		Answers			Scores
A	**Selection and restriction**				
	1 Description of inclusion and exclusion criteria	−	−/+	+	2
	2 Restriction to a homogeneous study population	−	−/+	+	2
B	**Treatment allocation**				
	1 Randomization	−	−/+	+	If yes, then
	2 Allocation procedure adequate	−	−/+	+	10
	3 Blinded allocation procedure	−	−/+	+	5
C	**Study size**				
	1 Smallest group bigger than 25 subjects	−	−/+	+	4
	2 Smallest group bigger than 50 subjects	−	−/+	+	6
	3 Smallest group bigger than 75 subjects	−	−/+	+	8
D	**Prognostic comparability**				
	1 Type of diagnosis	−	−/+	+	2
	2 Baseline scores for outcome measures	−	−/+	+	2
	3 Duration of the complaint	−	−/+	+	1
	4 Age	−	−/+	+	1
	5 Sex	−	−/+	+	1
	6 Previous medication	−	−/+	+	1
E	**Drop-outs**				
	1 No drop-outs, **or**	−	−/+	+	12
	2 Number of drop-outs given in each group	−	−/+	+	2
	3 Reasons for withdrawal (of drop-outs) given in each group	−	−/+	+	2
	4 Drop-outs not leading to bias (less than 5%)	−	−/+	+	8
F	**Intervention**				
	1 Type of intervention	−	−/+	+	1
	2 Dose	−	−/+	+	1
	3 Treatment frequency	−	−/+	+	1
	4 Duration of treatment	−	−/+	+	1
	5 Compliance presented	−	−/+	+	2
G	**Intervention**				
	1 Type of intervention	−	−/+	+	1
	2 Dose	−	−/+	+	1
	3 Treatment frequency	−	−/+	+	1
	4 Duration of treatment	−	−/+	+	1
	5 Compliance presented	−	−/+	+	2
H	**Extra treatment**				
	1 No co-intervention, **or**	−	−/+	+	5
	2 Co-intervention comparable between groups	−	−/+	+	5
I	**Blinding of patient**				
	1 Attempt at blinding	−	−/+	+	4
	2 Blinding evaluated and successful	−	−/+	+	2
J	**Blinding of therapist**				
	1 Attempt at blinding	−	−/+	+	4
	2 Blinding evaluated and successful	−	−/+	+	2
K	**Blinding of observer**				
	1 Attempt at blinding	−	−/+	+	4
	2 Blinding evaluated and successful	−	−/+	+	2
L	**Outcome measures**				
	1 Pain intensity	−	−/+	+	1
	2 Global improvement	−	−/+	+	1
	3 Functional status	−	−/+	+	1
	4 Medical consumption	−	−/+	+	1
	5 Other	−	−/+	+	0.5
	6 Other	−	−/+	+	0.5

TABLE 1. *(Continued)*

		Answers			Scores
M	**Timing of measurements**				
	1 Timing comparable	−	−/+	+	1
	2 Measurement just after the last treatment	−	−/+	+	1
N	**Side-effects**				
	1 Description of the side-effects in each group	−	−/+	+	5
O	**Analysis and presention of data**				
	1 Frequencies/mean and standard deviation/median and quartiles	−	−/+	+	2
	2 Intention to treat analysis, or	−	−/+	+	4
	3 Adequate correction for baseline differences or drop-outs	−	−/+	+	4

study was more effective, but not significant, the study was classified as 'positive not significant'.

A similar categorization was used for preventive treatments. These studies were classified positive if RSD/CRPS I was prevented significantly compared with placebo. If no prevention was achieved, then the study was classified as 'negative'. If the intervention applied in the study prevented the development of RSD/CRPS I more than placebo, but not significantly so, it was classified as 'positive not significant'.

We also investigated the influence of sponsorship of the reviewed studies on the methodological quality of the selected studies.

Statistics

Studies with similar interventions were pooled. A study was regarded as relevant if either pain intensity or prevention of CRPS I was the outcome measure. For methodological quality score we used a cut-off point of 50 as mentioned in the study of van Tulder *et al.* (1997). A trial was considered to be of high quality if the methodological score was 50 points or more and of low quality if the score was less than 50 points. The level of evidence for therapeutic intervention effectiveness was graded into four levels based on the quality, outcome and relevance of the studies (van Tulder *et al.*, 1997). The four levels were strong evidence, moderate evidence, limited evidence and no evidence. Strong evidence was based on multiple relevant, high quality trials; moderate evidence on one relevant, high quality trial and one or more relevant low quality trials. Limited evidence was classified as one relevant, high quality trial or multiple relevant, low quality trials whereas no evidence was classified as one relevant, low quality trial, no relevant trials or contradictory outcomes.

