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## Review of Treatment for Central Spinal Neuropathic Pain and Its Effect on Quality of Life: Implications for Neuromyelitis Optica Spectrum Disorder



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### ABSTRACT

**Objectives:** Neuromyelitis optica spectrum disorder (NMOSD) causes disabling and persistent central neuropathic pain (NP). Because the pain syndrome in NMOSD is severe and often intractable to analgesic treatment, it interferes with quality of life in patients. No interventional trials have been published looking at response to interventions for pain in NMOSD. This is a synthesis of the literature surveying the impact on quality of life of interventions in all mechanisms of central spinal NP. This review has important implications for management of pain in NMOSD.

**Methods and Data Sources:** A systematic database search was conducted using PubMed, Embase, and CINAHL Plus with keywords including “spinal cord,” “quality of life,” and “neuropathic pain” in an attempt to identify original research that targeted spinal NP treatment and used quality of life as an outcome measure. Both pharmacologic and nonpharmacologic treatments were sought out.

**Results:** Twenty-one studies meeting our eligibility criteria were identified and evaluated, 13 using pharmacologic treatments and 8 using nonpharmacologic interventions. Overall, sample sizes were modest, and effects on decreasing pain and/or improving quality of life were suboptimal.

**Conclusions:** This review provides researchers with a foundation from which to start a more thorough and thoughtful investigation into the management of NP in NMOSD and underscores the importance of including quality of life as a clinically meaningful outcome measure.

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Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disorder of the central nervous system (CNS) that preferentially targets the spinal cord and optic nerves, leading to blindness, paralysis, and death. NMOSD disproportionately affects non-Caucasians and females (Jarius et al., 2012; Mealy, Wingerchuk, Greenberg & Levy, 2012) and has a worldwide prevalence estimated to be 0.52 to 4.4 per 100,000 (Marrie & Gryba, 2013). It affects approximately 4,000–8,000 people in the United States, with a wide range of disease age at onset from infancy through old age (Jarius et al., 2012; Mealy et al., 2012). In contrast to

multiple sclerosis (MS), which primarily targets myelin, NMOSD causes irreparable neuronal cell death that leads to more severe disability and a poorer prognosis (Popescu & Lucchinetti, 2016). Historically, within 5 years of symptom onset, 60% of NMOSD patients were blind in at least one eye; 52% were weak in at least one limb, requiring gait assistance; and mortality was as high as 30% (Wingerchuk, Hogancamp, O'Brien & Weinshenker, 1999), though those data have improved with the identification of the highly specific AQP4 antibody (Mealy et al., 2018b; Wingerchuk, Lennon, Pittock, Lucchinetti & Weinshenker, 2006).

NMOSD causes severe, persistent pain that is more prevalent (83.8%–91%) than in MS (~47%) (Kanamori et al., 2011; Pellkofer et al., 2013; Qian et al., 2012) and most other neurologic diseases (Borsook, 2012). The most common type of pain in NMOSD is central neuropathic pain (CNP), which is characterized as agonizing burning, shooting, tingling, lancinating, and squeezing sensations that are distressing, persistent, and debilitating. Half of patients with NMOSD characterize their CNP as severe, and two thirds

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report constant pain (Pellkofer et al., 2013; Zhao, Mutch, Elson, Nurmikko, & Jacob, 2014). CNP typically presents weeks to months after the cord damage has occurred, long after the acute injury, and may be a result of secondary changes caused by reorganization of the damaged circuits of the somatosensory system (Sjolund, 2002). The pain can persist for years, decades, or throughout the patient's life. The presence and severity of pain in NMOSD may be influenced by lesion span and location: NMOSD lesions are generally transverse, involving both the central gray matter and dorsal horns. The dorsal horns are innervated by primary afferent fibers and contain a large number of excitatory (glutamatergic) and inhibitory ( $\gamma$ -aminobutyric acid-ergic or glycinergic) interneurons, as well as projection neurons that convey sensory information to the brain (Bradl et al., 2014; Todd, 2010). Damage to the central gray matter in NMOSD leads to astrocytic damage and tissue necrosis, thus disrupting sensory pain tracts going to and from the brain (Kanamori et al., 2011; Qian et al., 2012). As a consequence of ongoing spontaneous activity arising in the periphery, surviving neurons develop increased background activity and increased responses to ascending nerve impulses, including normally harmless tactile stimulation (Centonze, 2014).

Because many provider visits are dedicated to assessment and treatment of the underlying neurologic disease, treatment of CNP is lacking despite increasing awareness of its impact on quality of life (QoL). Table 1 shows a comprehensive overview that includes seven studies assessing pain and QoL in NMOSD to date, none of which focus on an intervention or treatment. However, three studies have found promising results when examining pain as a secondary outcome, two in patients receiving a humanized monoclonal antibody that targets interleukin-6 for disease suppression (Araki et al., 2014; Ringelstein et al., 2015), and one in patients receiving low-dose mycophenolate mofetil (Huang et al., 2018), though none of these studies investigated QoL outcomes.

