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Novel Approaches in Drug Discovery for Treatment of Radicular Pain

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Abstract— *Radicular pain is a form of pain that travels down your spine from your back and hip to your legs. The pain moves around the root of the spinal nerve. Radiculopathy is a condition in which nerve root conduction is blocked. Only radiating pain is present in radicular pain, while sensory and/or motor loss that can be objectified can be found in radiculitis. Lumbosacral radicular syndrome is described by radiates pain in one or more lumbar or sacral dermatomes. It may or may not be accompanied by other radicular irritation symptoms. The annual incidence of low back pain with leg pain moving below the knee in the general population ranged from 9.9% to 25%. A herniated disc is the most common cause of lumbosacral radicular syndrome in patients under the age of 50. Patients with radicular pain can be treated with a combination of NSAIDs, antibiotics, antidepressants, antiepileptic medications, corticosteroids, and benzodiazepines to enhance their physical and psychological well-being. However, for those patients with a herniate disc, there is a high percentage of those in pain for at least a year, if not longer. Chronic drug therapy for radicular pain has been found to be ineffective, especially when used alone. Muscle relaxants, benzodiazepines, and antidepressants are ineffective in controlling pain. Rare medications, such as anti-TNF therapy, have also been used, but their efficacy is still limited. New approaches are needed due to the failure of currently available medications*.

Keywords— *Radicular pain, Lumbosacral radicular syndrome*.

I. INTRODUCTION

Pain is an uncomfortable sensory and emotional sensation that occurs as a result of, or is related to, actual or imminent tissue injury. Patient anxiety is a kind of warning signal, and pain is the most common occurrence experienced by patients. There are several types of pain. It warns against bodily harm, which is critical for preventing accidents and, as a result, survival.[1] Radicular pain is a form of pain that travels down your spine from your back and hip to your legs. The pain moves around the root of the spinal nerve.[2] Pain elicited by stimulation of the sensory (dorsal) root of a spinal nerve, or its dorsal root ganglion (DRG), is the mechanism.[3,4] Radicular pain is described as pain felt in a limb or trunk that is triggered by ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots, as well as other neuropathic mechanisms.[5] Radiculitis implies that the inflammatory process is primarily responsible for radicular signs and symptoms, which is wrong. Radicular pain, more precisely, is a term used to describe pain caused by stimulation of, or a condition of, a nerve root. Radiculopathy is a concept that combines the terms radicular pain and radiculitis, implying that damage to the nerve root has resulted in a clinically relevant motor or sensory neurological deficit in the nerve root's distribution. As a consequence, radiculopathy is a condition in which nerve root conduction is blocked, resulting in objective neurologic symptoms like numbness or weakness, or the blood flow to a nerve root is impaired, resulting in paresthesia.[6] While they are not synonyms, the terms radicular pain and radiculopathy are often used interchangeably. Only radiating pain is present in radicular pain, while sensory and/or motor loss that can be objectified can be found in radiculopathy. Radiculopathy may be a continuum of radicular pain, and both syndromes often occur together.[7] A lumbosacral radicular syndrome (LSR) is described by radiating pain in one or more lumbar or sacral dermatomes, which may or may not be accompanied by other radicular irritation symptoms and/or functional symptoms.[7] Radicular pain is rare in the general population, with prevalence rates ranging from 1.2 to 43 percent of lumbar radiculitis, an annual age-adjusted incidence of 0.83 percent in the cervical spine, and radiculopathy in the thoracic spine being uncommon.[8,9] The annual incidence of low back pain with leg pain moving below the knee in the general population ranged from 9.9 percent to 25%. In addition, the point prevalence (4.6 percent to 13.4%) and lifetime prevalence (1.2 percent to 43 percent) are also very high [10], implying that lumbosacral radicular pain is presumably the most common form of neuropathic pain.[11, 12] Being male, obesity, smoking, lumbalgia history, anxiety and depression, work that involves long periods of standing and leaning over, heavy manual labour, carrying heavy items, and being exposed to vibration are the most significant risk factors.[13] In 60 percent of patients, pain heals fully or partially within 12 weeks of onset.[14] However, after 3 months to a year, about 30% of patients are still in pain. In comparison to the male population, the female population with LRS seems to have a significantly worse outcome. Female patients had a 3.3 times higher unadjusted chance of having a bad long-term outcome than male patients.[15] A herniated disc is the most common cause of lumbosacral radicular syndrome in patients under the age of 50. Radicular pain is often caused by degenerative changes in the spine after the age of 50 (e.g., stenosis of the foramen intervertebrale).[16] Regional pain was recorded to be 43 percent in the low back, 32 percent in the neck, and 13 percent in the thoracic spine in a population-based analysis of spinal pain.[17] Following an initial episode, 25–60% of patients experience chronic, recurrent spinal pain for at least a year, if not

