





**EVIDENCE-BASED REVIEW**

Update of evidence-based interventional pain medicine according to clinical diagnoses

### 3. Pain originating from the lumbar facet joints

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**Abstract**

**Introduction:** Pain originating from the lumbar facets can be defined as pain that arises from the innervated structures comprising the joint: the subchondral bone, synovium, synovial folds, and joint capsule. Reported prevalence rates range from 4.8% to over 50% among patients with mechanical low back pain, with diagnosis heavily dependent on the criteria employed. In well-designed studies, the prevalence is generally between 10% and 20%, increasing with age.

**Methods:** The literature on the diagnosis and treatment of lumbar facet joint pain was retrieved and summarized.

**Results:** There are no pathognomic signs or symptoms of pain originating from the lumbar facet joints. The most common reported symptom is uni- or bilateral (in more advanced cases) axial low back pain, which often radiates into the upper legs in a non-dermatomal distribution. Most patients report an aching type of pain exacerbated by activity, sometimes with morning stiffness. The diagnostic value of abnormal radiologic findings is poor owing to the low specificity. SPECT can accurately identify joint inflammation and has a predictive value for diagnostic lumbar facet injections. After “red flags” are ruled out, conservatives should be considered. In those unresponsive to conservative therapy with symptoms and physical examination suggesting lumbar facet joint pain, a diagnostic/prognostic medial branch block can be performed which remains the most reliable way to select patients for radiofrequency ablation.

**Conclusions:** Well-selected individuals with chronic low back originating from the facet joints may benefit from lumbar medial branch radiofrequency ablation.

**KEYWORDS**

diagnostic/prognostic block, evidence-based medicine, lumbar facet, radiofrequency ablation

## INTRODUCTION

This narrative review on pain originating from the lumbar facet joints is an update of the article published in 2010 in the series “Evidence-based Interventional Pain Medicine According to Clinical diagnoses.”<sup>1</sup>

Pain originating from the lumbar facets can be defined as pain that arises from the innervated structures comprising the joint: the subchondral bone, synovium,

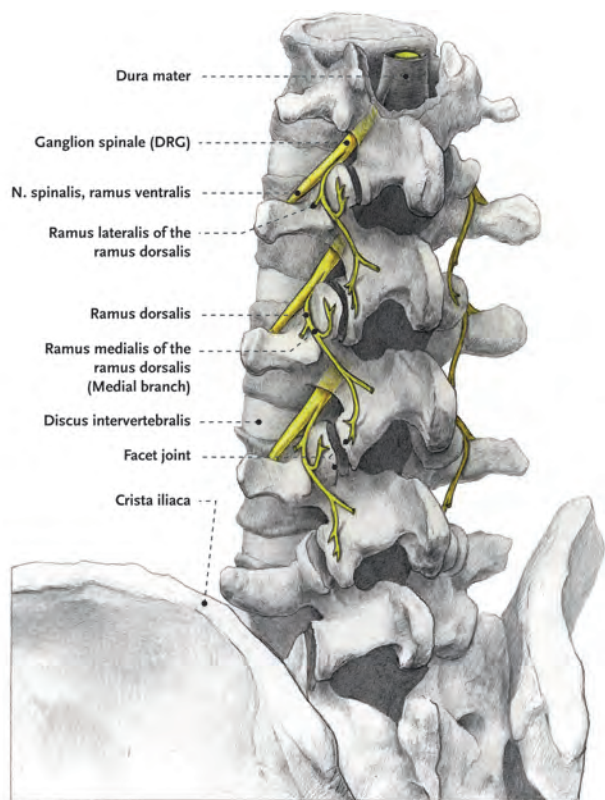
synovial folds, and joint capsule (the articular cartilage is aneural).<sup>2–4</sup> Although this definition is simple, the diagnosis and treatment of lumbar facet joint pain is controversial and complex. In the literature, the prevalence ranges from 4.8% to over 50% among patients with low back pain depending on the criteria used for diagnosis and selection of patients (i.e., more stringent criteria results in lower prevalence rates).<sup>5</sup> In high-quality studies that have utilized controlled blocks, the prevalence rate typically ranges between 10% and 20%, increasing in the

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elderly.<sup>2,6</sup> Lumbar facet joints are formed by the inferior articular process of the superior vertebra and the superior articular process (SAP) from the inferior vertebra, and the posterior articulation of the lumbar column (Figure 1). Progressing caudally from L3 to S1, the orientation of the facet joints gradually shifts from the sagittal plane (which protects against rotation) to the coronal plane (which better protects against forward flexion and shearing forces), with the maximal transverse articular orientation occurring distally. Unlike the cervical spine where the medial branches are named differently because the C8 spinal root exits between C7 and T1, each lumbar facet joint receives dual innervation by medial branches from the named nerve at the upper level and from one level above (i.e., L4-5 receives innervation from L3 and L4). Medial branches also innervate the multifidus muscle and the interspinous ligament and muscle.<sup>7,8</sup>

The medial branch runs from the ramus dorsalis of the spinal nerve, which also forms the source of the lateral (iliocostalis lumborum muscle and skin innervation) and intermediate branches (longissimus muscle innervation).<sup>9</sup> The L1–L4 medial branches run dorsal and caudally against bone over the base of the transverse process at the junction of the SAP. Subsequently, the medial branch passes under the mamillo-accessory ligament, which is partially responsible for its consistent location, from where branches to the facet joints above



**FIGURE 1** Anatomy of the lumbar spinal column. “Illustration: Rogier Trompert Medical Art”. [www.medical-art.eu](http://www.medical-art.eu). DRG, dorsal root ganglion.

and below are provided. The L5 dorsal branch runs in the groove between the SAP and the sacral ala, where it is amenable to treatment. L5 differs slightly in that it is traditionally held at the dorsal ramus itself, rather than the medial branch, though a recent cadaveric study has called this into question (i.e., the L5 medial branch is targeted between the sacral ala and articular process).<sup>10</sup> Opposite the caudal aspect of the L5/S1 facet joint the L5 dorsal ramus divides into a medial and intermediate branch; the L5 dorsal ramus has no lateral branch.<sup>7,8</sup>

The mamillo-accessory ligament can become ossified, which is most common at L5 (up to 26%), less frequent at L4 (up to 11%), and rare at more cephalad levels. Ossification can cause entrapment of the medial branch or the dorsal ramus.<sup>11,12</sup>

Lumbar facet joints play an important role in load transmission, restrict axial rotation, and stabilize the motion in flexion and extension.<sup>13,14</sup> Related to their function, lumbar facet joints are prone to degeneration, which is closely linked to degenerative disc disease and typically most prominent at L4/L5 and L5/S1.<sup>15,16</sup> Dehydration of the intervertebral disk results in decreased disc height and increased shearing forces on the facet joint, which also bear increased axial load.<sup>17</sup> Predisposing factors for accelerated facet degeneration are increased age, spondylolisthesis, obesity, facet joint tropism, poor posture, or adjacent to levels of previous surgery. Chronic shearing stress induces inflammation, joint effusion, and stretching of capsule, which stimulates nociceptive nerve endings innervating the facet joint and subsequently produces a pain response.<sup>18</sup> Lumbar facet joint pain sometimes results from a traumatic event like a sports injury or a fall and may be accelerated after fusion surgery.<sup>1,19,20</sup>

Recently, a multispecialty and international working group developed guidelines addressing clinically relevant questions, for example, the value of history and physical examination in selecting patients for blocks, the value of imaging, whether conservative treatment should be used before injections, the diagnostic and prognostic value of medial branch blocks (MBB). By approaching patients according to evidence-based guidelines, disparate treatments and controversies surrounding lumbar facet joint pain will hopefully diminish in the future.<sup>5</sup>

## METHODOLOGY

This narrative review is based on the article “Pain originating from the lumbar facet joints” published in 2010.<sup>1</sup> In 2015 an independent company, Kleijnen Systematic Reviews, performed a systematic review of the literature for the period 2009–2015, based on existing systematic reviews (SRs) and randomized controlled trials (RCTs).<sup>21,22</sup> For the current article an updated search was conducted for the period 2015–2022, using “lumbar” and “facet” and “pain” associated with the interventional pain management techniques, in this case, “injection” and

“intra-articular” or “medial branch block” and “radiofrequency.” Additionally, authors could select relevant missing articles.