Research on the impact of persistent pain on QoL in NMOSD has found that those patients with CNP experience more depression, less enjoyment of life, and more difficulty with ambulation (Mutch et al., 2014; Pellkofer et al., 2013; Zhao et al., 2014). CNP is particularly resistant to most currently available treatments (Qian et al., 2012; Zhao et al., 2014). The most common medication classes for the treatment of CNP, used off-label, are antiepileptics, antidepressants, and nonsteroidal anti-inflammatories, but many patients still require frequent opioid use (Qian et al., 2012; Zhao et al., 2014). Cannabinoids have been recently considered for CNP as they become more available for use, though no data specific to this population have been analyzed. Despite this analgesic armament, NMOSD patients continue to have pain, in contrast to nearly half of MS patients treated for their CNP who report being pain-free (Qian et al., 2012).

Another factor to consider is that the medications used for treatment of CNP have side effects, particularly at higher doses, and are independently associated with slower reaction times and fatigue (Qian et al., 2012). Acknowledging that randomized control trials have reported the efficacy of nonpharmacologic interventions for other pain conditions, researchers have sought to extend this work to spinal cord injury (SCI) and MS populations for the treatment of CNP, with interventions such as nerve stimulation, acupuncture, exercise, and massage therapy (Boldt et al., 2014; Namjooyan, Ghanavati, Majdinasab, Jokari, & Janbozorgi, 2014; Widerstrom-Noga & Turk, 2003). These studies are limited by small sample size and the potential bias of symptom self-report, and they often include therapies not generally covered by insurance.

Despite research of both pharmacologic and nonpharmacologic interventions in CNP, as well as research suggesting that CNP affects QoL, few studies have specifically examined whether a given

intervention that targets pain has any side benefit on QoL. This review sought to extract, evaluate, and synthesize the literature regarding the impact of CNP interventions on QoL. This review is subdivided by pharmacologic and nonpharmacologic interventions. Because no such literature exists specifically in NMOSD, central spinal pain was sought out broadly and included related conditions including MS and SCI from multiple causes.

## Methods

A research review was conducted by performing database searches of PubMed, Embase, and CINAHL Plus. Search terms included “neuropathic pain” and “quality of life” for each search, and the terms “spinal cord,” “myelitis,” and “multiple sclerosis” were each independently added to these terms in an effort to capture a comprehensive look at all causes for CNP of the spinal cord; this generated 975 citations (202 PubMed, 721 Embase, 52 CINAHL). Results were further limited to articles and book chapters, human subjects, English language, by adding to the search “treatment” OR “intervention” OR “therapy” and by searching for “pain” specifically in article titles, which narrowed the search to 326 (114 PubMed, 192 Embase, 20 CINAHL). Articles were not limited by date. Literature reviews that were not systematic, publications that were not peer reviewed, and descriptive case reports were excluded. Duplicate articles were removed. Treatments directed to non-spinal cord causes or those that did not differentiate among location (spinal cord versus supraspinal versus peripheral) and/or types (neuropathic versus nociceptive) of pain were also excluded, and clinical judgment was exercised when interpretable based on description and location of the pain, in an effort to be inclusive when appropriate. Articles were included only if QoL was considered as an outcome (primary or secondary) after an intervention for CNP treatment, leaving 153 abstracts and articles for analysis in this review.

## Results

Twenty-one interventional studies met inclusion criteria and were reviewed (Fig. 1). Across all studies, 910 patients were analyzed (438 SCI, 290 MS, 182 other). There were no studies focused on patients with NMOSD.

Sex was described in all but one study ( $n = 24$ ). Of the remaining aggregate sample of 886, 53% of participants were female. Demographic characteristics of race and ethnicity were described only in the three U.S. studies (aggregate  $n = 263$ ). Among these, 236 were White/Caucasian descent (90%), 22 were Black/African descent (8%), three were Hispanic/Latino descent (1%), one was Native American and one was classified as “other.”

### *Effect of Pharmacologic Interventions on QoL*

Thirteen studies examined the effect of a pharmacologic intervention or treatment on QoL as a primary or secondary outcome (Table 2). Five studies evaluated the benefit of antiepileptic medications (AEDs) for first-line treatment for CNP (Finnerup et al., 2015) in MS (two studies), SCI (two studies), and a heterogeneous group of patients with CNP, a subset of whom had an undifferentiated spinal etiology (one study). The rationale for using this class of medication for treatment of CNP was similar to the rationale for use in seizures: the drugs decrease hyperexcitability in damaged areas of the CNS caused by a sustained depolarization and inhibit voltage-dependent sodium channels, reducing the capacity of neurons to generate high-frequency action potentials (Salinas, Lugo, & Garcia, 2012). A randomized, double-blind, placebo-controlled clinical trial using early AED intervention with

