Narrative Review

Chronic Pain in Neurofibromatosis 1, Neurofibromatosis 2, and Schwannomatosis: A Review on Epidemiology, Pathophysiology, Symptomatology and Treatment

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Background: Neurofibromatosis (NF) is a group of neurogenetic disorders (including neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis) known for their tendency to induce the development of numerous nerve sheath tumors. Pain is a common symptom associated with NF, and the incidence of this pain can vary significantly, severely affecting the quality of life for many patients.

Objective: This narrative review aims to compile recent epidemiological data on NF1, NF2 and schwannomatosis, covering prevalence, incidence, and distribution across populations. It explores the disease's pathophysiology, highlighting the molecular mechanisms behind its development, and examines the diverse clinical manifestations and their impacts on patients. Additionally, the review evaluates current treatment approaches, synthesizing recent advancements to provide a comprehensive understanding. This review aims to offer researchers and health care professionals an updated perspective on managing NF effectively.

Study Design: A narrative review of peer-reviewed literature for NF, the management of its associated pain, and quality of life for patients who have the condition.

Methods: The MEDLINE and Embase databases were reviewed to identify peer-reviewed research that discussed factors relevant to NF-related pain and its management.

Limitations: This narrative review is not systematic and focuses primarily on existing literature without presenting new data.

Conclusions: While advances have been made in understanding pain associated with NF, particularly for NF1, NF2, and schwannomatosis, significant gaps in treatment and understanding remain. Future research should prioritize targeted therapies and improved pain management strategies to enhance the quality of life for NF patients.

Key words: Neurofibromatosis, schwannomatosis, chronic pain, quality of life, pain management, opioid, nerve sheath tumor, cancer pain, analgesia

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Neurofibromatosis (NF) encompasses a spectrum of neurogenetic disorders that commonly share susceptibility to multiple nerve sheath tumors. Among these, neurofibromatosis type 1 (NF1, previously known as von Recklinghausen disease) predominates, accounting for over 95% of all cases, followed by neurofibromatosis type 2 (NF2) with a prevalence of less than 5%, and schwannomatosis (SWN) representing less than one percent (1). NF1 is an autosomal dominant disorder affecting one in 3,000 to 4,000 people, whereas NF2 has been estimated to afflict one person in every 60,000 (1). While neurological impairments (such as neuropathy and motor dysfunction) are commonly documented within these populations, as are challenges with mental health and sleep, chronic pain and its profound impact on the quality of life remain uncharted and severely misunderstood consequences (2).

NF is a genetic condition marked by the growth of neurofibromas along nerves. These neurofibromas can compress or infiltrate neural structures, leading to chronic pain. This pain is often peripheral and neuropathic in nature, driven by ongoing nerve damage and inflammation that affects pain-processing pathways (2). Chronic peripheral neuropathic pain in NF patients can manifest as burning, stabbing, or electric-shock-like sensations, significantly impacting their quality of life (2). Additionally, the pain may be compounded by skeletal deformities or spinal tumors, which further contribute to pain and functional limitations, making management complex and requiring multimodal therapeutic approaches (2). Although the incidence of pain varies—ranging from 29-70% of all NF1 patients—in all types of NF, associated pain and its respective impact on quality of life are consistently reported in questionnaires that have been historically publicized (2-4).

Unfortunately, the underlying cause of pain in the SWN population is not entirely clear. Pain may present with a painful schwannoma tumor that can be addressed with surgical resection. However, in many instances, pain may return with or without the presence of an associated tumor (2). In other situations, pain may also be present in multiple concurrent areas without a specific pattern of an associated tumor (3). Currently, there is no specific therapy available to treat SWN-related pain effectively; there are many challenges and pitfalls to obtaining meaningful pain relief for NF and SWN patients (2,3).

