

# Sigma Antagonists for Treatment of Neuropathic Pain Syndromes in Cancer Patients: A Narrative Review

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**Abstract:** Almost 40% of cancer patients have neuropathic pain or mixed pain with a neuropathic component, which can be intense, debilitating, and challenging to treat. New studies on sigma receptors show these enigmatic ligand-binding protein chaperones may be helpful drug targets for new pharmacologic options to reduce many types of neuropathies, including chemotherapy-induced peripheral neuropathy (CIPN) and other cancer-related neuropathic pain syndromes. Our objective was to review the literature, including preclinical findings, in support of sigma-1 receptor (S1R) antagonists in reducing neuropathic pain and sigma-2 receptor (S2R) agonists for neuroprotection. The mechanisms behind these effects are not yet fully elucidated. The role of S1R antagonists in treating CIPN appears promising. In some cases, combination therapy of an opioid—which is a true analgesic—with a S1R antagonist, which is an anti-hyperalgesic and anti-allodynic agent, has been proposed. Of interest, but not well studied is whether or not S1R antagonists might be effective in treating CIPN in patients with pre-existing peripheral diabetic neuropathy. While neuropathic syndromes may occur with hematologic cancers, the role of S1R agonists may be effective. Sigma receptors are being actively studied now for a variety of conditions ranging from Alzheimer's disease to Parkinson's disease as well as neuropathic pain.

**Keywords:** Cancer-related neuropathic pain, chemotherapy-induced peripheral neuropathy, sigma 1 receptor, sigma 2 receptor, sigma receptor.

## INTRODUCTION

About 39% of all cancer patients have pure or mixed forms of neuropathic pain, which may be the result of the cancer itself and/or cancer treatments such as chemotherapy, radiation, or surgery [1, 2]. Neuropathic cancer pain includes plexopathy, radiculopathy, peripheral neuropathy, paraneoplastic sensory neuropathy, leptomeningeal metastasis, cranial neuralgia, and malignant painful radiculopathy together with chemotherapy-induced peripheral neuropathy (CIPN), chronic postsurgical pain, and post-radiation pain syndrome [1]. There are no effective strategies to prevent neuropathic pain from developing in cancer patients, and current clinical treatments focus on symptomatic relief of pain. Despite a large armamentarium of analgesic options, finding effective analgesic relief of neuropathic pain remains challenging [1].

The sigma-1 receptors (S1R) are protein chaperones that bind to many and diverse drugs, including psychotropic drugs [3]. They are localized around the endoplasmic reticulum of neurons and oligodendrocytes [4]. While their exact function remains enigmatic, they appear to be involved in many complex processes within the central nervous system, including higher-order brain activity [5]. Although S1Rs are protein chaperones, they respond to agonists and antagonists in the manner of traditional receptors [6].

The role of certain S1R agonist combinations may be an important treatment options for neuropathic pain in cancer patients. During tissue injury or as a result of cancer progression, S1Rs become activated with G-protein and ion channels their main clients [7]. Their emerging role as promising and novel drug targets has led to the term “neuropsychopharmacology” [4, 5]. It is known that they modulate ion channels; in addition, they may participate in membrane remodeling and cellular differentiation of the nervous system [5].

The objective of this narrative review is to present the current status of research on the role of agonists for S1Rs to help manage neuropathic pain in cancer patients. This is a very new field, there are few studies, and there are remain gaps in our understanding of the full range of sigma receptor activities.

## METHODS

The database of PubMed was searched in October 2022 for “sigma agonist combinations cancer neuropathic pain” (2 results), “sigma agonist combinations cancer” (21 results), “sigma agonist combinations neuropathy” (3 results), and “sigma agonist combinations” (159 results) with some overlap. The references in articles were also searched. Google Scholar was also searched.