**Table 1**  
Studies Evaluating Pain in NMOSD Patients (Listed Chronologically)

Author (year); Country	Patient Sample	Study Design	Pain Measure	QoL Measure	Findings & Comments <sup>a</sup>
Antiepileptics Kanamori et al. (2011); Japan	37 NMOSD patients (35 AQP4+; 36 female); 51 MS patients as comparator (37 female)	Descriptive comparative	BPI	SF-36	This was the first study that explored pain in NMO. Pain in NMOSD (83.8%) was more common than in MS (47.1%) and also more severe. QoL was also significantly poorer in the NMOSD group in the areas of body pain, physical functioning, and general health. Consecutive sampling was used for participant recruitment. Although this study did not investigate or account for medication use and was limited in the number of variables assessed, this pivotal study shed light on the issue of pain in NMO.
Qian et al. (2012); U.S.	29 NMOSD patients (24 AQP4+; 24 female; 14 White/Caucasian, 14 Black/African descent, 1 Asian descent); 66 MS patients as comparator (52 female; 56 White/Caucasian, 10 Black/African descent)	Descriptive comparative	MPQ; 10-point NRS	SF-36	This study assessed pain and other symptoms, neurologic function, spinal cord damage, and QoL. Pain in NMOSD (86.2%) was more common than in MS (40.9%) and also more severe, even after controlling for disability and spinal cord damage. Pain correlated with worse physical and mental scores on SF-36. This was the first study to examine medication use: Prescription pain medications were used significantly more frequently in NMOSD participants, who more often required multiple medications, and all treated patients experienced pain despite treatment.
Pellkofer et al. (2013); Germany	11 NMOSD patients (11 AQP4+; 9 female; all White/Caucasian)	Descriptive	10-point NRS	SF-36	This study aimed to investigate presence and clinical characteristics of pain, stress, and depression, and evaluated endocannabinoid levels and abnormalities in somatosensory functioning. Recruitment was through consecutive sampling. A total of 91% had NP within the previous 3 months and 72% reported ongoing NP; decreased QoL in 3 of 8 measures: physical functioning, general health, and body pain. This study also aimed to explore the role of endogenous cannabinoids and found plasma levels of 2-AG to be significantly higher in NMOSD patients, suggesting that central sensitization is controlled by it.
Zhao et al. (2014); U.K.	50 NMOSD patients (41 AQP4+; 39 female; no race/ethnicity data made available)	Descriptive	BPI	SF-36	This study specifically explored NP more in depth. Patients were assessed for pain and QoL through use of structured interviews and measurement

carbamazepine to prevent the onset of CNP in SCI did not find a significant difference between the intervention and control groups (Salinas et al., 2012) suggesting that preemptive analgesia does not prevent the subsequent onset of CNP. The other four studies were

conducted using patients after CNP onset, three of which found that reducing pain positively affected QoL. Gabapentin, pregabalin, and levetiracetam reduced pain by 50%–100% on average and improved self-reported Visual Acuity Scale ratings through the course of

Table 1 (continued)

Author (year); Country	Patient Sample	Study Design	Pain Measure	QoL Measure	Findings & Comments <sup>a</sup>
Mutch et al. (2014); U.K.	15 NMOSD patients (9 AQP4+; 11 female; no race/ethnicity data made available)	Qualitative descriptive	Semistructured interviews	Semistructured interviews	tools, and a retrospective record review was conducted to examine MRI data, medication use, and neurologic functioning. The study found that 62% of patients experienced NP, with 68% of those having constant pain affecting ADLs. Interestingly, 72% of female participants vs. 27% of male participants reported pain. A total of 25% of patients reported pain as their worst symptom, despite mobility and/or vision issues. Physical component of QoL was equally low in those patients with and without pain, specifically in the areas of physical functioning, general health, and body pain. The mental component was significantly lower in those with pain. This was the first qualitative study to explore QoL, including pain. Poor vision, reduced mobility, bladder dysfunction, and pain affected participants' independence and experience of living with NMO. Expressed anxiety regarding unpredictability of disease and desire for normalcy. Patients reported anxiety and low mood, particularly after diagnosis and after relapses. Twelve patients reported pain and indicated that it considerably affected their daily activities, mood, walking ability, enjoyment of life, and relationships.
Asseyer et al. (2018); Germany	49 NMOSD patients (29 AQP4+, 14 MOG+; 41 female; no race/ethnicity data made available)	Descriptive	painDETECT	SF-36	This study found that 86% of patients reported pain, regardless of antibody status. Pain correlated with QoL, but treatment of pain was not effective at improving QoL.
Eaneff et al. (2017); U.S., U.K., Sweden	522 NMOSD patients (self-reported; AQP4 status unknown; 283 female; race data available for 142 patients: 99 White/Caucasian, 22 Black/African descent, 15 Asian; 6 other)	Descriptive	Self-report	PLM Quality of Life Survey	This study reported the patient perspective of those with NMOSD via an online community called PatientsLikeMe and found that 53% of NMOSD patients reported moderate to severe pain; 59% reported that their health limited their work and activities all or most of the time. Physical and emotional health interfered with social activities.

ADLs = activities of daily living; AQP4+ = aquaporin 4+; BPI = Brief Pain Inventory; MRI = magnetic resonance imaging; MPQ = McGill Pain Questionnaire; MS = multiple sclerosis; NRS = numeric rating scale; NMOSD = neuromyelitis optica spectrum disorder; NP = neuropathic pain; QoL = quality of life; SF-36 = 36-Item Short Form Survey; 2-AG = 2-arachidonoylglycerol; PLM = PatientsLikeMe.

<sup>a</sup> Values were considered significant at  $p \leq .05$ , unless otherwise noted.

treatment (Levendoglu, Ogun, Ozerbil, Ogun, & Ugurlu, 2004; Rossi et al., 2009; Vranken et al., 2008) (Table 2). Overall, these findings support the use of AEDs for CNP treatment and improvement of QoL.

