



Review Article



Acupuncture and Spinal Stenosis: Considerations for Treatment

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Abstract

Acupuncture has been a staple of Eastern medicine for thousands of years. Recent evidence has shown that the benefits for spinal stenosis are strong. In this comprehensive review, the history and available literature will be reviewed. In addition, how the techniques have evolved, and their clinical utility will be discussed. The process and progression of spinal stenosis are addressed. The mechanism of action for acupuncture and the relevant treatment implications will be discussed. This is important in alleviating pain and providing a good quality of life. The findings in the pre-operative, peri-operative, and postoperative periods are highlighted. Finally, the preclinical data provide compelling evidence for novel pathways to be targeted. This resource could serve as a user-friendly guide for the clinician and scientist on this important topic. It might be the catalyst of ongoing investigation from clinical and preclinical sides.

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Introduction

Acupuncture as a practice is estimated to have been first developed approximately 3,000 years ago in China.^{1,2} It was, and has been, practiced by members of the culture since its inception. However, it was not until the late seventeenth century that acupuncture was first described in the medical literature in Europe.¹ Since then, the interest in acupuncture as a medical therapeutic modality waxed and waned until the late twentieth century, mainly due to the fundamental misunderstanding and perceived contradictions to scientific knowledge, with an overall uptrend in Western acceptance that has grown rapidly in the most recent decades as research endeavors looking into the utility of acupuncture as a medical treatment have increased

exponentially.^{3,4} In 1997, the National Institutes of Health issued a statement that approved the use of acupuncture as efficacious in reducing postoperative and chemotherapy-associated nausea and vomiting.⁵

Since then, the efficacy of acupuncture in the conservative management of a much wider array of diseases has been demonstrated, particularly in diseases notorious for causing chronic pain. One of the most common targets for acupuncture currently used in Western society is non-specific back pain. There is increasing evidence in the literature that shows the efficacy of acupuncture as an adjunct in the relief of non-specific back pain; however, the evidence is generally limited to showing low to moderate levels of pain relief and most pain relief comes from patients with acute back pain as opposed to chronic back pain.⁶⁻⁹ In addition, there is some conflicting evidence emerging that shows either no relief of this type of back pain or pain relief that is limited to the immediate term after acupuncture.^{10,11} Recent research has demonstrated significant promise in the treatment and prophylaxis of migraines.^{12,13} Migraine outcomes appear to be among the most positively affected by acupuncture.¹⁴ Musculoskeletal pain appears to be one of the most reported reasons for patients' utilization of acupuncture.¹⁵ One such condition with very high reported rates of musculoskeletal pain that has shown among the most favorable outcomes is fibromyalgia.¹⁴ The positive effect of acupuncture on fibromyalgia has been demonstrated as a decrease in reported pain, and a decrease in muscle stiffness, although these effects tend to be limited to the short-term.^{16,17} Although to a lesser degree, acupuncture has shown some evidence in the attenuation of neck pain, dental-associated pain, and pain associated with temporomandibular disorders.^{14,18,19} Acupuncture has been tested on pain relief associated with arthritic conditions, which include osteoarthritis and rheumatoid arthritis, and on depressive symptoms that are associated with posttraumatic stress disorder, generally with relatively little to no demonstrated positive effect.²⁰⁻²²

Multiple studies have now demonstrated that the prevalence of acupuncture use in the USA, in recent decades, has increased massively. In 2002, a National Health Interview Survey surveyed 31,044 adults in the USA inquiring about recent use (within the last 12 months) and lifetime use of acupuncture. The results indicated that 1.1% of adults, which represented an estimated 2.13 million American adults, had used acupuncture in the last 12 months with 4.1% reporting lifetime use.²³ A 2018 survey indicated that the total number of licensed acupuncturists in the USA had increased 257% in the 20-year period from 1998 to 2018, reflecting the large-scale growth and demand of acupuncture in the USA.²⁴ Another large-scale survey of acupuncture use in the

Keywords: Spinal stenosis; Acupuncture; Endocannabinoids; Novel treatment; Conservative management.

Abbreviations: AES, acupoint electrical stimulation; CB1, endocannabinoid receptor 1; GABA, γ -Aminobutyric acid; RCTs, randomized controlled trials; ST36, acupoint zusanli; TNF- α , tumor necrosis factor-alpha; VAS, visual analog scale.

