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Treatment modalities in brachioradial pruritis: a systematic review

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Abstract

Introduction: Brachioradial pruritis is a rare dysesthesia syndrome that is known to negatively impact quality of life. No consensus exists regarding optimal treatment strategies.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Collaboration Clinical Trials Registry from 1966 to 2021 for studies using the title word "brachioradial pruritis" with no language restriction. One author (A.Z.) screened and performed full article reviews of all randomized clinical trials, cohort studies, case-control studies, case reports, and case series describing treatment outcomes among patients with brachioradial pruritis.

Results: We identified 239 potential articles with a final set of 45 articles meeting inclusion criteria. Only a single randomized clinical trial was identified, finding no significant benefit of topical capsaicin cream. Treatment modalities with the greatest number of reported successful therapeutic trials include gabapentin and tricyclic antidepressants. In patients with confirmed cervical spine disease, spine-directed therapies such as epidural injections were found to be beneficial. Case reports and small case series describing less-common treatments were also identified.

Discussion: The literature is overall limited with the greatest support for gabapentin, pregabalin, tricyclic antidepressants, and spine-directed therapies in appropriate patients with brachioradial pruritis. Future randomized clinical trials are needed to compare the relative effectiveness of available treatments.

Keywords: brachioradial pruritis, capsaicin, cervical spine, gabapentin, systematic review, therapeutics, treatments, tricyclic antidepressants

Introduction

Chronic pruritis is a common presentation within dermatology and primary care clinics, with estimates that approximately 8% of cases have a neuropathic origin [1]. Brachioradial pruritis (BRP) is one of the more common causes of neuropathic itch and can lead to intractable pruritis that negatively impacts quality of life [2]. There remains disagreement whether BRP is primarily driven by sun exposure or cervical spine disease [3-5], but the condition classically presents with pruritis, burning, or stinging involving the upper extremities. Given lack of evidence as to the optimal treatment approach, we aimed to systematically review the current literature regarding described treatments for BRP to consolidate the evidence for efficacy of each treatment modality.

Methods

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. We conducted a search of MEDLINE, EMBASE, and the Cochrane Collaboration Clinical Trials Registry from 1966 to October 2021 for human studies using the title word "brachioradial pruritis" with no language restriction. One author (A.Z.) independently reviewed article titles to identify all potential randomized clinical trials, cohort studies,

case-control studies, cross-sectional studies, case reports, and case series of treatment results in persons with BRP. Articles were deemed potentially relevant if the title or abstract included the words "brachioradial pruritis" in addition to any mention of drug names, treatments, or therapeutic interventions. All articles that were deemed potentially relevant were located for full manuscript review. We included articles in the final set that had at least one patient with BRP with patient-level information regarding treatment received and therapeutic response. We excluded reviews and editorials. We also excluded articles describing patients with discrete spinal cord conditions (e.g., compressive tumor, transverse myelitis) because their treatment modalities would differ significantly from the standard patient with BRP. Reference lists from retrieved articles were visually scanned to identify other potentially relevant reports. We used a structured abstract form to record the author and year of the article, the type of study performed, treatment modality (type, dose, frequency, duration), follow-up and response to treatment, and any reported adverse effects. We also collected information regarding cervical spine disease. We summarized the cumulative evidence in support or opposition of each therapeutic option.

Results

Our search strategy identified 239 potential articles (96 MEDLINE, 143 EMBASE, 0 Cochrane Collaboration Clinical Trials Registry). Through our initial screen of article titles and abstracts, we excluded 157 studies (86 duplicates, 20 wrong article type, and 20 incorrect patient population, 31 unspecified therapeutic outcomes) and included 82 articles for full review. We excluded an additional 37 articles following full review (14 wrong article type, 10 unspecified therapeutic outcomes, 7 discrete spinal cord pathology, four unspecified patient-level outcomes, and two duplicate data), leaving a final set of 45 articles (Figure 1, Table 1). No additional articles were identified through reference list review.

Gabapentin/Pregabalin

Nineteen case studies and case series evaluated outcomes among patients receiving systemic gabapentin for BRP. Among 42 total patients, 26 (62%) reported improvement in symptoms with 18 reporting significant improvement or complete resolution [7-25]. Among 14 patients with confirmed spinal disease, 12 (86%) reported improvement in symptoms [8-11,13-19,22,24-25]. The mean daily dose among patients with improvement was 1121mg, with a range from 700mg to 1800mg. Two patients reported adverse effects, with one reporting diarrhea and sleeplessness at 1800mg per day [14] and one reporting moderate sedation at 1200mg per day [25].

