Spinal Targets for Interventional Pain Management

Lawrence R. Poree and Linda L. Wolbers

Key Points

- Interventional techniques that target specific nociceptive transmission sites can reduce pain without having the systemic impact that oral medication have on other organ systems.
- Convergence of nociceptive afferent signals in the spinal cord may explain the clinical observation that injury of different organs may produce the same pain sensations.
- Destruction of specific spinal neural targets with either neurolytic solutions or thermal probes provides long-term relief for a limited number of pain conditions.
- The primary pharmacological receptors that are targeted for intrathecal medication management of pain include opioid receptors, alpha-2 adrenergic receptors, sodium channel receptors, and calcium channel receptors.
- Electrical stimulation can provide effective analgesia by targeting various spinal targets including the spinal cord, nerve roots, and dorsal root ganglia.
- New minimally invasive percutaneous techniques have recently been developed to address some of the structural pathologies including spinal stenosis caused by ligamentum flavum hypertrophy.

L.R. Poree, M.D., MPH, Ph.D. (✉)
Department of Anesthesia and Perioperative Care,
University of Califoarnia San Francisco, San Francisco, CA USA

Pain Management, Pain Clinic of Monterey Bay,
8057 Valencia Street, Ste A, Aptos, CA 95003, USA
e-mail: lporee@painclinicofmontereybay.com

L.L. Wolbers, M.D., MPH
Pain Clinic of Monterey Bay, 8057 Valencia Street, Ste A,
Aptos, CA 95003, USA
e-mail: lwolbers@painclinicofmontereybay.com

Introduction

As noted in the previous chapter, the transmission of pain signals from the peripheral nervous system to the brain involves a variety of specialized neuronal and nonneuronal cells each with a host of specific receptors involved in the processing of these signals. The goal of this chapter is to briefly review the various image-guided interventional pain management techniques that target spinal structures aimed at reducing pain and improving patients' quality of life. Comprehensive medical management aims to accomplish these goals by utilizing systemic medications that target specific receptors throughout the peripheral and central nervous system. In many cases, this approach is successful with few untoward complications. However, in more severe pain conditions or higher doses of medications, patients may experience medication side effects and toxicities that limit the utility of a systemic approach. In contrast, interventional pain management techniques employ a variety of technologies to influence specific targets involved in nociceptive transmission while aiming to minimize the effects on systems not involved in the nociceptive process. For the purposes of this chapter, the interventional pain management techniques to be discussed will be limited to fluoroscopic procedures that target the structural and neural components in four distinctive spinal regions: the paraspinal region located immediately adjacent to the spine, the structural components of the spine including the bone and connective tissues, the intraforaminal region located within the spinal foramen, and the intraspinal region located within the spinal canal. Where appropriate, a distinction will be made between the epidural targets and intrathecal targets located within the intraspinal region. Knowledge of the spinal structures subject to interventional procedures is critical for all pain physicians, not just those who perform the interventions. For example, by understanding the spinal components involved in nociception and how they can be targeted, the clinician

can explain not only how a patient with cholecystitis can present with clinical complaints of angina but also why targeting the spinal cord may be beneficial [1, 2]. While this clinical observation was a mystery when first described over 100 years ago, animal studies characterized the convergent spinal pathways and processing centers responsible for this clinical observation [3, 4]. Armed with this knowledge, the interventionalist is able to target these centers with interventional techniques to disrupt the nociceptive processing at the spinal level. The techniques discussed here include both established as well as emerging technologies.

Paraspinal Targets for Interventional Pain Management

Chapter 1 described the role that the sympathetic nervous system plays in both the transmission and maintenance of pain. With efferent sympathetic fibers traversing along the paravertebral sympathetic chain adjacent to the cervical through sacral vertebral bodies, it is no surprise that these nerve bundles are a common target for neural blockade and ablation in patients diagnosed with sympathetically maintained pain. In addition, these same nerve bundles are often conduits of visceral nociceptive afferent fibers. Neural blockade with local anesthetic of nerve fibers in the cervical and lumbar sympathetic chain is a common therapeutic technique used in the treatment of complex regional pain syndrome (CRPS) of the upper and lower extremities, respectively. In a recent multicenter review of randomized clinical trials, sympathetic blockade for the treatment of CRPS was given a score of 2B+. This score indicates that one or more RCTs demonstrate effectiveness and that the treatment is recommended by the group [5]. In the cervical