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longer.[18,19] According to studies on the global burden of disability, the prevalence of low back pain is 9.4%, with 17 percent of these people suffering from extreme chronic low back pain and 25.8% suffering from severe chronic low back pain with leg pain.[20] The prevalence of neck pain was also reported to be 4.9 percent, with a large proportion of patients suffering from chronic neck and arm pain and having a high disability index.[21] As a result of the rising prevalence and impairment caused by spinal pain, a variety of treatment options have arisen. Patients with radicular pain are more likely to take medications than patients with just axial pain. Patients with radicular pain can be treated with a combination of NSAIDs, antibiotics, antidepressants, antiepileptic medications, corticosteroids, and benzodiazepines in clinical settings to enhance their physical and psychological well-being. However, the efficacy and safety of such treatments have yet to be determined. For patients presenting to chronic pain treatment centres, extensive combination therapy has been confirmed.[22] In general, pharmacotherapy is considered a first-line treatment in the early stages of radicular pain; however, pharmacotherapy has not been shown to be successful as a stand-alone treatment in the majority of cases of radicular pain, except in acute episodes. Chronic drug therapy for radicular pain has been found to be ineffective, especially when used alone.[6] The use of NSAIDs as a first-line treatment for radicular pain has been prescribed.[23] There was no substantial difference between conventional NSAIDs and COX-2 NSAIDs, except that traditional NSAIDs had more side effects. In radicular pain, systemic glucocorticoid therapy is also widely used, particularly for acute episodes. However, with moderate quality data, it has only been shown to be successful for a short period of time. Muscle relaxants, benzodiazepines, and antidepressants, while being effective in treating certain muscle spasms and underlying psychiatric conditions, are ineffective in controlling radicular pain. [23-25] Rare medications, such as anti-TNF therapy [26, 27], have also been used; however, their efficacy is still limited.[6] New approaches for radicular pain are needed due to the failure of currently available medications to provide effective clinical pain relief. The aim of this article is to look at some of the possible new treatments for the treatment of radicular pain that are on the horizon.

II. FACTORS THAT CAUSE RADICULAR PAIN

Foraminal stenosis and space-occupying lesions in the lumbar spine can cause lumbar radicular pain also known as sciatica [28], but lumbar disc herniation is the most common cause. Inflammation of the damaged nerve roots is implicated in the pain mechanism in laboratory studies.[29-35,36]

Other pathologic processes, such as infective, inflammatory, and neoplastic entities, can cause a clinical syndrome that is similar. The following is a detailed list of such causes:

Degenerative vertebral causes: Spinal stenosis, Lateral recess stenosis, Spondylolisthesis, Facet joint degeneration, and other degenerative vertebral causes Osteophytes of the discs, Paget's disease is a contagious disease that affects Laminae or pedicle abnormalities, The ligamentum flavum buckles, The posterior longitudinal ligament thickens, Infections (such as tuberculosis and brucellosis), and Infestations (e.g., hydatid), Radicular Pain Caused by Other Vascular, Cystic, Infectious, and Miscellaneous Causes Hematoma, Schistosomiasis, Hydatid cyst, Vascular malformations, Epidural abscess, Ligamentum flavum cyst Rheumatoid nodule, Dermoid tumours, Epidermoid cysts, Enteric cysts Malformations of the dural sac, Meningeal cysts, Metastases Nerve root defects are all neuromeningeal causes.[37]

Neoplastic causes: Primary benign, Osteoma, Osteoblastoma, Chondroma, Angioma, Hemangioma, Aneurysmal bone cyst, Primary malignant, Myeloma, Chordoma, Secondary, Metastases, Lipoma, Epidural, Meningioma, Neurinoma, Ganglioneuroma, Hodgkin disease, Intradural, Secondary malignant, Myeloma, Chordom Meningioma, Neurinoma, Ganglioneuroma, Ependymoma, Metastases, Lymphoma, Lipoma, Meningioma, Neurinoma, Ganglioneuroma, Ependymoma, Metastases, Lymphoma. [37,38]

Overweight, smoking, and C-reactive protein have all been linked to sciatic pain Cardiovascular and lifestyle risk factors can also play a role. [39, 40, 41, 42]

III. CLASSIFICATION

The duration and anatomical location of radicular pain can be used to classify it. Most doctors divide back pain into three categories based on how long it lasts:

Acute is defined as a period of less than six weeks.