Many of the currently available options for treating this population's pain are traditional pain medications, including antiepileptics, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids (5). These medications are often riddled with side effects and frequently require continued dose escalation (2). The use of prescription opioids for chronic pain is linked to an increasing concern of opioid misuse, dependence, overdose, and associated long-term toxicities. While a large majority of patients with NF and SWN use prescription pain medications regularly, many of the same patients continue to report intractable pain that significantly impacts their overall quality of life (1,2,5). Furthermore, although treatments such as surgery have traditionally been offered to this population, these procedures carry escalated risks of nerve injury and further worsening of pain, which may necessitate noninvasive treatment options (2).

The goal of this narrative review is to amalgamate the latest epidemiological information concerning NF1, NF2, and SWN, thereby providing a detailed analysis of prevalence, incidence, and distribution across diverse populations. In addition to exploring the epidemiology of NF, this review aims to delve into the intricate pathophysiology of the diseases it comprises, elucidating the underlying mechanisms and molecular factors contributing to the development of this genetic disorder. Furthermore, a comprehensive exploration of the symptomatology of NF will be undertaken, delineating its diverse clinical manifestations and their potential impacts on affected individuals. Lastly, the review will scrutinize contemporary treatment modalities, synthesizing recent advancements and evidence-based interventions to provide a holistic understanding of therapeutic approaches. By consolidating these crucial aspects, the review seeks to offer a nuanced and up-to-date perspective on NF, catering to both researchers and health care professionals in their pursuit of knowledge and effective management strategies for this complex disorder.

Methods

Literature Search

We conducted a systematic search in the databases Ovid MEDLINE and Ovid Embase for documents published in the English language from January 1st, 2007 to April 28th, 2024. The concepts and terms searched include "neurofibromatoses," "neurofibromatosis," "schwannomatosis," "pain," "pain management," "cancer pain," and "analgesia." Search structures, subject headings, and keywords were tailored to each

database. The terms were combined using AND/OR Boolean Operators. Conference abstracts were excluded from search results. The complete search strategies were detailed in Tables 1 and 2. We also added previously identified relevant research papers about NF therapies to the search results for this review.

Study Selection

The systematic database search retrieved 613 records. After duplicates were removed, 458 unique records were identified. Including previously identified references from other sources, we reviewed 507 references and included 82 papers in our narrative review. The review was done by 2 board-certified neurologists and one physical medicine and rehabilitation resident. Studies included in the analysis were further reviewed by a physician who was board-certified in neurology and pain medicine.

To meet the inclusion criteria, the publication needed to be an original research article, a case report, or a case series that detailed the use of treatment modalities aimed solely at pain relief in NF1, NF2, and SWN patients.

Studies on treatment modalities aimed primarily at curing NF-associated neoplasm/malignancy or treating pain related to NF complications (e.g. vascular rupture, hemothorax, scoliosis, etc.), studies without available abstracts or author lists, studies that gave no independent information on NF patients (even if the study population included NF patients among the others), studies on medical complications of NF, and studies that did not distinguish NF types from one another were excluded.

Table 1. *Ovid MEDLINE search strategy.*

#	Searches
1	exp Neurofibromatoses/
2	(neurofibromatosis or neurofibromatoses or Schwannomatosis).ti,ab,kf.
3	1 or 2
4	exp Pain/
5	exp Pain Management/
6	pain.ti,kf.
7	pain*.ab. /freq=2
8	4 or 5 or 6 or 7
9	3 and 8
10	limit 9 to (English language and yr="2007 -Current")

Table 2. *Embase search strategy.*

#	Searches
1	exp neurofibromatosis/
2	(neurofibromatosis or neurofibromatoses or Schwannomatosis).ti,ab,kf.
3	1 or 2
4	exp *pain/
5	exp analgesia/
6	exp cancer pain/
7	pain.ti.
8	pain*.ab. /freq=2 and exp pain/
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	limit 10 to (English language and yr="2007 -Current")
12	conference abstract.pt.
13	11 not 12