RESULTS

Methodological flaws

The major methodological flaws in the reviewed studies included poor description of the inclusion and the exclusion criteria, restriction to a homogeneous study population, small study size, lack of details about previous medications and inadequate patients' compliance description (Tables 2–4). In most studies it was not clear whether the therapist or the observer was blinded. Moreover, only one study tested whether the blinding procedure was adequate (Wu *et al.*, 1999). In 21 studies the treatment was defined as successful when the pain after intervention was significantly reduced compared with baseline (Adami *et al.*, 1997; Bickerstaff and Kanis, 1991; Bonelli *et al.*, 1983; Bounameaux *et al.*, 1984; Fialka *et al.*, 1993; Geertzen *et al.*, 1994; Gobelet *et al.*, 1992; Hanna and Peat, 1989; Jadad *et al.*, 1995; Kemler *et al.*, 2000; Kettler and Abram, 1988; Kho, 1995; Korpan *et al.*, 1999; Oerlemans *et al.*, 1999; Ramamurthy and Hoffman, 1995; Rauck *et al.*, 1993; Rocco *et al.*, 1989; Uher *et al.*, 2000; Varenna *et al.*, 2000; Wallace *et al.*, 2000; Wu *et al.*, 1999; Zuurmond *et al.*, 1996). Only in five studies was a pain reduction of 30% or more compared with baseline defined as a successful

TABLE 2. Hierarchical list of the quality score of the RCTs with a placebo group.

	Scores of the quality criteria															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Total
	4	15	8	8	12	6	6	5	6	6	6	5	2	5	6	100
RSD																
Rauck *et al*. (1993)	4	15	4	4	12	6	6	5	4	4	0	2	2	5	2	77
Gobelet *et al*. (1992)	4	15	4	8	12	4	4	5	4	4	0	3	2	5	2	76
Varenna *et al*. (2000)	4	15	0	8	12	4	4	5	4	4	4	4	2	5	2	75
Adami *et al*. (1997)	4	15	0	8	12	6	6	5	4	4	0	1.5	2	5	2	74.5
Zuurmond *et al*. (1996)	2	15	0	7	12	3	3	0	4	4	4	1.5	2	5	2	64.5
Verdugo and Ochoa (1994)	0	5	4	4	12	4	4	5	4	4	4	2	2	5	2	61
Bickerstaff and Kanis (1991)	0	15	0	7	4	4	4	5	4	0	0	2	2	5	2	54
Blanchard *et al*. (1990)	4	0	0	7	12	4	4	5	4	4	0	1.5	1	5	2	53.5
Kettler and Abram (1988)	2	5	0	7	4	4	4	5	4	4	4	2	1	5	2	53
Jadad *et al*. (1995)	0	15	0	4	12	4	4	5	4	4	0	2.5	2	5	2	51.5
Christensen *et al*. (1982)	2	5	0	7	12	4	4	5	0	0	0	3	1	0	2	45
Bounameaux *et al*. (1984)	4	0	0	7	12	4	4	0	2	2	0	2	2	0	2	41
Fialka *et al*. (1993)	2	5	0	2	12	3	3	0	4	0	4	1	0	0	2	38
Hanna and Peat (1989)	0	0	0	4	0	4	4	5	4	4	0	1.5	1	5	2	34.5
Kho (1995)	0	0	0	4	0	4	4	5	4	0	0	1.5	2	0	2	26.5
CRPS I																
Price *et al*. (1998)	4	5	0	8	12	4	4	5	4	4	4	1.5	2	5	2	64.5
Wu *et al*. (1999)	4	15	0	2	4	6	6	5	6	0	0	4	2	0	2	59
Korpan *et al*. (1999)	0	15	0	7	0	4	4	5	0	0	0	2.5	2	0	2	41.5

TABLE 3. Hierarchical list of the quality score of randomized active-controlled trials.

	Scores of the quality criteria															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Total
	4	15	8	8	12	6	6	5	6	6	6	5	2	5	6	100
RSD																
Hord *et al*. (1992)	2	15	0	8	4	4	4	5	4	0	4	2	1	5	2	60
Oerlemans *et al*. (2000)	4	15	4	7	10	4	4	0	0	0	0	4.5	1	0	6	59.5
Ramamurthy and Hoffman (1995)	4	15	0	8	12	4	4	0	2	0	2	3	2	0	2	58
Rocco *et al*. (1989)	4	15	0	8	0	4	4	0	2	2	0	1.5	2	5	0	47.5
Bonelli *et al*. (1983)	4	0	0	4	12	4	4	0	0	0	0	2	2	0	4	36
Geertzen *et al*. (1984)	2	0	0	6	12	4	4	0	0	0	0	0.5	2	5	0	35
CRPS I																
Uher *et al*. (2000)	2	15	0	5	12	5	5	5	0	0	0	2	2	0	2	55
Wallace *et al*. (2000)	0	0	0	8	12	6	6	5	2	0	2	1.5	2	5	2	49.5

TABLE 4. Hierarchical list of RCTs on the prevention RSD.

	Scores of the quality criteria															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Total
	4	15	8	8	12	6	6	5	6	6	6	5	2	5	6	100
Zollinger *et al*. (1999)	4	15	6	7	12	4	4	0	4	4	4	3	2	5	2	76
Gschwind *et al*. (1995)	4	15	4	7	12	4	4	5	4	4	0	3	2	0	2	70

treatment (Blanchard *et al.*, 1990; Christensen *et al.*, 1982; Hord *et al.*, 1992; Price *et al.*, 1998; Verdugo and Ochoa, 1994).

Randomized placebo-controlled trials

A total of 18 articles were included in this review. Tables 5 and 6 list these studies according their quality score. Fifteen studies used RSD criteria. From these studies five were published after 1994 (Adami *et al.*, 1997; Jadad *et al.*, 1995; Kho, 1995; Varenna *et al.*, 2000; Zuurmond *et al.*, 1996). Three studies used the diagnostic criteria for CRPS I (Korpan *et al.*, 1999; Price *et al.*, 1998; Wu *et al.*, 1999). The two investigators managed to resolve disagreements by consensus and the third investigator was never involved. Three trials investigated the effectiveness of acupuncture and used sham acupuncture as placebo. These studies were classified as placebo-controlled trials (Hanna and Peat, 1989; Kho, 1995; Korpan *et al.*, 1999) because it was not clear whether sham acupuncture was an active control or a placebo.