One case series and three case studies with a total of 6 patients evaluated patients receiving pregabalin. Five of the six patients (83%) reported significant improvement in symptoms or complete resolution [26-29]. No side effects were reported. Among five patients with cervical spine disease, four (80%) reported improvement [26-27, 29]. Doses ranged from 100mg to 225mg per day.

Topical capsaicin

A single randomized controlled trial (N=13) assigned patients with BRP to receive topical capsaicin 0.025% cream or a topical placebo [30]. Capsaicin reduced itch by 63% and placebo reduced itch by 66%, with no significant difference between the two therapies. Additionally, seven of thirteen patients in the capsaicin group reporting burning at the application site. A variation of a crossover study assigned 13 patients with bilateral BRP symptoms to apply topical capsaicin 0.025% cream to one arm and compare response to the untreated arm [31]. Two patients reported spontaneous resolution of symptoms in both arms, whereas ten of the eleven remaining patients reported significant relief from capsaicin compared to the untreated arm, with 7 reporting complete resolution. Nearly all patients complained of post-application burning sensation, causing two patients to discontinue use. In one large case series (N=30) of capsaicin cream of unspecified strength, two patients reported complete relief, two endorsed partial relief, and 26 endorsed no response [20]. In one case series (N=7) of topical capsaicin 0.025% cream, four patients endorsed significant relief with post-application burning being a common adverse effect [32]. In eight additional small case reports or case series, three of 10 patients (30%)

endorsed improvement with topical capsaicin cream of unspecified strength [10,12,19,24-25,33-35].

Three case series investigated the efficacy of an 8% capsaicin patch. In one large case series (N=25), the mean pruritis reduced significantly but data regarding the specific number of patients reporting benefit were not provided [36]. In two smaller case series with a combined 10 patients, all patients reported relief from the capsaicin patch with 5 endorsing complete resolution and 5 endorsing a reduction in pruritis symptoms by at least 85% [21,37]. Six of ten patients endorsed post-application burning and all ten reported post-application erythema. One case study of a capsaicin patch of unspecified strength described a single patient who endorsed no benefit [27].

Spine-directed therapies

One case series and two case studies evaluated chiropractic spinal manipulation among patients with BRP. The case series included 14 patients, with 6 endorsing a history of cervical spine disease with X-ray confirmation and 8 denying a history of cervical spine disease. All six patients (100%) with cervical spine disease reported complete resolution, whereas only four of eight patients (50%) without cervical spine disease benefitted [38]. In the two case studies spinal manipulation had no benefit [9, 24].

One case series and one case study evaluated physical therapy among four patients with imaging findings compatible with cervical spine disease, with all four patients (100%) reporting significant improvement or complete resolution of BRP symptoms [11,39].

Local epidural corticosteroid injections were evaluated in two case series and one case study among six patients with image-confirmed cervical spine disease [16,27,40]. All six patients reported improvement in BRP symptoms, with four achieving complete resolution and two endorsing an excellent response.

Two case studies described surgical interventions among patients with BRP and significant cervical spine disease. In one case study, a patient endorsed ninety-five percent improvement in pruritis symptoms following a multilevel anterior cervical diskectomy and fusion surgery [41]. In another study, a patient reported complete resolution in BRP symptoms following a C5-C6 diskectomy with C6 nerve root decompression and fusion between the C5 and C6 vertebrae [14].

Tricyclic antidepressants

A total of 6 case studies and case series reported on patients with BRP who received the tricyclic antidepressants amitriptyline or doxepin. In a large case series among patients with BRP without indication for decompressive surgery, twenty-two patients received amitriptyline with greater than ninety percent reporting a response and fifteen received doxepin with greater than ninety percent reporting a response [23]. Among 8 patients identified in the other case studies and small case series, two (25%) reported improvement in symptoms [10,12,16,27,32].

Topical corticosteroids

A total of 9 case studies and case series described patients who trialed topical corticosteroids to manage BRP. In one case series with 18 patients, 8 patients (44%) reported improvement with topical corticosteroids (two complete resolution, 6 partial response) whereas 10 reported no effect [21]. In 8 other case studies and case series reporting on 9 total patients, none of the patients reported benefit [17,19-20,33-35,42-43].

Antihistamines

A total of 14 case studies and case series reported on 17 patients who used antihistamines to manage BRP [7,9-10,12-13,17,21,25,33-35,37,42-43]. None of these patients reported improvement in symptoms.