## DIAGNOSIS

### History

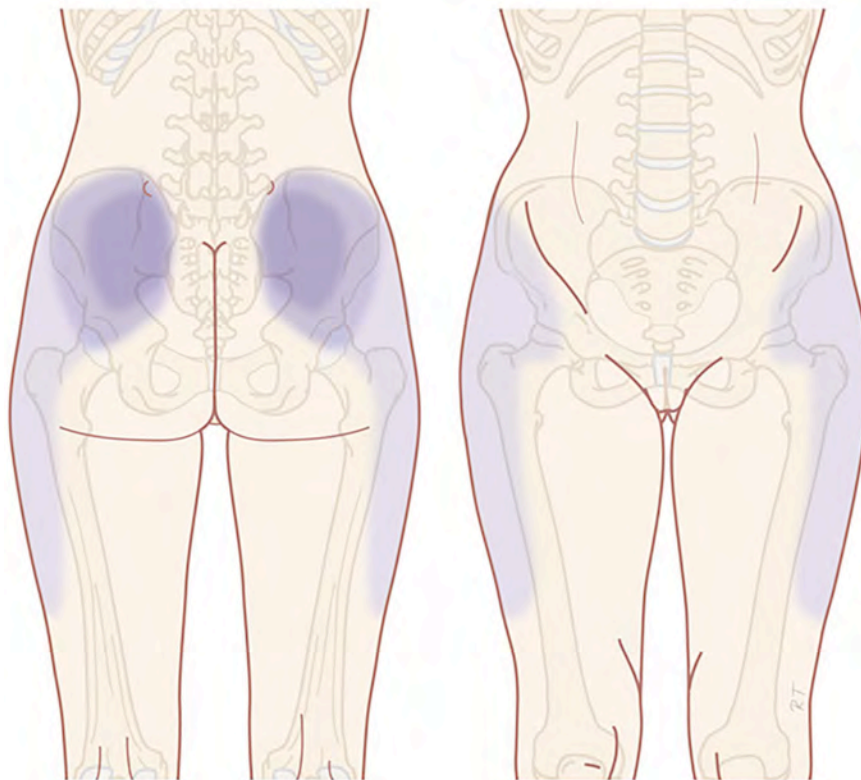
It is important to consider that (chronic) low back pain can be influenced by psychosocial factors.<sup>23–25</sup> Thus, history-taking should include a detailed multidimensional evaluation of the patients’ pain including its effects on daily activities and quality of life. Screening questions for red flags pointing to cancer, infection, trauma or underlying neurologic/systemic pathology should be evaluated.

There are no pathognomic signs or symptoms for pain originating from the lumbar facet joints, though location and referral patterns, onset, duration, quality of pain, aggravating and relieving factors, and imaging can all provide important clues. The most common reported symptom is uni- or bilateral axial low back pain. Pain originating from the upper facet joints can be referred to the flank, hip, groin, and thigh regions; pain from lower facet joints can refer to the posterior thigh (Figure 2). Pain referred distal to the knee is infrequently associated with facet pathology.<sup>1,26</sup>

Most patients report an aching type of pain worsening with an activity that typically has no neuropathic characteristics or radicular distribution pattern, though nociplastic characteristics such as tingling and allodynia may accompany all spine pain etiologies including lumbar facetogenic pain.<sup>28</sup> Since the facet joints are involved in all principal movements of the spine, pain can increase on extension, flexion, rotation, or walking uphill. It can also be provoked by static positions (like standing or sitting) or after a period of inactivity (like waking up from bed, morning stiffness).<sup>29,30</sup>

### Historical findings and clinical examination

A systematic review performed by Maas et al.<sup>31</sup> determined the diagnostic accuracy of history and physical examination to identify pain originating from the lumbar facet joints using a diagnostic block as a reference standard. One hundred and twenty-nine combinations of index tests and reference standards were studied, with most index tests having been evaluated in single studies with a high risk of bias. Only the results of Revel’s criteria (comprising seven clinical signs, with the presence of five out of seven during the assessment of the patient predicting an adequate response to lumbar facet block) could be pooled. Published sensitivities and specificities ranged from 0.11 (95% CI 0.02–0.29) to



**FIGURE 2** Pain referral pattern of lumbar facet pain adapted from McCall et al.<sup>27</sup> Illustration: Rogier Trompert Medical Art. <http://www.medical-art.eu>.

**TABLE 1** Diagnostic scale proposed by Gomez-Vega et al.<sup>32</sup>

Symptoms	Signs
Axial or bilateral axial lumbar pain	Kemp sign <sup>a</sup>
Improvement with rest	Pain induced in the articular or transverse process
Absence of a radicular pattern	Sign of facet stress or Acevedo sign <sup>a</sup>

<sup>a</sup>Kemp's test<sup>33</sup> and Acevedo sign have a poor diagnostic accuracy.<sup>32</sup>

1.00 (95% CI 0.75–1.00) and 0.66 (95% CI 0.46–0.82) to 0.91 (95% CI 0.83–0.96), respectively. They concluded that neither history nor physical exam could be used to identify a painful facet joint or to limit the need for a diagnostic block.<sup>31</sup>

Gomez Vega et al.<sup>32</sup> performed a pilot study following a systematic review and consensus meetings on the evaluation of lumbar facet joint pain. A total of 36 signs and symptoms were evaluated, of which 12 (8 symptoms and 4 signs) were included in the final survey and investigated in 31 patients with a positive diagnostic block. They proposed a diagnostic scale containing three symptoms and three signs as illustrated in Table 1.

In their pilot study, the occurrence of the facet stress sign was much lower (40.9%) compared with Kemp Sign (81.8%) in patients with a positive diagnostic block.<sup>32</sup> A 2014 systematic that included five studies evaluating the diagnostic accuracy of Kemp's test using response to intra-articular (IA) facet joint block or MBB as a reference standard found a sensitivity and specificity below 50% and a negative predictive value of ~60%.<sup>33</sup>

In a multicenter study, Cohen et al.<sup>5</sup> found a weak association between a positive response to lumbar facet radiofrequency ablation and paraspinal tenderness. In the most recent review on the use of diagnostic tests to identify painful structures in chronic low back pain that included 14 studies evaluating the facet joints, Han et al.<sup>34,35</sup> found no historical physical exam signs that were predictive of response to diagnostic blocks.