The quality score of the reviewed papers for RSD ranged from 26.5 to 79. Ten RCTs had a methodological quality score of 50 points or more (Adami *et al.*, 1997; Bickerstaff and Kanis, 1991; Blanchard *et al.*, 1990; Gobelet *et al.*, 1986; Jadad *et al.*, 1995; Kettler and Abram, 1988; Rauck *et al.*, 1993; Varenna *et al.*, 2000; Verdugo and Ochoa, 1994; Zuurmond *et al.*, 1996). These articles were considered to be of high quality. Three studies had a crossover design (Blanchard *et al.*, 1990; Jadad *et al.*, 1995; Kettler and Abram, 1988). The study populations varied between 6 and 66 patients. Treatment modalities included clonidine (Rauck *et al.*, 1993), calcitonin (Bickerstaff and Kanis, 1991; Gobelet *et al.*, 1986), clodronate (Varenna *et al.*, 2000), alendronate (Adami *et al.*, 1997), DMSO cream (Zuurmond *et al.*, 1996), phentolamine (Verdugo and Ochoa, 1994), phenylephrine (Verdugo and Ochoa, 1994), reserpine (Blanchard *et al.*, 1990), guanethidine (Blanchard *et al.*, 1990; Jadad *et al.*, 1995), droperidol (Kettler and Abram, 1988), prednisolone (Christensen *et al.*, 1982), acupuncture (Fialka *et al.*, 1993; Kho, 1995) and ketanserin (Bounameaux *et al.*, 1984; Hanna and Peat, 1989).

The methodological quality score of the CRPS I studies ranged between 41.5 and 64.5 and the study population between seven and 26 patients (Price *et al.*, 1998; Wu *et al.*, 1999; Korpan *et al.*, 1999). The studies of Price *et al.* (1998) and Wu *et al.* (1999) had scores of 64.5 and 59 respectively. These studies were considered to be of high quality. The treatment modalities included sympathetic ganglion blocks (Price *et al.*, 1998), qigong (Wu *et al.*, 1999), and acupuncture (Korpan *et al.*, 1999).

RSD

Sympathetic block. The study performed by Rauck *et al.* (1993) was classified as high quality. Epidural clonidine 700 μg and 300 μg both decreased pain significantly more than placebo.

The high quality study of Verdugo and Ochoa (1994) demonstrated that neither intravenous phentolamine 35 mg nor phenylephrine 500 μg given to achieve regional sympathetic block were effective for the treatment of RSD.

One study (Blanchard *et al.*, 1990) tested intravenous reserpine (0.5 mg for the upper extremity; 1 mg for the lower extremity) and intravenous guanethidine (20 mg for the upper extremity; 30 mg for the lower extremity). One further trial (Jadad *et al.*, 1995) on RSD investigated only intravenous guanethidine (10 mg and 30 mg for the upper extremity; 20 mg and 30 mg for the lower extremity). Both articles were of high quality and did not find any improvement compared with placebo.

The high quality study of Kettler and Abram (1988) showed that administration of intravenous droperidol (2.5 mg in 30 ml saline for the upper extremity and 2.5 mg in 50 ml saline for the lower extremity) did not result in any improvement in RSD patients.

Intravenous ketanserin was investigated in two studies (Bounameaux *et al.*, 1984; Hanna and Peat, 1989). Bounameaux *et al.* (1984) administered ketanserin 10 mg in one bolus. There was no significant improvement in pain intensity. Hanna and Peat (1989) did the same. However, they

TABLE 5. Hierarchical list of randomized placebo-controlled trials of RSD.

Authors	Year	Score	Cross-over	Patients	Treatment[a]	Treatment[a]	Measurements	Outcome for success	Follow-up (months)	Result	Result
Rauck *et al*.	1993	77	No	26	Clonidine 700 μg (epid)	Clonodine 300 μg (epid)	VAS, MPQ pain reduction scale	Significant differences improvement between groups ($p < 0.05$)	—	Positive significant	
Gobelet *et al*.	1992	76	No	66	Calcitonin 100 U thrice daily for 3 weeks (i.n.)		Pain scale at rest, pain scale during movement, ROM, oedema scale	Significant differences between groups ($p < 0.05$)	2	Positive significant	—
Varenna *et al*.	2000	75	No	32	Clodronate 300 mg daily for 10 days (i.v.)		VAS, global measure of improvement global assessmet, ROM, laboratory tests	Significant differences in improvement between groups ($p < 0.05$)	6	Positive significant	—
Adami *et al*.	1997	74.5	No	20	Alendronate 7.5 mg/day for 3 days (i.v.)		VAS, motor score, DXA	Significant differences in improvement between groups ($p < 0.05$)	12	Positive significant	—
Zuurmond *et al*.	1996	64.5	No	32	50% DMSO cream for 2 months		RSD score, VAS	Significant change of the median (between baseline and after2months) compared betweenboth groups	2	Negative	

