Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Optimal Delivery of Pain Management in Schwannomatosis: A Literature Review

Utaro Hino[1], Ryota Tamura[2], Masahiro Toda[2]

[1]Department of Neurosurgery, Saiseikai Yokohamashi Tobu Hospital, Kanagawa, Japan; [2]Department of Neurosurgery, Keio University School of Medicine, Tokyo, Japan

Correspondence: Ryota Tamura, Department of Neurosurgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan, Email moltobello-r-610@keio.jp

Abstract: Non-NF2 schwannomatosis is a rare syndrome characterized by multiple benign schwannomas that primarily affect nerve sheaths, with chronic, treatment-resistant pain as the most common symptom. No protocol has been established for pain management, and pharmacotherapies, including molecular target therapies, are being evaluated. Neuromodulation therapies such as scrambler therapy and surgical options are also employed; however, surgery may lead to persistent or recurrent pain caused by nerve damage or tumor recurrence. The lack of accurate animal models hampers understanding of pain mechanisms and tumor development, necessitating further basic research and clinical trials to improve treatment strategies.

Keywords: schwannomatosis, pain, surgery, medication, neuromodulation

Introduction

Traditionally, schwannomatosis is a syndrome characterized by the development of multiple schwannomas, distinct from neurofibromatosis type 1 and 2 (NF2).[1] In 2022, the nomenclature of NF2 and schwannomatosis was revised and defined by pathogenic mutations in multiple genes on chromosome 22.[2,3] Previously known as schwannomatosis, this syndrome is now called non-NF2 schwannomatosis, which is characterized by mutations of the tumor-suppressor genes *SMARCB1* and *LZTR1* and the loss of heterozygosity on chromosome 22q.[3–7] Non-NF2 schwannomatosis is a syndrome characterized by the occurrence of multiple benign schwannomas that primarily affect the nerve sheaths, with a lower incidence of vestibular schwannomas than NF2-schwannomatosis. It is an exceedingly rare disorder, with an annual incidence of 0.58 per million, approximately half that of NF2 schwannomatosis.[8,9] Most cases of non-NF2 schwannomatosis occur sporadically, although familial cases account for 13%–25%.[8,10,11]

Patients with non-NF2 schwannomatosis most frequently and initially complain of pain.[11–13] It is typically resistant to treatment, chronic, and often accompanied by anxiety and depression.[14] Unlike NF2 schwannomatosis, patients' average life expectancy is not typically reduced;[9] however, malignant transformation and shortened survival are causes of concern in some cases.[13,15] The management of patients with schwannomatosis is primarily symptomatic, with observation as the principal approach for asymptomatic schwannomas. In symptomatic cases, chronic, intractable pain significantly affects the quality of life (QOL), making pain control the primary therapeutic goal.[3,12,16] This review summarizes the latest information on pain management in non-NF2 schwannomatosis.

Tumor Distribution

In non-NF2 schwannomatosis, tumors typically arise in subcutaneous tissues and peripheral, spinal; cranial, and sciatic nerves, within the pelvic region.[17,18] Given that tumors may be nonpalpable or asymptomatic, clinically assessing all tumors in patients with non-NF2 schwannomatosis is challenging. A study using whole-body magnetic resonance imaging (MRI) revealed that out of 51 patients with non-NF2 schwannomatosis, 36 had one or more internal tumors.[18] The median number of tumors in affected patients was 4 (range, 1–27), and the median total tumor volume

Received: 29 August 2024
Accepted: 4 January 2025
Published: 17 January 2025

was 39 mL (range, 7–1372 mL). Spinal schwannomas in patients with non-NF2 schwannomatosis tend to cluster in the lumbar region, which contrasts with sporadic schwannomas that are more commonly found in the cervical and thoracolumbar regions.[12,19] *LZTR1* mutations were reported to increase the incidence of spinal schwannomas.[20]

Mechanisms of Pain Development in Non-NF2 Schwannomatosis

Despite reports indicating a correlation between the total tumor volume and pain intensity,[20] pain is not strictly associated with tumor growth or mechanical nerve compression.[11] Pain may be localized to the tumor site or may spread beyond the tumor's location,[21] reflecting the presence of pain-inducing mechanisms beyond mechanical compression.