spine, the cervicothoracic ganglion (aka stellate ganglion) sympathetic blockade is performed by advancing a needle to the anterior tubercle of the C7 vertebral body under fluoroscopic guidance. Injection of contrast confirms flow of the solution along the course of the cervical sympathetic chain in a craniocaudal direction and is followed by injecting 10 ml of local anesthetic (Fig. 2.1). Similarly, blockade of the lumbar sympathetic chain is performed by advancing a needle in the oblique fluoroscopic view to the anterior lateral surface of the L2 and/or L3 vertebral body under fluoroscopic guidance using a paramedian approach. Once proper needle placement is confirmed in the anterior-posterior and lateral views, 1 cc of contrast is injected and observed to spread in a craniocaudal direction and is followed by injecting 15 ml of local anesthetic (Fig. 2.2). In the thoracic spine, the sympathetic chain gives rise to the greater and lesser splanchnic nerves that provide sympathetic innervations of many visceral organs along with serving as a conduit for nociceptive afferents. As such, they are a favorite target for neural blockade and/or ablation in the treatment of visceral pain. For decades, the neural destruction of the celiac plexus with alcohol or phenol has been a mainstay in the treatment of pain associated with pancreatic cancer. While highly effective, this therapy is associated with significant risks, including inadvertent spread of neurolytic solution toward the nerve roots and lumbar plexus which may result in foot drop, paraplegia, sexual dysfunction, loss of anal and bladder sphincter tone, and dysesthesia [6]. To avoid these complications of chemical neurolysis, radiofrequency ablation is rapidly emerging as the preferred method for denervating the pancreas, especially in non-cancer patients [7]. The technique is accomplished by targeting the greater and lesser splanchnic nerves as they traverse along the lateral portion of the T11–T12 vertebral bodies (Fig. 2.3). Unlike the unpredictable
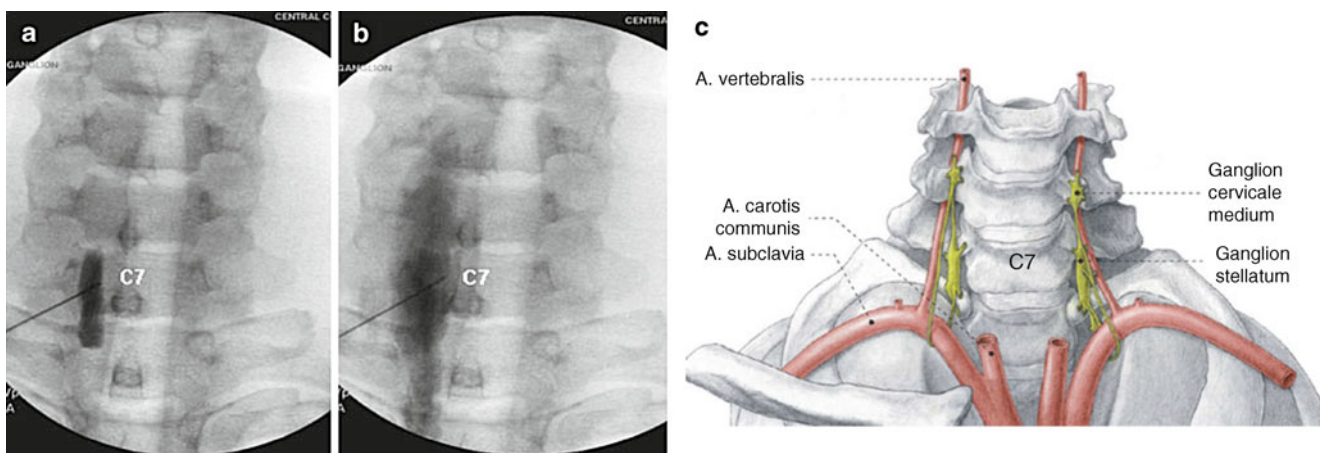

Fig. 2.1 (**a**) Right stellate ganglion block with needle at C7. (**b**) Contrast spreads from C5 to T2. (**c**) Anatomic illustration of the ganglion stellatum (aka cervicothoracic ganglion) (Fluoroscopic images courtesy of Lawrence Poree, MD Ph.D. Illustration courtesy of Rogier Trompert Medical Art. http://www.medical-art.nl; reprinted with permission from van Eijs et al. [5])

Fig. 2.2 Lumbar sympathetic block. (**a**) Needle placed on the anterolateral surface of the L3 vertebral body. (**b**) Contrast spreads from L2 to L4 (Fluoroscopic images courtesy of Lawrence Poree, M.D., Ph.D.)
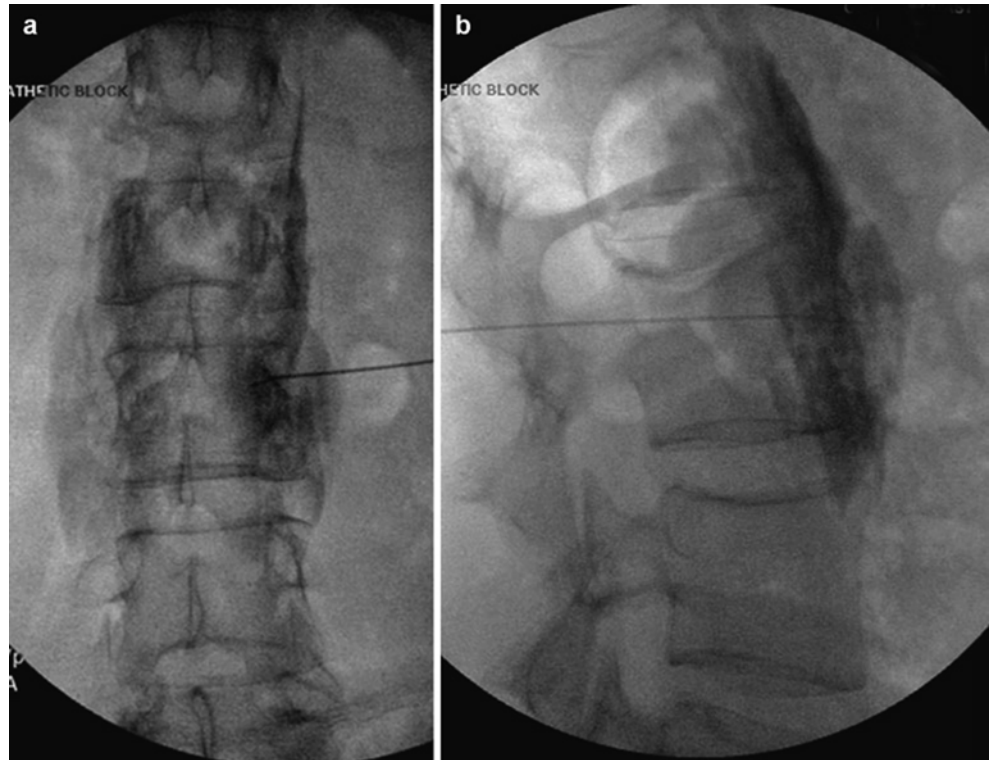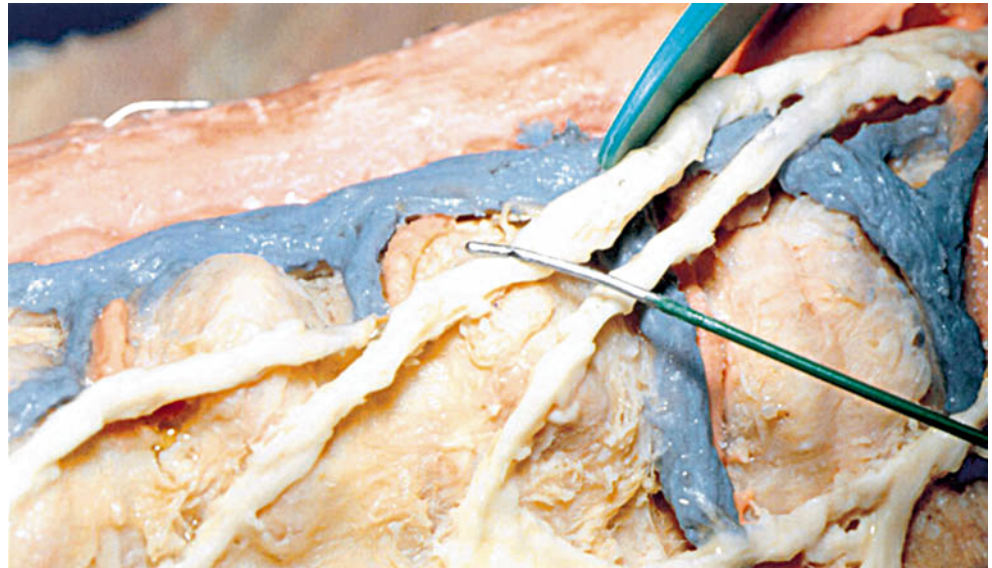

