

# Epidemiology and Treatment of Peripheral Neuropathy in Systemic Sclerosis

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**ABSTRACT. Objective.** The epidemiology and treatment of peripheral neuropathy in systemic sclerosis (SSc) is poorly understood. The objectives of this study were to evaluate the incidence, prevalence, risk factors, and treatments of peripheral neuropathy in SSc.

**Methods.** A systematic review of MEDLINE, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for literature reporting peripheral neuropathy in SSc was performed. Studies evaluating incidence, prevalence, risk factors, and treatments were synthesized. A metaanalysis using a random effects model was used to evaluate the prevalence of peripheral neuropathy.

**Results.** This systematic review identified 113 studies that reported 949 of 2143 subjects with at least 1 type of peripheral neuropathy. The mean age was 48.5 years. The mean time between SSc onset and detection of peripheral neuropathy was 8.85 years. The pooled prevalence of neuropathy was 27.37% (95% CI 22.35–32.70). Risk factors for peripheral neuropathy in SSc included advanced diffuse disease, anti-centromere antibodies, calcinosis cutis, ischemia of the vasa nervorum, iron deficiency anemia, metoclopramide, pembrolizumab, silicosis, and uremia. There were 73 subjects with successful treatments (n = 36 restoring sensation, n = 37 restoring motor or sensorimotor function). Treatments included decompression surgery, prednisone, cyclophosphamide, carbamazepine, transcutaneous electrical nerve stimulation, tricyclic antidepressants, and intravenous Ig.

**Conclusion.** All-cause peripheral neuropathy is not uncommon in SSc. Compression neuropathies can be treated with decompression surgery. Observational data reporting immunosuppressives and anticonvulsants to treat peripheral neuropathy in SSc are limited and conflicting. Randomized controlled trials are needed to evaluate the efficacy of these interventions.

*Key Indexing Terms:* epidemiology, peripheral neuropathy, scleroderma, systemic sclerosis

Peripheral neuropathy encompasses a wide spectrum of clinical disorders affecting sensory, motor, and autonomic peripheral nerve fibers. Most peripheral neuropathies affect all fiber types to some extent. However, a single fiber type may be predominantly

or exclusively affected in some disorders. Peripheral neuropathies are also defined by the pattern of nerve fiber involvement. Some disorders involve single individual peripheral nerves (mononeuropathies), and some involve numerous individual peripheral nerves (the mononeuritis multiplex syndrome). In addition, peripheral nerve disorders can involve the brachial plexus, lumbosacral plexus, or they can involve a single root, resulting in signs and symptoms in 1 limb. This diverse array of possible etiologies can make the diagnosis of peripheral neuropathies challenging. Nevertheless, the diagnosis can be facilitated with a systematic approach that classifies the peripheral neuropathy on the basis of clinical features, taking into account the type of peripheral nerve fiber that may be involved (i.e., sensory, motor, or autonomic), the distribution or pattern of peripheral nerve fiber involvement (generalized and symmetrical vs asymmetrical and multifocal), and the mode of evolution (acute, subacute, or chronic). Nerve conduction studies can be helpful in confirming the diagnosis, and in defining the nature and extent of the peripheral neuropathy. Peripheral nerve disorders are relatively common conditions that affect 2.4% of the population.<sup>1</sup> However, the prevalence increases to 8.0% with advancing age. Management of the peripheral neuropathy is directed first at the specific cause if it is treatable; and second at the alleviation of symptoms, including

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managing neuropathic pain, and bracing and physical therapy for weakness.

Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy, fibrosis, and immune abnormalities.<sup>2</sup> Affected organs include the skin, lungs, heart, digestive system, kidneys, muscles, joints, and nervous system. Neurologic involvement in SSc includes cranial, entrapment, peripheral, cutaneous, and autonomic neuropathies, whereas central nervous system (CNS) involvement includes headache, seizure, stroke, vascular disease, radiculopathy, and myelopathy. Estimates of the frequency of neurologic involvement in patients with SSc vary widely, but CNS involvement due to SSc is rare. A systematic review of the literature was conducted to synthesize data evaluating the epidemiology of peripheral neuropathy and treatment options used in SSc.

## METHODS

**Literature search.** A literature search was conducted through the University Health Network library with the assistance of an information specialist. The search included Ovid MEDLINE from 1946 to September 2020, including the Epub Ahead of Print and In-Process and Other Non-Indexed Citations (inception to September 2020); Embase (1974 to September 2020); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) with full text (inception to September 2020). The following keywords were used in the database search: scleroderma, systemic sclerosis, CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), sclerodactyly, Raynaud, calcinosis, peripheral nervous system diseases, peripheral neuropathy, tarsal tunnel, carpal tunnel, cubital tunnel, neuropathy, mononeuropathy, polyneuropathy, radiculopathy, and myelopathy. The search was restricted to humans, but no language restriction was applied.