## RESULTS

### What is Known

S1Rs interact with protein targets, such as G-protein coupled receptors and many ion channels,

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including the *N*-methyl-D-aspartate receptor (NMDAR) [8]. S1R antagonists can reduce the chaperone activity of the S1R and, in that way, increase opioid-induced signaling activity, while at the same time decreasing the responses of the NMDAR. This two-pronged effect is thought to boost opioid-related antinociception while at the same time decreasing hypersensitivity to sensory signals [8]. When S1R antagonism occurs, opioid analgesia is enhanced but opioid-associated side effects are not increased [8]. However, this activity neither confirms nor refutes the concept that S1Rs themselves may have a direct effect on pain.

Preclinical studies have shown that S1R antagonists reduce pain, and certain S1R antagonists are currently in clinical trials [8]. The S1R agonist, afobazole, has been approved in Russia as an anxiolytic but has not been evaluated by the Food and Drug Administration (FDA) [9]. To date, no S1R antagonists or agonists have been cleared to market in the United States.

In terms of neuropathic pain control, S1R antagonists should not be considered analgesics, but rather anti-allodynia and antihyperalgesics [10]. In a study of mice fed a high-fat diet to induce obesity-associated peripheral neuropathy, wild-type mice developed allodynia and thermal hypoalgesia at 24 weeks and multiple intrathecal administrations of BD1047, an S1R antagonist candidate drug, reduced peripheral neuropathy [11]. This suggests that S1R activity related to NMDAR expression may attenuate peripheral neuropathy [11]. While S1Rs are expressed in central sites, such as the spine and brain, their peripheral presence should not be overlooked. S1Rs are extensively expressed in the dorsal root ganglion (DRG) and along the nerves in the peripheral nervous system [12]. Thus, they play a role in both central and peripheral neural processes.

The S1R is a non-adenosine-triphosphate (non-ATP) binding membrane of a chaperone protein, mainly but not exclusively located in mitochondrial-associated endoplasmic reticulum membranes (MAM). In its resting state, its main function is to maintain proper conformation of the inositol triphosphate receptor type 3 (IP3R3), which allows for proper calcium ion signaling from the endoplasmic reticulum into the mitochondria. This mitochondrial communication is required for the production of ATP and to modulate the sensors in the inositol-requiring enzyme 1 in the endoplasmic reticulum [13]. In addition, the S1R also helps to attenuate the production of reactive oxygen species

[13]. When required, S1Rs can translocate within the membrane, allowing for interaction with other ion channels, receptors, and kinases, and to the nucleus, where it may be involved in gene transcription [14]. The modulating capacities of the S1R are pleiotropic, making it an intriguing new drug target [14].

Moreover, S1R agonists are known to confer neuroprotection in preclinical studies and it has been suggested this might be attributed to mitogen-activated protein kinases [15, 16]. S1R agonists were also shown to play a role in differentiating cutaneous mesenchymal stem cells into myelinating Schwann cells [17]. Thus, both S1R agonists and antagonists may play important roles in neuropathic pain syndromes.

### Neuropathic Pain and Sigma Receptors

Neuropathic pain has a prevalence of around 7% to 10% in the general population and its treatment has for years been deemed an urgent, unmet medical need [18]. The etiology of neuropathic pain involves aberrations in the signaling activity of the excitatory and inhibitory systems in ion channels rather than exogenous noxious stimuli [18]. Neuropathic pain can be intense, has been shown to be more distressing to patients than nociceptive pain, and is associated with worse quality of life than nociceptive painful conditions [19]. In neuropathic painful conditions, the molecular and electrophysiologic changes in the periphery travel to the central nervous system and result in a gain of function, such that the brain enters a hyperexcitable state at the same time its ability to inhibit this excitability is limited. Over a prolonged period of time, these neuronal changes may become chronic [18].

Following nerve injury, neuropathic pain traces back to the DRG, where the neuronal system interacts with the immune system [20]. S1Rs are expressed in the DRG, and S1R blockade appears to reduce neuropathic pain and modulate central sensitization [20]. In intact peripheral sensory neurons, the nuclei are centralized, but axotomized neurons have eccentric nuclei together with increased expression of ATF+3 [21, 22]. These injured neurons with eccentric nuclei secrete C-C motif chemokine ligand 2 (CCL2), stimulating peripheral macrophagy and launching an inflammatory response that can sensitize nearby intact neurons [23]. In this connection, it is important to note that S1R expression is higher in the DRG than in the dorsal spinal cord [24]. Thus, S1Rs may play a role in the development of peripheral neuropathy that is greater than previously suspected.