Fig. 2.3 15-mm active tip R-F (Racz-Finch) curved blunt needle for lesioning the splanchnics at T11–T12 placed over the splanchnic nerve dissected on a cadaver (With permission from Raj et al. [7])


flow of neurolytic solutions, RF lesions are limited to 1 mm lateral to the needle. Prior to lesioning, sensory stimulation at 50 Hz is performed up to 1 V to elicit stimulation in the epigastric region and motor stimulation at 2 Hz up to 3 V to rule out stimulation of the intercostal nerves as noted by lack of contraction of the intercostal muscles. Once the location is confirmed both fluoroscopically in the A/P and lateral projections and with sensory and motor stimulation, the area is

anesthetized with local anesthetic and then lesioned at 80 °C for 90 s. A second lesion is performed by turning the curved needle 180° to widen the lesion size. The primary complication of splanchnic nerve blocks/RF lesions is pneumothorax if the needle punctures the diaphragm [8].

Similarly, local anesthetic blocks and radiofrequency lesions of the lower portion of the sympathetic chain is targeted to treat pelvic and perineal pain. For bladder and

Fig. 2.4 Illustration of spinal innervation and targets for neural blockade/neurolysis including the sympathetic ganglia, ramus communicans, and ramus medialis (facet nerve) (Illustration courtesy of Rogier Trompert Medical Art. http://www.medical-art.nl. Reprinted with permission from Kallewaard et al. [20])
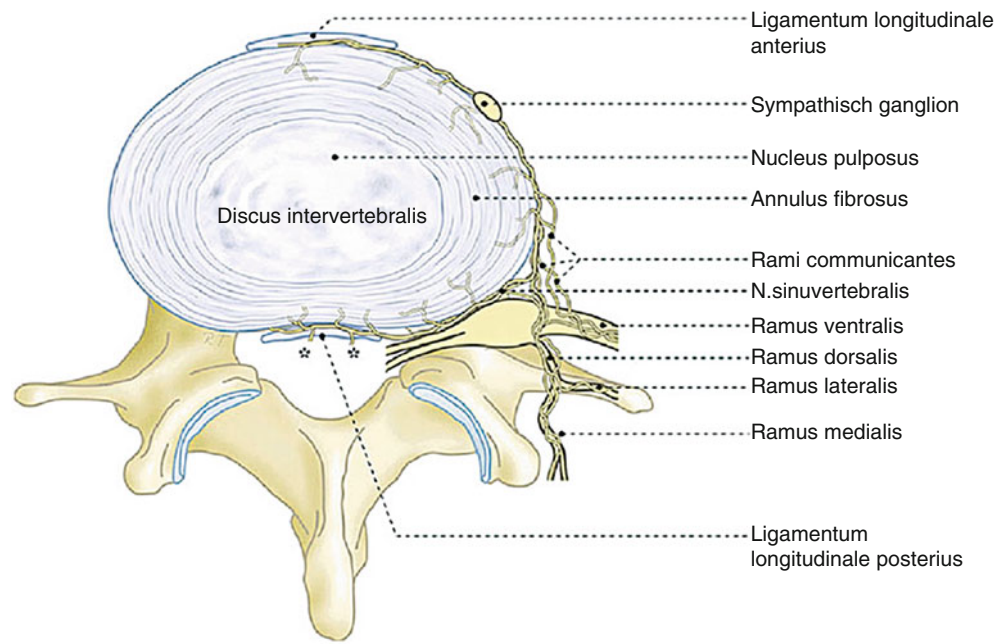
uterine pain, the superior hypogastric plexus block is employed, whereas for perineal, rectal, and vaginal pain, the ganglion of impar is the target. The superior hypogastric plexus is located on the anterior lateral border of the lower third of the L5 vertebral body and accessed via an oblique fluoroscopic view of the anterior lateral surface of the L5 vertebra or an L5–S1 transdiscal approach [9, 10]. The ganglion of impar is accessed by passing a needle through the sacrococcygeal ligament [11, 12]. Neurolysis of these structures with alcohol or phenol is typically reserved for those with cancer pain; however, botulinum toxin has emerged as a novel tool to aid in providing sympathetic neurolysis beyond the duration of local anesthetic but without the long-term sequel of alcohol or phenol [13, 14].