TABLE 5. *(Continued)*

Authors	Year	Score	Cross-over	Patients	Treatment[a]	Treatment[a]	Measurements	Outcome for success	Follow-up (months)	Result	Result
Verdugo and Ochoa	1994	61	No	77	First phase: i.v. placebo followed by i.v. phentolamine 35 mg for 30 min	Second phase: i.v. placebo was followed by i.v. phentolame 35 mg or phenylephrine 500 μg in random order	Pain, quantitative somatosensory thermotest, laser Doppler capillary flowmetry, hyperalgesy	Significant improvement within patients; change by 50% of more was considered as significant	—	Negative	Negative
Bickerstaff and Kanis	1991	54	No	40	Calcitonin 200 IU twice daily for 4 weeks (i.n.)		Chororimetry, pain questioner, hand volume, grip strength, finger stiffness	Significant differences in improvement between groups	3	Negative	—
Blanchard *et al*.	1990	53.5	Yes	21	UE, reserpine 0.5 mg 30–40 ml; LE, reserpine 1 mg 40–50 ml (i.v.)	UE,guanethidine 20 mg30–40 ml; LE,guanethidine 30 mg40–50 ml (i.v.)	VAS	Significant differences in improvement between groups; change by 50% of more was considered as significant	3	Negative	Negative
Kettler and Abram	1988	53	Yes	6	UE, droperidol 2.5 mg and heparin 500 U in 30 ml of normal saline (i.v.); LE, droperidol 2.5 mg and heparin 1000 U in 50 ml ofnormal saline(i.v.)		VAS	Differences improvement between pre- and afterblock between treatment and placebo, and time that pain returned to preblock intensity as determined by VAS	0.5	Negative	—
Jadad *et al*.	1995	51.5	Yes	16	UE, 10 mg guanethidine in 25 ml saline (i.v.);LE, 20 mg guanethidine in 50 ml saline(i.v.)	UE, 30 mg guanethidine in 25 ml saline (i.v.); LE, 30 mg guanethidine in 50 ml saline (i.v.)	VAS, total pain relief, mood, verbal rating scale	Significant differences in improvement between groups.	—	Negative	—

Christensen *et al*.	1982	45	No	23	Prednisone 10 mg (p.o.) thrice daily until clinical response was obtained (maximum 12 weeks)		Clinical scale	75% improvement in the clinical scale was classified as cured	3	Positive significant	Negative
Bounameaux *et al*.	1984	41	Yes	9	Ketanserin 10 mg (i.v.)		Scales for pain and cold sensation, skin temperature, blood flow	Significant differences in improvement between groups	—	Negative	—
Fialka *et al*.	1993	38	No	14	Acupuncture 5 times/week for 3 weeks	Sham	VAS	Comparison of mean pain reduction in both groups as measured by VAS	0.8	Positive not significant	—
Hanna and Peat	1989	34.5	Yes	16	Ketanserin 10 mg (i.v.)		VAS, temperature	Significant differences in improvement between groups	1	Positive significant	—
Kho	1995	26.5	No	28	Acupuncture 5 times a week for 3 weeks	Sham	VAS, sensory abnormality, temperature	Comparison of improvement between the groups	0.8	Positive not significant	—

[a]epid, epidural; i.n., intranasal; i.v., intravenous; UE, upper extremity; LE, lower extremity; p.o. per os.

TABLE 6. Hierarchical list of randomized placebo-controlled trials of CRPS I.

Authors	Year	Score	Crossover	Patients	Treatment	Treatment	Measurements	Outcome for success	Follow-up (months)	Result	Result
Price *et al*.	1998	64.5	Yes	7	Sympathetic ganglion block by 1% lidocane		VAS, allodynia	Significant differences between groups in peak analgesic effect and block duration (peak analgesic effect = VAS differences between baseline and the lowest VAS in the first hour of the block; block duration = time that the pain intensity returned to 50% of the difference between baseline and peak analgesic effect)	0.5	Positive not significant	—
Wu *et al*.	1999	59	No	26	Qigong 40 min twice a week for 3 weeks and 7 weeks at home		VAS, medication usage, SCL90, behaviour, bone scan	Significant differences in improvement between groups	2.5	Positive significant	—
Korpan *et al*.	1999	41.5	No	14	Acupuncture 5 times a week for 3 weeks	Sham	VAS, functional impairment, volumetric measurement, goniometry, temperature	Significant differences in improvement between groups.	6	Negative	—

found significant improvement by ketanserin compared with placebo.

Calcium-regulating drugs. Varenna *et al.* (2000) investigated the efficacy of intravenous clodronate 300 mg given for 10 days. Their trial was of high quality and resulted in a significant improvement in pain reduction in those patients given clodronate compared with the placebo group. Thus there is limited evidence for the efficacy of clodronate. Adami *et al.* (1997) administered intravenous alendronate 7.5 mg or placebo daily for 3 days. This was a high quality trial with a positive significant result.

Two articles (Bickerstaff and Kanis, 1991; Gobelet *et al.*, 1986) were identified using calcitonin (intranasal) as a therapeutic intervention. Both articles were of high quality. In the study with the highest quality score (76), performed by Gobelet *et al.* (1986), significant improvement in pain intensity was achieved after intranasal calcitonin 100 IU thrice daily for 3 weeks, whereas in the trial of Bickerstaff and Kanis (1991) no improvement was found after administering calcitonin 200 IU intranasally twice daily for 4 weeks.

Radical scavenging. Topical DMSO was tested by Zuurmond *et al.* (1996) in a high quality study which did not show significant pain reduction.