## Differential diagnosis

In patients presenting with chronic low back pain, the underlying disease should be ruled out with the help of red flags: malignancy, compression fracture, and spinal infection. However, most red flags lack specificity, with one retrospective study finding that while red flags increased the probability of serious spinal pathology, negative red flag screening did not lower the probability of diagnosing serious pathology.<sup>36</sup>

Since there are a large number of potential pain generators in the low back, the following pain syndromes which can resemble facet joint pain or concurrently exist should be considered and ruled out: myofascial pain,

ligamentous injury, discogenic low back pain, lumbosacral radicular pain, sacroiliac joint pathology, hip pathology, or inflammatory conditions (rheumatic disease, ankylosing spondylitis or gout).<sup>1,14,37</sup>

## Additional tests

### Imaging

Radiologic imaging can be used to rule out underlying disease and to identify facet pathology. Intervertebral disc height loss or facet degeneration is highly prevalent among patients without low back pain and therefore lack specificity.<sup>38</sup> The correlation between abnormal morphology on radiologic findings and pain originating from the facet joints (diagnostic value) and the prognostic value of abnormal radiologic findings and the effect of denervation is low.<sup>5,39–42</sup> Plain radiography, CT, MRI, scintigraphy imaging cannot accurately identify painful lumbar facet joint levels and are not routinely recommended before performing a diagnostic facet joint block.<sup>5</sup>

- Plain radiography is relatively inexpensive and widely available, but X-rays can be difficult to interpret and have high-rate false-positive and -negative findings. Standard views include an antero-posterior (AP) and lateral view for detecting spinal misalignments or tumors but are of limited value to visualize facet joints. In the oblique view, joint space narrowing, sclerosis and bone hypertrophy of the facet joints can be seen, especially in severe disease.<sup>29,40</sup>
- CT-imaging—is the most sensitive imaging technique for detecting degenerative changes in facet joints due to high contrast visibility between bony structures and soft tissue, and its capability to image the joint in multiple planes.<sup>39,40</sup>
- MRI is less sensitive than CT in detecting facet pathology but provides a superior delineation of soft tissues compared to other imaging modalities and has the advantage of detecting the consequences of facet degeneration on adjacent neural structures, for example, hypertrophy causing foraminal stenosis and radiculopathy.<sup>41,42</sup>
- Bone scintigraphy can be of use in patients in whom pain is unexplained by MRI or when there are so many abnormalities found on MRI that which structure is causing the pain is uncertain. Increased metabolic activity at a particular site may suggest it as the most likely origin of symptoms.<sup>40</sup>
- SPECT can detect active facet joint inflammation related to back pain.<sup>43</sup> It is the only imaging modality that provides any prognostic value prior to MBB, with weak evidence for its predictive value before intra-articular (IA) facet joint injections. The cost-effectiveness of SPECT warrants further



evaluation.<sup>5,44,45</sup> In a systematic review by Han et al.,<sup>34</sup> the authors found informative positive (2.80 [95% CI: 1.82–4.31]) and negative (0.44 [95% CI: 0.25–0.77]) likelihood ratios for predicting response to diagnostic injections based on 3 ( $n = 121$ ) studies.

## Diagnostic/prognostic blocks

When history taking and physical examination suggest pain originating from the lumbar facet joint, a diagnostic/prognostic MBB can be performed at the suspected painful lumbar level and from one level above (each facet joint receives dual innervation). Studies have shown that performing a MBB is the most reliable and appropriate way to diagnose lumbar facet joint pain and is part of the standard diagnostic protocol to select patients for radiofrequency ablation.<sup>5</sup> However, a diagnostic/prognostic MBB has some limitations. False negative and positive rates of a diagnostic/prognostic MBB vary from 25% to 49%, and are influenced by age, comorbid spinal pathology, opioid use, and psychosocial factors. High expectations (indicative of a strong placebo response), use of sedation, excessive use of superficial local anesthetic, and a non-selective block with leakage of injectate into surrounding pain-generating structures can cause false positive responses. A false negative response can result from aberrant innervation, inappropriate needle placement, failure to detect vascular uptake, and the inability of the patient to discern baseline from procedural pain. To reduce false positives, it is advised to administer the lowest volume of local anesthetic and carefully position the needle. In a cadaveric study ( $n = 6$ ), Wahezi et al.<sup>35</sup> found that both 0.25 and 0.5 mL of contrast bathed the 18 MBB and that using lower volumes significantly reduced aberrant spread to adjacent structures. However with inappropriate techniques, false negatives can occur with low volumes.<sup>46</sup> Dreyfuss et al. studied the most ideal needle tip position for a lumbar MBB, comparing a needle-end position at the upper edge of where the transverse process and articular process intersect to one midway between the upper border of the medial transverse process and at the mammiillo-accesory ligamentum. When a more caudad approach at the mammiillo-accesory ligamentum was used, lower rates of spread of local anesthetic to the ventral epidural space and spinal nerves were observed (using 0.5 mL injectate volume).<sup>47</sup> Incidences of intravascular uptake have been reported to range from 3.7% to even 22.5%.<sup>48</sup> Consequently, intravascular uptake needs to be ruled out with contrast before administration of the local anesthetic.<sup>5,49</sup> Digital subtraction enhances the ability to detect inadvertent vascular flow compared with live fluoroscopy,<sup>50</sup> but is not routinely available and coincides with increased radiation exposure. At least contrast should be administered during real-time fluoroscopy, which is more sensitive than intermittent fluoroscopy and aspiration.<sup>50</sup> In one study by Kaplan et al.<sup>51</sup>

performed in 18 individuals, if vascular uptake was appreciated during initial needle placement, re-direction of the needle failed to anesthetize the joint in 50% of cases. This same study found that 1 in 9 MBB failed to anesthetize the facet joint against capsular distention, suggesting aberrant innervation. Thus to improve the sensitivity and specificity of diagnostic/prognostic MBBs, patients should be properly selected and educated before the blocks and strict interventional criteria should be followed, including precise needle location and using low injectate volumes.<sup>1,5,26,35</sup>

A MBB can have a prognostic value for the effect of radiofrequency on lumbar facet joint pain. The number of blocks and what percent pain relief threshold that should be used as a cut-off has been discussed extensively. Using higher cut-offs for pain relief<sup>46,52–55</sup> and performing double MBBs, the number of false positives will be reduced, but the number of false negatives will increase. Consequently, the success rates of radiofrequency ablation can increase,<sup>52,56</sup> but at the cost of excluding patients who could potentially benefit from radiofrequency.