In addition to the sympathetic chain, another anterior column target for neurolysis is the ramus communicans (Fig. 2.4) [15, 16]. These nerves contribute to nociceptive innervation of the intervertebral disc. Radiofrequency ablation of these nerves at two adjacent levels was first reported to provide pain relief in patients with single level of discogenic pain over 20 years ago, but only one randomized clinical trial has been published on the procedure in that time period [17]. These nerves can be accessed via a 20° oblique fluoroscopic view with a 2-gauge spinal or RF needle advanced to the vertebral body just anterior to the posterior edge. The proper location is identified when sensory stimulation produces a sensation in the back at less than 1.5 V and motor stimulation at twice the sensory stimulation fails to cause contractions of the leg muscles. Once the proper location is identified, a radiofrequency lesion is made at 80 °C

for 60 s. One randomized clinical trial compared radiofrequency lesioning of the ramus communicans with a sham treatment. The RF-treated group had significantly lower VAS scores and improved SF-36 scores as compared to the sham-treated group 4 months after treatment [18]. Although there are few studies and only one RCT, the quality of evidence supporting this procedure secured it a level 2B+ positive recommendation using a modified grading system [19, 20]. This procedure is also reportedly effective in the treatment of pain due to vertebral fractures as the ramus communicans also innervates the vertebral bodies. However, further studies are needed to make this a recommended procedure [21].

In the posterior column, the most common targets for paraspinal neurolysis are the medial branches of the spinal posterior rami (aka ramus medialis or facet nerves). These nerves branch off the spinal nerves as they exit the intervertebral foramen to innervate the facet joints (aka zygapophyseal joint). With aging and injury, the facet joint may become sclerotic and hypertrophied and contribute to chronic back pain. Denervating the joint by ablating the medial branch nerves relieves the pain and improves range of motion. The primary target for denervation is the medial branch nerve as it passes over the junction of the transverse process and pedicle in the lumbar spine and in the middle of the facet pillar in the cervical spine [22, 23]. Pain relief after a local anesthetic blockade of these nerves is the diagnostic criteria used to determine which spinal segments are contributing to a patient's back pain. Two of these nerves are lesioned for each painful facet joint as each joint is innervated by two separate medial branches. Radiofrequency neurolysis at 80° for 90 s

is the most common technique for neurolysis although cryoneurolysis is also effective. Two recent analyses of the available literature using the Cochrane Musculoskeletal Review Group criteria for interventional techniques for randomized trials and the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies evaluated the efficacy of radiofreqency neurotomies of the medial branch nerves to treat facet joint pain and found that the available evidence supported recommending this procedure for the treatment of lumbar and cervical facet joint pain. This recommendation is based on quality of evidence reaching a level II-1 or II-2 when utilizing the grading criteria developed by the US Preventive Services Task Force [24, 25].

Percutaneous facet fusion, a new interventional pain management procedure, has recently been introduced as another technique to address facet joint pain. This fluoroscopically guided technique identifies the facet joint in an oblique view, and using a percutaneous portal system, a drill is advanced to the facet joint. A hole is made large enough to insert an 8-mm bone dowel into the joint which is allowed to fuse over the course of 6 weeks. This technique presumes that fusing the facet joint will relieve facet joint pain, but more clinical trials are needed to fully evaluate the effectiveness of this procedure as a stand-alone procedure for facet pain [26].

Spinal Bone and Connective Tissue Targets for Interventional Pain Management

As patients age, the bone and connective tissue components of the spine are subject to a wide array of degenerative processes that contribute to chronic pain, including but not limited to, vertebral fractures, disc herniations and ruptures, and hypertrophy and sclerosis of facets joints and ligamentum flavum. In the past 10–20 years, various minimally invasive image-guided interventional procedures have been developed to address each of these conditions with varying degrees of success.

Vertebral fractures, a condition common to patients with osteoporosis, can cause both acute and chronic pain. Two fluoroscopically driven procedures have emerged to address this condition, vertebroplasty and kyphoplasty. These vertebral augmentation procedures involve fluoroscopic placement of a needle into the fractured vertebral body and introduction of bone cement in an effort to stabilize the vertebral fracture and regain vertebral height and reduce pain [27]. A systematic review of the available studies from 1980 to 2008 graded the level of evidence using the North American Spine Society guidelines and concluded that there was good evidence to recommend vertebral augmentation in the treatment of vertebral fractures, although only one of the 74 studies was a randomized clinical trial. Subsequently, four additional randomized clinical trials were published that

offered conflicting recommendations, two supporting and two not supporting vertebral augmentation for vertebral fractures. The two in support were both open-label trials randomized to kyphoplasty versus medical management in one study [28] and vertebroplasty versus medical management in the other [29] with both having an inclusion criteria of edema noted on MRI. Each study reported significant decreases in VAS scores 1 month posttreatment in the augmented groups versus the medical management groups. Less of a difference was noted at the 1-year point, presumably due to fracture healing. In the kyphoplasty study, quality of life, mobility, and function also showed greater improvement in the surgical versus nonsurgical group. The two studies which did not support vertebral augmentation for vertebral fractures were sham versus vertebroplasty. All patients had radiographic evidence of vertebral fractures and back pain for less than a year, but not all had MRI evidence of edema [30, 31]. Each study reported trends of pain improvement in the vertebroplasty group at the 1-month time point that did not reach statistical significance. As each group continued to improve, there was no discernable difference between them in pain, physical functioning, or disability scores. The authors concluded that there was no significant difference between patients treated with vertebroplasty or a sham procedure. To help resolve these conflicting results, a more rigorous sham-controlled study was designed to include MRI evaluations by two independent radiologists, outcome measurements at 1 day, 1 week, 1,3,6, and12 months after treatment to include VAS, disability, and quality of life scores [32]. The results of this study are pending.