The translocation of S1Rs was observed clearly in a murine study. At baseline, S1R was observed in all DRG neurons evaluated. Following spared sciatic nerve injury, the S1R receptors had translocated to the soma near the nucleus [20]. This was most visible in injured ATF+3 neurons [20]. ATF+3 expression has been associated with deranged signaling pathways and can be used as a marker of DRG neuronal damage [25]. In wild-type mice, the injured DRG secreted chemokine CCL2, resulting in an influx of macrophages and monocytes to the sensory neurons [20]. At that point, the S1Rs translocated and the pro-inflammatory cytokine, interleukin-6 (IL-6), was produced. In S1R-knockout mice, there was less production of CCL2, less infiltration of macrophages and monocytes, and lower levels of IL-6 [20]. Again, this further supports the role of S1R in peripheral neuropathic syndromes.

Ligands of the S1R appear to regulate painful symptoms and pain behaviors in animal models [26]. S1R-knockout mice exhibit different phenotypic responses to the inflammatory cascade and the use of S1R antagonists in these mice reduced mechanical and thermal hypersensitivity in inflammatory injury, making them of interest for neuropathy and other neurological conditions [27].

### **Neuropathic Pain and Cancer**

About 20% of all cancer pain may be considered purely neuropathic [28] and neuropathic painful symptoms are prevalent among cancer patients, particularly if they have or have undergone certain chemotherapeutic regimens [18]. Neuropathic pain in cancer patients has been associated with worse outcomes [19, 29]. In a multicenter, observational study of 1,051 terminal cancer patients, 11% (n=113) reported painful neuropathic symptoms [19]. This group with self-reported neuropathic pain was more likely to be undergoing anticancer therapy and be taking strong opioids than the other cancer patients; neuropathic pain patients also had lower performance status and reported worse physical, cognitive, and social function than the terminal cancer patients without neuropathic pain [19].

Neuropathic pain in cancer patients has multiple causes. Malignant tumors, leukemia, and lymphoma have been known to metastasize to the peripheral nervous system [30]. Neoplasms may also metastasize into the brachial plexus or the lumbosacral plexus [31]. Involvement of the peripheral nerves is rare but may occur [30]. Neoplastic nerve lesions are likewise rare but can occur and result in peripheral pain [31]. But one

of the main causes of painful peripheral neuropathy in cancer patients remains chemotherapy.

### **Chemotherapy-Induced Peripheral Neuropathy**

Chemotherapy-induced peripheral neuropathy (CIPN) has a prevalence ranging from 19% to 85% of chemotherapy patients, depending on the antineoplastic agent used [32]. CIPN has been most associated with platinum-based agents (cisplatin, for example), taxanes (paclitaxel), vinca alkaloids (vincristine), and bortezomib, a proteasome inhibitor [33]. There is a wide range of variability among patients in terms of symptom severity [33]. Defined as a sensory neuropathy with motor and autonomic changes, it remains both one of the most common side effects of cancer treatments and one of the most challenging to treat [34].

Chemotherapeutic agents are neurotoxic, but non-neuronal cells, such as Schwann cells, may also play a role in CIPN [33]. The mechanisms underlying CIPN are plural: nuclear damage, damage to the mitochondrial DNA, and adverse effects on microtubules [33]. Antineoplastic agents damage nerve structures and can cause large- or small-fiber neuropathy, sensor and/or motor nerve demyelination, and axonal damage [34]. CIPN affects the longest axons and the most distal nerves first [35]. The dose-dependent toxicity of chemotherapeutic agents can be treatment limiting, but recent research suggests there may also be genetic factors, with biomarkers indicating higher-risk patients [35].