Numerous studies showing the efficacy of lumbar facet radiofrequency have used  $\geq 50\%$  pain relief from a single prognostic block as an inclusion criterion.<sup>46,57–59</sup> Studies evaluating health care costs and denervation success rates using 0, 1 or 2 blocks,<sup>46,60</sup> or with different thresholds<sup>60</sup> support a one-block paradigm with a threshold of  $\geq 50\%$ . In addition, the relative risks of radiofrequency ablation are less than those of some alternative treatments such as surgery, and often no other reliable treatment options are available. Some reviews have found superior outcomes when more stringent criteria are employed; however, studies directly comparing radiofrequency ablation outcomes between 50% pain relief following prognostic blocks and higher cutoff thresholds have consistently failed to detect a difference in outcomes, and clinical trials utilizing 2 or 3 blocks also adapted other more rigorous selection parameters, making head-to-head comparisons impossible.<sup>53,61,62</sup> Although not routinely recommended in clinical practice, for research purposes more stringent criteria in the diagnostic process have been endorsed.<sup>61</sup> Double blocks can be performed in a placebo-controlled or a blinded-comparative manner (long- versus short-acting local anesthetic), with the latter being shown to have low sensitivity.<sup>5,60,63</sup>

Weighing all aspects, the latest consensus advises practitioners to perform a single block with  $\geq 50\%$  pain relief (using low injectate volume) before deciding whether to perform radiofrequency treatment.<sup>5</sup> Using double-blocks can be considered for efficacy studies, and if a concern arises about the chance of success of radiofrequency (poor correlation between historical findings, physical exam and imaging, or when extensive psychological factors such as catastrophizing or anxiety emerge).<sup>61</sup>

Few studies have compared MBB with IA injections to identify painful facet joints and select patients for

radiofrequency.<sup>58,64,65</sup> Success rates of radiofrequency stratified by the type of prognostic block favor MBB, though whether the small difference is clinically meaningful is unclear. MBBs are easier to perform, have a lower technical failure rate, and are less painful than IA injections. Hence, numerous guidelines recommend MBBs as the preferred prognostic screening test before lumbar facet radiofrequency.<sup>5,66</sup> In selected cases when a corticosteroid may be of therapeutic (and diagnostic) value for inflammatory pain, and in whom radiofrequency is relatively contraindicated, IA injections can be considered. The total volume injected for IA injections should be limited to <1.5 mL to prevent capsular rupture and reduce spread to surrounding structures.<sup>5</sup>

## Diagnosis summary

Currently, there is no gold standard for diagnosing lumbar facet joint pain. History, physical examination, and diagnostic/prognostic blocks may suggest but not confirm the facet joints as the source of pain.

- *History:* Axial low back pain (not predominantly in the midline) radiating to the flank, posterolateral thigh, and hip.
- *Physical examination:* Lumbar paravertebral tenderness worsening with flexion and extension. Pain that is not predominantly in the midline and tenderness overlying the facet joints can have prognostic value for interventional treatment.
- *Imaging:* SPECT can predict the outcome of facet joint treatment, but its cost-effectiveness requires further study. Plain radiography MRI, CT, and scintigraphy have little or no diagnostic and prognostic correlation with pain originating from the facet joints or the effects of radiofrequency.
- *Interventional:* A single MBB using  $\geq 50\%$  pain relief as the threshold for a positive block has a diagnostic and prognostic value for lumbar facet joint pain.

## TREATMENT OPTIONS

### Conservative treatment

The general principles for the treatment of nonspecific low back pain can be applied, including self-care, patient education, simple analgesics, and physical therapy.<sup>67-70</sup> There is little evidence that paracetamol with or without codeine is effective in chronic low back pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered for a short period, and the patient should be monitored for risks and side effects. Duloxetine is approved for musculoskeletal pain in the U.S., with the pivotal studies being performed for axial low back pain and knee osteoarthritis, suggesting efficacy in individuals

with spinal arthritis. Physical therapy includes core strengthening, reducing stress on facet joint (reducing lumbar lordosis with pelvic tilting), and aerobic exercise.<sup>71,72</sup> It is recommended that conservative therapy is tried for at least 3 months to support the natural course of back pain.<sup>5,70</sup> However, there is no evidence that demonstrates the ideal timing or optimal duration of conservative treatments for chronic low back pain. Most studies for interventional treatments required a trial of conservative treatment before enrollment. In the elderly or otherwise frail patients, the effectiveness of conservative treatment can be limited by a reduced physical ability or comorbidities.

### Interventional pain treatment

The goals of interventional pain treatment include pain reduction, improved functionality and quality of life, and to reduce side effects from medications. Radiofrequency of the lumbar medial branch and in selected cases, IA corticosteroid injections can be considered after a positive diagnostic/prognostic block when conservative measures fail.

### Radiofrequency

Several systematic reviews have been performed which analyzed the efficacy of radiofrequency for pain originating from the lumbar facet joints. Included studies show heterogeneity regarding design, technique (eg, interventional procedural variations), population (eg, different criteria for diagnostic/prognostic blocks, patient selection), and outcome measures. However, they collectively show that well-selected individuals with chronic low back pain originating from the facet joints may benefit from lumbar medial branch radiofrequency. Kleijnen et al. performed an extensive review for interventions in chronic low back pain that included 8 trials assessing radiofrequency for lumbar facet pain. They found that a radiofrequency procedure might produce better outcomes than a sham procedure.<sup>22,73</sup> A Cochrane analysis in 2015 assessed the effectiveness of radiofrequency procedures for patients with chronic low back pain.<sup>74</sup> Twelve RCTs, including 5 placebo-controlled studies, were included that examined facet joint pain. In the overall cohort examining any study evaluating radiofrequency denervation for pain, 56% had a low risk of bias. The authors found moderate evidence for the effectiveness of radiofrequency on pain compared with placebo at <1 month follow-up (MD pain score -1.47 [95% CI -2.28 to -0.67]), and low-quality evidence for an effect on function as measured with Oswestry Disability Index (ODI) at <1 month (MD ODI -5.53 [95% CI -8.66 to -2.40]) and  $\geq 6$  months follow up (MD ODI -3.70 [95% CI -6.94 to -0.47]).<sup>74</sup> Several subsequent reviews have been published with somewhat different scopes. Lee

et al.<sup>75</sup> included 7 trials (4 of which were included in the Cochrane review) in a meta-analysis comparing radiofrequency to various control treatments such as sham and epidural injections. They found that radiofrequency for lumbar facet pain resulted in significant reductions in low back pain at 6 months (MD VAS 1.52 [95% CI 0.16 to -2.89]) and 12 months (MD VAS 3.55 [95% CI 0.51-6.59]) compared with the control group, but no significant differences at 1-3 month follow-ups, though there was a strong trend for a greater response rate at these time periods.<sup>75</sup> Chen et al.<sup>76</sup> performed a meta-analysis comparing radiofrequency to sham and conservative non-surgical approaches (IA injections, anti-inflammatory medications) for low back pain, with 11 of the 15 included studies evaluating lumbar facet radiofrequency ablation (6 of which were included in the Cochrane review). The authors found that the use of radiofrequency improves patients' functional outcomes (ODI -6.08 [95% CI -11.89 to -0.27]);  $p=0.04$  and pain scores (-1.14 [95% CI -1.97 to -0.31]) pooled difference on a 10-point scale) compared with other conservative nonsurgical treatments. QOL measures were significantly improved in the radiofrequency group as compared to the non-radiofrequency group, though only two studies were included, one for facet joint pain. Janapala et al. (2021) performed a systematic review and meta-analysis that included 12 trials (6 of which were included in the Cochrane review) evaluating patients with chronic low back pain who had at least one positive MBB, in which pain and function for  $\geq 6$  months were assessed. They cited level II evidence for radiofrequency compared with sham (5 trials) or other interventions (7 trials) for improvement  $\geq 6$  months.<sup>77</sup> Li et al.<sup>78</sup> performed a meta-analysis of 10 RCTs ( $n=715$ ) and found similar evidence for the effectiveness of radiofrequency in facet joint pain.