**Study selection.** Titles and abstracts were screened by 2 investigators independently to identify studies that described peripheral neuropathy in SSc. Inclusion criteria were (1) peer reviewed observational studies (cohort and case-control studies), randomized controlled trials (RCTs), case reports, or case series; and (2) report of peripheral neuropathy by symptoms and clinical examination, nerve conduction studies, or other detection tools. The 2 independent reviews were compared, and discrepancies were resolved by consensus or inclusion of a third investigator, as needed. Mixed connective tissue disease, central neuropathy, and myelopathies were excluded.

**Data abstraction.** Two investigators (BAA, FZT) independently reviewed each abstract and applied the inclusion and exclusion criteria to identify relevant studies for full review. A standardized data abstraction form was used to collect data on the study design, sample size, presence of control groups, incidence, prevalence, patterns of neuropathy, risk factors, and treatment.

**Outcomes.** A standardized form was used to abstract the prevalence, incidence, and risk factors of peripheral neuropathy in SSc, as well as treatments and outcomes.

**Statistical analysis.** Metaanalyses were evaluated for heterogeneity using the *Q* and *I*<sup>2</sup> tests.<sup>3</sup> Influential analysis was initially conducted to see the effect of each study; the Baujat plot identified identified 2 studies that were contributing to high heterogeneity. We used the suggested criteria of 25% (low), 50% (moderate), and 75% (high) for different levels of heterogeneity. A random effects metaanalysis was performed using the Paule-Mandel estimator on the final studies,<sup>4</sup> whereas the CIs of  $\tau$  and  $\tau^2$  were adjusted using the Biggerstaff and Jackson method. Prediction intervals are also reported for the random effects model.<sup>5</sup> Publication bias was assessed visually by inspecting a funnel plot and additionally by Egger test,<sup>6</sup> as well as Trim and Fill and Fail Safe N methods.<sup>7</sup> Multiple metaregression was also used to

assess the significance of different moderators. A *P* value < 0.05 was considered statistically significant. The data were analyzed using R Core Team (R Foundation for Statistical Computing).

## RESULTS

Of the 6342 studies identified through a systematic review of the literature, 113<sup>8-120</sup> were identified for full review (Figure 1). A total of 2143 subjects were included in the studies reviewed, of which 949 subjects were diagnosed with at least 1 type of peripheral neuropathy (Supplementary Table 1, available with the online version of this article). The mean age was 48.5 years. Fifty-one studies reported peripheral neuropathy in 1030 subjects with limited SSc<sup>8-15,17-29,31-33,35-40,42-60,68,74,80,83,85,88,93-95,98,99,107</sup> and 53 studies reported peripheral neuropathy in 607 subjects with diffuse SSc (dSSc).<sup>9,10,12,18,20,22,24,25,30,31,33,35,36,38,41,44,45,48,49,51,53-55,57,59,61-69,71,74,76-78,81,82,90,91,94,95,107,108,114-118,120</sup> At least 5 juvenile SSc subjects with peripheral neuropathy were found in 4 studies,<sup>78,79,116,120</sup> 4 studies reported peripheral neuropathy in 22 subjects with morphea,<sup>48,79,108,113</sup> and 3 studies reported peripheral neuropathy in 81 subjects with SSc sine scleroderma.<sup>36,54,70</sup> Study design included 49 case reports,<sup>8,14,15,17,23,27-31,37,39,40,42,43,47,52,56,58,60,61,63-67,69,70-73,76,78-91,115,117,118</sup> 23 case series,<sup>11,16,20,22,26,31,32,34,41,46,50,62,68,77,92-95,97-99,114,120</sup> 39 observational studies,<sup>9,10,12,13,18,19,21,24,25,33,35,36,38,44,45,48,49,51,53-55,57,59,74,96,100-106,108-113,116</sup> and 51 studies for therapeutics.<sup>8,11,14,15,17,21,23,29,31,32,34,37,39-43,46-48,60-62,64,66,68,69,71-74,76,81,84-86,88,90-95,99,101,102,107,114-116,118</sup> No RCTs were identified.