Two randomized controlled trials studied the effects of the serotonin noradrenaline reuptake inhibitor (SNRI) duloxetine use on pain (Vollmer, Robinson, Risser, & Malcolm, 2014; Vranken et al.,

2011), although SNRIs are not as commonly used for pain worldwide compared with tricyclic antidepressants (Finnerup et al., 2015). The stated rationale for using duloxetine was to inhibit the reuptake of serotonin and noradrenaline to potentiate monoamine neurotransmission in the descending inhibitory spinal pathways. This results in reduced nociceptive afferent transmission in the ascending spinal pain pathways to decrease the sensation of pain.

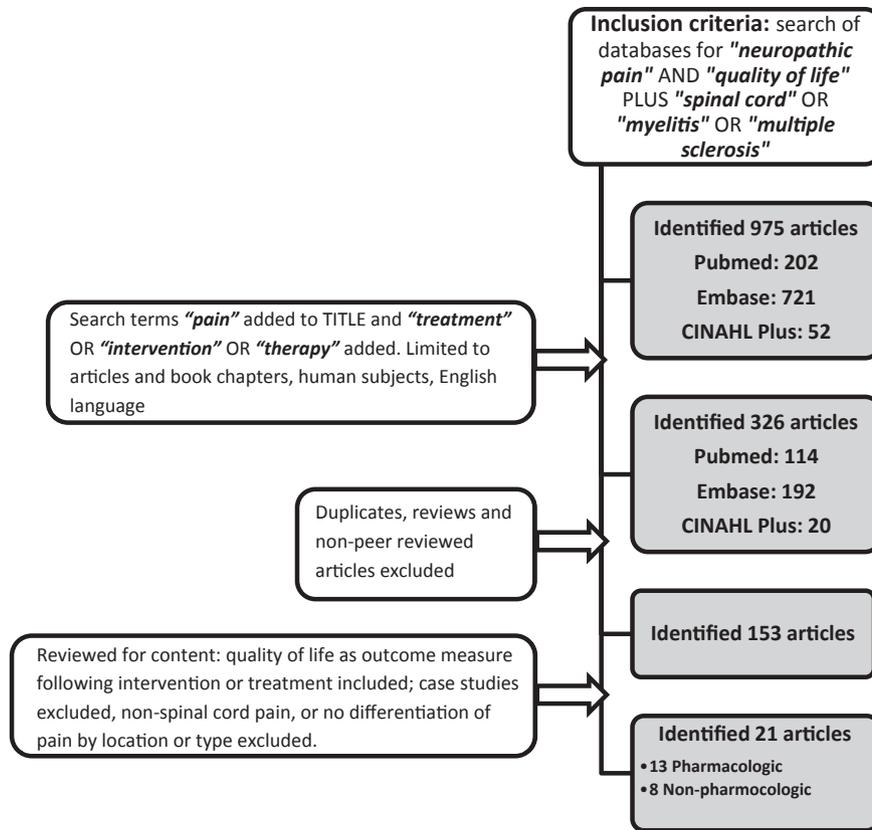


Figure 1. Flowchart depicting study selection procedure.

Potentiation of both serotonin and noradrenaline is required to produce effective analgesia (Lunn, Hughes, & Wiffen, 2014). The smaller of these studies ( $n = 40$ ) examined the effects of duloxetine in SCI-induced pain showed improvements in QoL including in the area of pain, but no improvement in independent pain scales (Vranken et al., 2011). In the larger study ( $n = 239$ ), duloxetine in MS patients with CNP resulted in significant reductions in pain throughout the end of the extension phase, without effecting any change in QoL (Vollmer et al, 2014). These seemingly conflicting results may be because the studies used different survey tools, highlighting the importance of using standardized, validated measures of pain and quality of life.

Cannabinoid agents were investigated in two small RCTs, both in MS (Svendsen et al., 2004; Turcotte et al., 2015). Cannabinoids are ligands that bind on the presynaptic cannabinoid receptor, resulting in reduced calcium influx from voltage-gated calcium channels and hyperpolarization, thus decreasing cellular excitability (Turcotte et al., 2015). Both of the cannabinoid agents used in these studies uncovered a significant impact on pain, with the larger of the two additionally affecting QoL. The smaller, more recent study evaluated the use of nabilone, a synthetic tetrahydrocannabinol, in patients who were already on stable doses of gabapentin (Turcotte et al., 2015). As used this study, multimodal approaches to CNP treatment that target dual mechanisms of CNP treatment may be more effective at improving both pain and QoL.

Two opioids were assessed for treatment of CNP: tramadol and oxycodone. Opioids bind to an opioid receptor, causing inhibition of adenylyl-cyclase, hyperpolarization of neurons, and decreased excitability (Ordóñez Gallego, González Baron, & Espinosa Arranz, 2007). One of the medications, tramadol, has a second mechanism of action similar to SNRIs, as described earlier (Norrbrink &

Lundeberg, 2009). Both studies reported improvement in pain, though a limitation of the oxycodone study (Ordóñez Gallego et al., 2007) was that it was an observational study and oxycodone dosing was not standardized by the study protocol.

Another study examined the effect of botulinum toxin type A (BTX-A) for CNP treatment in patients with SCI ( $n = 40$ ). The mechanism of action proposed in CNP is based on its mechanism in nociceptive pain, which suggests that BTX-A may inhibit neurogenic inflammation and the peripheral sensitization of nerve fibers by inhibiting the release of local neuropeptides, thereby reducing pain. The study reported a significant reduction in pain, though only a marginal trend toward significance on QoL.