A pragmatic controlled study estimated the added value of radiofrequency to a standardized exercise program for patients with chronic mechanical low back pain (facet joint pain, sacroiliac joint pain, and a combination group). The primary outcome parameter was pain intensity at 3 months. The study on facet joint pain did not find a statistically significant difference in pain reduction, defined as  $\geq 2$  points on Numeric Rating Scale (NRS, 0-10) between the 2 groups. The outcomes show that the mean difference in pain intensity between the radiofrequency procedure group and controls at 3 months was NRS (-0.18 [95% CI -0.76 to 0.40]). There were also no differences in other outcomes or at other follow-up moments.<sup>57</sup> This study was the subject of numerous criticisms regarding design, technique, and analysis.<sup>79-81</sup>

#### *Biopsychosocial factors influencing outcome of radiofrequency*

Consistent with the biopsychosocial model of pain, studies have shown that some psychological, social factors and biological factors (previous surgery, radicular signs, predominantly midline pain) have a greater

risk for poorer radiofrequency outcomes.<sup>82-84</sup> Studies have found depression, substance misuse, younger age, a greater Cobb angle and more non-organic (Waddell) signs to be associated with negative lumbar facet radiofrequency outcomes.<sup>82</sup> In one study evaluating outcomes in 101 Worker's compensation cases, retaining an attorney was associated with a  $>7$ -fold increased risk of post-treatment physical disability, along with greater bodily pain, functional impairment, and less vitality.<sup>83</sup> Since most chronic low back pain patients present with concomitant lumbar pain generators and psychosocial risk factors, one should ideally consider an interdisciplinary, multimodal treatment approach that includes addressing the most pressing and impactful conditions. An older age has been found to be associated with improved pain relief after radiofrequency.<sup>61,85,86</sup>

Signs during physical examination or response to diagnostic investigations can provide a direction of radiofrequency outcomes. A multi-center study by Cohen et al.<sup>87</sup> in 192 patients found that "facet loading" was associated with a negative outcome, and paraspinal tenderness was associated with a positive outcome. In another large, multi-center, case-controlled study ( $n=424$ ), a higher success rate for radiofrequency was found in patients who received a MBB compared to an IA injection.<sup>65</sup>

#### *Imaging for facet joint blocks*

For lumbar facet joint injections, image guidance provides accurate needle placement and improves safety through direct visualization of bony elements. Fluoroscopy is the preferred technique for lumbar MBB, with CT guidance occasionally used. CT is associated with more radiation exposure, is more expensive, and is unable to detect real-time intravascular uptake, but may be especially useful in the performance of IA injections where it has been shown to have a higher technical success rate than fluoroscopically-guided injections.<sup>88</sup>

The use of ultrasound has garnered dramatic interest over the past 15 years since it is not associated with radiation exposure, it provides real-time visualization of targeted tissues and is portable and relatively inexpensive. Disadvantages include limited field visualization, especially in obese patients, a lengthy learning curve, the potential for unrecognized inadvertent vascular uptake, and the need to count lumbar vertebral levels, especially in patients with transitional lumbar anatomy, to avoid treating non-targeted levels.<sup>89</sup> A systematic review and meta-analysis ( $n=22$  studies) compared ultrasound-guided MBB and IA injections using fluoroscopy and CT as the reference standards, respectively, Ashmore et al. found pooled risk differences for inaccurate needle placement of 11% for MBB and 13% for IA injections, with slightly longer procedure times.<sup>5,90</sup>

#### *Alternative radiofrequency administration possibilities*

The small size of the target nerves and the limited size of radiofrequency ablation zone necessitates the need for

optimizing radiofrequency, which can be performed using conventional, cooled or bipolar ablation, or pulsed radiofrequency (PRF). During conventional radiofrequency nerve tissue is ablated by increasing the temperature of nerve tissue which interrupts nociceptive signaling. Cooled radiofrequency, wherein water is circulated through the probe tip to regulate temperature at the tissue-tip interface and reduce tissue charring that can limit lesion expansion, creates a spherical, forward-projecting lesion. Bipolar radiofrequency utilizes two symmetrically situated electrodes serving as the anode and cathode, through which current flows to heat the intervening tissue. Similar to cooled radiofrequency, bipolar radiofrequency creates large lesions that may increase the nerve capture rate compared to conventional radiofrequency, but requires precision placement and involves greater tissue trauma. PRF utilizes brief pulses of radiofrequency current to induce voltage fluctuations at the treatment site, thereby minimizing neurotrauma. In multiple randomized trials, conventional radiofrequency has been shown to be superior to PRF for lumbar facet joint pain.<sup>91,92</sup> In a meta-analysis of 21 studies comparing the effectiveness of pulsed, cooled, or conventional radiofrequency for lumbar facet joint or sacroiliac joint pain, Shih et al. found cooled radiofrequency to be superior to conventional radiofrequency, with PRF providing the least benefit through 12 months follow up. No serious complications were reported after receiving treatment using the three techniques.<sup>93</sup> Another systematic review confirmed that PRF is less effective than conventional radiofrequency in reducing pain and functional deficits in patients with lumbar facet pain.<sup>94</sup>

New application forms of radiofrequency are currently under investigation (eg, cooled RF and multi-tined electrodes).<sup>95,96</sup>

## Other treatment options

### *Intra-articular injections*

The evidence for IA facet joint injections in low back pain is limited, with most systematic reviews failing to demonstrate therapeutic utility because of high study heterogeneity and a very small effect size.<sup>5,97,98</sup> A systematic review evaluated 6 RCTs comparing IA facet joint injections with (various) active drug or placebo/inactive injection and found significant between-group differences for pain, disability, and outcomes in only 2 of the included studies.<sup>98</sup> However, there was a wide range in quality (eg, only two studies provided information on sample size calculation) and no consistent pattern of benefit among the 6 trials, with most patients improving with or without the intervention.<sup>98</sup> A recent meta-analysis included 7 studies comparing IA corticosteroid injection versus radiofrequency ablation.<sup>97</sup> They found lower pain scores at 3, 6, and 12 months and improved functioning at 6 months in patients treated with radiofrequency. Despite the conceptual plausibility, there is little evidence that suggests some

subpopulations experiencing acute facet joint inflammation respond better to IA blocks.<sup>99</sup> Ackerman and Ahmad found that IA lumbar injections were more effective than MBBs in SPECT-positive patients ( $n=46$ ).<sup>100</sup> The study found  $\geq 50\%$  pain relief in 14/23 IA group vs. 6/23 MBB group and greater disability reduction at 12 weeks in the IA group.<sup>100</sup> Another important issue is the high technical failure rate for IA injections which ranges between 29% and 38% per joint, and 46% and 64% per procedure.<sup>58,101</sup>

In addition to corticosteroids, lumbar facet joint injection using autologous platelet-rich plasma,<sup>102</sup> hyaluronic acid,<sup>103</sup> and medical ozone<sup>104</sup> have yielded mixed results based on low-quality studies, and are currently not recommended outside of clinical studies.<sup>5,105</sup> Other treatments for lumbar facet joint pain such as fluoroscopy-guided high-intensity focused ultrasound and percutaneous fixation techniques are also devoid of high-quality data and are not recommended at this time.<sup>106,107</sup>

## COMPLICATIONS

MBB have a low complication rate, in part because no vulnerable structures lie near the target region or along the intended track of the needle. Nevertheless, side effects/complications can occur and may be related to general procedural interventions, or lumbar facet interventions in particular including equipment malfunction. All described side effects and complications should be discussed with the patient.