Neurofibromatosis 1

NF1 Epidemiology/Pathophysiology

NF1 is an autosomal dominant tumor disposition syndrome for neurofibromas, taking place in approximately one per 3000 live births (Table 3) (6). NF1 consists of 96% of all NF cases, occurring equally between genders and races, with half of NF1 cases arising from spontaneous mutations (1). These mutations are loss-of-function mutations on the neurofibromin 1 gene, located on band 17q11.2. The neurofibromin 1 gene codes for neurofibromin, a tumor suppressor that functions in the RAS/MAPK and mTOR pathways (6). Without neurofibromin, this pathway becomes overactive, causing unchecked cell proliferation and tumor formation, particularly of neurofibromas (5,6). Alongside RAS/MAPK dysregulation, the mTOR pathway is also activated significantly in cases of NF1, playing a crucial role in cell growth, survival, and metabolism, and further contributing to tumor development (5,6). The resulting tumor growth from these dysregulated pathways can lead to nerve compression, causing neuropathic pain.

NF1 mutations have a 100% penetrance and show variable expressivity and mosaicism. Specific genotype-phenotype correlations have also been reported in certain mutations, such as 17q11.2 microdeletion and severe disease (earlier onset and death) or mosaicism and other presentations of NF1 (1,5). Mosaicism results in segmental, generalized, or gonadal NF1. Segmental NF1 presents with pigment changes and limits tumors to body segments, whereas the generalized variety

Table 3. *Comparative epidemiology and pain characteristics of NF1, NF2, and schwannomatosis.*

Condition	Prevalence	Incidence	Chronic Pain Prevalence	Common Demographics
NF1	96% of NF cases	1:3,000 live births	35% to 53% of patients	Occurs equally in genders and races; 50% arise from spontaneous mutations.
NF2	3% of NF cases	1:87,410 live births	47% of patients	50% de novo mutations; mutations on 22q12 affect merlin protein and tumor suppression pathways.
SWN	< 1% of NF cases	1:126,000 live births	> 50% of patients	20% familial cases; involve multiple schwannomas, incomplete penetrance

NF1: neurofibromatosis type 1; NF2: neurofibromatosis type 2; SWN: schwannomatosis