Studies have reported that Schwann cells contribute to pain by secreting cytokines such as tumor necrosis factor-α and prokineticin 2, which sensitize nociceptors.[22,23] The nerve growth factor (NGF), initially identified as a neurotrophic factor, has increasingly been recognized as a key mediator, particularly in inflammatory and neuropathic pain.[24,25] NGF is also expressed in Schwann cells and is involved in the sustained hyperalgesia observed in non-NF2 schwannomatosis.[26–28] NGF expression has been detected in schwannomas resected from patients with non-NF2 schwannomatosis and in conditioned media from schwannoma cultures,[29] indicating its involvement in schwannomatosis-associated pain responses. Similarly, fibroblast growth factors are associated with neuropathic pain.[30,31] Schwannomas secrete high mobility group box 1, which stimulates surrounding dorsal root ganglion neurons, leading to CCL2 expression, macrophage recruitment, and interleukin (IL)-6 overproduction, a process implicated in pain generation.[32]

Patients with non-NF2 schwannomatosis carrying *LZTR1* mutations tend to experience more severe pain than those carrying *SMARCB1* mutations, indicating the potential association of germline mutations with pain severity.[20] The cause of the pain differences between these mutations is unclear but is hypothesized to be caused by the distinct functions of *SMARCB1* and *LZTR1*. *SMARCB1* is associated with the SWI/SNF human chromatin remodeling complex and is involved in the regulation of genome-wide gene expression,[33] whereas *LZTR1* functions as an adaptor protein for the Cullin-3 ubiquitin ligase complex, mediating the ubiquitin-dependent degradation of proteins such as epidermal growth factor receptor (EGFR) and anexelekto (AXL). LZTR1 mutations result in the abnormal accumulation of these proteins, leading to the aberrant activation of growth factor signaling. Schwannoma-like tumors have been shown to form in *LZTR1*-deficient mice.[34–36]

Pain Management

Medications

To date, no pharmacotherapy specifically for non-NF2-Schwannomatosis has been established, and medications commonly used for neuropathic pain, such as gabapentin, pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (such as amitriptyline), serotonin–norepinephrine reuptake inhibitors (such as duloxetine), anticonvulsants (such as topiramate and carbamazepine), and short-acting opioids, are also employed in managing pain in non-NF2 schwannomatosis.[37–42] In addition, the following drugs have been suggested to be effective in pain management in patients with non-NF2 schwannomatosis.

Cannabinoids

A case report indicated that the administration of tetrahydrocannabinol/cannabidiol crystals led to improvements not only in pain but also in the mood and QOL of a patient whose previous pain management, including opioids and antineuropathic drugs, had been completely ineffective.[38] Cannabidiol is thought to exert analgesic effects by acting on the transient receptor potential vanilloid subtype 1 receptors, which are primarily expressed on nociceptive neurons.[43,44] These receptors are nonselective nociceptive cation channels that take on a crucial role in pain transmission by promoting Ca2+ influx into peripheral sensory neurons.[45,46]

Bevacizumab

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, has shown early promising results in clinical trials that target vestibular schwannomas in patients with NF2 schwannomatosis.[47] A study reported

bevacizumab may reduce the tumor size and alleviate pain in non-NF2 schwannomatosis.[48] However, its use is associated with side effects, such as thrombosis, bleeding, visceral perforation, hypertension, and renal impairment.[49–51]

Brigatinib

Brigatinib, an inhibitor of anaplastic lymphoma kinase and several other tyrosine kinases, has demonstrated radiographic responses in multiple tumor types in NF2 schwannomatosis, with notable effects on meningiomas and nonvestibular schwannomas.[52] It has also demonstrated clinical benefits, including pain reduction. Given that *LZTR1* mutations are implicated in tumorigenesis through the dysregulation of tyrosine kinase pathways, including those involving EGFR and AXL,[35] brigatinib may exert similar effects on non-NF2 schwannomatosis. Its use is associated with side effects such as gastrointestinal symptoms (diarrhea and nausea), respiratory symptoms, hypertension, and hepatic dysfunction.[53–55]

Siltuximab

Siltuximab is a chimeric monoclonal antibody against human interleukin-6 (IL-6) and is currently used as a therapeutic agent for Castleman disease.[56,57] Given the influence of IL-6 in schwannoma-related pain, a Phase II trial (NCT05684692) has been initiated to evaluate siltuximab for pain relief in patients with non-NF2 schwannomatosis.[32] Side effects of siltuximab include lymphopenia, thrombocytopenia, neutropenia, anemia, upper respiratory infections, nausea, and headache.[56,58]

Tanezumab

Tanezumab is a humanized monoclonal antibody designed to inhibit NGF. It was developed primarily to treat chronic pain conditions such as osteoarthritis and chronic low back pain.[59–61] NGF is involved in the sensitization of nociceptors, which are nerve cells responsible for transmitting pain signals to the brain. By inhibiting the interaction between NGF and tropomyosin receptor kinase A, tanezumab is believed to prevent nociceptor sensitization and suppress the transmission of pain signals.[62] Its efficacy in alleviating pain associated with non-NF2 schwannomatosis is currently being investigated in a Phase 2, randomized, double-blind, placebo-controlled study (NCT04163419).[63] The results of this trial could offer a new therapeutic option for pain management in patients with non-NF2 schwannomatosis.