In a study of rats, CIPN was associated with a significant reduction in S1R expression in the spine [26]. In this study, SA4503, an S1R agonist, inhibited oxaliplatin- and paclitaxel-associated neuropathy, but the S1R antagonist NE-100 did not [26].

A theory has been put forth that certain transient receptor potential (TRP) channels acting as nociceptors in primary sensory neurons are crucial to the development of CIPN. Among those TRPs is ankyrin 1 (TRPA1). TRPA1, a nonselective cation-permeable channel present in nociceptors, has been associated with cold pain and cold-pain-associated neuropathy [36]. S1R antagonism by the drug S1RA has been shown to reduce CIPN in a phase 2 clinical trial, but the mechanisms behind this remain unclear [37]. However, antagonism of the S1R impaired the receptors' ability to traffic TRPA1 to the plasma membrane. In a mouse model of oxaliplatin chemotherapy, the administration of S1RA reduced

inward current and lowered the firing of action potentials in response to TRPA1 agonists and prevented the development of painful neuropathy [37].

In a murine study, the administration of BD-1063 or S1RA about half an hour before administration of paclitaxel prevented cold allodynia and mechanical allodynia in wild-type mice [38]. Another preclinical study found that paclitaxel treatment did not result in allodynia in S1R-knockout mice, suggesting that S1R activity is necessary for the development of painful neuropathic syndromes [39]. Treating these paclitaxel-dosed mice with BD-1063 prevented neuropathic pain [39].

Neuroprotection is an important component in preventing chemotherapy-induced peripheral neuropathy. The S1R antagonist MR309 (formerly known as E-52862) is a selective S1R antagonist and has been shown to reduce neuropathic pain in animal models [13].

The majority of colorectal patients treated with oxaliplatin as part of a chemotherapeutic regimen typically experience an acute phase of cold hypersensitivity, which usually resolves on its own in a matter of days [40]. This is followed by a chronic sensory peripheral neuropathy that is cumulative and may persist long after chemotherapy has ceased [40]. In a study of 124 chemotherapy-naïve colorectal cancer patients who received oxaliplatin chemotherapy, patients were randomized to receive by mouth 400 mg a day of MR309, an S1R antagonist, or placebo for the first five days of each chemotherapy cycle, up to 12 cycles total. Fewer MR309 patients than controls developed severe chronic peripheral neuropathy and the MR309 patients were able to tolerate higher doses of chemotherapy [41]. A limitation of this study was that disease progression compelled a large number of patients to drop out before the study concluded.

In a randomized, double-blind, phase 2 study of 124 cancer patients treated with oxaliplatin chemotherapeutic regimens, patients were randomized to be treated with placebo or an S1R antagonist (MR309) [42]. The S1R antagonist decreased significantly both cold pain threshold and suprathreshold stimulus-evoked pain intensity. Severe chronic neuropathy rates were significantly lower in the MR309 patients than the controls and MR309 patients were able to receive significantly larger amounts of oxaliplatin than controls. Study withdrawal due to disease progression occurred more often in the MR309 than placebo groups (7.4% vs. 25.0%,  $p=0.054$ ) [42].

More MR309 patients experienced at least one adverse event related to the study drug (24.8% vs. 11.9%,  $p=0.051$ ) [42].

Most studies of S1R antagonists and agonists related to CIPN are preclinical and the early human studies offer glimpses of the potential of the S1R antagonist's role. Further study is warranted, particularly as CIPN is one of the main forms of neuropathic pain in cancer patients.

### **Paraneoplastic or Neoplastic Neuropathy**

Subacute sensory neuronopathy is the most common type of peripheral paraneoplastic neurological syndrome [43]. Other syndromes include sensory polyneuropathy, sensorimotor polyneuropathy, demyelinating neuropathy, autonomic neuropathy, focal nerve lesions, and plexus nerve lesions [43]. Paraneoplastic neuropathy is associated with onconeural or intracellular antibodies or neuronal surface antibodies [43]. In late-stage cancer, patients may experience sensory-motor neuropathy, a relatively mild condition distinct from CIPN [43]. There are multiple mechanisms underlying these various paraneoplastic neuropathies, including the autoimmune hypothesis that maintains that the body's immune response to cancer mounts a defense using antibodies against neural antigens [43]. Treatment for these various types of neuropathies involves addressing symptoms [43]. It is not clear if there is a role for S1R antagonists for these forms of cancer-related neuropathies.