Other

Case studies and case reports of positive results for less common treatments among patients with refractory BRP symptoms were described. These included strict photoprotection (N=1), [44], aprepitant (N=1), [19], naltrexone and pregabalin combination therapy (N=1), [45], dupilumab with soak-and-smear regimen (N=1), [43], lamotrigine (N=1), [12], botulinum toxin injection (N=2), [46-47], thalidomide (N=2), [48], and topical amitriptyline and topical ketamine combination therapy (N=2), [24,35]. One case study reported on a patient who

did not have a response to systemic corticosteroids [7]; two case studies reported on patients who did not have response to a lidocaine patch [25,27]; one case study reported on a patient without a response to carbamazepine [12]; one case series reported on three patients without response to an unspecified anticonvulsant medication [37]. One case series described 6 patients who received risperidone, with one reporting no improvement, one reporting adequate reduction in pruritis, and four reporting excellent reduction in pruritis [23]. Another case series described 9 patients who tried cutaneous field stimulation, with all patients reporting improvement in BRP symptoms without adverse effects and four (44%) reporting a greater than fifty percent reduction in pruritis [49]. One case study of a patient receiving transcutaneous electronic nerve stimulation found seventy percent reduction in pruritis [50].

Discussion

Through our systematic review, we determined that only a single randomized controlled trial has evaluated the efficacy of therapeutic interventions for BRP and that most evidence relies upon case series and case studies. Although no consensus exists regarding an optimal treatment modality, commonly used medications predominated in the literature. Gabapentin and pregabalin were found to be effective in more than half of patients with a modest average dose. Given the known safety profile of these medications, they should be considered as possible first-line agents among patients with BRP. Tricyclic antidepressants also appear favorable overall and are known to be effective in cases of neuropathic pain or itch. However, given the possibility of sedation and other side effects, it is important to consider risks and benefits especially among elderly patients who may be particularly sensitive. The literature supporting capsaicin cream remains weak, with the only randomized clinical trial detecting no significant difference between active medication and placebo. The other publications cumulatively demonstrated that only seven of forty patients endorsed benefit with adverse effects being a common limiting factor. In contrast, the literature supporting the 8% capsaicin patch appears more promising with recent studies among patients with neuropathic pain finding the capsaicin patch to be a cost-effective option [51]. Therefore, in patients with BRP who have unilateral or well-circumscribed pruritis, the 8% capsaicin patch may be a reasonable second-line agent. Additionally, our findings suggest that antihistamines and topical corticosteroids are minimally effective in BRP. These results highlight the importance of distinguishing BRP from primary dermatologic causes of pruritis, such as eczema, for which these treatments are commonplace.

A continued controversy regarding BRP is whether it is primarily triggered by cervical spine disease, sun exposure, or a combination of the two [3-5]. Although there were insufficient data to delineate the appropriate treatment based on presence sun-related symptoms, photoprotection should be considered as a component of BRP management given that it has the potential to eliminate symptoms [44], does not contribute additional cost, and can decrease other risks associated with excessive sun exposure (e.g., skin cancer). In addition, our results suggest that spine-directed therapies may be useful among patients with confirmed cervical spine disease. Therefore, among patients with suspected cervical spine disease in the setting of BRP, collaboration with the departments of neurosurgery, neurology, or physical medicine and rehabilitation should be considered to determine whether imaging should be undertaken and to determine whether local epidural spine corticosteroid injections, physical therapy, or surgical intervention are indicated. Although our findings suggest chiropractic spinal manipulation may be useful, the potential risks associated with the activity, including dissection of arteries in the head and neck [52], need to be thoroughly considered.

Given the lack of high-quality evidence, our conclusions remain limited. One major limitation in the setting of case series and case reports is publication bias, with positive results being more likely to receive publication. Overall, this would cause a positive bias to exist for most treatments in the literature and makes it difficult to accurately evaluate the potential utility of less commonly used

medications that showed promise in a limited set of published articles, such as dupilumab and botulinum toxin. Second, no head-to-head trials comparing the effectiveness of different medications currently exist in the literature, so we are unable to determine the optimal first-line treatment among patients with BRP. Third, the articles were not all using the same outcomes and the use of certain instruments to quantify itch may not be fully validated in BRP.

Based upon its current state, the greatest support exists for gabapentin, pregabalin, tricyclic antidepressants, the capsaicin 8% patch, and spine-directed therapies in appropriate patients. Future randomized clinical trials are needed to determine the best therapeutic intervention among patients with BRP and to investigate the relative utility of other less commonly used treatments, such as dupilumab, in this setting.