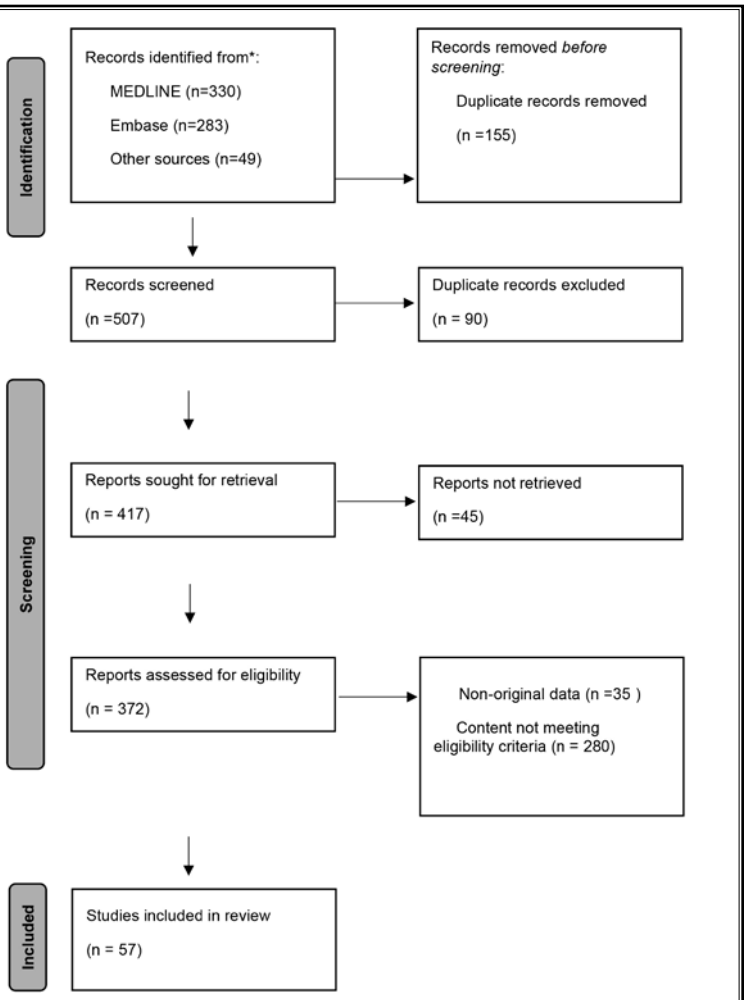

Fig. 1. *Flowchart demonstrating the process of study selection.*

is similar to classic NF1 without the mutation of the neurofibromin 1 gene. Gonadal NF1 affects only ova or sperm (5). These mutations result in the formation of neurofibromas consisting of various cell types, including Schwann cells, perineural cells, mast cells, and fibroblasts. Other formations include plexiform (muscle nerve fascicles neurofibromas) and schwannomas (7).

Studies in animal models with NF1 mutations have shown that dysregulated RAS/MAPK and mTOR signaling are associated with increased neuronal excitability and hyperalgesia, which reflects the heightened pain sensitivity observed in NF1 patients. Various studies have found increased heat sensitivity, which can be induced by capsaicin, substance P, or calcitonin gene-related peptides, in heterozygous neurofibromin 1 gene knockout mice (NF1+/-) (8-10). In some cases, these neuropeptide releases were 3-5 times greater in NF1+/- than wild types (9). Wang et al further isolated these NF1+/- mice to test the effects on sensory neuron nociceptive signaling (11). They found a greater number of action potentials, reduced firing latency, and decreased firing thresholds in NF1+/- mice, suggesting NF1 genotypes generated increased sensory action potentials more quickly in hyperpolarized states (i.e., pain) than in controls. Subsequent studies on the potassium and sodium channels in NF1+/- mice suggest an increased ion channel remodeling and heightened excitability of sensory neurons to promote hyperalgesia. Similar findings with dysregulated collapsing response mediatory proteins due to neurofibromin 1 deletion influence on voltage-gated ion channels have been reported in NF1 rat and porcine models (12-15). Immunofluorescence analyses have also found cutaneous NF1 hyperalgesia and chronic itch to be promoted by dysplastic cutaneous C-fiber sensory

endings and Schwann cells due to abnormal neurturin and artemin signaling through cRET kinase and GFRα2 and GFRα3 co-receptors (16,17).

NF1 Presentation

NF1 is a clinical diagnosis that presents cutaneous and non-cutaneous manifestations. Approximately 70% of persons with NF1 show signs of disease by their first birthday, 97% by their 8th birthday, and 100% by their 20th birthday (17). To receive a diagnosis of NF1, the patient must meet 2 of the 7 diagnostic criteria for the condition. These include: 1) at least 6 café au lait spots greater than 5 mm in the prepubertal stage and greater than 15 mm in the postpubertal stage, 2) at least 2 neurofibromas or at least one plexiform neurofibroma, 3) axillary or groin freckling, 4) optic glioma, 5) at least 2 Lisch nodules, 6) sphenoid dysplasia, dysplasia or thinning of long bone cortex, or 7) a parent with NF1 (5,17).

Cutaneous manifestations of NF1 are common. Café au lait spots are flat, uniformly hyperpigmented macules that present during the first year of life, with an increased number during early childhood (18). Patients whose café au lait spots presented at a younger age (under 2 years old) and numbered 6 or more were associated with a greater risk of NF1 (80.4%) than were patients over the age of 2 years or who had fewer than 6 café au lait spots (0.9%) (18). Other cutaneous presentations include freckles (Crowe sign), cutaneous neurofibromas, plexiform neurofibromas, and nodular neurofibromas (19). Freckles are also a diagnostic criterion, usually smaller in size than café au lait spots, and present in axillary and inguinal areas when the patient is between 3 and 5 years old. Cutaneous neurofibromas regularly appear as non-tender, pedunculated, or soft, sessile tumors that move with skin manipulation. Plexiform neurofibromas located superficially in skin and soft tissues usually have indiscernible nerve fibers or small plaques; deeper-tissue plexiform neurofibromas can grow into complex enlarged nerve masses. Nodular neurofibromas are firm, rubbery, sometimes tender masses. Lisch nodules are raised, tan-colored hamartomas of the iris that appear specifically in NF1 cases and are seen in more than 90% of adults with the condition (20).