Paresthesia, arthralgia, hypoesthesia, and peripheral edema are common adverse events of tanezumab.[61,64,65] The primary safety issues with tanezumab are rapidly progressive osteoarthritis and the increased likelihood of joint replacement surgery, particularly when used in combination with NSAIDs.[59]

Nerve and Ganglionic Block

Common non-pharmacological treatments for neuropathic pain include nerve and ganglion blocks.[66,67] Corticosteroids, neurolytic agents such as alcohol, and local anesthetics including lidocaine, bupivacaine, and clonidine are the agents of choice for nerve blocks.[68,69] Local anesthetics provide temporary analgesia by blocking sodium channels and may also exert long-term effects on chronic pain through modulation of NGF-mediated pathways, influencing neuronal growth and sensitization.[70,71] Reports indicate that nerve blocks can offer significant symptomatic relief for drug-resistant neuropathic pain, particularly following Schwannoma removal.[72,73]

Nerve blocks are associated with complications, including infection, hemorrhage due to vascular injury, and neurological impairments such as unintended sensory disturbances and motor dysfunction.[69,74] To minimize these risks, procedures are performed under ultrasound or fluoroscopic guidance.[68,75]

Neuromodulation

Scrambler therapy, a relatively new neuromodulation treatment, noninvasively alleviates neuropathic pain through transcutaneous electrical stimulation.[76,77] Its mechanism is attributed to the replacement of endogenous "pain" signals with artificial "non-pain" signals transmitted along the same neural pathways. These artificial signals are conveyed through local electrical stimulation channels that interact with surface receptors on C-fibers.[76,78,79] Typical treatment involves daily sessions of 30–45 min for 10 consecutive days[76,80] to induce neuroplastic changes in the spinal and cerebral pain pathways, resulting in prolonged analgesic effects even after the treatment sessions.[76,77] A study using MRI suggested that scrambler therapy induced changes in cerebral blood volume in specific brain

regions associated with pain processing, such as the frontal lobe, precentral gyrus, and postcentral gyrus, indicating its central effects.[81] Furthermore, studies have reported that scrambler therapy led to significant reductions in the levels of inflammatory neuropeptides, such as NGF, in the blood.[82] This therapy alleviates neuropathic and cancer-related pain resistant to other treatments, and studies have reported its efficacy in alleviating pain in non-NF2 schwannomatosis.[83]

Surgery

Surgery is indicated for symptomatic schwannomas, such as those causing refractory pain, localized neurological deficits, or spinal cord compression, and tumor resection is often associated with significant pain relief.[84,85] The complete excision of schwannomas outside the tumor capsule is associated with a higher risk of postoperative complications related to nerve function. Therefore, intracapsular resection, which relieves tumor-induced compression and preserves the nerve, is generally preferred for better preservation of neurological function.[86,87] However, some patients experience persistent or recurrent pain postoperatively, which may be caused by preoperative nerve damage from tumor compression, iatrogenic nerve injury during surgery, postoperative soft tissue scarring, or tumor recurrence.[85,88] In non-NF2 schwannomatosis, given the multifocal nature of schwannomas, patients may require an average of 3.4 surgical procedures in 10 years.[11]

Ongoing Clinical Trials

Table 1 presents the ongoing trials that focused on molecular target therapies. These include the humanized monoclonal antibody tanezumab, which inhibits NGF, and siltuximab, a human-mouse chimeric monoclonal antibody that binds to human IL-6. These studies aim to provide valuable insights into the pain mechanisms in non-NF2 schwannomatosis and explore potential therapeutic options.

Future Direction

Although pain does not affect survival, it is associated with non-NF2 schwannomatosis is chronic and refractory, significantly impairing the QOL of patients. No treatment protocol has been established for pain management in non-NF2 schwannomatosis, and therapy is typically tailored to the clinical situation using a combination of the aforementioned methods (Figure 1) based on the discretion of individual institutions. Despite reports of *LZTR1*-deficient, *SMARCB1*-deficient, and patient-derived xenograft model mice that develop schwannoma-like tumors, currently, no animal model faithfully replicates the tumor formation and pain mechanisms of non-NF2 schwannomatosis.[32,35,89] Thus, new animal models are anticipated. Further elucidation of the detailed molecular mechanisms and large-scale clinical trials for various treatment options are needed.

Putting in Perspective

Non-NF2-Schwannomatosis is a rare disorder causing chronic, treatment-resistant pain that significantly impacts patients' quality of life. This review highlights the roles of NGF and IL-6 in pain mechanisms, with emerging therapies like Tanezumab and Siltuximab offering promise. Non-invasive approaches, such as Scrambler Therapy, also show potential.