Conclusion

The literature on therapeutic interventions among patients with BRP is overall limited and of low quality.

Potential conflicts of interest

The authors declare no conflicts of interest.

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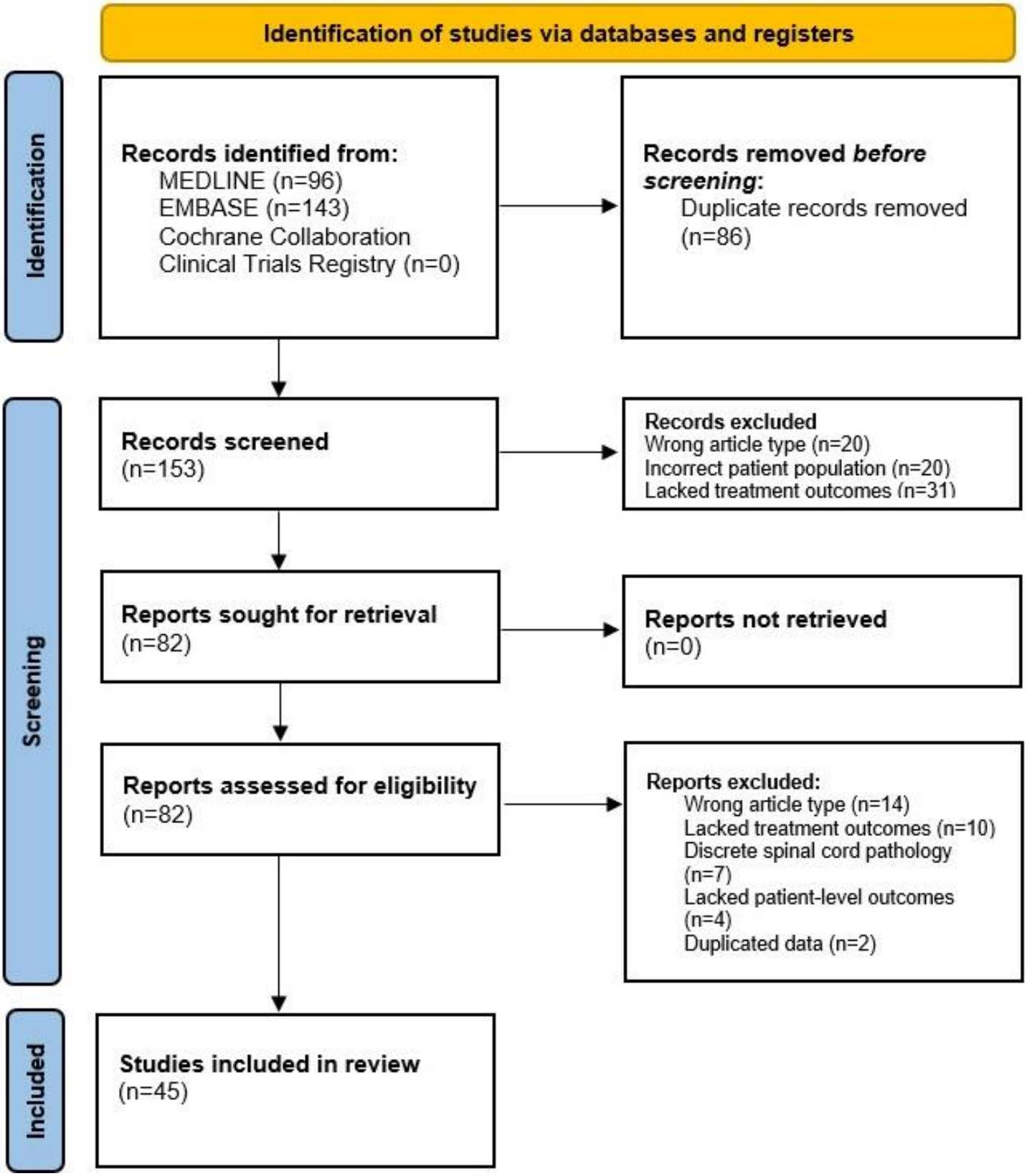