Subacute: between 7 and 12 weeks

Chronic: lasting more than three months

Depending on the anatomical position of the affected nerve root, radicular pain is known as cervical, thoracic, or lumbar. Seven vertebrae make up the cervical spine. The point at which spinal nerves emerge from the spinal canal is where they are named and numbered. C1-C7 emerge above their respective vertebrae in the cervical zone, and C8 emerges between the seventh cervical and first thoracic vertebra. The cervical plexus (roots C1-C4) innervates and transmits sensitivity to the skin of the face, neck, and shoulders by innervating the anterior and posterior musculature of the neck. The shoulder muscles, lower scalenes, and upper limb muscles and skin are all innervated by the brachial plexus (roots C5-C8 and T1).

There are twelve vertebrae and twelve nerve roots in the thoracic spine. Each thoracic nerve emerges from beneath the vertebra it corresponds to.

The lumbar spine is made up of five vertebrae and five nerve roots, each of which is numbered after the vertebra above it. As a result, nerve root L1 emerges from the L1-L2 region, while nerve root L5 emerges from the space between L5 and S1. Cervical nerve roots run horizontally to meet the intervertebral foramen since the spinal cord is not the same length as the vertebral column, while thoracic and lumbar nerve roots descend obliquely. The cauda equina is formed by the sacral and coccygeal nerve roots.[43]

IV. COMPLICATIONS

Disruption of the intervertebral disc causes discogenic leg pain [44,45], which has historically been treated with open

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discectomy.[46,47] By reducing pressure within the intervertebral disc and adjacent nerve root, open discectomy has gained acceptance.[47, 48] However, depending on the amount of annular invasion necessary, the effectiveness of this method can be limited by reherniation and/or reoperation.[49] As a result, open discectomy can be unsuccessful in minimising discogenic leg pain [46, 50, 51] and has risks.[52] Despite its widespread acceptance, open discectomy is a major surgical procedure with a history of complications.[53-56] Stolke, Sollman, and Siefert found a 13 percent complication rate, with one death, three nerve root injuries, and 1% discitis.[54] According to Ramirez and Thisted, 1 in 64 patients had a significant complication, 1 in 335 had a neurological complication, almost 1 in 500 had a cardiovascular complication, and 1 in 1,700 died as a result of the operation.[55,56]

V. CURRENT TREATMENT

Drugs Derived from Nature

Those with a higher level of education, a lower health status, and a holistic approach to health are more likely to use herbal therapies; those seeking relief from symptoms or an improvement in their overall condition; and those who have had a life-changing experience.[57] Echinacea, ginseng, ginkgo biloba, and garlic supplements are the most widely used herbal products.[58]

Herbal goods are worth around $4 billion a year in the United States, with an annual growth rate of more than 30%.[59] The selling of herbal substances increased by 380 percent in the 1990s, according to estimates. In a 2002 poll, 19% of adults said they had used natural products like herbal medicine, functional foods (garlic), or animal-based supplements.[58]

Herbal treatments have potential risks that users of herbs for medicinal purposes should be aware of. Herbal therapies and medications contain active ingredients that can trigger harmful herb/herb or herb/drug interactions.[60,61] Kava, when taken with levodopa, can increase the amount and length of "off" periods; St. John's wort, when taken with sertraline (Zoloft), can cause nausea, vomiting, and anxiety.[61] Herbal remedies and medications often contain several active ingredients. This makes determining the pharmacologic ingredient is causing the interaction or unfavourable side effect much more difficult.[62]

Clinical Drugs

Patients with radicular pain are more likely to take medications than patients with just axial pain. NSAIDs, skeletal muscle relaxants, opioid analgesics, benzodiazepines, systemic corticosteroids, antidepressants, and anticonvulsants are some of the most commonly prescribed medications. In general, pharmacotherapy is considered a first-line treatment in the early stages of radicular pain; however, pharmacotherapy has not been shown to be successful as a standalone treatment in the majority of cases of radicular pain, except in acute episodes. Chronic drug therapy for radicular pain has been shown to be ineffective, especially when used alone. The length and form of radicular symptoms are essential factors in deciding which medications to use to treat radicular pain. Radicular pain is primarily nociceptive in the acute phase and may respond to NSAIDs as well as corticosteroids. Antidepressants and antiepileptic drugs have been considered for chronic pain with a neuropathic dimension. The use of NSAIDs as a first-line treatment for radicular pain has been prescribed.[23] There was no substantial difference between conventional NSAIDs and COX-2 NSAIDs, except that traditional NSAIDs had more side effects. As a result, complications are common; gastrointestinal complications have been identified in over 2% of users, resulting in over 120,000 hospital admissions and over 17,000 deaths each year in the United States alone.