The intervertebral disc is another source of chronic spinal pain targeted by interventional procedures [33]. Derangements of the intervertebral disc can become a source of both acute and chronic back pain and is estimated to constitute up to 45 % of all cases of low back pain [19].

Herniated disc or extruded disc fragments can create pain as a result of a mass effect on neural structures including the spinal cord and exiting nerve roots. In addition, annular tears can allow leakage of the acidic nucleus pulposus leading to neural irritation of the sinuvertebral nerves that innervate the outer annulus as well as spinal nerves if the nucleus pulposus extends beyond the borders of the disc (Fig. 2.4). Diagnosis of this discogenic pain is most often determined by provocative discograms whereby 1–2 ml of contrast is injected into the disc and observed to reproduce concordant pain. The structural integrity of the disc is also evaluated by measuring intradiscal pressure to see if and at what pressure contrast may leak outside the normal boundaries of the nucleus pulposus up to a maximum of 100 psi, the normal pressure of a lumbar disc in the seated position (Fig. 2.5) [15, 19, 34]. Early interventional procedures attempted to treat discogenic pain with intradiscal injections of chymopapain, but anaphylaxis and clinical benefit less than that obtained with surgical discectomy lead

Fig. 2.5 (**a**) A/P fluoroscopic image of needles placed within lumbar disc. (**b**) Lateral view with injection of contrast, note posterior leakage of contrast at the L3–4 disc (Fluoroscopic images courtesy of Lawrence Poree, MD Ph.D)
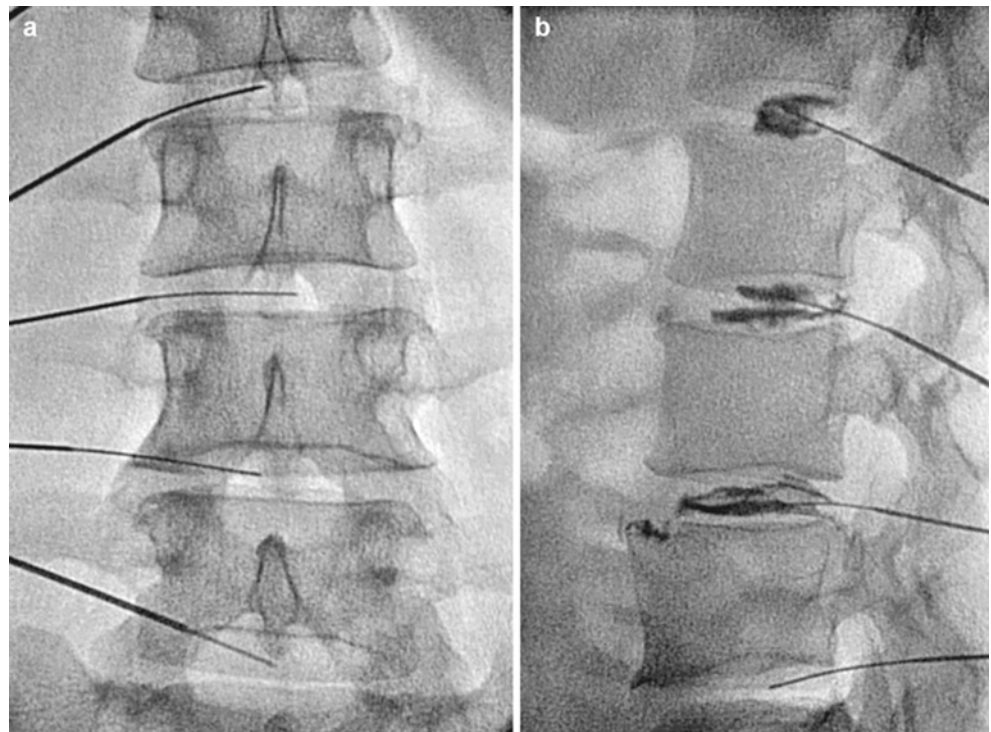
to the abandonment of this chemonucleolysis technique [35]. In the intervening 20 years, a number of intradiscal procedures have been introduced utilizing a variety of lesioning, injection, and decompressive technologies, including intradiscal electrothermal therapy (IDET), annuloplasty and other radiofrequency lesioning techniques, injection of corticosteroids, ozone, hypertonic dextrose, and methylene blue, as well as nucleoplasty and other percutaneous disc decompression techniques [36–38]. A recent multicenter analytical review of the available studies of these procedures made the following recommendation [19]: "Intradiscal corticosteroid injections and RF treatment of the discus are not advised for patients with discogenic low back pain. The current body of evidence does not provide sufficient proof to recommend intradiscal treatments, such as IDET and biacuplasty for chronic, nonspecific low back complaints originating from the discus intervertebralis. We are also of the opinion that at this time, the only place for intradiscal treatments for chronic low back pain is in a research setting. RF treatment of the ramus communicans is recommended." (See section above on paraspinal targets for a review of RF lesioning of the ramus communicans.) The authors went on to conclude "…provocative discography remains the gold standard for the determination of the diagnosis of discogenic pain."