The average duration between SSc onset and the detection of peripheral neuropathy was 8.85 years. Twenty-four studies reported a neuropathy onset ranging from 3 months to 5 years before SSc was diagnosed,<sup>8,11,22,29,31,46,48,50,56,58,63,64,66,69,71,77,78,80,82,83,87,89,94,114</sup> 4 studies reported diagnosing SSc and neuropathy at the same time,<sup>34,62,93,98</sup> and the remaining studies reported neuropathy 1 month to 59 years after the diagnosis of SSc. The most frequent modalities used to detect and assess neuropathy were history and physical examination in symptomatic subjects (*n* = 339),<sup>8,11,13-17,20-32,34,37,40-48,50,52,53,56-64,66-74,76-91,93-95,97-99,101,103-105,109-111,114-116,118,120</sup> nerve conduction studies (NCS; *n* = 173),<sup>8,11,13-17,20-34,37,40-50,52,53,56-64,66-74,76-84,86,88,93,94,98,100,105,108,114,115,120</sup> and nerve and skin biopsies (*n* = 117).<sup>19,21,31,35,41,42,49,52,56,64,79,82,88,89,93,94,112,113,116,117</sup> Imaging techniques included radiographs (6.3%),<sup>17,47,60,65,81,85,91</sup> computed tomography scans (5.4%),<sup>17,23,72,81,90,91</sup> ultrasound (4.5%),<sup>10,13,57,92,105</sup> and magnetic resonance imaging (4.5%).<sup>42,57,69,91,120</sup> Imaging modalities were mostly used where compression neuropathy was suspected.

Peripheral neuropathies were categorized as compression vs noncompression neuropathies. Compression neuropathies were reported in 26.5% of the studies.<sup>10,11,13,17,23,30,31,34,40,43,46,47,50,56,57,60,64,72,74,77,81,84,85,90,91,95,101,105,118,120</sup> Median nerve entrapment (carpal tunnel syndrome [CTS]) was the most common form of compression neuropathy (*n* = 216; Table 1).<sup>10,11,13,31,34,46,50,56,57,64,74,77,84,95,101,105,118,120</sup> Causes of entrapment included calcinosis cutis (most common)<sup>17,47,57,60,72,85,91</sup> and soft tissue thickening.<sup>10,13,40,74,84</sup> Trigeminal neuralgia may also occur as a result of nerve entrapment secondary to calcinosis or tissue fibrosis.<sup>8,14,17,19,30,31,34,35,37,43,46,47,52,57-60,63,70,72-74,80-82,84,85,90,91,93,94,99,104,111,113,116,118,120</sup>

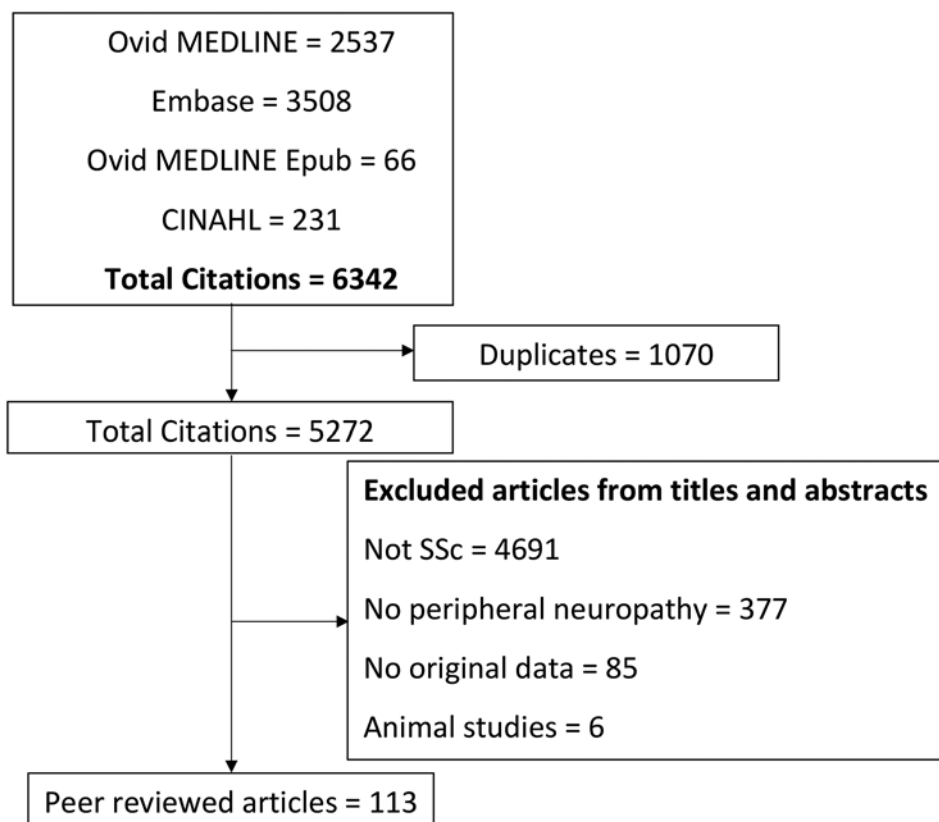


Figure 1. PRISMA flow diagram of systematic review results. CINAHL: Cumulative Index to Nursing and Allied Health Literature; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; SSc: systemic sclerosis.