Figure 1. *Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.*

Table 1. *Studies assessing therapeutics for brachioradial pruritis.*

Reference, Year Published	Specific Therapy	Study type	Number of patients	Number of patients reporting benefit, No. (%)	Description of overall outcomes	Considerations related to cervical spine disease	Adverse effects
Gabapentin or pregabalin							
Małek, 2017 [7]	Gabapentin	Case study	1	1 (100)	>50% improvement in symptoms	N/A	None
Szewka, 2016 [8]	Gabapentin	Case study	1	1 (100)	Excellent response	Cervical radicular compression on MRI	None
Bueller, 1999 [9]	Gabapentin	Case study	1	1 (100)	Complete resolution	Spondylosis with impingement at C6 on MRI	None
Winhoven, 2004 [10]	Gabapentin	Case series	2	2 (100)	Excellent response	1 patient with degenerative changes in cervical spine on MRI	None
Schürmeyer-Horst, 2006 [11]	Gabapentin	Case study	1	1 (100)	Complete resolution	C6 nerve root compression on MRI	None
Crevits, 2005 [12]	Gabapentin	Case study	1	0 (0)	No change in symptoms	Normal MRI of cervical spine	N/A
Kanitakis, 2006 [13]	Gabapentin	Case study	1	1 (100)	90% improvement in symptoms	Disc arthrosis at C5-C6 and C6-C7 levels on spine X-ray	Diarrhea, sleeplessness
Binder, 2008 [14]	Gabapentin	Case study	1	1 (100)	50% improvement in symptoms	Intervertebral osteochondrosis at C5-C6 level with compression of right C6 nerve root on MRI	None
Mataix, 2008 [15]	Gabapentin	Case series	4	3 (75)	Complete resolution	Three patients had imaging consistent with degenerative spinal disease, did not provide data on whether patients who benefitted had spinal disease	N/A
De Ridder, 2010 [16]	Gabapentin	Case study	1	1 (100)	Partial response	Multilevel degenerative disease with neuroforaminal stenosis at C3-	None

						C4, C4-C5 and C5-C6 on MRI	
Yilmaz, 2010 [17]	Gabapentin	Case study	1	1 (100)	Complete resolution	Osteophytes at C4-C5 and degenerative changes at C6-C7 on MRI	None
Uldal Pallesen, 2012 [18]	Gabapentin	Case study	1	1 (100)	Complete resolution	Cervical radiculopathy on spinal imaging	None
Ally, 2013 [19]	Gabapentin	Case study	1	0 (0)	No change in symptoms	Bilateral neuroforaminal stenosis between C4 and C6 on MRI	N/A
Mirzoyev, 2013 [20]	Gabapentin	Case series	13	4 (31)	2 with complete resolution and 2 with partial response	Data regarding imaging findings specifically among patients receiving certain treatments not provided	N/A
Misery, 2015 [21]	Gabapentin	Case series	2	1 (50)	1 with initial improvement with waning effect and 1 with no response	N/A	None
Carvalho, 2015 [22]	Gabapentin	Case study	1	1 (100)	Significant improvement	Right cervical disc herniation with nerve root compression at C6-C7 on MRI	None
Wachholz, 2017 [23]	Gabapentin	Case series	7	6 (86)	3 with excellent response, 2 with good response and 1 with minimal response	N/A	N/A
Magazin, 2019 [24]	Gabapentin	Case study	1	0 (0)	No change in symptoms	Moderate-severe degenerative changes between C4-C7 on MRI	N/A
Berger, 2019 [25]	Gabapentin	Case study	1	1 (100)	Significant improvement in symptoms	Long-standing history of neck pain with imaging-confirmed cervical	Moderate sedation

						radiculopathy (C3 to C6)	
Szczech, 2017 [26]	Pregabalin	Case study	1	1 (100)	Significant improvement in symptoms	Herniated discs at C3-C4 and C5-C6 on MRI	None
Kumar, 2014 [27]	Pregabalin	Case study	1	0 (0)	No change in symptoms	Cervical facet disc degenerations with disc protrusions compressing cervical nerve roots	N/A
Vestita, 2016 [28]	Pregabalin	Case study	1	1 (100)	Complete resolution	N/A	None
Atış, 2017 [29]	Pregabalin	Case series	3	3 (100)	Complete resolution	All 3 patients had imaging-confirmed degenerative disease affecting C3 to C7	N/A
Topical capsaicin							
Winhoven, 2004 [10]	Capsaicin cream	Case series	1	0 (0)	No change in symptoms	1 patient with degenerative changes in cervical spine on MRI	N/A
Crevits, 2005 [12]	Capsaicin cream	Case study	1	0 (0)	No change in symptoms	Normal MRI of cervical spine	N/A
Ally, 2013 [19]	Capsaicin cream	Case study	1	0 (0)	No change in symptoms	Bilateral neuroforaminal stenosis between C4 and C6 on MRI	N/A
Mirzoyev, 2013 [20]	Capsaicin cream	Case series	30	4 (13)	2 with complete resolution and 2 with improvement in symptoms	Data regarding imaging findings specifically among patients receiving certain treatments not provided	N/A
Misery, 2015 [21]	Capsaicin 8% patch	Case series	5	5 (100)	Complete resolution	N/A	All had mild erythema and one patient had post-application burning
Magazin, 2019 [24]	Capsaicin cream	Case study	1	0 (0)	No change in symptoms	Moderate-severe degenerative changes between C4-C7 on MRI	N/A