Minimally invasive lumbar decompression (MILD) is another new interventional pain management technique that targets the hypertrophic ligamentum flavum in patients with lumbar spinal stenosis and neurogenic claudication [39]. As patients age, the ligamentum flavum hypertrophies in part due to replacement of the normal elastin with collagen in the posterior fibers of the ligamentum flavum [40]. Mechanical stress of the ligament causes an inflammatory response with infiltration of macrophages and fibroblast that in turn leads to scar formation. In addition, loss of disc height leads to buckling of the ligament and further narrows the spinal canal [41]. In later stages, calcification and ossification of the ligament develops and contributes even further to thickening and inflexibility of the ligamentum flavum [42]. Until recently, this condition was treated initially with epidural steroid injections, and when this therapy no longer provided significant benefit, patients were treated with an open surgical decompression. The MILD procedure, performed with local anesthetic and minimal sedation, uses the placement of epidural contrast and fluoroscopy to outline the anterior border of the ligamentum flavum in a region where ligamentum flavum hypertrophy was identified on MRI images (Fig. 2.6). A small 5.1-mm trocar is advanced to the inferior lamina of interlaminar space to be treated. Removal of the trocar's stylet leaves a working portal through which instruments are passed and are used to remove osteophytes and the posterior fibers of the hypertrophied ligamentum flavum. Initial clinical trials revealed that this procedure showed statistically and clinically significant reduction of pain and improvement in the mobility as measured by VAS, ZCQ, SF-12v2, and ODI [43]. These improvements persisted at the 1-year follow-up [44]. A multicenter, randomized clinical trial is currently underway to compare the long-term benefits of the MILD procedure compared with epidural steroid treatments.

Fig. 2.6 (**a**) Axial MRI of lumbar spine showing spinal stenosis secondary to hypertrophy of the ligamentum flavum (LF). (**b**) Fluoroscopic image in contralateral oblique view showing epidurogram and failure of contrast to flow cephalad. (**c**) Tissue sculptor used to remove posterior portion of hypertrophic ligamentum flavum. (**d**) Epidurogram after decompression shows improvement in epidural flow (Images courtesy of Vertos Medical Aliso Viejo, CA)
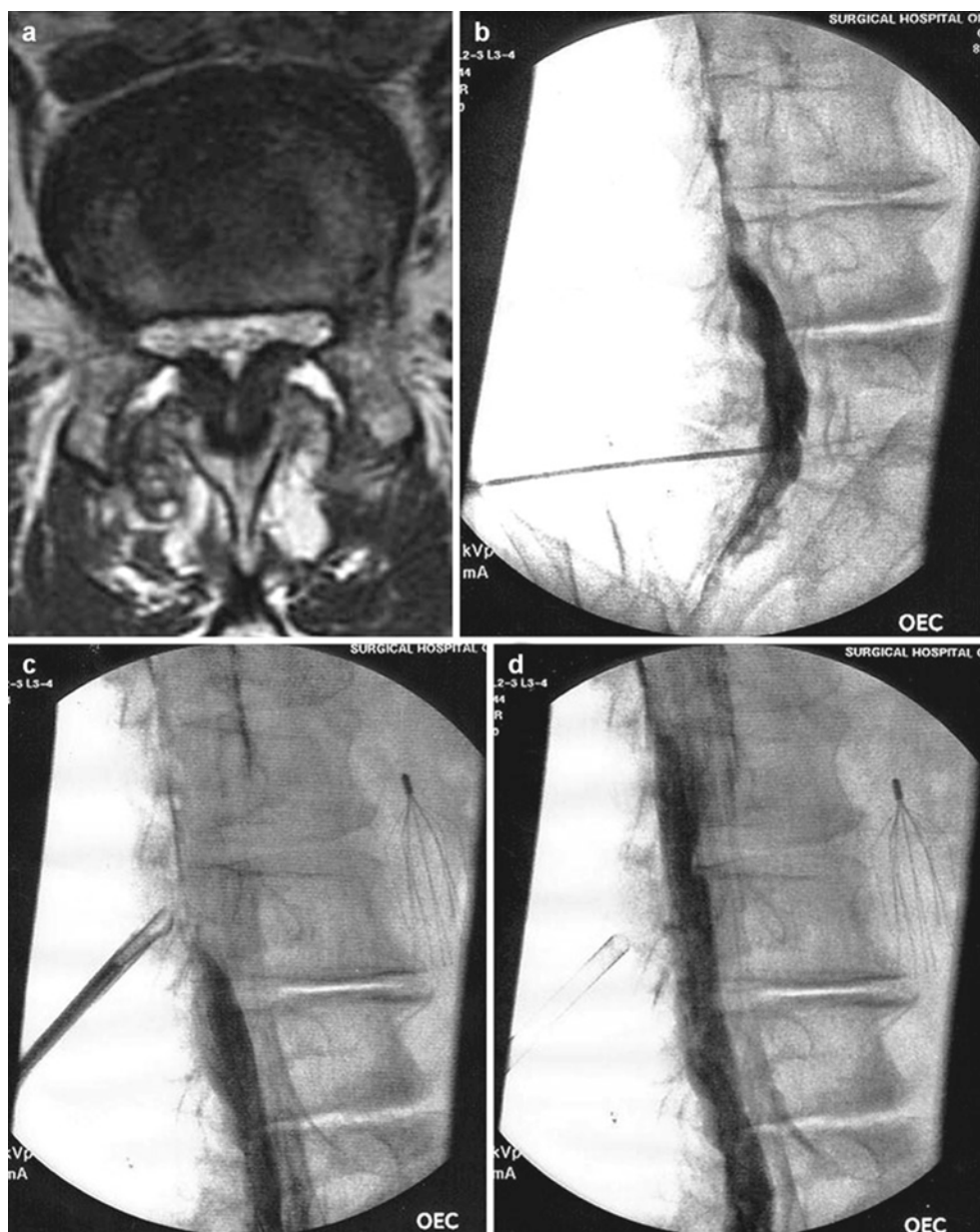
Intraforaminal Targets for Interventional Pain Management