Table 1 Ongoing Clinical Trials for Pain Related to Non-NF2 Schwannomatosis

ClinicalTrials.Gov Identifier	Initiation date	Responsible Party	Estimated Enrollment	Age	Treatment Strategy
NCT04163419	April 2020	Massachusetts General Hospital	46	≧18	Tanezumab
NCT05684692	August 2023	Massachusetts General Hospital	40	≧18	SiltuximabErenumab-Aooe

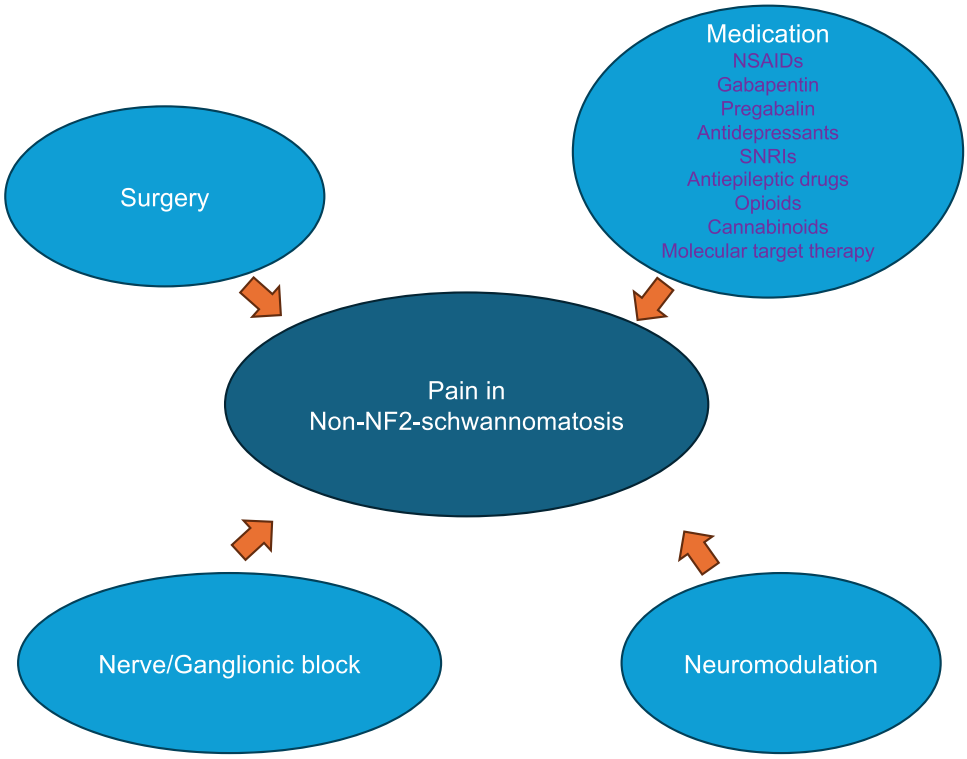

Figure 1 Multidisciplinary treatment using a combination of several methods.

However, the lack of accurate models and limited treatment options remain challenges. Future research should focus on uncovering pain mechanisms and developing effective therapies. This review provides a foundation for advancing treatment strategies and improving patient outcomes.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the English language review.

Disclosure

The authors report no conflicts of interest in this work.

References

1. MacCollin M, Woodfin W, Kronn D, Short MP. Schwannomatosis: a clinical and pathologic study. *Neurology*. 1996;46(4):1072–1079. doi:10.1212/WNL.46.4.1072
2. Plotkin SR, Messiaen L, Legius E, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: an international consensus recommendation. *Genet Med*. 2022;24(9):1967–1977. doi:10.1016/j.gim.2022.05.007
3. Planet M, Kalamarides M, Peyre M. Schwannomatosis: a Realm Reborn: year one. *Curr Opin Oncol*. 2023;35(6):550–557. doi:10.1097/CCO.0000000000000994
4. Melean G, Velasco A, Hernández-Imaz E, et al. RNA-based analysis of two SMARCB1 mutations associated with familial schwannomatosis with meningiomas. *Neurogenetics*. 2012;13(3):267–274. doi:10.1007/s10048-012-0335-8
5. Paganini I, Chang VY, Capone GL, et al. Expanding the mutational spectrum of LZTR1 in schwannomatosis. *Eur J Hum Genet*. 2015;23(7):963–968. doi:10.1038/ejhg.2014.220
6. Hutter S, Piro RM, Reuss DE, et al. Whole exome sequencing reveals that the majority of schwannomatosis cases remain unexplained after excluding SMARCB1 and LZTR1 germline variants. *Acta Neuropathol*. 2014;128(3):449–452. doi:10.1007/s00401-014-1311-1
7. Mohammad A, Iqbal M, Wadhwania A. Schwannomas of the head and neck region: a report of two cases with a narrative review of the literature. *Cancer Res Stat Treat*. 2020;3(3):517. doi:10.4103/CRST.CRST_149_20
8. Antinheimo J, Sankila R, Carpén O, Pukkala E, Sainio M, Jääskeläinen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. *Neurology*. 2000;54(1):71–76. doi:10.1212/WNL.54.1.71
9. Evans DG, Bowers NL, Tobi S, et al. Schwannomatosis: a genetic and epidemiological study. *J Neurol Neurosurg Psychiatry*. 2018;89(11):1215–1219. doi:10.1136/jnnp-2018-318538