In radicular pain, systemic glucocorticoid therapy is also widely used, particularly for acute episodes. However, with moderate quality data, it has only been shown to be successful for a short period of time.[24] Antiepileptic drugs have been emphasised, especially in chronic radiculitis with a neuropathic aspect, but without evidence. As a result, antiepileptics are widely used, not just for generalised pain but also for radicular pain.

Muscle relaxants, benzodiazepines, and antidepressants, while being effective in treating certain muscle spasms and underlying psychiatric conditions, are ineffective in controlling radicular pain.[23-25] Rare medications, such as anti-TNF therapy [26, 27] have also been used; however, their efficacy remains limited.

Finally, opioids are the most widely prescribed medications, not just for chronic low back pain but also for radicular pain, and they have a slew of side effects that have sparked a lot of debate and criticism. In the majority of patients with chronic low back pain, the magnitude of pain relief and functional status change tends to be about 30%, with substantial negative implications. Patients with radicular pain can be treated with a combination of NSAIDs, antibiotics, antidepressants, antiepileptic medications, corticosteroids, and benzodiazepines in clinical settings to enhance their physical and psychological well-being. However, the efficacy and safety of such treatments have yet to be determined. For patients presenting to chronic pain treatment centres, extensive combination therapy has been confirmed.[63,6]

VI. NEW APPROACHES

Despite the fact that different methods of treating root pain have been identified over the years, we currently lack adequate evidence to make recommendations on the best treatment. Radicular pain is currently treated conservatively with a combination of surgical, pharmacological, and physiotherapeutic management.

Radicular pain is treated with a lumbar transforaminal steroid injection (LTFIS). Because of their anti-inflammatory effects, steroids are thought to have a therapeutic effect. In vitro studies show that steroids can reduce inflammatory mediators including cytokines and chemokines [64, 65] another study indicates that steroids can stabilise nociceptive signalling in C-fibers and inhibit ectopic neural discharges.[66] Researchers have discovered that patients with radicular pain have elevated levels of the neuro-inflammation marker 18 kDa translocator protein in both the neuroforamina (which contains

the dorsal root ganglion and nerve roots) and the spinal cord [67], and that an epidural steroid injection can help reduce these levels. Radicular pain caused by an intervertebral disc herniation responds well to LTFIS.[68]

Dexamethasone is a glucocorticoid used in clinical practise that has anti-inflammatory and analgesic properties. It reduces lipocalin type prostaglandin D synthase, which is triggered by lumbar disc herniation, and thus relieves radicular pain caused by lumbar disc herniation. Meanwhile, the phosphoinositide 3-kinase/protein kinase B pathway activity was reduced, presumably as a result of the reduced inflammation caused by dexamethasone.[69]

Ginger is a natural pain reliever that works via a variety of mechanisms, including inhibition of prostaglandins through the COX and LOX pathways, antioxidant activity, inhibition of the transcription factor nf–kB, and acting as an agonist of the vanilloid nociceptor. It has been used to treat musculoskeletal pain as an anti-inflammatory and anti-rheumatic agent.[70,71] Despite the fact that chronic low back pain is more common in older people, only one study has looked into the effects of Swedish massage with aromatic ginger oil to see if it can reduce disability.[72]

Even though further research is required to reach a consensus on the amount of ginger that is effective for long-term therapy, the use of ginger for pain relief is safe and promising.[72] Interventional medical treatments are reserved for patients who have root pain that has not responded to other treatments. With the Pulsed Radio frequency (PRF) modality, radio frequency (RF) may be a successful treatment choice.[73] It has the potential to be a useful treatment for refractory chronic cervical radicular pain.[74] For patients with axial back pain, with or without radicular pain, new stimulation waveforms and frequencies can provide a higher likelihood of pain relief than traditional spinal cord stimulation.[75]

VII. Conclusion

Radicular pain, more precisely, is a term used to describe pain caused by stimulation of, or a condition of, a nerve root. There are various treatment approaches for this particular condition. In current pharmacotherapy, various drugs used for the treatment of pain are NSAIDs, skeletal muscle relaxants, opioid analgesics, benzodiazepines, systemic corticosteroids, antidepressants, and anticonvulsants. Some drugs are in clinical trials which could be effective in the treatment, such as natural drugs like ginger is effective for the treatment even though further research is required to reach a consensus on the amount of ginger that is effective for long-term therapy. More research is being conducted to find novel pain-relieving treatment strategies.

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