Table 1. Compression and noncompression neuropathies in systemic sclerosis.

Compression Neuropathy	Noncompression Neuropathy
Trigeminal neuropathy	Trigeminal neuropathy
Carpal tunnel syndrome	Sensorimotor neuropathy
Ulnar nerve entrapment	Brachial plexopathy
Tarsal tunnel syndrome	Sensory ataxic neuropathy
Ilioinguinal nerve entrapment	Multiple mononeuropathies
Popliteal nerve palsy	Sensory motor plexopathy
Cutaneous neuropathy	Optic neuropathy
	Digital neuropathy
	Sensory neuropathy
	Polyneuropathy
	Cutaneous neuropathy
	Axonal polyneuropathy
	Fourth cranial nerve palsy
	Meralgia paraesthetica
	Damaged cutaneous peripheral nerves
	Digital neurovascular dysfunction
	Neuropathic fecal incontinence
	Painful feet paresthesia

The most common type of noncompression neuropathy was trigeminal neuropathy (n = 100).<sup>9,22,23,25,26,29,31,58,61-63,66-69,73,78,79,83,87,95,97,99,120</sup> Several etiologies were proposed including nerve fibrosis secondary to tissue edema and

vasculitis,<sup>8,13,15,19,21,27,32,34,35,39,40,48,56,57,63,73,80,88,99,113,117</sup> as well as nerve ischemia due to microangiopathy.<sup>9,10,14,15,23,24,31,33,37,44,49,52,53,57,59,73,88,94,105</sup> Mononeuropathy was found in the majority of subjects (n = 369),<sup>9,11,13,16-19,22-24,26,27,29-34,37,39,40,46,47,50,57-60,62-70,73,74,77,78,83-85,87,95,97-99,101,103,105,118,120</sup> multiple mononeuropathies in 143 subjects,<sup>14-16,21,31,34,35,41,53,61,79,82,92,95,98,100,102</sup> and polyneuropathy in 202 subjects.<sup>16,25,26,28,31,38,40,42-44,48,49,51,52,55,56,68,71,72,76,80,81,86,88-91,94,96,104,105,109-111,114,115,117,120</sup> When neuropathies were assessed based on small and large fibers, the most common type found was small fiber neuropathy (n = 556),<sup>9-16,18,19,21-24,26,27,29-31,34,35,38,41,43,44,46-51,53,55,57,58,62-64,66-70,73,74,77-79,83,87,92,95,97-104,106,109,111,113,118,120</sup> whereas large fiber neuropathy was found in 231 subjects (data not shown).<sup>8,16,17,21,25,26,28,31-33,37,39-42,48,49,52,56,59-61,65,68,71,72,74,76,79-82,84-86,88-92,94,96,98,100,102,105,110,111,115,120</sup>

**Risk factors.** The most frequent risk factor for compression neuropathy in SSc was calcinosis cutis.<sup>17,72,88</sup> Risk factors for noncompression neuropathies include advanced diffuse disease, anticentromere antibodies, ischemia of the vasa nervorum, iron deficiency anemia, reduced nerve density, metoclopramide, pembrolizumab, silicosis, and uremia (Table 2).

**Treatment.** There were 68 patients with reported success of treatments in the literature, including 41 patients who had success in restoring sensation.<sup>8,11,14,15,17,23,34,40,42,43,48,56,60,64,73,74,84,88,90,91,101</sup> These patients had CTS, brachial plexopathy, optic neuropathy, ulnar nerve compression, trigeminal neuropathy, axonal

Table 2. Risk factors for noncompression peripheral neuropathy in SSc.

Study	Neuropathy Risk Factor	Method of Assessment
Manneschi 2005 <sup>35</sup>	Advanced dSSc	N/A
Del Rosso 2003 <sup>18</sup>	Anticentromere antibody	Indirect immunofluorescence
Bandinelli 2010 <sup>10</sup>	Ischemia of vasa nervorum	Ultrasound
Ostojic 2013 <sup>44</sup>	Metoclopramide and iron deficiency anemia	N/A
Barbosa 2017 <sup>114</sup>	Pembrolizumab	N/A
Bignotti 2015 <sup>13</sup>	Reduced nerve density	Ultrasound
Agarwal 1987 <sup>61</sup>	Silicosis	N/A
Averbuch-Heller 1992 <sup>120</sup>	Uremia	Blood level

dSSc: diffuse systemic sclerosis; N/A: not applicable; SSc: systemic sclerosis.