Corticosteroids. We found one trial (Christensen *et al.*, 1982) that investigated the efficacy of prednisolone 10 mg thrice daily for a maximum period of 12 weeks. Christensen *et al.* (1982) found a significant improvement after administering prednisolone. However, this trial was of low quality.

Complementary therapies. Two trials (Hanna and Peat, 1989; Kho, 1995) studied the efficacy of acupuncture five times a week for 3 weeks in patients with RSD. They found an improvement compared with sham acupuncture (Hanna and Peat, 1989; Kho, 1995). However, this improvement was not significant. Both articles were of low quality.

CRPS I

Sympathetic block. Sympathetic ganglion block in CRPS I patients by 1% lidocaine was tested in one high quality study performed by Price *et al.* (1998). The results demonstrated that there was a slight improvement after lidocaine, but this improvement was not significant compared with saline.

Complementary therapies. The efficacy of 40 min of qigong exercises twice a week for 4 weeks was investigated by Wu *et al.* (1999) in a high quality study and significant improvement was noted when compared with sham exercises.

One low quality trial investigated the efficacy of acupuncture five times a week for 3 weeks on CRPS I patients and did not find any improvement (Korpan *et al.*, 1999).

Randomized active-controlled trials

Eight studies were identified investigating the effectiveness of the treatment modalities by comparing different treatment interventions. The results are shown in Tables 7 and 8. In six studies RSD diagnostic criteria were used. Two of these studies were published after 1994 (Oerlemans *et al.*, 2000; Ramamurthy and Hoffman, 1995). Two studies were identified performing the CRPS I diagnostic criteria (Uher *et al.*, 2000; Wallace *et al.*, 2000).

The quality score of the RSD studies ranged between 35 and 65.5. Three studies proved to be of high quality. The interventions consisted of regional intravenous sympathetic blocks (Bonelli *et al.*, 1983; Hord *et al.*, 1992; Ramamurthy and Hoffman, 1995; Rocco *et al.*, 1989), physical therapy (Oerlemans *et al.*, 1999), stellate ganglion block (Bonelli *et al.*, 1983) and DMSO application (Geertzen *et al.*, 1994).

The methodological quality scores of the studies on CRPS I were 55 and 49.5 (Uher *et al.*, 2000; Wallace *et al.*, 2000). The studies investigated the efficacy of lymph drainage (Uher *et al.*, 2000) and intravenous lidocaine (Wallace *et al.*, 2000).

TABLE 7. Hierarchical list of randomized active-controlled trials on RSD.

Authors	Year	Score	Crossover	Patients	Intervention	Intervention	Intervention	Measurement	Outcome for success	Follow-up (months)	Result
Hord *et al*.	1992	60	Yes	12	RIS block by 1.5 mg/kg bretylium and 0.5% lidocaine	RIS block by 40–60 ml of 0.5% lidocaine		VAS, vital signs, skin temperature	Pain reduction of more than 30% was considered as significant	3.5	Maximal bretylium and lidocaine resulted in significantly better improvement than lidocaine alone
Oerlemans *et al*.	1999	59.5	No	135	Physical therapy	Occupational therapy	Social work (no therapy)	VAS, MPQ, AROM, skin temperature, volumetry	Differences between baseline and subsequent observations for each group and within groups ($p < 0.05$)	12	Significant improvement compared with baseline and control group
Ramamurthy and Hoffman	1995	58	Yes	60	UE, 20 mg guanethidine (i.v.) LE, 40 mg guanethidine (i.v.)	UE, 2 ml saline in 0.5% 30–50 ml lidocaine; LE, 4 ml saline in 0.5% 40–75 ml lidocaine		MPQ, global evaluation scale, ROM, skin temperature	The primary efficacy variable was the pain rating index of the MPQ between placebo and treatment	6	No significant improvement

Rocco *et al.*	1989	47.5	Yes	12	RIS block by 20 mg guanethidine in 50 ml 0.5% lidocaine	RIS block by 1.25 mg reserpine in 50 ml 0.5% lidocaine	50 ml 0.5% lodocaine	VAS, NRS, pain diary, skin temperature	Differences between baseline and subsequent observations for each group and within groups	24	No significant improvement
Bonelli *et al.*	1983	38	No	19	Stellate ganglion block with bupivacaine 0.5% 15 ml to a total of 8 blocks	20 mg guanethidine (i.v.), every 4 days to a total of 4 blocks		VAS, skin temperature, skin plethysmo-graphy	Differences between baseline and subsequent observations for each group and within groups ($p < 0.05$)	3	Significant improvement compared with baseline, no differences between groups
Geertzen *et al.*	1994	35	No	26	DMSO 50% in water, 4 times a day for 3 weeks	RIS block twice a week for 3 weeks		VAS, daily activity, oedema, discoloration, ROM, finger function, psychological aspects	Differences between baseline and subsequent observations for each group and within groups ($p < 0.05$)	3	Significant improvement compared with baseline, no differences between groups

TABLE 8. Hierarchical list of randomized active-controlled trials on CRPS I.