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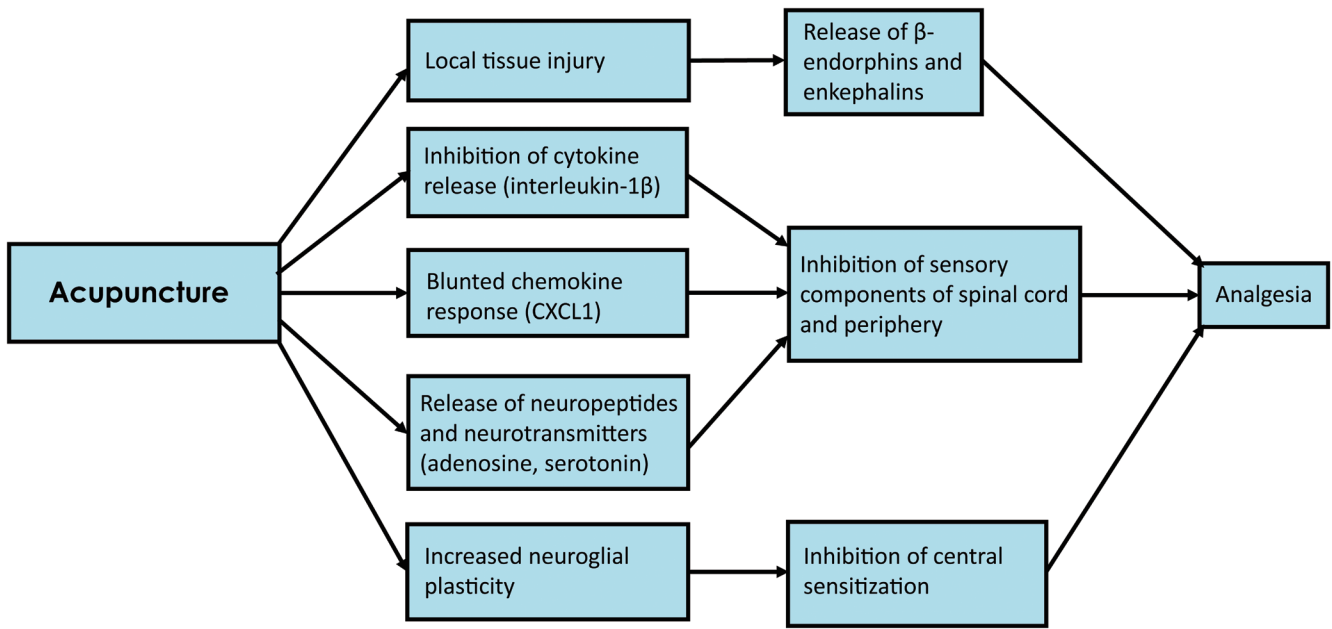


Fig. 1. Proposed biochemical mechanisms for acupuncture-induced analgesia.

USA in 2012 reported sociodemographic information of these adults, showing that females (69.6%), aged between 41 and 65 years, non-Hispanic (85.3%), and white (78.1%) were all predictors of acupuncture utilization in the USA.²⁵ In addition, a study in 2015 of 6,068 chronic musculoskeletal pain patients in the USA revealed that 32% of responders reported that they had pursued acupuncture use for pain relief.²⁶

As described previously, significant research has been carried out on the efficacy of acupuncture in several chronic pain disorders and is continuing to be researched at an increasing pace. A newer area where acupuncture is beginning to demonstrate significant efficacy is in the conservative management of degenerative spinal disease, particularly in spinal stenosis. Because patients with spinal stenosis often exhibit pain that is difficult to control with other conservative treatment measures, such as manual therapy and exercise, there a large marginal benefit currently exists for these patients when finding other more conservative treatment options for chronic pain management, such as acupuncture.²⁷

The following discussion will begin with an outline of the proposed pathophysiology behind the role of acupuncture in the treatment of spinal stenosis. Subsequently, the clinically relevant evidence regarding the efficacy of acupuncture in spinal stenosis patients will be divided into several sections. First, the pre-operative aspect of acupuncture for these patients will account for most of the discussion, which reflects the bulk of research carried out on acupuncture in this context as a conservative measure to help reduce or eliminate the need for surgical intervention. For patients who previously underwent surgical intervention for spinal stenosis, a relevant discussion of existing evidence on peri-operative care and postoperative care will be included. A discussion of when advanced care (surgical intervention) is recommended, and a discussion of emerging studies on this topic, will be provided.