Berger, 2019 [25]	Capsaicin cream	Case study	1	0 (0)	No change in symptoms	Long-standing history of neck pain with imaging-confirmed cervical radiculopathy (C3 to C6)	N/A
Kumar, 2014 [27]	Capsaicin patch	Case study	1	0 (0)	No change in symptoms	Cervical facet disc degenerations with disc protrusions compressing cervical nerve roots	N/A
Wallengren, 1998 [30]	Capsaicin cream	Randomized clinical trial	13	12 (92)	Capsaicin treatment reduced the itch by 63.1% ± 2%, whereas placebo reduced the itch by 65.5% ± 2.9% (no significant difference)	N/A	7 of 13 patients in capsaicin group reported burning at application site
Knight, 1994 [31]	Capsaicin cream	Crossover Trial Variation (patients with bilateral symptoms applied placebo to one arm and capsaicin cream to other arm)	13	Unclear	10 of 13 patients found significant relief from capsaicin on treated arm compared to untreated arm with 7 having complete resolution; 2 patients had spontaneous resolution of both arms	N/A	Majority of patients endorsed post-application burning, causing 2 patients to drop out of study
Barry, 2004 [32]	Capsaicin cream	Case series	7	4 (57)	Significant relief	Five of 7 patients had imaging-confirmed cervical degenerative disease; did not provide sufficient data to determine status of cervical spine disease among responders	Post-application burning endorsed by some patients

Goodless, 1993 [33]	Capsaicin cream	Case series	2	2 (100)	Complete resolution	No imaging findings consistent with cervical spine disease	None
Lane, 2008 [34]	Capsaicin cream	Case study	1	1 (100)	Moderate response	Left-sided osteophyte at C3-C4 with history of prior anterior discectomy and fusion from C4 to C6	None
Poterucha, 2013 [35]	Capsaicin cream	Case study	1	0 (0)	No change in symptoms	Narrowing of C3 and C5 foramina on spinal x-ray	N/A
Pereira, 2018 [36]	Capsaicin 8% patch	Case series	25	Unclear	Significant reduction in mean pruritis among patient group, but unclear how many benefitted and how much they benefitted	All patients had pathologic findings on MRI (6 with degenerative changes, 5 with cervical stenosis, and 14 with both)	N/A
Zeidler, 2016 [37]	Capsaicin 8% patch	Case series	5	5 (100)	Significant relief (>85% reduction in symptoms)	N/A	All patients complained of post-application erythema and burning
Spine-directed therapies							
Bueller, 1999 [9]	Spinal manipulation	Case study	1	0 (0)	No change in symptoms	Spondylosis with impingement at C6 on MRI	N/A
Schürmeyer-Horst, 2006 [11]	Physical therapy	Case study	1	1 (100)	Complete resolution	C6 nerve root compression on MRI	None
Binder, 2008 [14]	C5-C6 discectomy and C6 nerve root decompression, followed by fusion between the C5 and C6 vertebrae	Case study	1	1 (100)	Complete resolution	Intervertebral osteochondrosis at C5-C6 level with compression of right C6 nerve root on MRI	None
De Ridder, 2010 [16]	Epidural steroid injection	Case study	1	1 (100)	Complete resolution	Multilevel degenerative disease with neuroforaminal stenosis at C3-C4, C4-C5 and C5-C6	None

Magazin, 2019 [24]	Chiropractic manipulation	Case study	1	0 (0)	No change in symptoms	Moderate-severe degenerative changes between C4-C7 on MRI	N/A
Kumar, 2014 [27]	Cervical facet and epidural steroid injections	Case study	1	1 (100)	Excellent response	Cervical facet disc degenerations with disc protrusions compressing cervical nerve roots	None
Tait, 1998 [38]	Cervical spine manipulation	Case series	14	10 (71)	Among 6 patients with reported and imaging-confirmed cervical spine disease, all 6 had resolution of symptoms. Among 8 patients denying cervical spine disease, 4 had resolution of symptoms.	6 patients had symptoms and imaging consistent with cervical spine disease, with all 6 endorsing complete resolution of symptoms	None
Heyl, 1983 [39]	Orthopedic therapy or physiotherapy	Case series	3	3 (100)	Significant improvement in symptoms	14 patients were included in study with 5 patients receiving lateral x-rays. Among these 5, 4 showed cervical degenerative changes between C4 and C7. Unclear whether 3 patients receiving orthopedic therapy or physiotherapy had cervical spine disease	None
Weinberg, 2018 [40]	CT-guided epidural steroid injections	Case series	3	3 (100)	2 patients had near complete resolution after 1 treatment, while 1	All 3 patients had foraminal stenosis on spinal imaging	None