Noncutaneous presentations include optic pathway gliomas, which occur in approximately 15% of children with NF1 (20). These gliomas can involve the optic nerves, chiasm, and post-chiasmal optic tracts, but only a minority of NF1 children have impaired vision. Additionally, optic chiasm involvement by optic pathway gliomas can cause premature or delayed puberty via mass effect. These derangements can also influence linear skeletal growth, bone dysplasia, and scoliosis, all warranted concerns within NF1 pediatric populations (21). Central nervous system neoplasms, such as low-grade astrocytomas, brainstem gliomas, and high-grade gliomas, are also present, as are soft tissue sarcomas, such as malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, and rhabdomyosarcoma (22).

Neurological and painful presentations of NF1 also exist between 35% to 53% of patients, which severely limit activities of daily living and overall quality of life. Cognitive deficits and learning disabilities, especially in pediatric NF1 populations, occur with higher frequency into adulthood (23). Intelligence quotient scores have been reported to be 5-10 points lower for children with NF1 than for the general population (23). NF1 patients are also twice as likely as the general population to suffer from seizures (24). Peripheral neuropathy and chronic pain can be seen in a subset of NF1 patients throughout their truncal anatomy and extremities (5). These pains can be experienced with cutaneous neurofibromas, superficial and deep plexiform neurofibromas, neuropathy, radiculopathy, or malignant peripheral nerve sheath tumors, and have been reported by children, adolescents, and adults throughout a continuum of time, the pain worsening with age (19). Craniofacial pain, including headache and pain in the temporomandibular joint area, is also common (25). These headaches present as the tension-type, chronic idiopathic, analgesic-abuse, and migraine varieties (25). The relationship between chronic NF1 pain and heart rate variability was also elicited, with the population of NF1 patients having lower heart rate variability (3). With heart rate as an index of autonomic nervous system function, lower heart rate variability suggests poorer adaptability and psychological flexibility to pain presentation. Unsurprisingly, this neuropathic pain, compounded by the diverse physical, psychological, and neurological manifestations of NF1, results in poorer quality of life as well as reduced functionality and activities of daily living (26).

Neurofibromatosis 2

NF2/SWN Epidemiology/Pathophysiology

NF2 is also an autosomal dominant tumor disposition syndrome for schwannomas found in one in

87,410 births (Table 3) (5). Seen in approximately 3% of all NF cases, NF2 is characterized by a loss-of-function mutation of the neurofibromin 2 gene on band 22q12, which serves as a negative regulator of cell growth and proliferation by interacting with several signaling pathways, including PI3K/Akt and RAS/MAPK (27). With 50% of cases from de novo mutations (and half from inheritance), this loss of function of the merlin protein in 22q12 affects tumor suppression in the PI3kinase/Akt, Raf/MEK/ERK, and mTOR pathways. This mutation, though fully penetrant, has variable mosaic presentations throughout the population, with worse clinical presentations seen with truncated proteins from a frameshift or nonsense mutation, point pathogenic variations, promoter methylation, or mitotic recombination (5). Generally, these mutations present with bilateral vestibular schwannomas and intradermal and neurogenic tumors (e.g., meningiomas).

Previously aggregated with NF2, SWN was distinguished from it in the 1990s and should be discussed as a separate entity (5,6). Further distinction as a spectrum of schwannoma (and not neurofibroma) predisposition syndromes was updated in 2022, with variants defined as SMARCB1 gene-related, LZTR1 gene-related, 22q-related SWN, and SWN—not otherwise specified (5,6,28). While the exact molecular mechanisms vary, evidence shows that disruptions in these pathways contribute to tumor formation and small fiber neuropathies; inactivation of these chromosome 22 tumor-suppressor genes has resulted in multiple schwannomas and pain (5,6). These presentations are considered incomplete penetrance, with an estimated prevalence of one in 126,000 NF patients and approximately 20% of cases due to familial history (Table 3) (28). This incomplete penetrance suggests pathogenic variants and additional genetic alterations requiring multiple genetic hits are also seen in SMARCB1 and LZTR1 gene-related schwannoma formation (29). Similarly, compared to NF1, the presentation of neuropathic pain in SWN is linked to small fiber neuropathies and reduction of epidermal nerve fiber density in C-fibers, perpetuating pain signaling (30).