Intravenous immunoglobulin (IVIG) contains the pooled polyvalent immunoglobulin G antibodies extracted from the plasma of thousands of blood donors and is generally used to decrease inflammation. The exact mechanism of action has not been well elucidated, but it is theorized that a high load of exogenous antibodies leads to a robust antibody recycling process that turns over both exogenous and endogenous antibodies (Sapir & Shoenfeld, 2005). This therapy was examined in post-polio syndrome ( $n = 142$ ; 75 with CNP): polio causes acute inflammation of the spinal cord, leading to weakness, fatigue, and pain persisting long after the acute infection has resolved (Gonzalez et al., 2006). Ongoing denervation has been suggested to be the most important reason for progressive muscle weakness associated with poliomyelitis infection. Patients with post-polio syndrome have increased expression of messenger RNA for proinflammatory cytokines in cerebrospinal fluid, which may suggest an ongoing inflammatory process in the CNS (Gonzalez et al., 2006). As such, the researchers hypothesized that targeting inflammation with IVIG may improve weakness or stop its progression. Pain was a secondary study

**Table 2**  
Trials Examining the Effect of Pharmacologic Interventions on QoL (Grouped by Mechanism)

Author (year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments <sup>a</sup>
Anti-Epileptics Levendoglu et al. (2004); Turkey	SCI patients with NP; n = 20 (7 female; no race data made available)	RCT with crossover	Gabapentin, titrated up to 3,600 mg/day	Modified Lattinen Test	Significant decrease in intensity and frequency of most descriptors of pain (sharp, hot, unpleasant, deep, and surface) and disability and sleep were significantly better in the GBP treatment group. This was the first RCT to include QoL measures with one of the most commonly used medications for NP treatment; however, another measure of QoL would be helpful to capture a fuller picture of effects on health status.
Breuer et al. (2007); US	MS patients with spinal NP; n = 12 (10 female; 8 white, 8 African descent)	RCT with crossover	Lamotrigine in addition to stable regimen, titrated up to 400 mg	MSQoL-54	Pilot study found no significant difference in pain or QoL. The results did not support the need for a larger trial.
Vranken et al. (2008); Netherlands	Patients with NP; subset was spinal; n = 40 (19 female; 20 in treatment group; no race data made available); 21 patients with spinal cause	RCT	Pregabalin in addition to stable regimen, titrated up to 600 mg/day	EQ-5D; SF-36; PDI	There was a significant decrease in mean pain score for the pregabalin treatment group compared with placebo. No difference in PDI was found between groups, but the treatment group had significant improvement in the EQ-5D utility score and EQ-5D VAS score compared with the placebo group, and SF-36 indicated that treatment led to a significant improvement in the body pain domain only.
Rossi et al. (2009); Italy	MS patients with spinal NP; n = 20 (15 female; 12 in treatment group; no race data made available)	RCT	Levetiracetam, 500 mg/day	MSQoL-54	A significant reduction in pain was reported for the treatment group; no difference was found in reported QoL, except for the item "overall rating of quality of life."
Salinas et al. (2012); Colombia	SCI patients with NP; n = 46 (4 female; 24 in treatment group; no race data made available)	RCT	Carbamazepine, titrated up to 600 mg/day	SF-36	This novel study looked at prevention of NP with early treatment, rather than treatment in those who already experience it. Early intervention did not decrease incidence of NP over time, and there was no difference in QoL between groups, despite appropriate power.
Antidepressants Vranken et al. (2011); Netherlands	SCI and stroke patients with NP; n = 48 (24 in treatment group; Table 1, Demographics, is missing from manuscript)	RCT	Duloxetine in addition to stable regimen, titrated up to 60 mg/day	EQ-5D; SF-36; PDI	The study found no difference in pain intensity with treatment. The treatment group found a significant

(continued on next page)

Table 2 (continued)