Patients commonly report some postprocedural pain, which can be from performing the procedure itself, or post-procedure neuritis, which can last several weeks and occurs in between 1% and 10% of individuals.<sup>108</sup> The cervical and lumbar facet guidelines found mixed evidence for prevention with gabapentin, and Grade C evidence for the use of post-radiofrequency perineural steroids or oral NSAIDs.<sup>5,109</sup> Patients can also experience a vasovagal (less common than in the cervical region) or allergic reactions, and one should be prepared for its treatment.

Temporary paresthesia in the legs and loss of motor function can be caused by extravasation of local anesthetics to the segmental nerves or a needle inadvertently placed into a foramen. As noted above, inadvertent intravascular injection or overflow of local anesthetic can be responsible for false-negative diagnostic/prognostic block but the low volumes injected have not been reported to cause systemic toxicity.<sup>47,49</sup> In rare cases, puncturing a blood vessel may result in bleeding and a retroperitoneal hematoma. After radiofrequency numbness and/or neuropathic-type pain in the skin overlying the lumbar paraspinal muscles separate from medial branch neuritis has been reported, possibly resulting from transection of the lateral branches of the lumbar dorsal rami.<sup>110,111</sup> Unintentional spinal nerve root paresthesia or foot drop have been described in medicolegal



cases after radiofrequency.<sup>112</sup> Improper needle placement, insertion of multiple electrodes simultaneously with no motor testing, and performing the procedure under deep sedation and general anesthesia are factors that contribute to permanent nerve injury.<sup>112</sup>

Infection is a risk common to all invasive procedures, though severe infections like epidural abscess, and vertebral osteomyelitis are rare after radiofrequency and have only been described in case reports.<sup>113</sup>

Multifidus atrophy has been observed following radiofrequency. A small study ( $n=5$ ) observed diffuse lumbar multifidus atrophy on a MRI 17–26 months after radiofrequency; however, radiologists could not reliably determine the laterality and levels of treatment.<sup>114</sup> A retrospective study ( $n=27$ ) found a trend ( $p=0.06$ ) toward measurable segmental changes in multifidus morphology after lumbar medial branch radiofrequency. The notable change in cross-sectional area measured with MRI was  $<10\%$  and more pronounced in females and the elderly.<sup>16</sup> Another retrospective study ( $n=20$ ) found no differences in the paraspinal intramuscular adipose tissue volume and distribution before and after RFN.<sup>115</sup> An analysis of aforementioned studies on behalf of the Spine Intervention Society Patient Safety Committee concluded that despite inconclusive evidence for multifidus atrophy after MBB radiofrequency, some degree of atrophy is plausible but requires further study.<sup>116</sup>

## Recommendations

Well-selected individuals with chronic low back originating from the facet joints may benefit from lumbar medial branch radiofrequency. Patients should be treated in accordance with guidelines, and stringent interventional techniques should be used to reduce technical treatment failure (i.e., missed nerves) and complications.<sup>5</sup> The recommendations are summarized in [Table 2](#).

## Clinical practice algorithm

A practice algorithm for the management of lumbar facet pain is illustrated in [Figure 3](#).

## TECHNIQUES

### Procedure for diagnostic/prognostic block and radiofrequency of the lumbar medial branch

There are several ways to perform lumbar facet radiofrequency, and this section elaborates on one technique that has been previously described.<sup>1,8,26</sup> We also refer to the book “Interventional Pain: A step-by-step guide for FIPP exam”.<sup>117</sup>

When the proximity of the electrode is confirmed with sensory stimulation, it is important that a near-parallel/parallel positioning of the electrode is achieved to envelop the targeted nerve in the radiofrequency, as randomized and large retrospective studies have found superiority to a perpendicular approach for lumbar facet joint pain<sup>118,119</sup> ([Figure 4](#)). In addition to a greater nerve capture rate (especially in cases where the medial branch is trapped beneath the mamillo-accessory ligament) and effectiveness, animal studies suggest that larger lesions result in longer-lasting structural changes, which may translate to longer benefit.<sup>5,120</sup> Lesions expand in a spheroid shape around the active tip of the electrode; hence perpendicular placement has the highest chance of missing the nerve. Strict parallel placement to the nerve can theoretically produce the largest lesions, though it is important that sensory thresholds are tested because if the electrode is placed exactly parallel to but adjacent to the nerve outside of the lesion circumference, it can miss it altogether.<sup>5</sup> Inserting electrodes at an oblique and cephalad angle results in a larger active tip-bony target interface and therefore greater chance of nerve capture, but the precise angle that optimizes electrode contact has yet to be determined (and may differ based on individual anatomy).<sup>121</sup> Although indirect results of randomized trials also support a near-parallel approach, these results should be interpreted with caution considering the differences in patient selection, criteria for designating the diagnostic/prognostic blocks as positive, and other technical parameters.<sup>119</sup>

### Procedure for diagnostic medial branch block

The patient is positioned in a prone position, with a pillow placed under the abdomen to reduce lumbar lordosis, if necessary. Routinely, 3 lumbar levels are treated at the same time. These are identified by counting downward from Th12. The C-arm is then angled approximately 15–20° obliquely to the ipsilateral side until the joint line between the SAP and inferior articular process opens up. For the L5 dorsal ramus, the C-arm can be turned less oblique (0–10°). The entry point on the skin is marked a few millimeters caudad to the junction between the SAP and transverse process (L1–L4), or sacral articular process and ala (L5).<sup>122</sup>

The procedure is performed in a sterile manner and the skin is anesthetized before needle (10-cm 22-G needle with connection tubing) placement. The needle is slowly advanced in a co-axial (tunnel) view until bony contact is achieved, with regular use of lateral, oblique, and anteroposterior fluoroscopic images to ensure safe and accurate needle manipulation. In a lateral view, the needle should be at the base of the SAP posterior to the middle of the facet line. True lateral images occur when the iliopectineal lines overlap. In an AP view, the needle should touch the base of the SAP.