10. Jacoby LB, MacCollin M, Parry DM, et al. Allelic expression of the NF2 gene in neurofibromatosis 2 and schwannomatosis. *Neurogenetics*. 1999;2(2):101–108. doi:10.1007/s100480050060
11. MacCollin M, Chiocca EA, Evans DG, et al. Diagnostic criteria for schwannomatosis. *Neurology*. 2005;64(11):1838–1845. doi:10.1212/01.WNL.0000163982.78900.AD
12. Merker VL, Esparza S, Smith MJ, Stemmer-Rachamimov A, Plotkin SR. Clinical features of schwannomatosis: a retrospective analysis of 87 patients. *Oncologist*. 2012;17(10):1317–1322. doi:10.1634/theoncologist.2012-0162
13. Gonzalvo A, Fowler A, Cook RJ, et al. Schwannomatosis, sporadic schwannomatosis, and familial schwannomatosis: a surgical series with long-term follow-up. Clinical article. *J Neurosurg*. 2011;114(3):756–762. doi:10.3171/2010.8.JNS091900
14. Alaidarous A, Parfait B, Ferkal S, Cohen J, Wolkenstein P, Mazereeuw-Hautier J. Segmental schwannomatosis: characteristics in 12 patients. *Orphanet J Rare Dis*. 2019;14(1):207. doi:10.1186/s13023-019-1176-4
15. Carter JM, O'Hara C, Dundas G, et al. Epithelioid malignant peripheral nerve sheath tumor arising in a schwannoma, in a patient with "neuroblastoma-like" schwannomatosis and a novel germline SMARCB1 mutation. *Am J Surg Pathol*. 2012;36(1):154–160. doi:10.1097/PAS.0b013e3182380802
16. Lu-Emerson C, Plotkin SR. The neurofibromatoses. Part 2: NF2 and schwannomatosis. *Rev Neurol Dis*. 2009;6(3):E81–6.
17. Chick G, Victor J, Hollevoet N. Six cases of sporadic schwannomatosis: topographic distribution and outcomes of peripheral nerve tumors. *Hand Surg Rehabil*. 2017;36(5):378–383. doi:10.1016/j.hansur.2017.07.001
18. Plotkin SR, Bredella MA, Cai W, et al. Quantitative assessment of whole-body tumor burden in adult patients with neurofibromatosis. *PLoS One*. 2012;7(4):e35711. doi:10.1371/journal.pone.0035711
19. Li P, Zhao F, Zhang J, et al. Clinical features of spinal schwannomas in 65 patients with schwannomatosis compared with 831 with solitary schwannomas and 102 with neurofibromatosis Type 2: a retrospective study at a single institution. *J Neurosurg Spine*. 2016;24(1):145–154. doi:10.3171/2015.3.SPINE141145
20. Jordan JT, Smith MJ, Walker JA, et al. Pain correlates with germline mutation in schwannomatosis. *Medicine*. 2018;97(5):e9717. doi:10.1097/MD.0000000000009717
21. Ostrow KL, Donaldson KJ, Caterina MJ, Belzberg A, Hoke A. The Secretomes of Painful Versus Nonpainful Human Schwannomatosis Tumor Cells Differentially Influence Sensory Neuron Gene Expression and Sensitivity. *Sci Rep*. 2019;9(1):13098. doi:10.1038/s41598-019-49705-w
22. Campana WM, Li X, Shubayev VI, Angert M, Cai K, Myers RR. Erythropoietin reduces Schwann cell TNF-alpha, Wallerian degeneration and pain-related behaviors after peripheral nerve injury. *Eur J Neurosci*. 2006;23(3):617–626. doi:10.1111/j.1460-9568.2006.04606.x
23. Lattanzi R, Maftei D, Marconi V, et al. Prokineticin 2 upregulation in the peripheral nervous system has a major role in triggering and maintaining neuropathic pain in the chronic constriction injury model. *Biomed Res Int*. 2015;2015:301292. doi:10.1155/2015/301292