Pathophysiology

To understand the usefulness of acupuncture as a viable treatment for pain relief for spinal stenosis patients, it is imperative to examine the potential mechanisms behind

which acupuncture is purported to cause pain relief. There are currently a wide variety of proposed mechanisms outlining the basis by which acupuncture provides pain relief on a biochemical level. Among the most widely cited mechanisms likely to play the most significant roles in acupuncture-induced analgesia are the release of neurotransmitters, endogenous opioid-like substances, and the activation of descending inhibitory systems.^{28,29} In medical scientific research, the release of endogenous peptides that manifest opioid-like analgesia was one of the first hypotheses postulated for the mechanism of action of acupuncture-induced analgesia.³⁰ Because beta/β-endorphins, enkephalins, and their respective receptors are increased at sites of tissue injury, this could be a logical initial and primary explanation for pain relief seen with acupuncture treatment.³¹

In addition, acupuncture has been shown to inhibit sensory components of the spinal cord and periphery by a complex interaction between numerous neuropeptides and neurotransmitters other than endogenous opioid-like peptides, including cytokines, serotonin, substance P, n-methyl-d-aspartic acid receptors, and signaling molecules, such as janus kinase-2 and signal transducer and activator of transcription-3.³² Acupuncture has been demonstrated to inhibit the action of several cytokines, such as interleukin-1β and tumor necrosis factor-α (TNF-α), and attenuating the response of chemokines and their respective receptors, such as chemokine ligand 1 (CXCL1)/CXC chemokine receptor 2 (CXCR2).³³ Another theory is the inhibition of central sensitization mediated by neuroglial plasticity.³³ Evidence has implicated adenosine, adenosine A1 and A2 receptors, and transient receptor potential vanilloid-1 in acupuncture-induced analgesia.^{34,35} Therefore, as it currently stands, acupuncture appears to mediate its analgesic effects through a multitude of mechanisms, which is currently evolving at a rapid pace and is very challenging to pinpoint with specificity due to this complex and multifactorial nature. However, it is most important to note in the context of this discussion that scientific evidence behind the efficacy of acupuncture treatment in pain relief of several different disorders is beginning to gain traction. An overview of the currently proposed biochemical mechanisms for acupuncture-induced analgesia is shown in Figure 1.

In addition to the induction of analgesia, acupuncture may have other methods by which it is effective in treating spinal stenosis. One method is the stimulation of peripheral receptive fields of neurons by acupuncture needles. The peripheral receptive fields that are activated may differ depending on the location of the acupuncture needles such as, for example, depending on the different acupuncture points used in traditional Chinese medicine.³⁶ Indeed, in traditional Chinese medicine, a wide variety of acupoints exist, which are often chosen in practice based on several factors, including patient history and physical findings, and practitioner preference.^{37,38} Although not yet fully understood from a mechanistic standpoint, the effect of specific, previously characterized acupuncture points on peripheral receptor field stimulation might serve as a target for future investigation, and facilitate replicable clinical recommendations for acupuncture in the treatment of spinal stenosis. Evidence is beginning to emerge that suggests acupuncture may facilitate increased physiological expression at neuron level, with a recent study suggesting that electroacupuncture at the acupoint zusanli (ST36) in particular may increase the expression of axonal growth-associated protein in sensory neurons located at the level of the dorsal root ganglion.³⁹ In addition, the demonstrated anti-inflammatory role that acupuncture mediates may be a mechanism by which it is effective in this patient population.⁴⁰ Therefore, although acupuncture-induced analgesia is a widely cited mechanism by which acupuncture may be effective in the conservative treatment of spinal stenosis, evidence behind several other mechanisms is beginning to accumulate, which could demonstrate potential functional efficacy on neurons. More investigation into each of these mechanisms is warranted to better elucidate their role in the efficacy of acupuncture treatment in spinal stenosis.

Pre-operative care

Acupuncture for spinal stenosis has previously been used as one of the last-line conservative treatment options before surgical interventions are considered in patients that do not meet criteria for urgent surgical intervention. In 2000, Witzmann described the efficacy of acupuncture as being derived more from the concurrent attenuation of psychological disturbance rather than from the pain relief itself.⁴¹ The American College of Physicians presented new clinical recommendations in 2017 for acute, subacute, and chronic low back pain. For chronic back pain, it is recommended with moderate-quality evidence that patients initially do a trial of nonpharmacologic treatment, including acupuncture. For acute or subacute low back pain, acupuncture has low-quality evidence, because pain of this nature generally self-resolves.⁴² Recent studies have suggested that acupuncture utilization in lumbar spinal stenosis patients, a condition seen in >200,000 adults in the USA alone, may now be as high as 63%.^{43,44} Because spinal stenosis is a common form of low back pain in the USA, a current understanding of the evidence in the literature on the conservative management, including acupuncture, could help to guide clinical treatment recommendations.