**TABLE 2** Summary of recommendations from Cohen et al.<sup>5</sup> with permission of the publisher.

Topic	Recommendation/findings	Level of evidence and certainty
Value of history and physical examination to select patients for blocks	There are no examination or historical signs that reliably predict response to lumbar facet blocks. Paraspinal tenderness and radicular symptomatology may be weakly predictive of positive and negative blocks, respectively. The levels targeted should be based on clinical presentation (eg, tenderness, pain patterns, imaging if available)	Grade C, low level of certainty
Correlation between imaging and facet block and RF outcomes, and whether imaging is necessary before blocks	There is moderate evidence for SPECT before MBB	Grade C, moderate level of certainty
	There is weak evidence for SPECT before IA blocks	Grade D, low level of certainty
	There is weak evidence for MRI, CT, and scintigraphy before MBB and IA blocks	Grade D, low level of certainty
Requirement of conservative treatment including physical therapy before facet blocks	Consistent with clinical practice guidelines, we recommend a 3-month trial of different conservative treatments before facet joint interventions	Grade C, low level of certainty
Necessity of image guidance for lumbar facet blocks and RFA	We recommend CT or preferably fluoroscopy be used for lumbar MBB, although ultrasound may be considered in certain contexts. For IA injections, we recommend CT, although fluoroscopy can be considered in some cases	Grade C, low level of certainty
	For RF, we recommend using fluoroscopy	Grade B, low level of certainty
Diagnostic and prognostic value of facet blocks	IA injections are theoretically more diagnostic than MBB, although they are characterized by a high technical failure rate and poorer predictive value before RF. Both MBB and IA injections are better than saline injections as prognostic tools before RFA	Grade B, low level of certainty
MBB vs. IA injections before RF	MBB should be the prognostic injection of choice before RF. IA injections may be used for both diagnostic and therapeutic purposes in some individuals (eg, young people with inflammatory pain, people at risk of RFA complications)	Grade C, moderate level of certainty
Effect of sedation on diagnostic and prognostic utility	Consistent with guidelines, sedation should not be routinely used in the absence of individual indications	Grade B, low-to-moderate level of certainty
Ideal volume for facet blocks	Lumbar MBB should be performed with a volume <0.5 mL to prevent spread to adjacent structures, and IA injections should be done with a volume <1.5 mL to prevent aberrant spread and capsular rupture	Grade C, low level of certainty
Therapeutic benefit from MBB and IA injections	We recommend against the routine use of both therapeutic MBB and IA injections, although we acknowledge there may be some contexts in which these can be useful (eg, prolonged relief from prognostic blocks, contraindications to RF)	Grade D, moderate level of certainty
Cut-off for designating a prognostic block as positive and use of non-pain score outcome measures	We recommend that >50% pain relief be used as the threshold for designating a prognostic block as positive but recognize that using higher cut-off values may result in higher RF success rates. Secondary outcomes such as activity levels may also be considered when deciding whether to proceed with RFA	Grade B, moderate level of certainty
Number of prognostic blocks performed before RF	We recommend a single block. Although using multiple blocks may improve RFA success rates, it will also result in patients who might benefit from RFA being denied treatment	Grade C, low-to-moderate level of certainty
Evidence for large RF lesions	There is indirect evidence, and limited direct evidence, that techniques that result in larger lesions (eg, larger electrodes, higher temperatures, longer heating times, proper electrode orientation, fluid modulation) improve outcomes	Grade C, low level of certainty that larger lesions increase the chance of capturing nerves
		Grade I, low level of certainty that larger lesions increase the duration of pain relief

TABLE 2 (Continued)

Topic	Recommendation/findings	Level of evidence and certainty	
Electrode orientation	We recommend positioning the electrode in an orientation near parallel to the nerve	Grade B, low level of certainty	
Use of sensory and motor stimulation before RFA	Sensory stimulation should be used when single lesions are anticipated.	Grade C, low level of certainty	
	When multiple lesions are planned, the evidence for sensory stimulation is inconclusive	Grade I, moderate level of certainty	
	Motor stimulation may be beneficial for safety and effectiveness purposes	Grade B, low level of certainty	
Mitigating complications	Intravascular uptake can adversely affect the validity of MBB and we recommend aspiration and real-time contrast injection	Grade C, low level of certainty	
	Anticoagulation medications should be continued for facet blocks and RF, and cases that might warrant discontinuation should be discussed with relevant healthcare providers	Grade B, moderate level of certainty	
	Injection of steroids after RFA may prevent neuritis	Grade C, low level of certainty	
	Confirming electrode placement in multiple views and using sensorimotor testing may reduce the risk of nerve root injury	Grade B, low level of certainty	
	RF can result in paraspinal muscle degeneration and possibly disc degeneration, though the clinical relevance of this is unclear. We recommend a discussion of this possibility with patients, and consideration of physical therapy before and after RF to reduce the risk	Grade C, low level of certainty	
	Interference with implanted electrical devices can occur, and physicians should consult with relevant healthcare teams regarding recommendations (eg, programming pacemakers to asynchronous mode, turning off neurostimulators). Bipolar modes may be safer than monopolar, and grounding pads should be placed away from implanted cardiac devices, but not too close to the neurotomy site (risk of tissue burn). Avoid excessive sedation	Grade C, low level of certainty	
	Burns may occur from equipment malfunction or lesion extension to the skin (less likely). Checking equipment, and properly positioning the grounding on a dry, clean-shaven lower extremity devoid of scars may minimize this risk	Grade B, moderate-to-high level of certainty	
	Spine surgery is associated with lower RFA success rates, and physicians should check the placement of RF probes in multiple fluoroscopic views and avoid contact with hardware to prevent thermal injury	Grade C, low level of certainty	
	Difference in standards between clinical trials and clinical practice	Providers involved in clinical trials and clinical practice may have different goals that warrant different selection and performance criteria. Areas that might warrant discrepancies include the use of contrast during MBB, number of blocks performed, prognostic block cut-off for identifying an RF candidate, and use of sensorimotor stimulation	Grade A, moderate level of certainty
Repeating RF	We recommend repeating RFA in individuals who obtained at least 3 (and preferably 6) months of relief, up to two times per year. The success rate for repeat RFA decreases for successive procedures but remains above 50%	Grade B, moderate level of certainty	
	Repeating prognostic blocks is not routinely necessary in patients who experience a recurrence of their baseline pain in a physiological timeframe	Grade C, low level of certainty	

Abbreviations: IA, intra-articular; LA, local anesthetic; MBB, medial branch block; RF, radiofrequency; SPECT, single photon emission computed tomography.

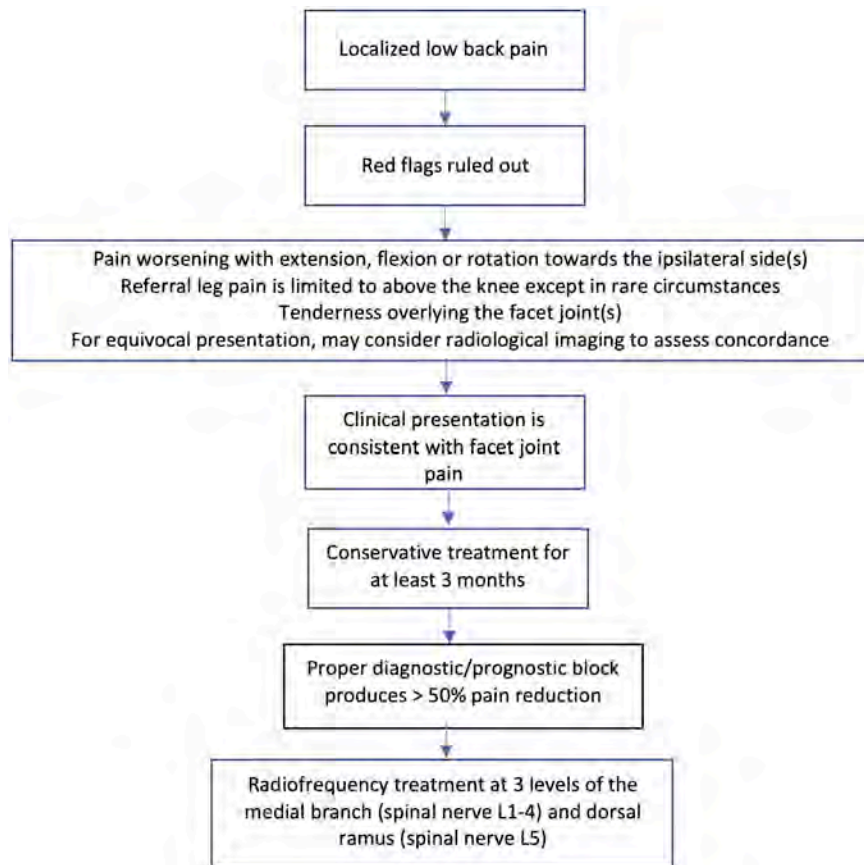


FIGURE 3 Clinical practice algorithm for the treatment of lumbar facet pain.