sensory neuropathy, lumbosacral plexopathy, cervical radiculopathy, and cauda equina. Thirty-three patients had improvement in motor or sensorimotor neuropathies.<sup>31,37,40,64,75,88,91,94,107,115</sup> These patients had neuromyotonia, CTS, 4th nerve palsy, lumbosacral plexopathy, cauda equina, and gastric myoelectric activity abnormalities (Table 3). Out of the 68 patients, 17 had documented successful surgeries (14 for sensory neuropathies<sup>11,17,34,40,43,60,64,74,84,90,91</sup> and 3 for sensorimotor<sup>40,64,91</sup>), and all the surgeries were performed on neuropathies caused by nerve compression.<sup>17,31,34,40,43,47,60,72,74,84,90,91,118</sup>

Immunosuppression was the treatment of choice for noncompression neuropathies caused by tissue edema, vasculitis, and microangiopathy.<sup>8,15,21,32,34,39,40,73,88,94</sup> The most commonly used medication in cases of neuropathy with successful outcomes was prednisone (n = 11), where it was used in 7 patients with sensory neuropathies (5 as monotherapy,<sup>34,48,73,88</sup> 1 in combination with cyclophosphamide [CYC],<sup>8</sup> and 1 in combination with azathioprine<sup>15</sup>), and in 4 patients with motor neuropathies (3 as

monotherapy<sup>31,88,94</sup> and 1 in combination with CYC<sup>75</sup>). Only complete resolution of symptoms was considered a successful outcome. CYC use was reported in 4 case reports.<sup>8,65,75,119</sup> Nonimmunosuppressive therapy for noncompression neuropathies included amitriptyline, pregabalin, gabapentin, tricyclic antidepressants, and transcutaneous electrical nerve stimulation. Treatments for compression and noncompression peripheral neuropathies are summarized in Tables 3 and 4.

*Metaanalysis.* The pooled prevalence of neuropathy using the random effects model was 27.37% (95% CI 22.35–32.70) with the 95% prediction interval of 17.54–38.47%. The  $I^2$  was 19% (95% CI 0.00–58.50) with  $P = 0.27$ . Results are presented in a forest plot (Figure 2). Egger test ( $P = 0.65$ ) and funnel plot showed that publication bias was not an issue in this research. The results of the Fail Safe N method ( $N = 1720$ ,  $P = 0.05$ ) further suggest that the conclusion of our metaanalysis may not be susceptible to publication bias. We tested different moderators (sex, publication year, age, duration of disease, and study

Table 3. Treatment of compression peripheral neuropathy in systemic sclerosis and outcomes.

Study	Treatment Drug	Sensory Outcome	Motor Outcome	MRC at Baseline	MRC Posttreatment	Assessment Tool/Parameter
Barr 1988 <sup>11</sup>	Decompression surgery	Partial improvement	N/A	N/A	N/A	Symptoms
Barr 1988 <sup>11</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Berth-Jones 1990 <sup>64</sup>	Decompression surgery	Success	Success	N/A	N/A	Symptoms
Chammas 1995 <sup>17</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Ko 1996 <sup>84</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Lima 2005 <sup>72</sup>	Posterior cervical-thoracic laminectomy	Failure	Failure	N/A	N/A	Symptoms
Machet 1992 <sup>34</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Machet 1992 <sup>34</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Machet 1992 <sup>34</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Mondeli 1995 <sup>74</sup>	Decompression surgery	Failure	N/A	N/A	N/A	Symptoms
Mondeli 1995 <sup>74</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Mondeli 1995 <sup>74</sup>	Decompression surgery	Success	N/A	N/A	N/A	Symptoms
Mouthon 2000 <sup>40</sup>	Ulnar arcade resection	Success	Success	N/A	N/A	Symptoms
Ortiz 1991 <sup>43</sup>	Surgery (aneurysm)	Success	N/A	N/A	N/A	Symptoms
Pinstein 1989 <sup>90</sup>	Surgery	Success	N/A	N/A	N/A	Symptoms
Polio 1989 <sup>47</sup>	Surgery	Partial improvement	N/A	N/A	N/A	Symptoms
Shibuya 2006 <sup>91</sup>	Surgery	Success	Success	3 to 4	5	Symptoms
Thurman 1991 <sup>60</sup>	Surgery	Success	Partial improvement	N/A	N/A	Symptoms

N/A: not applicable; MRC: Medical Research Council.

Table 4. Treatment of noncompression peripheral neuropathy in systemic sclerosis and outcomes.