Author (year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments <sup>a</sup>
Vollmer et al. (2014); U.S.	MS patients with spinal NP; n = 239 (189 female; 221 white, 15 African descent, 2 Hispanic, 1 Native American; 118 in treatment group); 209 in OLE	Multicenter RCT, with OLE	Duloxetine in addition to stable regimen, titrated up to 60 mg/day in RCT and up to 120 mg/day in OLE	MSQoL-54	improvement for the body pain domain only of the SF-36. No significant differences were identified in other QoL indices. The distribution of spinal versus supraspinal NP was said to be in Table 1 (Demographics), but no such table was included in the manuscript and spinal NP could not be separately assessed. This well-conceived, well-executed, international study found significant pain reduction in the treatment group; QoL was not affected. In OLE, pain reduction was reported in patients in both groups, with greater improvement reported by patients who had received placebo during the acute phase.
Cannabinoids Svendsen et al. (2004); Denmark	MS patients with spinal NP; n = 24 (14 female; no race data made available)	RCT with crossover	Dronabinol, titrated up to 10 mg	SF-36	Pain intensity and reduction significantly improved on treatment; the only improvements to QoL were in body pain and mental health.
Turcotte et al. (2015); Canada	MS patients with NP refractory to GBP; n = 15 (13 female; 8 in treatment group; no race data made available)	RCT	Nabilone, titrated up to 1 mg, in addition to stable GBP dose	VAS <sub>impact</sub>	This small but well-designed study explored the important need for combining medication therapies and found that a combination of GBP with nabilone significantly reduced pain. No change in pain impact was noted; however, the use of a VAS to capture the impact of pain may have been inadequate and a more comprehensive measure of QoL would have been prudent.
Opioids Norrbrink & Lundeberg (2009); Sweden	SCI patients with NP; n = 35 (7 female; 23 in treatment group; no race data made available)	Multicenter RCT	Tramadol in addition to stable regimen, titrated up to 400 mg/day	LiSat-9	Decrease in pain intensity in treatment group compared with those on placebo. Global life satisfaction improved in the placebo group only.
Barrera-Chacon et al. (2011); Spain	SCI patients with NP refractory to AED treatment; n = 54 (10 female; no race data made available)	Multicenter, observational descriptive	Oxycodone, usually in conjunction with AED use	Modified EQ-5D	Significant decrease in pain intensity, improved health-related QoL, and diminished impact of pain on physical activity and sleep were reported. Because doses of oxycodone were not investigated, further

Table 2 (continued)

Author (year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments <sup>a</sup>
Other					research in controlled trials assessing appropriate dosing for NP treatment is warranted.
Han et al. (2016); Korea	SCI patients with NP; n = 40 (14 female; 20 in treatment group; no race data made available)	Multicenter RCT	BTX-A, 200 U subcutaneous injection, in addition to stable regimen	WHOQOL-BREF	The BTX-A group had significant reductions in pain score at 4 and 8 weeks after injection compared with placebo. A trend toward significant impact in the physical health domain of QoL only was found.
Gonzalez et al. (2006); Sweden	Post-polio syndrome patients; subset had NP; n = 142; 75 patients with NP (33 of whom are in treatment group; 92 females in total group, not differentiated by pain status; no race data made available)	RCT	IVIG, 90 g over 3 days with second equal dose at 3 months	SF-36	Pain assessment was a secondary endpoint of this study that primarily assessed strength, and not all patients included had NP. In the subcohort of patients with significant pain, those receiving IVIG had a greater pain reduction. QoL did not differ between groups.

AED = antiepileptic drug; BTX-A = botulinum toxin type A; EQ-5D = EuroQoL 5 Dimensions instrument; GBP = gabapentin; IVIG = Intravenous immunoglobulin; LiSat-9 = Life Satisfaction Questionnaire 9; MS = multiple sclerosis; MSQoL = Multiple Sclerosis Quality of Life instrument; NP = neuropathic pain; OLE = open-label extension; PDI = Pain Disability Index; QoL = quality of life; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Survey; VAS = Visual Analog Scale; SCI = spinal cord injury; WHOQOL-BREF = World Health Organization Quality of Life—Abbreviated.

<sup>a</sup> Values were considered significant at  $p \leq .05$ , unless otherwise noted.

outcome, but notably it was reduced in this patient population. QoL was not significantly affected.

#### Effect of Nonpharmacologic Interventions on QoL

Eight studies were identified that examined the effect of a nonpharmacologic intervention for CNP on QoL. Nonpharmacologic interventions included the use of physical therapy and exercise, transcutaneous electrical nerve stimulation (TENS), cognitive behavioral therapy (CBT), and complementary and alternative medicine (CAM) approaches (Table 3).

In rats, regular moderate aerobic exercise reversed signs of CNP and increased endogenous opioid content in brainstem regions important in pain modulation (Stagg et al., 2011). This approach was translated to a small human study in SCI that found significant improvements in both QoL and pain, suggesting that a larger study with physical therapy and exercise is warranted (Norrbrink, Lindberg, Wahman, & Bjerkefors, 2012). TENS uses electric current to stimulate denervated nerves through electrodes placed on the skin (Norrbrink, 2009). Effectiveness has been found for use in peripheral neuropathy, but results in the treatment of central NP have been equivocal. Sites in the spinal cord and brainstem that use opioid, serotonin, and muscarinic receptors have been found to be activated by peripheral nerve stimulation by TENS, but lack of standards on ideal frequency and stimulation amplitude needed to achieve pain reduction has hampered the use of TENS in clinical trials of CNP (Norrbrink, 2009; Sluka, Bjordal, Marchand, & Rakel, 2013).

Psychological factors are believed to influence the maintenance and aggravation of CNP, suggesting that psychological interventions with traditional biomedical interventions may reduce the burden of CNP (Heutink et al., 2014). Four studies evaluated the effectiveness

of CBT for CNP treatment, all in patients with SCI (Heutink et al., 2012, 2014; Nicholson Perry, Nicholas, Middleton, & Siddall, 2009; Norrbrink Budh, Kowalski, & Lundberg, 2006). CBT focuses on modifying an individual's beliefs, expectations, and coping abilities (Norrbrink Budh et al., 2006). One study reported reduced pain without improving QoL, two studies reported improved QoL only, and one found no impact on pain or QoL. CBT is aimed at modifying a patient's response to pain rather than directed at the pain itself, explaining the finding that treatments in three of the studies did not affect pain significantly. Interestingly, all four studies reported some impact on anxiety and/or depression, adding strength to the argument that this intervention improves pain responses rather than the physical experience of pain itself.