24. Pezet S, McMahon SB. Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci*. 2006;29(1):507–538. doi:10.1146/annurev.neuro.29.051605.112929
25. Watson JJ, Allen SJ, Dawbarn D. Targeting nerve growth factor in pain: what is the therapeutic potential? *BioDrugs*. 2008;22(6):349–359. doi:10.2165/0063030-200822060-00002
26. Lewin GR, Ritter AM, Mendell LM. Nerve growth factor-induced hyperalgesia in the neonatal and adult rat. *J Neurosci*. 1993;13(5):2136–2148. doi:10.1523/JNEUROSCI.13-05-02136.1993
27. Mills CD, Nguyen T, Tanga FY, et al. Characterization of nerve growth factor-induced mechanical and thermal hypersensitivity in rats. *Eur J Pain*. 2013;17(4):469–479. doi:10.1002/j.1532-2149.2012.00202.x
28. Rukwied R, Mayer A, Kluschina O, Obreja O, Schley M, Schmelz M. NGF induces non-inflammatory localized and lasting mechanical and thermal hypersensitivity in human skin. *Pain*. 2010;148(3):407–413. doi:10.1016/j.pain.2009.11.022
29. Ostrow KL, Donaldson K, Blakeley J, Belzberg A, Hoke A. Immortalized Human Schwann Cell Lines Derived From Tumors of Schwannomatosis Patients. *PLoS One*. 2015;10(12):e0144620. doi:10.1371/journal.pone.0144620
30. Forouzanfar F, Sadeghnia HR. Fibroblast Growth Factors as Tools in the Management of Neuropathic Pain Disorders. *Curr Drug Target*. 2020;21(10):1034–1043. doi:10.2174/1389450121666200423084205
31. Kukutla P, Ahmed SG, DuBreuil DM, et al. Transcriptomic signature of painful human neurofibromatosis type 2 schwannomas. *Ann Clin Transl Neurol*. 2021;8(7):1508–1514. doi:10.1002/acn3.51386
32. Yin Z, Wu L, Zhang Y, et al. Co-Targeting IL-6 and EGFR signaling for the treatment of schwannomatosis and associated pain. *bioRxiv*. 2023;2023:527377. doi:10.1101/2023.02.06.527377
33. Kalimuthu SN, Chetty R. Gene of the month: SMARCB1. *J Clin Pathol*. 2016;69(6):484–489. doi:10.1136/jclinpath-2016-203650
34. Piotrowski A, Xie J, Liu YF, et al. Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. *Nat Genet*. 2014;46(2):182–187. doi:10.1038/ng.2855
35. Ko A, Hasanain M, Oh YT, et al. LZTR1 Mutation Mediates Oncogenesis through Stabilization of EGFR and AXL. *Cancer Discov*. 2023;13(3):702–723. doi:10.1158/2159-8290.CD-22-0376
36. Bigenzahn JW, Collu GM, Kartnig F, et al. LZTR1 is a regulator of RAS ubiquitination and signaling. *Science*. 2018;362(6419):1171–1177. doi:10.1126/science.aap8210
37. Tamura R. Current Understanding of Neurofibromatosis Type 1, 2, and Schwannomatosis. *Int J Mol Sci*. 2021;22(11):5850. doi:10.3390/ijms22115850
38. Iorno V, Roberto A, Colantonio LB, Landi L, Corli O. Including cannabinoids in the treatment of painful schwannomatosis. *Brain Behav*. 2018;8(7):e01011. doi:10.1002/brb3.1011
39. Eisenberg E, River Y, Shifrin A, Krivoy N. Antiepileptic drugs in the treatment of neuropathic pain. *Drugs*. 2007;67(9):1265–1289. doi:10.2165/00003495-200767090-00003
40. Cayley Jr WE. Antidepressants for the treatment of neuropathic pain. *Am Fam Physician*. 2006;73(11):1933–1934.
41. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007;2007(4):CD005454. doi:10.1002/14651858.CD005454.pub2
42. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database Syst Rev*. 2013;2013(8):CD006146. doi:10.1002/14651858.CD006146.pub2