Authors	Year	Score	Crossover	Patients	Intervention	Intervention	Measurement	Outcome for success	Follow-up (months)	Result
Uher *et al.*	2000	55	No	35	Exercise in combination with manual lymph drainage 3 times a week for 6 weeks	Exercise 3 times a week for 6 weeks	VRS, ROM, skin temperature, volumetry, scintigraphy	Differences between baseline and subsequent observations for each group and within groups ($p < 0.05$)	1.5	Significant improvement compared with baseline, no differences between groups
Wallace *et al.*	2000	49.5	Yes	16	Plasma concentration of 1, and 2 and 3 μg/ml lidocaine were targeted and maintained for 20 min i.v.	Diphenhydramine	Vas, allodynia, neurosensory testing	Differences between baseline and subsequent observations for each group and within groups ($p < 0.05$)	0.25	Significant decreased response to stroking and cool stimuli, and spontaneous pain at high lidocaine plasma level

RSD

Sympathetic block. Three cross over studies have investigated the effectiveness of sympathetic blockade. Hord *et al.* (1992) administered bretylium 1.5 mg/kg together with 0.5% lidocaine or only 0.5% lidocaine without bretylium. They defined a pain reduction of more than 30% compared with baseline as significant. This high quality study demonstrated that the combination of both treatments resulted in significant pain reduction.

Ramamurthy and Hoffman (1995) compared the effectiveness of guanethidine in a high quality trial. The patients were enrolled to receive four intravenous regional blocks at 4 day intervals with either guanethidine or 0.5% lidocaine. Each patient was randomized to receive one guanethidine and three lidocaine blocks, two guanethidine and two lidocaine blocks or four guanethidine blocks without any lidocaine block. The sympathetic blocks for the upper extremity were done with either 2 ml (20 mg) guanethidine or 0.5% lidocaine 30–50 ml. For the lower extremity the blocks were performed with 4 ml (40 mg) guanethidine or 0.5% lidocaine 40–75 ml. The results did not demonstrate any significant differences between the interventions. In addition, Rocco *et al.* (1989), in a low quality randomized crossover study, investigated the effectiveness of guanethidine and reserpine. All patients successively received 20 mg guanethidine in 50 ml 0.5% lidocaine, 1.25 mg reserpine in 50 ml 0.5% lidocaine and 50 ml 0.5% lidocaine with a 1 week interval between medications. No significant reduction in pain was found with either combination therapy.

Stellate ganglion block using 15 ml 0.5% bupivacaine was compared with regional intravenous sympathetic block using guanethidine 20 mg every 4 days to a total of four blocks (Bonelli *et al.*, 1983) in a low quality study. This study did not demonstrate any differences between these treatments.

Radical scavenging vs Sympathetic block. Geertzen *et al.* (1994) compared in a low quality study the effectiveness of dermal application of DMSO 50% four times daily for 3 weeks with regional intravenous sympathetic blockade thrice weekly for 3 weeks. No differences were found between these interventions.

CRPS I

Sympathetic block. Wallace *et al.* (2000) administered lidocaine and compared its effectiveness with diphenhydramine. Plasma lidocaine concentration steps of 1 μg/ml, 2 μg/ml and 3 μg/ml were targeted and maintained for 20 min. In this low quality study lidocaine proved to achieve significant improvement.

Complementary therapies. In a study by Uher *et al.* (2000) the effectiveness of lymph drainage combined with exercise was compared with exercise alone. This high quality study did not show any differences between these interventions.

Prevention of CRPS I

The search for relevant studies concerned with prevention of RSD/CRPS I resulted in two randomized placebo-controlled studies (Gschwind *et al.*, 1995; Zollinger *et al.*, 1999) that describe preventive modalities in RSD patients (Tables 4 and 9). Both articles were of high quality. In the

TABLE 9. Hierarchical list of RCTs on the prevention of RSD.

Authors	Year	Score	Crossover	Patients	Treatment	Treatment	Outcome	Follow-up (months)	Result
Zollinger *et al.*	1999	76	No	123	Vitamin C, 500 mg for 50 days	Placebo	RSD criteria	12	Significantly less incidence of RSD with vitamin C
Gschwind *et al.*	1995	70	No	71	Guanathidine 20 mg i.v.	Placebo	RSD criteria	1.5	Negative

study by Zollinger *et al.* (1999) either placebo or vitamin C 500 mg was administered daily for 50 days in patients with RSD after a Colles' fracture. At 1 year the incidence of RSD in those patients given vitamin C was significantly less than in those in the placebo group. In the other study (Gschwind *et al.*, 1995) either saline or intravenous guanethidine 20 mg was administered in patients undergoing faciectomy for Duputyren's disease. They concluded that it is not possible to prevent RSD by giving intravenous guanethidine pre-operatively.

The influence of sponsorship on methodological quality

To investigate the influence of sponsorship on the quality of the selected studies we combined all studies of treatment modalities to one study population. Seven studies of 26 studies were funded (Bickerstaff and Kanis, 1991; Gobelet *et al.*, 1992; Hord *et al.*, 1992; Oerlemans *et al.*, 2000; Ramamurthy and Hoffman, 1995; Rauck *et al.*, 1993; Verdugo and Ochoa, 1994). The mean methodological quality of the funded studies was significantly higher than the other studies (*t*-test; $p<0.02$).

DISCUSSION

We designed the present review to provide a consensus in the treatment or prevention of RSD or CRPS I. RCTs that have examined the effectiveness of treatments and prevention of this disabling disease were reviewed.