Several retrospective studies have shown a potential positive effect of acupuncture on spinal stenosis patient outcomes. A retrospective case series by Kim *et al.* on 33 lumbar spinal stenosis patients who received acupuncture combined with other conventional Korean nonsurgical medical therapy, including herbal supplements and pharmacopuncture, showed significant levels of pain reduction measured using a visual analog scale (VAS) for pain ($p<0.01$) and an increase in walking duration ($p<0.01$) after this combination treatment.⁴⁵ Lee *et al.* conducted a retrospective study on 47 patients with lumbar spinal stenosis treated with an

alternative method of acupuncture called Wonli acupuncture, which utilizes unique acupuncture needles in combination with a direct approach to the intervertebral foramen. The results indicated decreased VAS pain scores ($p<0.01$), and better functional status indicated by decreased Oswestry disability index scores ($p<0.01$) post-treatment.⁴⁶ This suggested the potential utility of this method of acupuncture for the conservative treatment of lumbar spinal stenosis for pain reduction and functional status. In 2020, Kim *et al.* conducted a long-term follow-up (2–5 years) on 378 spinal stenosis patients who received inpatient, nonsurgical integrative Korean medical treatment including acupuncture, electroacupuncture, herbal medicine, pharmacopuncture, and Chuna manipulation. The results indicated that scores for back and leg pain decreased significantly on initial discharge from the hospital ($p<0.001$) and remained reduced in the 2–5 year follow-up period ($p<0.001$).⁴⁷ Of note, these studies evaluated the efficacy of several different types of acupuncture, including traditional acupuncture, electroacupuncture, and Wonli acupuncture, although a direct comparison between these types was not made.

Prospective studies have shown some promise. Inoue *et al.* conducted a prospective case series on 17 patients with spinal stenosis who had failed a trial of conventional acupuncture treatment for symptomatic relief. The 17 patients were subjected to 3–5 separate sessions of electroacupuncture administered under X-ray guided fluoroscopy directly to the nerve roots and evaluated for pain level and walking distance before and immediately after treatment sessions, then again after 3 months post-treatment. The results showed reduction in back ($p<0.01$) and leg pain ($p<0.01$) with improvement in continuous walking distance after treatment completion, which was sustained at 3 months post-treatment ($p<0.01$).⁴⁸ Although a relatively small sample size, this study highlights that electroacupuncture may be an efficacious option for patients that do not achieve pain relief with traditional acupuncture methods. Of note, Inoue *et al.* demonstrated that pudendal nerve electroacupuncture might be efficacious in these patients, with noticeable reductions in pain levels, particularly in the lower extremities.⁴⁹ Furthermore, a 2019 study showed significant VAS pain scores ($p<0.001$) in 24 lumbar spinal stenosis patients who were treated with a combined conventional therapeutic approach including traditional acupuncture, pharmacopuncture, and applied kinesiology.⁵⁰

A 2016 Cochrane Systematic Review that evaluated five randomized controlled trials (RCTs) that compared surgical versus non-surgical treatment (including acupuncture) of spinal stenosis concluded that there is a very low amount of confidence in asserting whether surgical or conservative nonsurgical management of spinal stenosis has better outcomes. However, the authors found that the conservative treatment options, such as acupuncture had no reported side effects, and the side effects from surgical management were from 10% to 24%.⁵¹ Therefore, these results highlight that acupuncture as a conservative treatment option for spinal stenosis may offer similar outcomes to surgical intervention, and offer a considerably lower risk of side effects. Since this Cochrane Systematic Review was published, several other trials evaluating the efficacy of acupuncture on spinal stenosis patients have been published. Hadianfard *et al.* randomly selected 24 patients with lumbar spinal stenosis and symptoms of neurogenic claudication who subsequently completed 10 sessions of acupuncture. Several measures, including quality of life and pain score, were measured before and after the intervention period and at 6 weeks post-intervention. The results indicated significantly reduced pain scores immediately after cessation of intervention ($p<0.001$) and at 6 weeks postintervention ($p=0.01$). Further, patients reported significant improvements in quality of life immediately after intervention and 6 weeks postintervention, including significant improvements