Of course, the most important interventional pain management target within the vertebral foramen is the dorsal root ganglion (DRG). The primary sensory afferent neurons in the ganglion are the principle link between peripheral nociceptors and the processing centers of the central nervous system. Injury of these nerves is common from mechanical trauma resulting from lateralized herniated disc or spondylolisthesis, chemical irritation from leakage of nucleus pulposus [45–48], and injury caused by infectious agents such as herpes zoster. All of these injuries can initiate a cascade of inflammatory mediators including cytokines that contribute to the development and maintenance of chronic pain [49]. Thus, it comes as no surprise that foraminal injection of glucocorticoids is a common target for interventional pain physicians [50, 51]. A recent analysis of the available literature using the Cochrane Musculoskeletal Review Group criteria for interventional techniques for randomized trials and the criteria developed by the Agency for Healthcare Research and Quality (AHRQ) criteria for observational studies evaluated the efficacy of transforaminal epidural steroid injections and found that the available evidence supported recommending this procedure for the treatment of lumbar radiculitis. The quality of this evidence was ranked utilizing the US Preventive Services Task Force and found to reach a level

II-1 for the short term and level II-2 for long-term management of lumbar nerve root and low back pain [52].

More recently, patients with acute lumbosacral radiculopathy due to intervertebral disc herniation have reportedly improved with transforaminal injections of clonidine [53]. The mechanism for this improvement remains uncertain; however, there may be multiple targets for intraforaminal clonidine. Chung and others observed that peripheral nerve injury leads to sympathetic nerve fiber spouting around the DRG, and this observation was hypothesized to contribute to the development of sympathetically mediated neuropathic pain [54]. Thus, clonidine, an alpha-2 agonist with sympatholytic actions on sympathetic nerve endings, may reduce the effects of increased sympathetic innervation of the DRG after nerve injury. Another possibility is via direct anti-inflammatory action. Liu and Eisenach demonstrated decreased hyperexcitability in rodent-injured nerves after clonidine was applied perinurally and attributed this to inhibition of pro-inflammatory cytokines and prostaglandins [55]. A peripheral site of action for the antinociception activity of an alpha-2 agonist was also suggested by Poree et al. in an animal model of neuropathic pain. In this model, the antinociceptive actions of dexmedetomidine, an alpha-2 agonist, was antagonized by prior treatment with a peripherally restricted alpha2AR antagonist that does not cross the blood-brain barrier. The authors suggested the DRG as a possible peripheral site of action for dexmedetomidine after nerve injury [56].

The DRG has also been targeted for electrical and pulsed radiofrequency stimulation. Although high temperature lesioning radiofrequency energy is successfully employed to denervate medial branch nerves, this technique is avoided in the larger mixed nerves as it may lead to deafferentation pain and painful neuromas. Pulsed and low temperature radiofrequency treatments do not cause neural destruction but instead expose the nerves to a high voltage low to moderate temperature environment. In a prospective randomized double-blind study, 67 °C RF was reported to provide long-term relief of cervical brachial pain [57]. A recent retrospective chart review of 50 patients who received pulsed (42 °C) and moderate temperature (56 °C) radiofrequency treatment of the DRG for lumbar radiculitis reported that all patients received at least a 50 % improvement in their pain [58]. Another group reported that when low temperature (42 °C) pulsed RF was used alone, 30 % of the patients received greater than 50 % pain relief [59]. The observation that even low temperature electric fields applied to the DRG could provide long-lasting pain relief has prompted the recent development of an implantable DRG stimulation system to provide a continuous electric field around the DRG [60]. Excellent results from multiple prospective clinical trials have resulted in approval of DRG stimulation for the treatment of chronic pain in Europe and Australia with clinical trials currently underway in the USA (Fig. 2.7).
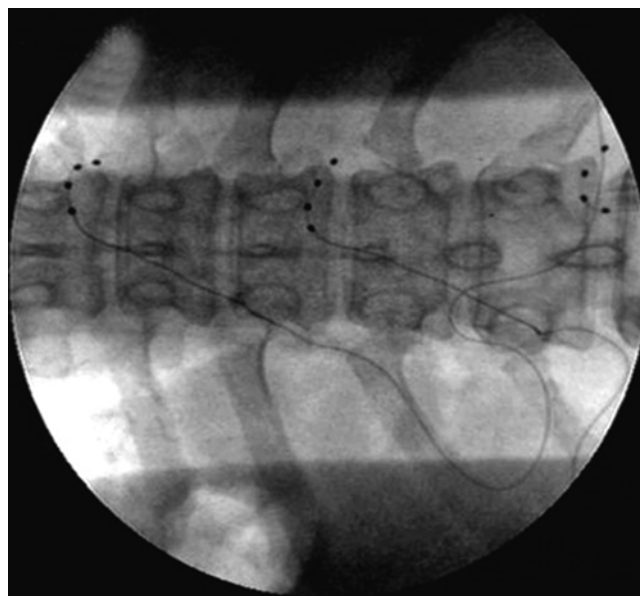

Fig. 2.7 Stimulating electrodes placed over dorsal root ganglia within the right T8–9, T10–11, and T12–L1 foramen. Stimulating electrodes placed over dorsal root ganglia within the right T8–9, T10–11, and T12–L1 foramen (Courtesy of Eric Grigsby MD, Napa Pain Institute, Napa, CA. and Jeff Kramer, Ph.D. Spinal Modulation, Menlo Park, CA [60]