Generally, the value of a review of the literature depends on the success in obtaining the results of all studies that have been conducted on the subject at issue. Reviews are subject to bias caused by the outcomes of published and unpublished studies differing (publication bias). Although we put much effort into obtaining all the available studies, we may have missed important published and unpublished trials. Furthermore, we were not blinded for the outcomes of the publications in this review, which means that some degree of reviewer bias cannot be excluded. Any reader, however, can check our point assignment and apply different weights to different criteria.

We identified 27 randomized trials, of which 18 were placebo controlled (Adami *et al.*, 1997; Bickerstaff and Kanis, 1991; Blanchard *et al.*, 1990; Bounameaux *et al.*, 1984; Christensen *et al.*, 1982; Fialka *et al.*, 1993; Gobelet *et al.*, 1992; Hanna and Peat, 1989; Jadad *et al.*, 1995; Kettler and Abram, 1988; Kho, 1995; Korpan *et al.*, 1999; Price *et al.*, 1998; Rauck *et al.*, 1993; Varenna *et al.*, 2000; Verdugo and Ochoa, 1994; Wu *et al.*, 1999; Zuurmond *et al.*, 1996). The heterogeneity of the studies and the small sample sizes precluded the drawing of firm conclusions about the efficacy or effectiveness of any of the interventions studied on RSD or CRPS I patients. On basis of our review we conclude that there is limited to no evidence for efficacy of sympathetic blocks (stellate ganglion block or RIS block), radical scavenging, prednisolone administration, acupuncture and manual lymph drainage. Calcium-regulating drugs and qigong exercises seem to be promising treatment modalities. However, further high quality studies are required before the place of these treatments in pain therapy can be established. Further, it is demonstrated that funded studies have better methodological quality than non-funded studies.

The search for eligible trials about prevention resulted in two high quality randomized placebo-controlled studies in which vitamin C and intravenous guanethidine were investigated for RSD patients (Gschwind *et al.*, 1995; Zollinger *et al.*, 1999). Vitamin C prevented RSD while guanethidine did not prevent the development of RSD. Both studies had small sample sizes and no other randomized placebo-controlled studies were identified. Therefore there is limited evidence whether any interventions can significantly prevent RSD.

The major methodological flaws in the reviewed studies included poor description of the inclusion and the exclusion criteria, restriction to a homogeneous study population, small study size, lack of details about previous medications and inadequate patients' compliance description. Mostly, it was not clear whether the therapist or the observer was blinded and only one study

(Wu *et al*., 1999) tested whether the blinding procedure was adequate. Except for five studies (Blanchard *et al*., 1990; Christensen *et al*., 1982; Hord *et al*., 1992; Price *et al*., 1998; Verdugo and Ochoa, 1994) in all studies the treatment was defined as successful when the pain after intervention was significantly reduced compared with baseline and the control (Adami *et al*., 1997; Bickerstaff and Kanis, 1991; Bonelli *et al*., 1983; Bounameaux *et al*., 1984; Fialka *et al*., 1993; Geertzen *et al*., 1994; Gobelet *et al*., 1992; Hanna and Peat, 1989; Jadad *et al*., 1995; Kemler *et al*., 2000; Kettler and Abram, 1988; Kho, 1995; Korpan *et al*., 1999; Oerlemans *et al*., 1999; Ramamurthy and Hoffman, 1995; Rauck *et al*., 1993; Rocco *et al*., 1989; Uher *et al*., 2000; Varenna *et al*., 2000; Wallace *et al*., 2000; Wu *et al*., 1999; Zuurmond *et al*., 1996). In these studies it is not clear whether a significant pain reduction is classified as improvement according the patients. Therefore the results of these studies are questionable. Furthermore, after the introduction of the CRPS I diagnostic criteria in 1994 (Merskey and Bogduck, 1994) only five studies (Korpan *et al*., 1999; Price *et al*., 1998; Uher *et al*., 2000; Wallace *et al*., 2000; Wu *et al*., 1999) of the 14 studies (Adami *et al*., 1997; Gschwind *et al*., 1995; Jadad *et al*., 1995; Kho, 1995; Korpan *et al*., 1999; Oerlemans *et al*., 1999; Price *et al*., 1998; Uher *et al*., 2000; Varenna *et al*., 2000; Verdugo and Ochoa, 1998; Wallace *et al*., 2000; Wu *et al*., 1999; Zollinger *et al*., 1999; Zuurmond *et al*., 1996) performed after 1994 used these criteria.

In conclusion, there is limited evidence to support the effectiveness of commonly used interventions for treating or preventing RSD or CRPS I. More prospective controlled trials are needed in this field.

REFERENCES

Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; **56**: 201–204.

Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* 2000; **16**: S12–S20.

Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *Br J Rheumatol* 1991; **30**: 291–294.

Blanchard J, Ramamurthy S, Walsh N, Hoffman J, Schoenfeld L. Intravenous regional sympatholysis: a double-blind comparison of guanethidine, reserpine, and normal saline. *J Pain Symptom Manage* 1990; **5**: 357–361.

Bonelli S, Conoscente F, Movilia PG, Restelli L, Francucci B, Grossi E. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial. *Pain* 1983; **16**: 297–307.

Bounameaux HM, Hellemans H, Verhaeghe R. Ketanserin in chronic sympathetic dystrophy. An acute controlled trial. *Clin Rheumatol* 1984; **3**: 556–557.

Christensen K, Jensen EM, Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir Scand* 1982; **148**: 653–655.