NF2/Schwannomatosis Presentation

NF2 is diagnosed in patients with one of the following: 1) bilateral vestibular schwannomas, 2) identical NF2 pathogenic variations in a minimum of 2 anatomically distinct NF2-related tumors (schwannoma, meningioma, or ependymoma), 3) a combination of major (unilateral vestibular schwannomas, parent with NF2-related SWN, 2+ meningiomas, or NF2 pathogenic variant) and minor (bilateral cortical cataracts or multiple ependymomas, meningiomas, or schwannomas) criteria (5,6). Typically, NF2 patients present around 20-25 years of age. These presentations include 90-95% with bilateral vestibular schwannomas (often by 30 years of age), 24-51% have schwannomas of other cranial nerves, 70% show cutaneous schwannomas (usually with sensory or motor disturbances rather than pain), 50% have meningiomas, 33-53% with ependymomas, 47% with peripheral neuropathy, and 80% have subcapsular cataracts (5).

Vestibular schwannomas are typically bilateral in NF2 and cause tinnitus, hearing loss, and balance dysfunction (5). This hearing loss eventually leads to deafness. However, no obvious correlation exists between tumor growth and hearing loss. Left untreated, vestibular schwannomas can worsen balance dysfunction through medial extension and compression of the brain stem. In terms of pain, NF2 patients will eventually develop a spinal tumor (either schwannomas, meningiomas, or ependymomas) that can impinge neuronal pathways and cause significant nerve damage, leading to chronic neuropathic pain, weakness, and paresthesia (31). Additionally, dysregulated mTOR signaling, particularly in the context of NF2, is thought to play a key role in neuropathic pain by affecting nerve excitability and sensitivity (31). However, in terms of neuropathic symptoms, NF2 patients more often report sensorimotor symptoms rather than painful presentations; in the case of pain, cutaneous manifestations with nodules or lesions afflicting nerves are occasionally seen (1).

SWN clinically presents in adulthood (25-30 years old) with schwannomas and chronic neuropathic pain rather than sensorimotor deficits. Over 50% of SWN patients report pain as an initial onset that may or may not localize to specific, palpable tumors (28,29). These symptoms can be compounded with mass effects causing focal numbness, weakness, and muscle atrophy. Nearly all of these pain symptoms are due to peripheral nerve schwannomas found in the arms, legs, head, or neck regions (29). Cranial nerves can also be involved, with specific nerves resulting in specific symptoms (e.g., trigeminal schwannoma presenting with pain, numbness, and paresthesia like trigeminal neuralgia) (32). Radicular pain can also arise from spinal nerve root schwannoma-induced compression of dorsal sensory roots (33). These chronic neuropathic pains persist despite multiple interventions; in one population of 87 patients, 72% reported trialing up to

5 different chronic medications (neuropathic, opiate, anti-inflammatory, etc.), 20% trialed between 6-10 medications, and 7% reported trying more than 10 medications (34). Surgical interventions in these 87 patients were also trialed, with 217 surgeries for schwannoma resection completed. Forty patients underwent 72 spinal surgeries, while 70 underwent 145 peripheral resections. These surgical interventions relieved pain in only 39% of patients, with pain recurrence seen in 75% of patients at either the original tumor site or new tumor growth (34). Ultimately, the presence of pain in these patients, despite multimodal management and surgical interventions, also indicates reduced quality of life and functional ability (35). The delay in diagnosis, especially with factors such as intermittent, nonspecific presentations, delayed initial presentation, or delayed confirmatory genetic workup can lead to misdiagnosis, promoting perceptions of illness, inspiring coping mechanisms, and affecting patients' overall quality of life (36).