					patient required 3 treatments to achieve complete resolution		
Salzmann, 2020 [41]	Multilevel anterior cervical diskectomy and fusion surgery	Case study	1	1 (100)	95% resolution in pruritis	Multilevel foraminal stenosis from C3 to C7 on spine MRI	None
Tricyclic antidepressants							
Winhoven, 2004 [10]	Doxepin	Case series	2	0 (0)	No change in symptoms	1 patient with degenerative changes in cervical spine on MRI	N/A
Crevits, 2005 [12]	Amitriptyline	Case study	1	0 (0)	No change in symptoms	Normal MRI of cervical spine	N/A
De Ridder, 2010 [16]	Amitriptyline	Case study	1	0 (0)	No change in symptoms	Multilevel degenerative disease with neuroforaminal stenosis at C3-C4, C4-C5 and C5-C6	N/A
Wachholz, 2017 [23]	Amitriptyline	Case series	22	>90% with a response	About half of patients with a response noted excellent reduction in pruritis	N/A	N/A
Wachholz, 2017 [23]	Doxepin	Case series	15	>90% with a response	About one-third of patients with a response noted excellent reduction in pruritis	N/A	N/A
Kumar, 2014 [27]	Amitriptyline	Case study	1	0 (0)	No change in symptoms	Cervical facet disc degenerations with disc protrusions compressing cervical nerve roots	N/A
Barry, 2004 [32]	Amitriptyline	Case series	3	2 (67)	Symptom relief	Five of 7 patients had imaging-confirmed cervical degenerative disease; did not	N/A

						provide sufficient data to determine status of cervical spine disease among responders	
Topical steroids							
Yilmaz, 2010 [17]	Unspecified topical steroid	Case study	1	0 (0)	No change in symptoms	Osteophytes at C4-C5 and degenerative changes at C6-C7 on MRI	N/A
Ally, 2013 [19]	Unspecified topical steroid	Case study	1	0 (0)	No change in symptoms	Bilateral neuroforaminal stenosis between C4 and C6 on MRI	N/A
Mirzoyev, 2013 [20]	Unspecified topical steroid	Case series	18	8 (44)	2 with complete resolution and 6 with improvement in symptoms	Data regarding imaging findings specifically among patients receiving certain treatments not provided	N/A
Misery, 2015 [21]	Unspecified topical steroid	Case series	3	0 (0)	No change in symptoms	N/A	N/A
Goodless, 1993 [33]	Unspecified topical steroid	Case series	1	0 (0)	No change in symptoms	No imaging findings consistent with cervical spine disease	N/A
Lane, 2008 [34]	Unspecified topical steroid	Case study	1	0 (0)	No change in symptoms	Left-sided osteophyte at C3-C4 with history of prior anterior discectomy and fusion from C4 to C6	None
Poterucha, 2013 [35]	Unspecified topical steroid	Case study	1	0 (0)	No change in symptoms	Narrowing of C3 and C5 foramina on spinal x-ray	N/A
Fisher, 1997 [42]	Unspecified topical steroid	Case study	1	0 (0)	No change in symptoms	No imaging, but history of severe whiplash injury preceding disease	N/A
Abel, 2021 [43]	Triamcinolone 0.1% cream	Case study	1	0 (0)	No change in symptoms	Bulging cervical disc on spine MRI	N/A
Oral antihistamines							
Małek, 2017 [7]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	N/A	N/A