in overall bodily pain and vitality ($p < 0.05$).⁵² A 2019 RCT by Kim et al. examined 36 patients randomly allocated to one of three groups, two of which received acupuncture and one that received no acupuncture but received other conventional treatment therapy including epidural steroid injection, non-steroidal anti-inflammatory drugs, and physiotherapy. The results showed that the groups that received acupuncture showed significant improvements in back and leg pain, and functional capacity measured using treadmill walking at 3 and 6 months post-treatment compared with the group that received only other conventional therapy.⁵³ In 2019, Oka et al. published the first comparative trial of different conservative treatment options for lumbar spinal stenosis. Researchers allocated approximately 40 patients each into medication, exercise, and acupuncture groups. Reduction in symptom severity and improvement in physical function were measured using Zurich claudication questionnaire scores before and after a total of 4 weeks of treatment. Results indicated a significant improvement in symptom severity in the medication ($p = 0.048$), acupuncture ($p = 0.04$), and exercise ($p = 0.003$) groups. However, significant improvements in physical function were only seen in the acupuncture group ($p = 0.045$). In addition, patients reported significantly higher levels of satisfaction with their treatment regimen in the acupuncture group compared with the medication group. Although limited by a small sample size, this study suggests potential overall superiority of acupuncture compared with exercise and medication as conservative treatment options.⁵⁴

However, it is important to note that there is still debate in the literature regarding the efficacy of acupuncture for conventional treatment of spinal stenosis, with several studies deeming its effect as nonexistent or inconclusive regarding functional outcomes and pain relief.⁵⁵ A 2013 Cochrane Systematic Review by Ammendolia et al. utilizing data from 1,851 patients with lumbar spinal stenosis with neurogenic claudication from 21 trials concluded that moderate-high quality evidence for nonoperative treatment for lumbar spinal stenosis patients in general is lacking.⁵⁶ A 2013 systematic review and meta-analysis by Kim et al. utilizing six RCTs and six controlled clinical trials reported generally favorable outcomes for pain reduction and functional capacity in acupuncture treatment groups compared with controls that lasted ≤ 6 months. However, the authors noted that all of the RCTs used different methods, including combinations of acupuncture points and techniques, and all of the studies included were conducted in China.⁵⁷ These might introduce bias and limit the generalizability of the results. Therefore, the authors asserted that no firm evidence for either the safety or efficacy of acupuncture for lumbar spinal stenosis could be concluded.⁵⁷ Kim et al. conducted an RCT in 2016 on 50 patients with lumbar spinal stenosis who were allocated to receive either usual conservative management (physical therapy) alone or usual care in conjunction with 12–16 individual sessions of acupuncture (manual acupuncture with or without concurrent electroacupuncture) over 6 weeks. The outcomes of the functional status of the back were measured using the Oswestry disability index and improvements in pain levels were assessed at 3 months postintervention. The results showed no significant difference in back-specific functional status between the acupuncture and control groups, although mild improvement in back and leg pain were noted at the 3-month follow-up.⁵⁸ In 2021, Bussieres et al. reported very low quality evidence for the recommendation of traditional acupuncture on a trial basis for spinal stenosis patients.⁵⁹

Of note, the selection of acupuncture points may influence the efficacy of acupuncture treatment in these patients. Some studies specifically report which acupoints were used, many of them do not specify. Further, researchers report using an individualized approach to which acupoints are

used during their trials, making it difficult to objectively assess the efficacy of any one acupoint or series of acupoints used. In the 2015 retrospective case series by Kim et al., the semi-individualized selection of acupuncture points was utilized in the study's 33 patients, including the acupuncture points BL23, BL25, GV3, GV4, and GB30. Utilization of these points leads to a significant reduction in pain and an increase in functional status.⁴⁵ In the aforementioned study by Hadinfard et al., a significant reduction in pain and an improvement in several measures of quality of life were achieved using many acupuncture points including BL-23, BL-25, BL-26, DU-3, DU-4, DU-20, LI-4, BL-37, BL-40, BL-54, BL-57, and BL-60.⁵² Furthermore, the 2019 RCT by Kim et al. reported the use of acupoints BL22, BL23, BL24, BL25, LI4, ST36, and LV3 that resulted in the alleviation of pain and increased functionality in 36 symptomatic spinal stenosis patients.⁵³ Although it appears that certain acupoints, such as BL-23 and BL-25, can consistently achieve positive results in this patient population, it is difficult to draw strong conclusions in the absence of direct, large-scale, controlled comparisons of different acupoints. In the future, the most effective combination of acupuncture points may become evident as the research continues to progress at an increasing rate. Specifically, future studies should consider dividing the use of different acupoints into separate trial groups to obtain clearer evidence on which acupoints are most effective in the treatment of spinal stenosis, which may subsequently help guide clinical recommendations.