Sensory stimulation is applied after confirming the proper needle position and checking impedance. Needle position is generally deemed adequate if concordant stimulation is obtained at  $\leq 0.5$  V for the lower back. After confirmation of correct needle position, intravascular needle placement needs to be ruled out with real-time contrast injection and fluoroscopic observation. After negative aspiration and administration of contrast have confirmed a lack of vascular (or intramuscular) uptake, a low volume of local anesthetic is administered.

### Procedure for radiofrequency ablation of the lumbar medial branch

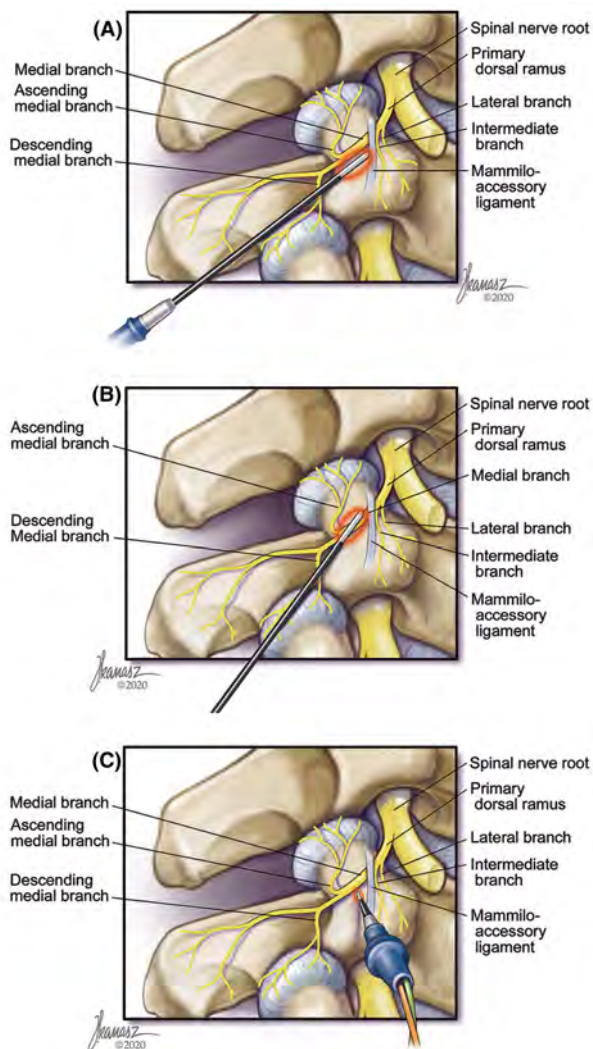
Imaging for radiofrequency can either be similar to that used for a diagnostic MBB, but a co-axial view is desirable, the image intensifier is rotated sharply caudally ( $30^\circ$ ) so that the electrode can be positioned in a near-parallel orientation to facilitate a cephalad trajectory. The insertion point for radiofrequency is at the junction between SAP and transverse process, or sacral articular process and ala (L5).

The electrode is slowly advanced in a co-axial (tunnel) view until bony contact is achieved, with intermittent use of fluoroscopic images. Once on bone, the

electrode is slowly wiggled over the transverse process. To prevent spinal nerve root injury, the trajectory of the electrode is kept over bone as it is advanced. In the lateral view, the electrode tip should lie at the base of SAP and approximately 1 mm to the posterior border of the foramen intervertebral. In anteroposterior view, the electrode should touch down along the lateral neck of the SAP, just cephalad to the superior border of the transverse process.

Sensory stimulation is performed as discussed above, with most studies using concordant stimulation at  $\leq 0.5$  volts as the cutoff threshold. In one prospective study, no correlation was found between sensory stimulation and lumbar medial branch radiofrequency ablation outcomes, which was attributed to numerous other confounding factors (eg, sedation, age, presence of neuropathy) mitigating any small effect.<sup>123</sup> Next, motor stimulation at 2 Hz is performed, usually up to 1.5–2 V or at least  $3\times$  the sensory threshold, to confirm sufficient proximity to the medial branch as well as to rule out proximity to the exiting nerve-root by confirming the absence of lower extremity muscle stimulation. In one retrospective study, a higher success rate was observed when paraspinal muscle contraction was observed at all treated levels than when no twitches were observed.<sup>124</sup> At the L5 level (ramus dorsalis) 2 Hz stimulation does not always produce prominent contraction of the multifidus





**FIGURE 4** Insets illustrate closeup views of the bony and neural anatomical landmarks and a schematic representation of the effect electrode orientation has on nerve ablation. Artistic renditions by Joe Kanasz ([joekanasz@att.net](mailto:joekanasz@att.net)). (A) Parallel insertion of electrodes. Parallel placement may result in a higher likelihood of missing the nerve than with near-parallel orientation. (B) Near-parallel insertion of electrodes. This may result in the highest likelihood of medial branch nerve ablation. (C) Perpendicular insertion of electrodes. This theoretically results in the highest chance of missing the nerve, which may be more likely when the medial branch is entrapped beneath the mammillo-accessory ligament. From Cohen et al.<sup>5</sup> With permission of the publisher.

muscle. If leg movement is observed, the needle must be repositioned.

After confirmation of correct electrode placement, local anesthetic is administered. Before radiofrequency, higher volumes than those administered during diagnostic/prognostic blocks are sometimes used since local anesthetic may not only reduce procedure-related pain, but has also been shown to enhance radiofrequency lesion size. After a brief time interval waiting for the local anesthetic to take effect, an 80° burn is created for

at least 90s, which reduces lesion variability.<sup>125,126</sup> The goal of radiofrequency is to capture the medial branch with an adequate lesion size and avoid unnecessary injury to non-targeted tissues. Medial branches can vary in location and even in the number of branches that innervate the facet joint. Some practitioners perform multiple lesions.<sup>127</sup> The effect of temperature and duration of lesioning were studied in 96 patients with lumbar facet joint pain using a single block. No difference was found in categorical outcomes at 1 and 6-month follow-ups between lesioning at 90°C for 50s, 85°C for 60s, or 70°C for 90s.<sup>84</sup> However, this study was underpowered and experimental studies have found larger lesions when higher temperatures and longer heating times are employed, as recommended in the lumbar facet guidelines.<sup>5,126</sup>

## SUMMARY

Lumbar facet joint pain is a common source of low back pain in which controversy exists regarding prevalence, diagnosis, and treatment, including radiofrequency parameters. There is no gold standard for diagnosing pain originating from the lumbar facet joints. Unilateral localized back pain without referral to the lower leg, worsened with movement, and with paravertebral tenderness on palpation are suggestive for diagnosis. A single diagnostic/prognostic MBB (and in selected cases an IA block) should be used to confirm the diagnosis. If  $\geq 50\%$  pain reduction is achieved, radiofrequency can be performed. As for all patients with chronic low back pain, patients should be treated using a step-wise, multidimensional approach before moving to interventional techniques.

## AUTHORS CONTRIBUTIONS

Sandra van den Heuvel performed the literature search and wrote the manuscript. Van Zundert Jan, Koen Van Boxem, and Kallewaard Jan Willem assisted in the selection of the literature and revised the manuscript. Jan Van Zundert is the final responsible for this manuscript. Cohen Steven and Javier de Andr es Ares, revised and edited the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.


## DATA AVAILABILITY STATEMENT

This narrative review is based on the existing literature, therefore, data on the used publications are available through PubMed and libraries.

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