43. Anand U, Jones B, Korchev Y, et al. CBD Effects on TRPV1 Signaling Pathways in Cultured DRG Neurons. *J Pain Res*. 2020;13:2269–2278. doi:10.2147/JPR.S258433
44. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1–3):75–83. doi:10.1016/j.ejphar.2006.11.006
45. Moriello AS, De Petrocellis L. Assay of TRPV1 Receptor Signaling. *Methods Mol Biol*. 2016;1412:65–76.
46. Pecze L, Blum W, Schwaller B. Mechanism of capsaicin receptor TRPV1-mediated toxicity in pain-sensing neurons focusing on the effects of Na +/Ca2+ fluxes and the Ca2+-binding protein calretinin. *Biochimi Biophys Acta Mol Cell Res*. 2013;1833(7):1680–1691. doi:10.1016/j.bbamcr.2012.08.018
47. Plotkin SR, Stemmer-Rachamimov AO, Barker II FG, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med*. 2009;361(4):358–367. doi:10.1056/NEJMoa0902579
48. Blakeley J, Schreck KC, Evans DG, et al. Clinical response to bevacizumab in schwannomatosis. *Neurology*. 2014;83(21):1986–1987. doi:10.1212/WNL.0000000000000997
49. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. *Semin Oncol*. 2006;33(5 Suppl 10):S26–34. doi:10.1053/j.seminoncol.2006.08.001
50. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol*. 2010;117(3):497–504. doi:10.1016/j.ygyno.2010.02.021
51. Tol J, Cats A, Mol L, et al. Gastrointestinal ulceration as a possible side effect of bevacizumab which may herald perforation. *Invest New Drugs*. 2008;26(4):393–397. doi:10.1007/s10637-008-9125-4
52. Plotkin SR, Yohay KH, Nghiemphu PL, et al. Brigatinib in NF2-Related Schwannomatosis with Progressive Tumors. *N Engl J Med*. 2024;390(24):2284–2294. doi:10.1056/NEJMoa2400985
53. Xing P, Hao X, Zhang X, Li J. Efficacy and safety of brigatinib in ALK-positive non-small cell lung cancer treatment: a systematic review and meta-analysis. *Front Oncol*. 2022;12:920709. doi:10.3389/fonc.2022.920709
54. Ng TL, Narasimhan N, Gupta N, Venkatakrishnan K, Kerstein D, Camidge DR. Early-Onset Pulmonary Events Associated With Brigatinib Use in Advanced NSCLC. *J Thorac Oncol*. 2020;15(7):1190–1199. doi:10.1016/j.jtho.2020.02.011
55. Omar NE, Fahmy Soliman AI, Eshra M, Saeed T, Hamad A, Abou-Ali A. Postmarketing safety of anaplastic lymphoma kinase (ALK) inhibitors: an analysis of the FDA Adverse Event Reporting System (FAERS). *ESMO Open*. 2021;6(6):100315. doi:10.1016/j.esmoop.2021.100315
56. Tonialini L, Bonfichi M, Ferrero S, et al. Siltuximab in relapsed/refractory multicentric Castleman disease: experience of the Italian NPP program. *Hematol Oncol*. 2018;36(4):689–692. doi:10.1002/hon.2532
57. van Rhee F, Casper C, Voorhees PM, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. *Oncotarget*. 2015;6(30):30408–30419. doi:10.18632/oncotarget.4655
58. Suzuki K, Ogura M, Abe Y, et al. Phase 1 study in Japan of siltuximab, an anti-IL-6 monoclonal antibody, in relapsed/refractory multiple myeloma. *Int J Hematol*. 2015;101(3):286–294. doi:10.1007/s12185-015-1743-y
59. Schnitzer TJ, Ekman EF, Spierings ELH, et al. Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or Hip osteoarthritis pain. *Ann Rheum Dis*. 2015;74(6):1202–1211. doi:10.1136/annrheumdis-2013-204905
60. Walicke PA, Hefti F, Bales R, et al. First-in-human randomized clinical trials of the safety and efficacy of tanezumab for treatment of chronic knee osteoarthritis pain or acute bunionectomy pain. *Pain Rep*. 2018;3(3):e653. doi:10.1097/PR9.0000000000000653
61. Markman JD, Bolash RB, McAlindon TE, et al. Tanezumab for chronic low back pain: a randomized, double-blind, placebo- and active-controlled, Phase 3 study of efficacy and safety. *Pain*. 2020;161(9):2068–2078. doi:10.1097/j.pain.0000000000001928
62. Gondal FR, Bilal J, Kent Kwoh C. Tanezumab for the treatment of osteoarthritis pain. *Drugs Today*. 2022;58(4):187–200. doi:10.1358/dot.2022.58.4.3352752
63. JLW Da, Merker VL, Jordan JT, et al. Design of a randomized, placebo-controlled, phase 2 study evaluating the safety and efficacy of tanezumab for treatment of schwannomatosis-related pain. *Contemp Clin Trials*. 2022;121:106900. doi:10.1016/j.cct.2022.106900
64. Chen J, Li J, Li R, et al. Efficacy and Safety of Tanezumab on Osteoarthritis Knee and Hip Pains: a Meta-Analysis of Randomized Controlled Trials. *Pain Med*. 2017;18(2):374–385. doi:10.1093/pm/pnw262
65. Balanescu AR, Feist E, Wolfram G, et al. Efficacy and safety of tanezumab added on to diclofenac sustained release in patients with knee or Hip osteoarthritis: a double-blind, placebo-controlled, parallel-group, multicentre Phase III randomised clinical trial. *Ann Rheum Dis*. 2014;73(9):1665–1672. doi:10.1136/annrheumdis-2012-203164
66. Gharaei H, Gholampoor N. The role of interventional pain management strategies for neuropathic pelvic pain in endometriosis. *Pain Phys*. 2023;26(5):E487–E495. doi:10.36076/ppj.2023.26.E487
67. Lin CS, Lin YC, Lao HC, Chen CC. Interventional treatments for postherpetic neuralgia: a systematic review. *Pain Phys*. 2019;22(3):209–228. doi:10.36076/ppj/2019.22.209
68. Gunduz OH, Kenis-Coskun O. Ganglion blocks as a treatment of pain: current perspectives. *J Pain Res*. 2017;10:2815–2826. doi:10.2147/JPR.S134775
69. Datta R, Agrawal J, Sharma A, Rathore VS, Datta S. A study of the efficacy of stellate ganglion blocks in complex regional pain syndromes of the upper body. *J Anaesthesiol Clin Pharmacol*. 2017;33(4):534–540. doi:10.4103/joacp.JOACP_326_16
70. Costa YM, Exposto FG, Castrillon EE, Conti PCR, Bonjardim LR, Svensson P. Local anaesthesia decreases nerve growth factor induced masseter hyperalgesia. *Sci Rep*. 2020;10(1):15458. doi:10.1038/s41598-020-71620-8
71. Takatori M, Kuroda Y, Hirose M. Local anesthetics suppress nerve growth factor-mediated neurite outgrowth by inhibition of tyrosine kinase activity of TrkA. *Anesth Analg*. 2006;102(2):462–467. doi:10.1213/01.ane.0000194334.69103.50
72. Naja Z, Naja AS, Rajab O, Mugharbil A, Shatila AR, Al Hassan J. Repetitive nerve block for neuropathic pain management: a case report. *Scand J Pain*. 2018;18(1):125–127. doi:10.1515/sjpain-2017-0155
73. Paiva A, Ferreira JB, Serrano S. Does interventional pain management play a role in the treatment of cervical post-surgical neuropathic pain? *Cureus*. 2023;15(11):e48996. doi:10.7759/cureus.48996
74. Mohamed SAE, Ahmed DG, Mohamad MF. Chemical neurolysis of the inferior hypogastric plexus for the treatment of cancer-related pelvic and perineal pain. *Pain Res Manag*. 2013;18(5):249–252. doi:10.1155/2013/196561