### **Neuropathy with Hematological Cancer**

Neuropathy may occur with various hematological cancers. These rare conditions include the POEMS syndrome, anti-myelin-associated glycoprotein (anti-MAG) peripheral neuropathy, and amyloid light chain or primary amyloidosis, which presents in a way that resembles paraneoplastic neuropathy [43]. Multiple mechanisms underlie these various conditions including axonal neuropathy, demyelinating neuropathy, hyper-viscosity, and amyloid deposits [43].

Of interest in this context is that novel small molecule inhibitors of pro-survival proteins involved with the B-cell lymphoma family (Bcl-2) have produced promising results in hematologic cancers [44]. Their mechanism of action is to cause apoptosis by binding to the pro-survival proteins and mimicking the pro-death Bcl-2 homology 3 (BH3) proteins [44]. These

agents are sometimes called BH3 mimetics [44]. These agents resemble sigma receptor ligands, and Bcl-2 protein families are located in the endoplasmic reticulum in proximity with the sigma receptors. It has been suggested that S1R agonists act in a neuroprotective fashion and promote cell survival because they increase Bcl-2 [44, 45]. S2R agonists increase the pro-apoptotic actions of Bcl-2s, which results in cytotoxicity [44]. This work suggests a close interrelationship between BH3 proteins and sigma receptors [44].

Treatment of these neuropathies is mainly supportive, based on pharmacologic pain control. Gabapentinoids, antidepressants, and opioids may be used [46]. The role of S1R agonists or antagonists in pain control with neuropathies associated with hematological cancers is not known.

### **Diabetes and the Risk of Peripheral Neuropathy in Cancer Patients**

While pre-existing type 2 diabetes mellitus (T2DM) may increase a cancer patient's risk of developing CIPN, metabolic or endocrine neuropathies are not usually the cause of peripheral neuropathy in cancer patients, [33] although it is true that high serum glucose levels may adversely affect peripheral nerves [47]. Since peripheral neuropathy is prevalent among people with T2DM, they are often excluded from CIPN clinical trials, which explains the paucity of information about CIPN in the T2DM population.

Thus, the interrelationships between T2DM, cancer, and peripheral neuropathy are not well known. A systematic analysis of 259 articles (n=768 cancer patients with T2DM versus 5,247 controls without T2DM) undergoing chemotherapy found that more severe neuropathic signs and symptoms occurred in T2DM patients compared to controls and those symptoms lasted longer, even up to two years after chemotherapy [48]. While there have been no studies of the use of an S1R antagonist in T2DM patients with cancer, a study in mice indicated that S1Rs together with NMDA receptors, were involved in obesity-related peripheral neuropathy. Animals were fed a high-fat diet and at 24 weeks, intrathecal S1R antagonists reduced thermal hypoalgesia and tactile allodynia [11]. Since people with T2DM are at elevated risk for cancer, [49] this is an important avenue for future research. It is intriguing that T2DM and cancer have certain biological commonalities which remain incompletely understood. Many anti-hyperglycemic medications have been linked with increased or also decreased risk of cancer [49].

### **Combination Therapy**

Multimechanistic analgesia targeting pain sources through different agents with distinct mechanisms of action has become recognized as an important pain control strategy in different medical disciplines [50]. S1R antagonists may be a particularly good adjuvant agent to opioids for cancer pain [51]. Pain signals in the body travel through tissue which has dense expression of S1Rs and S2Rs, which appear to modulate pain signaling across these tissues by affecting the various proteins involved in the neurotransmission [52]. Among those signaling participants are  $\mu$ -opioid receptors (MORs), NMDARs, and cannabinoid 1 receptors (CB1R). S1R antagonism results in anti-hyperalgesia and can reduce the intensity of neuropathic, inflammatory, and chemically induced pain syndromes [52].