CAM refers to treatments that are outside of conventional medicine, which for the most part have not been rigorously tested and often evolve from traditional Asian medicine. The American public's use of CAM therapeutic modalities has grown exponentially in recent years, including for CNP (Namjooyan et al., 2014). This may be a product of the fact that CNP is often not affected in a clinically meaningful way, leading patients to look for other options. Common examples of these are acupuncture and massage therapy. Acupuncture is the stimulation of specific points through which the life-energy flows along the skin of the body using thin needles, in an attempt to achieve balance. Healing Touch (HT) similarly aims to achieve balance in life-energy through touch. Progressive muscle relaxation is a technique focused on controlling the state of muscular tension and involves learning to monitor tension in each specific muscle group in the body by deliberately inducing and releasing tension in each group. The study examining HT versus progressive muscle relaxation was the only mixed methods study reviewed; no significant impact was found on pain and QoL differences favoring HT were captured in the qualitative

**Table 3**  
Trials Examining the Effect of Nonpharmacologic Interventions on QoL (Grouped by Mechanism)

Author (year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments <sup>a</sup>
<b>Physical Medicine and Rehabilitation Medicine</b>					
Norrbrink (2009); Sweden	SCI patients with NP; n = 24 (4 female; no race data made available)	RCT with crossover	High- vs. low- frequency TENS	LiSat-9	In this study with high attrition and difficulty with enrollment, pain intensity was unchanged compared with baseline values on a group level and no differences were found between the two modes of stimulation; no effect on secondary measures, including life satisfaction, was noted.
Norrbrink et al. (2012); Sweden	SCI patients with musculoskeletal pain and/or NP; n = 8; 7 patients with NP pain (1 of whom was female; no race data made available)	Observational descriptive	10-week exercise program	SCI QoL data set	Descriptive statistics were used alone because inferences could not be made in this small cohort. For those with neuropathic pain, median pain intensity ratings decreased from 5 on a 0-10 numerical rating scale at baseline to 3 at the end of study. All median ratings of QoL had improvement. Results in this exploratory study were promising and need to be further explored in a larger controlled study.
<b>Cognitive Behavioral Therapy Programs</b>					
Norrbrink Budh et al. (2006); Sweden	SCI patients with NP; n = 38 (24 female; 27 in treatment group; no race data made available)	Quasi-experimental	CBT	NHP	In this nonrandomized study, no difference from baseline in pain or QoL was found in treatment group or between groups. Improvement in sleep quality and mood were detected in the treatment group but did not affect the composite score.
Nicholson-Perry et al. (2009); Australia	SCI in patients with NP; n = 36 (8 female; 19 in treatment group; no race data made available)	Quasi-experimental	CBT	Modified SF-36 with physical and mental domains	No changes in pain intensity between or within groups over time were identified, though there was significant improvement in pain catastrophizing for the treatment group. QoL improved for mental but not physical status.
Heutink et al. (2012); Netherlands	SCI patients with NP; n = 61 (22 female; 31 in treatment group; no race data made available)	Multicenter unblinded RCT	CBT	LiSat-9	In the first RCT of CBT, a short-term decrease in pain was detected, but this was not sustained at 3-month follow-up. No change in life satisfaction was identified, but anxiety and depression decreased in the intervention group.
Heutink et al. (2014); Netherlands	SCI patients with NP; n = 29 (9 female; no race data made available)	Multicenter extension study of Heutink et al. (2012) (treatment group only)	CBT	LiSat-9	Pain intensity was significantly decreased at 12-month follow-up; no changes in life satisfaction or depression over time

Table 3 (continued)

Author (year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments <sup>a</sup>
Complementary and Alternative Medicine					
Wardell et al. (2006); U.S.	SCI patients with NP; n = 12 (0 female; 4 white, 3 African descent, 1 Hispanic, 1 other; 7 in HT group)	Quasi-experimental; convergent mixed methods	Healing Touch (energy-based program) vs. guided progressive relaxation	SWLS; unstructured focus groups & interviews, written responses	were identified, though a significant decrease in anxiety was noted. This small pilot study of male veterans did not reveal significant changes in pain or life satisfaction. However, the HT group had variable responses and the qualitative component indicated that a subset of patients experienced benefit, suggesting that although this pilot study was not powered appropriately to find differences, a larger study may.
Norrbrink & Lundeborg (2011); Sweden	SCI patients with NP; n = 30 (6 female; 15 in treatment group; no race data made available)	Quasi-experimental; sequential controlled-trial	Acupuncture vs. massage therapy	LiSat-9	This small exploratory study found a significant difference between the two groups at end of treatment in favor of acupuncture but no within-group differences in pain at follow-up. No impact on life satisfaction was reported.

CBT = Cognitive Behavioral Therapy; HT = Healing Touch; LiSat-9 = Life Satisfaction Questionnaire 9; NHP = Nottingham Health Profile extension; NP = neuropathic pain; QoL = quality of life; RCT = Randomized Controlled Trial; SCI QoL = Spinal Cord Injury Quality of Life instrument; SCI = spinal cord injury; TENS = transcutaneous electrical nerve stimulation; SWLS = Satisfaction with Life Scale.