Davidoff G, Werner R, Cremer S, Jackson MD, Ventocilla C, Wolf L. Predictive value of the three-phase technetium bone scan in diagnosis of reflex sympathetic dystrophy syndrome. *Arch Phys Med Rehabil* 1989; **70**: 135–137.

de Vet HCW, de Bie RA, Verhagen AP, Sijpkes P, Knipschild PG. Systematic reviews on the basis of methodological criteria. *Physiotherapy* 1997; **83**: 284–289.

Fialka V, Resch KL, Ritter-Dietrich D, Alacamlioglu Y, Chen O, Leitha T, Kluger R, Ernst E. Acupuncture for reflex sympathetic dystrophy [letter]. *Arch Intern Med* 1993; **153**: 661, 665.

Geertzen JH, de Bruijn H, de Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: early treatment and psychological aspects. *Arch Phys Med Rehabil* 1994; **75**: 442–446.

Gobelet C, Meier JL, Schaffner W, Bischof-Delaloye A, Gerster JC, Burckhardt P. Calcitonin and reflex sympathetic dystrophy syndrome. *Clin Rheumatol* 1986; **5**: 382–388.

Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain* 1992; **48**: 171–175.

Gschwind C, Fricker R, Lacher G, Jung M. Does perioperative guanethidine prevent reflex sympathetic dystrophy? *J Hand Surg* 1995; **20**: 773–775.

Hanna MH, Peat SJ. Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial. *Pain* 1989; **38**: 145–150.

Hord AH, Rooks MD, Stephens BO, Rogers HG, Fleming LL. Intravenous regional bretylium and lidocaine for treatment of reflex sympathetic dystrophy: a randomized, double-blind study. *Anesth Analg* 1992; **74**: 818–821.

Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manage* 1995; **10**: 13–20.

Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000; **343**: 618–624.

Kettler RE, Abram SE. Intravenous regional droperidol in the management of reflex sympathetic dystrophy: a double-blind, placebo-controlled, crossover study. *Anesthesiology* 1988; **69**: 933–936.

Kho HK. The impect of acupuncture on pain in patients with reflex sympathetic dystrophy. *Pain Clin* 1995; **8**: 59–61.

Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73**: 123–139.

Korpan MI, Dezu Y, Schneider B, Leitha T, Fialka-Moser V. Acupuncture in the treatment of posttraumatic pain syndrome. *Acta Orthop Belg* 1999; **65**: 197–201.

Kozin F, Soin JS, Ryan LM, Carrera GF, Wortmann RL. Bone scintigraphy in the reflex sympathetic dystrophy syndrome. *Radiology* 1981; **138**: 437–443.

Merskey KR, Bogduck N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle, WA: IASP Press, 1994.

Oerlemans HM, Goris JA, de Boo T, Oostendorp RA. Do physical therapy and occupational therapy reduce the impairment percentage in reflex sympathetic dystrophy? *Am J Phys Med Rehabil* 1999; **78**: 533–539.

Oerlemans HM, Oostendorp RA, de Boo T, van der Laan L, Severens JL, Goris JA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. *Arch Phys Med Rehabil* 2000; **81**: 49–56.

Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. *Clin J Pain* 1998; **14**: 216–226.

Ramamurthy S, Hoffman J. Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a randomized, double-blind study. Guanethidine Study Group. *Anesth Analg* 1995; **81**: 718–723.

Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J. Epidural clonidine treatment for refractory reflex sympathetic dystrophy [see comments]. *Anesthesiology* 1993; **79**: 1163–1169, discussion 27A.

Rocco AG, Kaul AF, Reisman RM, Gallo JP, Lief PA. A comparison of regional intravenous guanethidine and reserpine in reflex sympathetic dystrophy. A controlled, randomized, double-blind crossover study. *Clin J Pain* 1989; **5**: 205–209.

Schurmann M, Gradl G, Andress HJ, Furst H, Schildberg FW. Assessment of peripheral sympathetic nervous function for diagnosing early post-traumatic complex regional pain syndrome type I. *Pain* 1999; **80**: 149–159.

Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. A review. *Arch Neurol* 1987; **44**: 555–561.

Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995; **63**: 127–133.

Uher EM, Vacariu G, Schneider B, Fialka V. Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome, type I. A comparative randomized controlled therapy study. *Wien Klin Wochenschr* 2000; **112**: 133–137.

van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. *Spine* 1997; **22**: 2128–2156.

Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, Sinigaglia L. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *J Rheumatol* 2000; **27**: 1477–1483.

Verdugo RJ, Ochoa JL. 'Sympathetically maintained pain.' I. Phentolamine block questions the concept. *Neurology* 1994; **44**: 1003–1010.

Verdugo RJ, Ochoa JL. Reversal of hypoaesthesia by nerve block, or placebo: a psychologically mediated sign in chronic pseudoneuropathic pain patients. *J Neurol Neurosurg Psychiatry* 1998; **65**: 196–203.

Wallace MS, Ridgeway BM, Leung AY, Gerayli A, Yaksh TL. Concentration–effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology* 2000; **92**: 75–83.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999; **353**: 1959–1964.

Wu WH, Bandilla E, Ciccone DS, Yang J, Cheng SC, Carner N, Wu Y, Shen R. Effects of qigong on late-stage complex regional pain syndrome. *Altern Ther Health Med* 1999; **5**: 45–54.

Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet* 1999; **354**: 2025–2028.

Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van Loenen AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand* 1996; **40**: 364–367.