Study	Treatment Drug	Sensory Outcome	Motor Outcome	MRC at Baseline	MRC Posttreatment	Assessment Tool/Parameter
<b>Immunosuppressives</b>						
Agarwal 1987 <sup>61</sup>	D-penicillamine	Partial improvement	Partial improvement	N/A	N/A	Symptoms
Allanore 2002 <sup>8</sup>	Prednisone and cyclophosphamide	Success	Partial improvement	3 of 5	4 of 5	Symptoms
Andreadou 2012 <sup>119</sup>	Cyclophosphamide	N/A	Partial improvement	N/A	N/A	Gait
Andreadou 1971 <sup>62</sup>	Prednisone	N/A	No change	N/A	N/A	Blink reflex
Ashworth 1971 <sup>62</sup>	Prednisone	N/A	No change	N/A	N/A	Blink reflex
Barbosa 2017 <sup>114</sup>	IVIg and mycophenolic acid	N/A	Failure	N/A	N/A	Power
Barbosa 2017 <sup>114</sup>	Prednisone	N/A	Failure	N/A	N/A	Power
Birk 1995 <sup>65</sup>	Prednisolone and cyclophosphamide	N/A	Failure	N/A	N/A	Symptoms
Boschi 1993 <sup>15</sup>	Prednisone and azathioprine	Success	N/A	N/A	N/A	Visual acuity
Boschi 1993 <sup>15</sup>	Prednisone and azathioprine	Failure	N/A	N/A	N/A	Visual field
Burke 1979 <sup>66</sup>	D-penicillamine	Failure	N/A	N/A	N/A	Examination
Knupp-Oliviera 1999 <sup>71</sup>	Prednisone	Failure	Partial improvement	N/A	N/A	Writing and walking
Lecky 1987 <sup>95</sup>	Prednisone	Failure	N/A	N/A	N/A	Symptoms
Lee 1984 <sup>31</sup>	Prednisone	Not documented	Success	Not documented	4+	Walking
Levy 2005 <sup>86</sup>	IVIg	Partial improvement	Partial improvement	N/A	N/A	EMG and symptoms
Levy 2005 <sup>86</sup>	Prednisone	Failure	Failure	N/A	N/A	Symptoms
Machet 1992 <sup>34</sup>	Local corticotherapy	Partial improvement	N/A	N/A	N/A	Symptoms
Machet 1992 <sup>34</sup>	Local corticotherapy	Success	N/A	N/A	N/A	Symptoms
Miguel 2017 <sup>3</sup>	Prednisone	Success	N/A	N/A	N/A	Symptoms
Mondeli 1995 <sup>74</sup>	Local injections of 40 mg triamcinolone acetonide	Failure	N/A	N/A	N/A	Symptoms
Moore 1989 <sup>88</sup>	Prednisone 40 mg	Success	Success	3 of 5	5 of 5	Symptoms
Moulick 2013 <sup>39</sup>	Prednisone 1 mg/kg	Partial improvement	N/A	N/A	N/A	Vision
Mouthon 2000 <sup>75</sup>	Cyclophosphamide and prednisone	Failure	Success	N/A	N/A	Symptoms
Nitra 1996 <sup>41</sup>	Prednisone 40 mg and prostaglandin E	Failure	N/A	N/A	N/A	Symptoms
Nitra 1996 <sup>41</sup>	Prednisone 40 mg and prostaglandin E	Partial improvement	N/A	N/A	N/A	Symptoms
Nobuhara 2006 <sup>62</sup>	IVIg	Success	N/A	N/A	N/A	Symptoms
Sukemik 1987 <sup>36</sup>	Penicillamine	Failure	N/A	N/A	N/A	Impotence
Sukemik 1987 <sup>36</sup>	Penicillamine	Success	N/A	N/A	N/A	Carpal tunnel symptoms
Poncellet 2003 <sup>48</sup>	Prednisone	Success	N/A	N/A	N/A	Symptoms
Poncellet 2003 <sup>48</sup>	Prednisone	Success	N/A	N/A	N/A	Symptoms
Rudusky 1964 <sup>76</sup>	Prednisone	Failure	Failure	0	0	Symptoms
Di Trapani 1986 <sup>94</sup>	Prednisone	N/A	Success	2 to 3	5	Symptoms
<b>Nonimmunosuppressives</b>						
Benito-León 1999 <sup>115</sup>	Carbamazepine	N/A	Success	N/A	N/A	Symptoms
Benito-León 1999 <sup>115</sup>	Hydroquinine and tetrazeepam	N/A	Failure	N/A	N/A	Symptoms
Bondavalli 1997 <sup>14</sup>	Amitriptyline	Failure	N/A	N/A	N/A	Sensation
Bondavalli 1997 <sup>14</sup>	Amitriptyline	Success	N/A	N/A	N/A	Pain
Butt 2015 <sup>92</sup>	Sacral nerve stimulation	N/A	10 failures	N/A	N/A	Fecal incontinence
DeLea 2011 <sup>101</sup>	Hydrodissection with lidocaine followed by injection of triamcinolone	12 successes	N/A	N/A	N/A	Pain score
Fischhoff 2000 <sup>23</sup>	Gabapentin	Success	N/A	N/A	N/A	Pain
Jimenez-Moreno 1998 <sup>69</sup>	Carbamazepine	Failure	N/A	N/A	N/A	Symptoms

Table 4. Continued.