Overall, in the past 5 years, there appears to be more convincing evidence for the utility of acupuncture as a potentially effective adjunct treatment in the conservative management of spinal stenosis. Additional prospective studies are needed, and RCTs and studies with larger sample sizes. Furthermore, most of these trials are still being conducted in Asian countries, potentially limiting generalization to patients in other geographic locations, such as the USA. In general, evidence for the utility of acupuncture seems to be most significant in the short-term (immediate-6 weeks). The results reported that longer times (3 months or longer) were less convincing, especially for improvements in functional status. Therefore, studies incorporating longer follow-ups would be beneficial. In addition, since some forms of acupuncture may be more efficacious than others, more direct comparisons between them may help to determine the superiority of certain forms over others, helping to further guide clinical recommendations for these patients.

Peri-operative/postoperative care

Acupuncture has shown some efficacy in alleviating postoperative pain from several types of procedures, including cardiac, abdominal, and joint replacement surgery.^{60–62} Although relatively less prevalent in the literature, a few studies have investigated the effect of acupuncture on peri-operative and postoperative pain relief in patients who underwent lumbar surgery for spinal stenosis and other diseases that affect the spine that were indicated for surgical intervention.⁶³ In 2011, Yeh et al. conducted a randomized placebo- and sham-controlled trial on patients who received lumbar spine surgery, including spinal stenosis patients. Patients were divided into three equal groups ($n = 30$ each): the intervention group that received acupoint electrical stimulation (AES) therapy with true acupoints, a group that received AES at sham acupoints, and a group that received no AES intervention. The results showed that postoperative VAS pain scores were significantly lower in the group that received AES with true acupoints than either the control group ($p < 0.007$) or the sham group ($p = 0.005$).⁶⁴ Yeh et al. conducted another similarly constructed study in lum-