Bueller, 1999 [9]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Spondylosis with impingement at C6 on MRI	N/A
Winhoven, 2004 [10]	Unspecified antihistamine	Case series	2	0 (0)	No change in symptoms	1 patient with degenerative changes in cervical spine on MRI	N/A
Crevits, 2005 [12]	Cetirizine	Case study	1	0 (0)	No change in symptoms	Normal MRI of cervical spine	N/A
Kanitakis, 2006 [13]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Disc arthrosis at C5-C6 and C6-C7 levels on spine X-ray	N/A
Yilmaz, 2010 [17]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Osteophytes at C4-C5 and degenerative changes at C6-C7 on MRI	N/A
Misery, 2015 [21]	Unspecified antihistamine	Case series	1	0 (0)	No change in symptoms	N/A	N/A
Berger, 2019 [25]	Diphenhydramine	Case study	1	0 (0)	No change in symptoms	Long-standing history of neck pain with imaging-confirmed cervical radiculopathy (C3 to C6)	N/A
Goodless, 1993 [33]	Unspecified antihistamine	Case series	1	0 (0)	No change in symptoms	No imaging findings consistent with cervical spine disease	N/A
Lane, 2008 [34]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Left-sided osteophyte at C3-C4 with history of prior anterior discectomy and fusion from C4 to C6	None
Poterucha, 2013 [35]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Narrowing of C3 and C5 foramina on spinal x-ray	N/A
Zeidler, 2016 [37]	Unspecified antihistamine	Case series	2	0 (0)	No change in symptoms	N/A	All patients complained of post-application erythema and burning
Fisher, 1997 [42]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	No imaging, but history of severe whiplash injury	N/A

						preceding disease	
Abel, 2021 [43]	Unspecified antihistamine	Case study	1	0 (0)	No change in symptoms	Bulging cervical disc on spine MRI	N/A
Other therapies							
Małek, 2017 [7]	Systemic Steroid (unspecified)	Case study	1	0 (0)	No change in symptoms	N/A	N/A
Crevits, 2005 [12]	Lamotrigine	Case study	1	1 (100)	Complete resolution	Normal MRI of cervical spine	N/A
Ally, 2013 [19]	Aprepitant	Case study	1	1 (100)	Improvements in excoriations and erosions	Bilateral neuroforaminal stenosis between C4 and C6 on MRI	None
Wachholz, 2017 [23]	Risperidone	Case series	6	5 (83)	4 with excellent response and 1 with good response	N/A	N/A
Magazin, 2019 [24]	Amitriptyline 1% cream and ketamine 0.5% cream	Case study	1	1 (100)	Complete resolution	Moderate-severe degenerative changes between C4-C7 on MRI	Sensation of tightness at application site
Berger, 2019 [25]	Topical lidocaine	Case study	1	0 (0)	No change in symptoms	Long-standing history of neck pain with imaging-confirmed cervical radiculopathy (C3 to C6)	N/A
Kumar, 2014 [27]	Lidocaine patch	Case study	1	0 (0)	No change in symptoms	Cervical facet disc degenerations with disc protrusions compressing cervical nerve roots	N/A
Poterucha, 2013 [35]	Topical amitriptyline hydrochloride and ketamine hydrochloride	Case study	1	1 (100)	Complete resolution	Narrowing of C3 and C5 foramina on spinal x-ray	None
Zeidler, 2016 [37]	Unspecified anticonvulsant	Case series	3	0 (0)	No change in symptoms	N/A	N/A
Abel, 2021 [43]	Dupilumab and soak-and-smear regiment	Case study	1	1 (100)	95% improvement in symptoms	Bulging cervical disc on spine MRI	None
Armstrong, 1997 [44]	Strict photoprotection	Case study	1	1 (100)	Complete resolution	Normal neurologic exam with complete range	None

						of motion of cervical spine	
Zeidler, 2014 [45]	Naltrexone and pregabalin	Case study	1	1 (100)	Symptom improvement by over 50%	Degenerative changes in cervical spine MRI (consistent with age)	None
Haenen, 2013 [46]	Botulinum toxin injection	Case study	1	1 (100)	Excellent response	N/A	N/A
Kavanagh, 2012 [47]	Botulinum toxin injection	Case study	1	1 (100)	Significant symptom relief	Normal cervical x-ray	N/A
Pereira, 2005 [48]	Thalidomide	Case series	2	2 (100)	Complete resolution	One patient had reduced disc space between C5 and C6 and One patient had cervical spondylarthrosis of C5-C6 and C6-C7	None
Wallengren, 2001 [49]	Cutaneous field stimulation	Case series	9	9 (100)	Improvement in all patients, with 4 having >50% reduction in symptoms	N/A	None
Alai, 2018 [50]	Transcutaneous electronic nerve stimulation	Case study	1	1 (100)	Patient-reported 70% clinical improvement	Severe central cervical canal stenosis at C3-C4, C4-C5 and C5-C6	N/A

N/A, not applicable and/or information not provided.