Study	Treatment Drug	Sensory Outcome	Motor Outcome	MRC at Baseline	MRC Posttreatment	Assessment Tool/Parameter
Kabadi 1977 <sup>29</sup>	Carbamazepine	Partial improvement	N/A	N/A	N/A	Symptoms
Kabadi 1977 <sup>29</sup>	Levodopa	Failure	N/A	N/A	N/A	Symptoms
Kabadi 1977 <sup>29</sup>	Phenytoin	Failure	N/A	N/A	N/A	Symptoms
Lecky 1987 <sup>95</sup>	Carbamazepine	Failure	N/A	N/A	N/A	Symptoms
Lecky 1987 <sup>95</sup>	Carbamazepine	Failure	N/A	N/A	N/A	Symptoms
Lecky 1987 <sup>95</sup>	Carbamazepine	Failure	N/A	N/A	N/A	Symptoms
McNearney 2013 <sup>107</sup>	Transcutaneous electrical nerve stimulation (TENS)	N/A	17 successes	N/A	N/A	Improved GMA scores, lowered plasma VIP, motilin and IL-6 levels and improved association between GMA and sympathovagal balance
Mejias 1986 <sup>37</sup>	Lens prism	N/A	Success	N/A	N/A	Improved vertical diplopia
Miguel 2017 <sup>73</sup>	Pregabalin, duloxetine, repeated infusions of procaine and lidocaine, and local therapy with capsaicin, red light therapy, connective tissue massages or transcutaneous electrical nerve stimulation of the face	Failure	N/A	N/A	N/A	Symptoms
Mouthon 2000 <sup>40</sup>	Ulhar arcade resection	Success	Success	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Failure	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Failure	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Gabapentin or tricyclic antidepressants	Success	N/A	N/A	N/A	Symptoms
Poncelet 2003 <sup>48</sup>	Lidocaine patch	Success	N/A	N/A	N/A	Symptoms
Vicente 1991 <sup>99</sup>	Carbamazepine and amitriptyline	Failure	N/A	N/A	N/A	Symptoms

EMG: electromyography; IL: interleukin; IVIG: intravenous immunoglobulin; GMA: gastric myoelectrical activity; MRC: Medical Research Council; N/A: not applicable; VIP: vasoactive intestinal peptide.

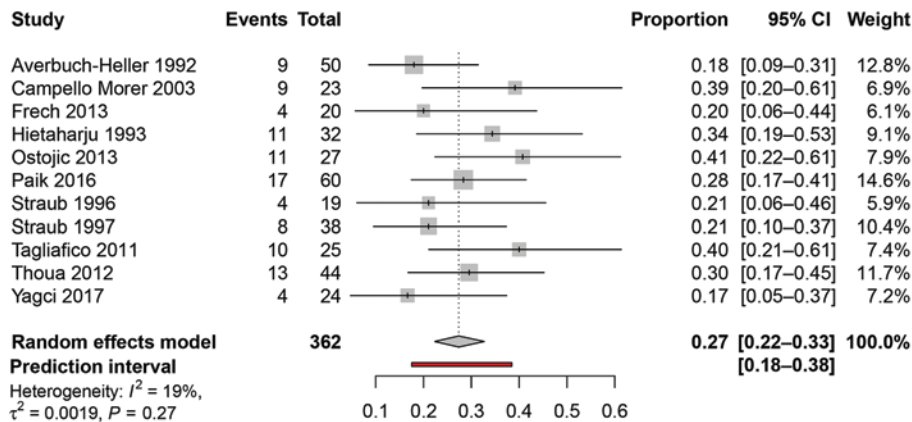


Figure 2. Forest plot of random effects model showing the pooled prevalence and prediction interval.

design) to explain the 19% heterogeneity. Results of metaregression showed that collectively the amount of heterogeneity explained by all these moderators was  $R^2 = 98.77\%$ , but overall the tests for moderators was not significant ( $P = 0.67$ ). When multimodel inference was applied to observe which predictors were important, results showed that age was the most important predictor of neuropathy, followed by male sex, then female sex, and last, duration of disease.