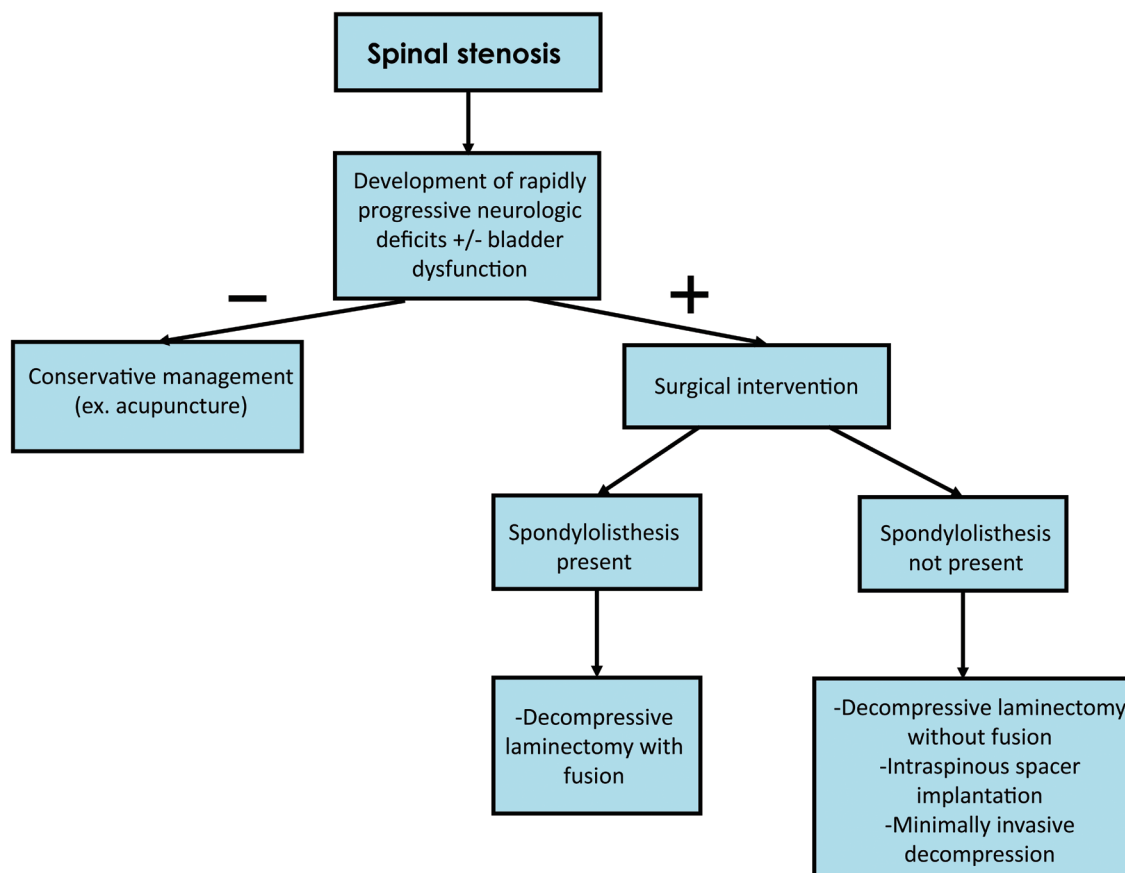


Fig. 2. Advanced care surgical algorithm for spinal stenosis patients.

bar spine surgical patients, where results demonstrated reduced pain scores in patients who received postoperative AES. However, the results showed that patients who received AES and control patients had no significant difference in the postoperative utilization of opioids for pain management.⁶⁵ No studies that involve classical acupuncture on postoperative pain for patients who underwent surgery for spinal stenosis were identified in the literature. However, a related study was performed on 132 patients who received classical acupuncture following surgical intervention for lumbar disc protrusion. The results demonstrated significantly decreased VAS pain scores in back ($p < 0.0001$) and leg pain ($p < 0.0001$) 6 h after acupuncture administration.⁶⁶ Although these results are significant, it is important to note that their applicability to lumbar spinal stenosis surgical patients may be limited due to the different disease processes and surgery involved. Overall, there appears to be little research into the use of acupuncture, especially classical acupuncture, on the relief of postoperative pain in spinal stenosis patients. Future research into this area, particularly with larger sample sizes, is warranted.

Advanced care

As discussed previously, several studies have shown that there does not appear to be a significant difference in outcomes between surgical and nonsurgical treatment for spinal stenosis; therefore, nonsurgical management is currently recommended for most spinal stenosis patients on an elective basis with a strong reliance on patient pref-

erence.^{67,68} However, it is important to note the criteria for when conservative management has failed and when surgical intervention is needed. This criterion includes the emergence of rapidly progressive neurologic deficits with or without bladder dysfunction or the emergence of bladder dysfunction in isolation.⁶⁷

Several options for surgical approaches exist and the choice of which to use depends on a variety of factors. For spinal stenosis without spondylolisthesis, the most preferred approach is decompressive laminectomy without fusion.⁶⁷ The preference for not undergoing concurrent fusion in these patients is based on the fact that outcomes between both appear to be similar, with decompressive laminectomy without fusion demonstrating less complications than decompressive laminectomy with fusion in these patients.⁶⁹ Another surgical option for lumbar spinal stenosis patients without spondylolisthesis is an intraspinous spacer implantation.⁶⁷ This method appears to be most appropriate and effective when intermittent claudication is present, which is classically worsened with spine extension and relieved with spine flexion.⁷⁰ Another option for patients without spondylolisthesis is minimally invasive decompression. Some studies have suggested lower complication rates with this procedure compared with its counterparts; however, the relative functional and symptom outcomes with this procedure remain unclear.^{67,71,72} However, if spondylolisthesis is present, fusion is generally recommended.⁶⁷ To date, studies have generally shown improvements in outcomes, including overall quality of life, in spinal stenosis patients with spondylolisthesis who underwent spinal fusion.⁷³ A surgical algorithm for spinal stenosis patients has been provided in [Figure 2](#).

Emerging studies

As discussed previously, acupuncture has been demonstrated to facilitate the release of several molecules, including a multitude of neuropeptides, in the central nervous system. The more well-known and better characterized of these include β -endorphins and enkephalins. However, pre-clinical trials that involve newer targets, which could play a mechanistic role in acupuncture-induced analgesia, are emerging.