75. Ahmed DG, Mohamed MF, Mohamed SAE. Superior hypogastric plexus combined with ganglion impar neurolytic blocks for pelvic and/or perineal cancer pain relief. *Pain Phys*. 2015;18(1):E49–56. doi:10.36076/ppj/2015.18.E49
76. Marineo G. Inside the Scrambler Therapy, a Noninvasive Treatment of Chronic Neuropathic and Cancer Pain: from the Gate Control Theory to the Active Principle of Information. *Integr Cancer Ther*. 2019;18:1534735419845143. doi:10.1177/1534735419845143
77. Tomasello C, Pinto RM, Mennini C, Conicella E, Stoppa F, Raucci U. Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: a preliminary study. *Pediatr Blood Cancer*. 2018;65(7):e27064. doi:10.1002/pbc.27064
78. Majithia N, Smith TJ, Coyne PJ, et al. Scrambler Therapy for the management of chronic pain. *Support Care Cancer*. 2016;24(6):2807–2814. doi:10.1007/s00520-016-3177-3
79. Yarchoan M, Naidoo J, Smith TJ. Successful Treatment of Scar Pain with Scrambler Therapy. *Cureus*. 2019;11(10):e5903. doi:10.7759/cureus.5903
80. Smith TJ, Razzak AR, Blackford AL, et al. A Pilot Randomized Sham-Controlled Trial of MC5-A Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN). *J Palliat Care*. 2020;35(1):53–58. doi:10.1177/0825859719827589
81. Lee SY, Park CH, Cho YS, et al. Scrambler Therapy for Chronic Pain after Burns and Its Effect on the Cerebral Pain Network: a Prospective, Double-Blinded, Randomized Controlled Trial. *J Clin Med Res*. 2022;11(15):4255. doi:10.3390/jcm11154255
82. Starkweather AR, Coyne P, Lyon DE, Elswick Jr RK, An K, Sturgill J. Decreased low back pain intensity and differential gene expression following Calmare®: results from a double-blinded randomized sham-controlled study. *Res Nurs Health*. 2015;38(1):29–38. doi:10.1002/nur.21632
83. Murphy T, Erdek M, Smith TJ. Scrambler Therapy for the Treatment of Pain in Schwannomatosis. *Cureus*. 2022;14(3):e23124. doi:10.7759/cureus.23124
84. Huang JH, Simon SL, Nagpal S, Nelson PT, Zager EL. Management of patients with schwannomatosis: report of six cases and review of the literature. *Surg Neurol*. 2004;62(4):353–361. doi:10.1016/j.surneu.2003.11.020
85. Niepel AL, Steinkellner L, Sokullu F, Hellekes D, Kömürcü F. Long-term Follow-up of Intracapsular Schwannoma Excision. *Ann Plast Surg*. 2019;82(3):296–298. doi:10.1097/SAP.0000000000001812
86. Date R, Muramatsu K, Ihara K, Taguchi T. Advantages of intra-capsular micro-enucleation of schwannoma arising from extremities. *Acta Neurochir*. 2012;154(1):173–178. doi:10.1007/s00701-011-1213-0
87. Zheng Z, Li J, Shen Y, Xu L, Sun J. Radical intracapsular microenucleation technique for exclusively intraparotid facial nerve schwannoma: long-term follow-up review. *J Craniomaxillofac Surg*. 2016;44(12):1963–1969. doi:10.1016/j.jcms.2016.09.012
88. Kim SM, Seo SW, Lee JY, Sung KS. Surgical outcome of schwannomas arising from major peripheral nerves in the lower limb. *Int Orthop*. 2012;36(8):1721–1725. doi:10.1007/s00264-012-1560-3
89. Vitte J, Gao F, Coppola G, Judkins AR, Giovannini M. Timing of Smarcb1 and Nf2 inactivation determines schwannoma versus rhabdoid tumor development. *Nat Commun*. 2017;8(1):300. doi:10.1038/s41467-017-00346-5