## DISCUSSION

Our study synthesizes the literature on the epidemiology and treatment of peripheral neuropathy in SSc. First, we found that peripheral neuropathy is not uncommon in SSc, with a pooled prevalence of 27.37%. Compared to a general population prevalence of 2–8%, peripheral neuropathy appears to occur more frequently in SSc. Peripheral neuropathy in SSc has several different etiologies including nerve compression by soft tissue swelling, tissue fibrosis or calcinosis cutis, traumatic injury, medication adverse effects, metabolic sequelae, and ischemia. Peripheral neuropathy was detected mostly in the first decade of the disease course (mean 8.85 yrs from the onset of SSc). Modalities most frequently used to detect peripheral neuropathy in SSc were physical examination, NCS, electromyography, and biopsy.

Peripheral neuropathy in the context of SSc can be categorized as compression or noncompression neuropathies. Calcinosis was the most-reported cause of compression neuropathy, but other causes of compression included soft tissue thickening, edema, and fibrosis. The most common entrapment neuropathy in SSc was CTS, which may present prior to the diagnosis of SSc. Compression neuropathies were mostly successful when treated by surgical decompression. Compression neuropathies, such as CTS, are well recognized in SSc and treatment well established.

In contrast, noncompression peripheral neuropathies in SSc may occur secondary to traumatic injury, adverse effects of medication, metabolic sequelae, or ischemia, and therefore have different risk factors. The noncompression peripheral polyneuropathies, consisting of sensory, mixed sensory and motor, and mononeuritis multiplex, were more common in dSSc. A symmetric, sensory polyneuropathy was the noncompression

neuropathy most frequently associated with SSc. A number of risk factors and etiologies have been implicated in the development of noncompression peripheral neuropathy in SSc. Complications of organ damage in SSc have also resulted in peripheral neuropathy, including renal involvement with hypertensive and/or uremic neuropathy; gastrointestinal tract involvement with malabsorption and subsequent myelopathy; and vitamin E, cyanocobalamin, or calciferol deficiency.<sup>74,120</sup> Peripheral neuropathy may also be caused by microangiopathy leading to nerve ischemia,<sup>14,21,35,53,68,73,74,88,94,120</sup> or as a result of therapies used in SSc, such as colchicine and penicillamine.<sup>74,120</sup>

Mononeuropathy, or mononeuritis multiplex, may occur as a manifestation of vasculitis and was more frequent in patients with limited SSc. Since vasculitis is an uncommon manifestation of SSc, other overlapping diseases such as systemic lupus erythematosus, or a concomitant disease such as cryoglobulinemia due to hepatitis C infection, should be considered. Cranial neuropathies have also been reported in SSc. The most commonly involved cranial neuropathy was the trigeminal nerve, with dysfunction of the optic, oculomotor, trochlear, abducens, facial, glossopharyngeal, and auditory nerves. Symptoms of trigeminal neuropathy included slowly progressive unilateral or bilateral facial numbness, frequently with associated pain and paresthesia.

There are few reports of peripheral nerve pathology in patients with SSc. Findings include increased collagen and amorphous substance in the endoneurium, loss of myelinated fibers, intimal thickening, adventitial edema, diffuse hyalinosis of endoneurial and perineurial blood vessels, and necrotizing vasculitis (very rare).<sup>21,121,122</sup> The treatment for compression peripheral neuropathy is most frequently decompression surgery. Medications used in the treatment of noncompressive peripheral neuropathies have included corticosteroids, CYC, amitriptyline, gabapentin, methotrexate, and anticonvulsants.

This comprehensive systematic review synthesizes what is known about the epidemiology and treatment of peripheral neuropathy on SSc. This may be of value to clinicians who face this clinical challenge. However, this study has a few limitations that should be considered. First, the literature reporting peripheral neuropathy in SSc is limited by the large number of case reports and the lack of RCTs. The literature describing the

frequency of peripheral neuropathy in SSc is largely descriptive and of poor methodological quality. As a result, our estimate of the frequency of all-cause peripheral neuropathy is imprecise. Attempts to make estimates of peripheral neuropathy by etiology would be even more imprecise. Second, the studies were variable in their use of physician diagnosis or classification criteria for SSc as inclusion criteria. Nearly all the studies predated the most recent 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for SSc. The main messages we wish to express is that all-cause peripheral neuropathy occurs in SSc and is not uncommon. Peripheral neuropathy in SSc warrants better investigation of epidemiology and treatment. We have found evidence of potential therapeutic benefit of immunosuppressive and anticonvulsive medications, and demonstrated clinical equipoise regarding the preferred treatment regimen.<sup>123</sup>

In conclusion, all-cause peripheral neuropathy appears to be more common in SSc than in the general population. Observational data suggest that compression neuropathies can be successfully treated with decompression surgery. The evidence supporting immunosuppressives and anticonvulsants to treat peripheral neuropathy in SSc is limited and conflicting. These data provide enough evidence of effect to justify RCTs to evaluate the efficacy of these interventions.

#### ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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