Treatment Options for Pain Management

Pharmacological Treatments

Although numerous medical and surgical options for NF1-associated tumors are being studied, studies that evaluate the options specifically for the management of pain caused by this condition are rare (Table 4) (37). Literature shows that various evidence-based methods are employed to manage pain associated with NF1. Among those, a 2019 cross-sectional study by Buono et al showed that after over-the-counter options, gabapentinoids were the most commonly used type of medication for treating neuropathic pain in NF1 patients (38). However, the use of gabapentinoids may be limited by side effects, such as dizziness and sedation, and larger studies focusing on long-term efficacy and optimal dosing are needed. Different cannabinoid formulations with varying THC-to-CBD ratios are among the medications reported to manage pain successfully in NF1-related patients (39,40). Some reports also show improvement in other parameters affecting quality of life, such as anxiety (40). A case series showed that high-intensity topical capsaicin might be beneficial in the treatment of NF1 patients' neuropathic pain (41). Bevacizumab, sirolimus, and ketamine treatments were also tried in the management of pain complaints presented by NF1 patients. A retrospective cohort study by Linda et al showed a small cohort of NF1 patients whose pain complaints were successfully managed with bevacizumab infusions. Anecdotal evidence from case reports suggests that sirolimus and ketamine infusions may help with NF1-associated pain (42-44). In a study of the effects of transdermal buprenorphine on children with cancer caused by NF1, the substance was shown to improve pain levels, sleep, and opioid needs (45). On the other hand, for pediatric NF1 patients suffering from migraines, Carotenuto et al showed in a prospective open-label study that a nutraceutical combination including ginkgolideB, coenzyme Q10, riboflavin, and magnesium proved to be successful as a preventive medication and led to improvements in migraine frequency, duration, intensity, and disability (46).

Complementary and Physical Treatments

Studies and case reports on the use and success of physical therapy and chiropractic care that suggest these treatments might be helpful also exist, although

Table 4. *Summary of treatment modalities for pain management in NF1, NF2, and SWN.*

Treatment Category	Intervention/Medication	Effectiveness	Limitations	Gaps in Research
Pharmacological	Gabapentinoids	Efficacious for neuropathic pain	Side effects (sedation, dizziness)	Long-term efficacy studies needed
	Cannabinoids	Positive outcomes in pain/anxiety	Inconsistent dosing, cognitive side effects	Larger trials needed
	Topical capsaicin	Efficacious for localized pain	Local irritation	Lack of large-scale studies
Complementary Therapies	Yoga, meditation	Improves physical and psychological outcomes	Mixed results, small sample sizes	Need for larger, controlled trials
	Physical therapy, acupuncture	Some reported pain relief	Limited evidence	Controlled trials needed
Interventional/Surgical	Lesion excision, motor cortex stimulation	Targeted pain relief	Risk of recurrence and complications	Larger trials needed to optimize approaches
NF2/SWN-Specific	Bevacizumab, nerve blocks, spinal fusion	Pain relief in select cases	Limited evidence, recurrence of pain	Need for larger randomized trials

there is no established evidence to assess their efficacy (38). The same study by Buono et al also showed that physical exercise, physical therapy, counseling, yoga mindfulness, meditation, and acupuncture were among the complementary treatment modalities employed for NF1-related pain (38). In addition to these established and evidence-based treatment modalities for pain, there are studies investigating other medical, behavioral, and interventional modalities used to treat NF1-associated pain symptoms. Case reports on other complementary options used for pain management in NF1 include methods such as scrambler therapy and transcutaneous electromagnetic stimulation (TENS) (52,53).

A study by Grau et al (47) to assess a pain self-management application called iCanCope showed that NF1 patients endorsed its use, although the main aim of the study was to evaluate the strengths and weaknesses of the application. Notably, NF1 patients were shown to be interested in tracking their pain in a detailed way on the application, among other functions (47). A meta-analysis including 6 trials focusing on the efficacy of mind-body interventions for pain in patients with NF1 showed that these interventions improved the patients' physical, psychological, and environmental quality of life (48). A small cohort study that evaluated the improvement in pain with acceptance and commitment therapy (ACT) had shown benefits over the baseline levels of pain; however, the study lacked a control group, so the placebo effect could not be evaluated (49). A mind-body skills-based intervention, "the relaxation response resiliency program (3RP)," was also shown to result in improvements in multiple psychosocial parameters related to coping with pain (50). Furthermore, a study by Varni et al (51) on pain interference and HRQOL argues that cognitive behavioral therapy may improve the quality of life for NF1 patients suffering from pain.