A balance of S1R antagonism and MOR agonism has been proposed to offer improved pain control [52]. While MOR agonists affect sensory thresholds, S1R antagonists do not. However, S1R antagonists appear to be able to reduce "sensory gain" that can occur in certain pathological states such as cancer. Such "sensory gains" include allodynia and hypoalgesia [52]. Thus, the combination of MOR agonists to lower sensory thresholds with S1R antagonists to reduce sensory gains warrants investigation. Of course, opioid receptors can be activated by endogenous opioids, such as enkephalins, dynorphins, endorphins, and nociceptin [52]. Potentially beneficial interactions between the MOR and S1R systems had been observed as early as 1993 [53]. Bifunctional MOR/S1R ligands have been proposed with the dual goals of augmenting analgesic effect while reducing potential adverse effects, but have not yet been investigated in clinical studies [52].

S1R antagonism has been associated in animal studies with decreased pain signaling resulting in lower pain intensity. When S1R antagonists are combined with opioid pain relievers, there is a synergistic effect on analgesia but not on side effects [10]. This may be explained partly by the fact that an S1R antagonist is actually an anti-allodynic and anti-hyperalgesic agent rather than a true analgesic, although they do have a modulating effect on chronic neuropathic pain [10]. Thus, S1R antagonists enhance opioid analgesia without increasing their associated adverse effects [54].

S1R antagonists are not analgesics but modulate opioid analgesic effects. Conversely, S1R agonists decrease opioid analgesia [55]. In a murine study, it

was found that S1R antagonists did not potentiate morphine analgesia in knockout mice, although it had that effect in wild-type mice [56]. The combination did not increase opioid tolerance or physical dependence [56].

### Sigma-2 Receptors

Far less is known about sigma-2 receptors (S2R) than S1Rs. S2Rs are known to regulate intracellular calcium levels and to modulate cholesterol homeostasis, [57] but their role in nociception, if any, remains unclear [58].

### DISCUSSION

The S1Rs and S2Rs are important and enigmatic receptors under active investigation. Our study examined the role of such agents—many of which are currently in development—in reducing neuropathic pain associated with cancer. However, S1R and S2R agonists and antagonists may play a role as anticancer drugs as well. It is known that S2Rs are overexpressed in cancer cells [59].

Sigma receptors are a subject for new and intensive investigation but the range of applications for sigma-related pharmacotherapy is so vast and diverse, it is often challenging to explore very specific applications. For instance, S1R agonists are neuroprotective and are being studied in amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease [60]. Their role in neurophysiology is expanding the horizons of possibility for a range of diverse conditions that are currently considered challenging to treat effectively [60].

Neurological conditions are impacted by neuronal plasticity allowing symptoms to sometimes outlast their causes. For instance, in a meta-analysis of 4,179 cancer patients, CIPN prevalence was 68% in the first month after chemotherapy had concluded but remained at 30% at six months or more after cessation of chemotherapy [61]. While distinct from cancer-related neuropathies, protracted neurological symptoms can occur in any number of conditions, including benzodiazepine withdrawal and long COVID, and may resist treatment [62, 63]. Thus, effective treatments for cancer-related neuropathies have been limited and sigma receptors hold great promise.

### CONCLUSIONS

Neuropathic pain is prevalent among cancer patients and may be related to the cancer or anticancer

treatments. Such neuropathic pain in cancer patients is associated with poor outcomes, pain that can be severe, and worse quality of life, yet treatment options have been limited. Chemotherapy-induced peripheral neuropathy is a painful and prevalent condition that can persist long after the treatments have ceased. Recent work into drugs targeting sigma receptors (S1R and S2R) hold great promise in numerous applications, particularly in the management of cancer-related neuropathic pain. To this end, they may be paired with opioids. New drugs are in development and while studies to date have been primarily in animal models of neuropathic pain, the use of S1R antagonists alone or with opioids for neuropathic pain in cancer patients holds great promise.

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