One of these newer targets being explored is endocannabinoid receptor 1 (CB1). In 2021, Wang *et al.* conducted a study to determine if CB1 participates in pain relief in electroacupuncture. Researchers made neck incisions along the cervical spinal cord in rats, and subsequently measured the levels of CB1 protein, mRNA, and the immunoreactivity of CB1 in rats who received electroacupuncture compared with those who did not. The results indicated that rats receiving electroacupuncture had elevated levels of CB1 protein, mRNA, and heightened immunoreactivity of CB1 ($p < 0.05$) which corresponded to alleviated allodynia in the rats who received electroacupuncture. In addition, the relief of allodynia in rats that received electroacupuncture was reversed when a CB1 antagonist (AM251) was given, suggesting upregulation of CB1 due to electroacupuncture as a potential mechanism of subsequent pain relief.⁷⁴ Zheng *et al.* conducted a similar study that demonstrated an increase in CB1 protein levels following electroacupuncture. In addition, researchers demonstrated a concurrent reduction in ERK1/2 activity, suggesting CB1 activation at least partially regulating the ERK1/2 signaling pathway was a potential mechanism of action for CB1-induced antinociception in electroacupuncture.⁷⁵ Another potential newer target is angiopoietin 1. In 2021, Wu *et al.* measured the mechanical withdrawal threshold, thermal withdrawal latency, and levels of angiopoietin-1 in 45 rats randomly allocated into a model group that underwent spinal nerve ligation of L5 to establish a neuropathic pain model with no subsequent electroacupuncture treatment, a model group that underwent electroacupuncture treatment, and a sham group.⁷⁶ The results indicated a significantly elevated mechanical withdrawal threshold and thermal withdrawal latency in the electroacupuncture group at 2 weeks postintervention ($p < 0.05$), signifying decreased allodynia, along with increased levels of assumed to assist in nerve regeneration, further investigation into this protein is warranted to elucidate its mechanistic role in acupuncture-induced pain relief.⁷⁷ The downregulation of toll-like receptor 4 and upregulation of heat shock protein 90 have recently been shown to be associated with a reduction in thermal hyperalgesia in rat spinal injury models.⁷⁸

Studies aimed at further characterizing some targets that have previously been described in the literature are ongoing. Wang *et al.* conducted a study in 2019 where levels of several different cytokines and subsequent pain thresholds were measured in 84 rats randomly allocated into four different groups: model groups that received cervical incisions (two groups received electroacupuncture treatment, one did not) and a control group that received neither an incision nor electroacupuncture treatment. The results showed that TNF- α and interleukin-10 mRNA levels were significantly lower ($p < 0.05$) in the groups that received electroacupuncture treatment compared with the model group that did not receive electroacupuncture. In addition, one of the electroacupuncture groups showed a significantly elevated pain threshold and elevated levels of interleukin-4 and interleukin-4R mRNA levels compared with the model group that did not receive electroacupuncture ($p < 0.05$).⁷⁹ These results add credence to the notion that the mechanism of pain relief with acupuncture treat-

ment may be at least partially mediated through alterations in the levels of cytokines. As previously mentioned, studies have tended to show that acupuncture is associated with a decrease in cytokine levels, as seen in the results in this experiment; however, this study shows the potential for acupuncture to increase certain cytokine levels (interleukin 4). The mechanism of γ -Aminobutyric acid (GABA) on acupuncture-induced analgesia continues to be explored in the literature, with a recent study demonstrating the upregulation of GABA and several GABA receptor subtypes, including GABA-A α 2 and GABA-A β 3, with an increased thermal pain threshold in rat models who underwent cervical neck incisions and subsequent electroacupuncture treatment compared with models who did not undergo electroacupuncture treatment.⁸⁰

The number of preclinical studies examining the effects of a multitude of different neuropeptides and other proteins has increased significantly recently. Due to the complex nature of the mechanisms, because they relate to acupuncture-induced analgesia, interest in these studies will continue to increase and might help to elucidate the potential pathways by which acupuncture is effective in reducing pain in a multitude of disease processes.

Conclusions

The use of acupuncture as a therapeutic approach for the conservative management of spinal stenosis has historically been met with much trepidation, particularly in the Western world. However, clinical trials are beginning to emerge with the majority demonstrating the efficacy of acupuncture techniques, particularly electroacupuncture, when providing pain relief and, to a lesser extent, improving functional outcomes in spinal stenosis patients. Currently, acupuncture is a very safe treatment option with several studies demonstrating pain relief at least on par with surgical interventions for patients that do not meet the criteria for urgent surgical intervention. Therefore, acupuncture is viable and effective as an adjunct conservative treatment option in these patients. Clinical trials using larger sample sizes, longer follow-ups, and a wider variety of geographical locations are required to further guide clinical recommendations for these patients.

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Author contributions

AC wrote and organized the manuscript, BL conceptualized and critical editing. All authors have made a significant contribution to this article and have approved the final manuscript.

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