Interventional Treatments

Interventional and surgical options for treating NF1-associated pain are mostly specific to symptomatic lesions. Case reports illustrate instances in which the successful excision of culprit lesions resulted in the complete resolution of pain symptoms (54). The extent of these surgical interventions varied depending on the lesion, ranging from minimally invasive techniques to amputations and spinal fusions. Lefaucher et al (55) investigated the use of motor cortex stimulation as an interventional option in a randomized controlled trial that included 3 NF1 patients; however, the results for these patients were unclear.

NF2 and SWN-Related Pain Management

Literature on pain management specific to NF2 was scarcer. In a case report similar to a case series for NF1, Kollar et al (56) reported complete pain relief with bevacizumab in a patient with NF2. One study reports a case in which the selective posterior tibial nerve and saphenous nerve blocks were used successfully to treat recurrent schwannoma pain in the foot (57). Surgical interventions targeting individual lesions were reported to relieve SWN-related pain (58,59). Our search criteria were unable to include any further studies solely aimed at pain management in NF2 or SWN patients.

Discussion

This systematic review and narrative synthesis highlight the challenges and complexities in managing pain associated with NF1, NF2, and SWN. A critical observation is the significant impact of chronic pain on the quality of life for patients with these conditions, further potentiated by the limitations and side effects of currently available treatments.

Pain management strategies for NF1 range from pharmaceutical interventions to complementary therapies. The use of gabapentinoids, cannabinoid formulations, and high-intensity topical capsaicin has shown promise in alleviating NF1 patients' pain symptoms (17,42). Mind-body interventions, such as mindfulness, yoga, and ACT, have also demonstrated efficacy in improving physical and psychological aspects of pain management for NF1 patients (51). However, the variable efficacy and lack of controlled studies for some of these therapies underscores the need for further investigation.

For NF2 and SWN patients, the management of pain remains a difficult challenge. Although surgical interventions may provide relief, the recurrence of pain and the growth of new tumors limit long-term effectiveness. The case of bevacizumab providing complete relief for a patient with NF2 is noteworthy but represents a single-case scenario, emphasizing the need for continued exploration into targeted therapies (56).

The overarching issue in pain management for NF and SWN is the heterogeneity of pain among patients, necessitating individualized treatment approaches. In 2016, the Numeric Rating Scale-11, Pain Interference Index (6-24 years) and the Patient-Reported Outcome Measurement Information System (PROMIS) Pain In-

terference Scale, and the PROMIS Physical Functioning Scale were recommended by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration to assess pain in NF patients during clinical trials (60). The REiNS International Collaboration's 2016 recommendation to standardize pain assessment tools is a step toward further understanding and management of the pain associated with these conditions. Standardization in this format may facilitate greater efficacy in clinical trials and the development of tailored pain management strategies.

Conclusions

In conclusion, while there have been advancements in understanding and treating the pain of NF1, NF2, and SWN patients, significant care gaps remain. Future research should prioritize the development of targeted therapies, such as gene editing or modulation approaches that specifically address pain pathways in these conditions. Exploring advanced neuromodulation techniques like transcranial magnetic stimulation and deep brain stimulation may offer promising alternatives for pain relief. Furthermore, the identification of biomarkers to predict the onset and progression of pain in these disorders could greatly enhance the ability to tailor individualized treatments. These biomarkers could influence options in regenerative medicine, including stem cell therapies aimed at repairing nerve tissue damaged by tumors. Moreover, research should also focus on improving patient-reported outcomes and quality of life by considering the broader impact of pain on daily activities and emotional well-being. Together, these efforts will be crucial in bridging the existing care gaps and ultimately improving the clinical management of pain in NF patients.

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