<sup>a</sup> Values were considered significant at  $p \leq .05$ , unless otherwise noted.

component alone (Wardell, Rintala, Duan, & Tan, 2006). In the study investigating the effects of acupuncture versus massage therapy, no differences in amount of pain were found but the data suggest that acupuncture may have prevented worsening of pain compared with therapeutic massage (Norrbrink & Lundeborg, 2011).

The concept of integrative medicine combines evidence-based treatments with alternative and nonpharmacologic options, in an attempt to approach treatment in a more holistic manner, and may be a promising next step in this arena. There are no trials or studies that systematically used a combination of pharmacologic and nonpharmacologic treatments for central spinal CNP using QoL as an outcome measure.

## Discussion

This is a comprehensive literature review examining the state of the science in spinal CNP treatment using QoL as a primary or secondary measure. Hundreds of articles were found that examined the impact of a given intervention on CNP or the impact of CNP on QoL, but only these 21 could be identified that included an examination of the impact of a pain intervention on QoL. However, affecting pain alone may not be clinically meaningful to a patient if QoL is not also enhanced. Given that pain affects QoL (Kanamori et al., 2011; Newland, Naismith, & Ullione, 2009), it seems reasonable that an objective of pain treatment should be aimed at improving QoL in patients as well. It is striking that so few studies have applied QoL measures as an outcome. To meet patient-

centered goals of improving QoL, future studies should include measures of both pain and QoL.

Also notable is the seeming mismatch between reported effects on pain levels and QoL, such that improvement in pain did not necessarily translate to improvement in QoL: of the 21 studies examined, 6 were found to positively affect both pain and QoL, 4 failed to affect either, 7 affected pain only, and 4 affected QoL only. There are several possible explanations for why half of the studies had a mismatch between effects on pain and effects on QoL. First, many of the studies were relatively small, with a median sample size of 29.5 (range 8–239). Thus some studies may have been adequately powered to address the primary outcome but not sufficiently powered to identify significant differences in secondary outcomes, including QoL. Second, a wide array of both pain measures and QoL measures were used, and although most have been validated in some populations, not all have been validated specifically in the populations that were investigated; see reviews of instruments for SCI, MS, and NP (Breivik et al., 2008; Kuspinar & Mayo, 2014; Stadhouder, Buckens, Holtslag, & Oner, 2010). Using validated measurement tools or combining tools may draw out significant findings.

Another possible explanation for the mismatch between treatment of NP and its effect on QoL could be explained by recent research on symptom clusters. Symptom clusters consist of two or more related symptoms that co-occur and that may or may not share a common cause (Kim, Abraham, & Malone, 2013). In chronic disorders, patients often present with multiple interrelated symptoms, which may explain why treating one symptom does not necessarily affect quality of life. Although much of the research in

symptom clusters has focused on cancer, the concept is applicable to a wide array of chronic conditions, including NMOSD, MS, and SCI. The implication for NMOSD is that treating CNP in isolation may not affect QoL in a disease that causes other debilitating symptoms, including anxiety, depression, fatigue, sleep dysfunction, and bladder dysfunction (Hollinger et al., 2016; Mealy, Boscoe, Caro, & Levy, 2018a; Mutch et al., 2015; Pan et al., 2015; Shi et al., 2016).

There was relative balance in the number of female to male participants represented overall (54%). SCI patients made up 39% of the total number of participants among trials, which has a high male-to-female ratio of 2.6-7:1 internationally (Singh, Tetreault, Kalsi-Ryan, Nouri, & Fehlings, 2014). Counterbalancing this were the MS patients (42% of the total sample), where the female-to-male ratio is 2-3:1 (Koch-Henriksen & Sørensen, 2010). Only three studies reported on race and ethnicity, and all of these were from the United States and all predominantly white. Although many of the countries represented are fairly homogenous groups, demographic characteristics continue to change worldwide and it is problematic to fail to report on social determinants of health and inequities between groups, especially among groups in whom health inequities are known to be present and where perceptions of pain differ (Bernardes, Keogh, & Lima, 2008; Rahim-Williams, Riley, Williams, & Fillingim, 2012). Some research suggests that biopsychosocial mechanisms may underlie these differences (Paller, Campbell, Edwards, & Dobs, 2009). Of interest would be a comparison of responses to nonpharmacologic interventions and particularly to CBT, which is guided by the biopsychosocial model (Heutink et al., 2012, 2014; Nicholson Perry et al., 2009).

## Conclusions

NMOSD causes damage to CNS pathways in the spinal cord as occurs in MS and SCI, suggesting that it is reasonable to extrapolate data from MS and SCI to guide therapy in NMOSD while also recognizing that different outcomes may result in part because of disparities in sex and race in NMOSD. CNP is difficult to treat and is pervasive in NMOSD. Treatments are ineffective, and individual pain interventions are not sufficient to affect QoL. These factors only further underscore the need for broadening treatment options and using a multimodal approach in this population. It is important to focus attention on what symptoms form clusters and on comprehensive treatment regimens that address these clusters. A practical and potentially clinically meaningful trial for future research may examine a combination of an AED, an antidepressant, CBT, and an exercise program. This may highlight how the cluster of symptoms is affected differently between the two groups, with emphasis on how this translates to improved quality of life.

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