Intraspinal Targets for Interventional Pain Management

Targeting the intrathecal space with opioids and local anesthetic has been available for cancer pain management since it was first reported in 1899 [61]. However, widespread utilization of intraspinal (epidural and intrathecal) analgesics outside of the operating room was not practical until the advent of long-term catheters and implantable pumps in the 1980s [62]. Dupen epidural catheters had an antimicrobial sleeve located at the skin exit site, thereby reducing the risk of infection and allowing for intraspinal delivery via an external pump for more than a year. While these catheters are no longer commercially available, they have been replaced by long-term epidural catheters attached to subcutaneous ports which provide even greater protection from infection [63]. For even longer-term intrathecal infusions and even greater protection against infection, implantable pumps have emerged as the preferred method for intrathecal delivery in the past 30 years. While these pumps are initially more expensive than externalized systems, they become cost neutral after 3 months and actually provide a cost savings thereafter as compared with externalized pumps [64, 65]. Most of the current systems are computer controlled, and some have the option for patient-controlled activation of programmed bolus doses [66]. The advantage of intrathecal management over systemic administration is one of

inhibition of nociceptive transmission at the spinal level and reduced systemic toxicity. In a randomized clinical trial comparing intrathecal drug delivery systems (IDDS) to comprehensive medical management (CMM), cancer patients treated with IDDS had less medication-induced toxicity, greater pain control, and longer survival than did CMM patients [67]. Nonetheless, it is estimated that only 10–20 % of patients with cancer-related pain fail comprehensive medical management using the World Health Organization guidelines and require more advanced pain management interventions such as IDDS [68]. Guidelines on appropriate selection of patients and intrathecal medication admixtures for patients with intractable cancer-related pain has recently been updated and includes the use of medications approved by the FDA for approved IDDS, medications that are by expert consensus, commonly used for IDDS therapy, and medications that are experimental and are recommended only as a means to provide greater analgesia in the final stages of life (Fig. 2.8) [70–72]. The common pharmacological targets for IDDS therapy include the mu-opioid receptors, calcium channels, sodium channels, and α-2 adrenergic receptors. Figure 2.9 shows the presynaptic and postsynaptic location of the receptors in the dorsal horn that forms the pharmacological basis of IDDS therapy, although, only morphine and ziconitide (aka SNX-111), a novel N-type voltage-sensitive calcium channel antagonist, are currently FDA-approved analgesics for IDDS therapy [70, 73–75]. As IDDS therapy gains greater acceptance for the treatment of intractable cancer pain, the appropriate position in a continuum of care for chronic non-cancer pain remains a source of debate. A recent review aimed at addressing this issue systematically evaluated the available literature using the Agency for Healthcare Research and Quality (AHRQ)
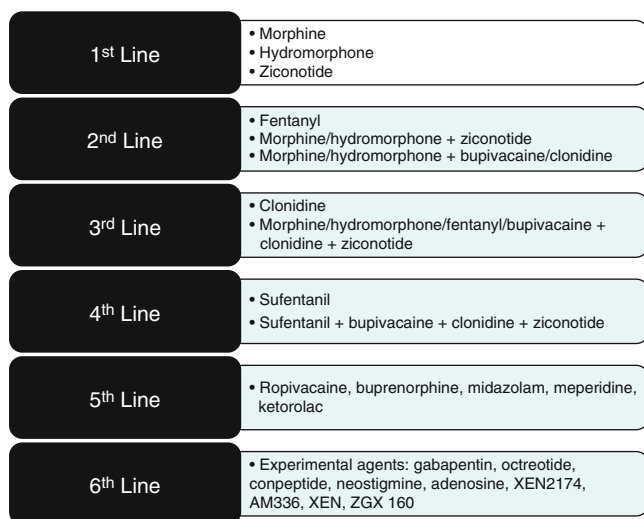
criteria for observational studies and the Cochrane Musculoskeletal Review Group criteria for randomized trials. The level of evidence was determined using five levels of evidence, ranging from level I to III with three subcategories in level II, based on criteria developed by the US Preventive Services Task Force (USPSTF) [76]. The authors found 20 studies that met both the inclusions and exclusion criteria. Based on their analysis, they concluded that high-quality evidence supported a moderate recommendation for intrathecal infusion systems for cancer-related pain and that moderate quality of evidence supported a limited to moderate recommendation for non-cancer-related pain.

In addition to pharmacological receptors, intraspinal neural structures are also targeted with electrical stimulation. Although the first spinal cord stimulator was implanted in 1967, the exact mechanism for electrical stimulation-induced analgesia remains elusive [77]. It is currently hypothesized that the analgesic effects of spinal cord stimulation are explained in part by the gate control theory proposed by Melzack and Wall whereby activation of large-diameter afferents activate segmental GABAergic interneurons [78, 79]. However, recent findings also suggest that supraspinal pathways are also involved in spinal cord stimulation analgesia [80]. Successful analgesia with spinal cord stimulation is dependent most upon proper placement of epidural electrodes over the spinal cord that are programmed to deliver the amplitude, frequency, and pulse width that successfully provides analgesia without untoward stimulation in areas that are not painful. The distance between electrodes being placed in an area that provides good analgesia ("sweet spot") and an area that does not can be as small as a few millimeters. Thus, successful stimulation can be lost if an electrode migrates even a few millimeters away from the ideal target. To circumvent this problem, most manufactures have devised more complex electrode arrays that allow for greater maneuverability of the electric field. While earlier systems employed as few as two or four electrode contacts per array, more recent spinal cord stimulation systems employ 16–20 contact arrays (Fig. 2.10b). In addition to spinal cord stimulation, intraspinal nerve roots can also be individually targeted (Fig. 2.10a). As with DRG stimulation discussed above, this technique is advantageous when the region of neuropathic pain has a small focal distribution and spinal cord stimulation activates areas outside the region of pain that is uncomfortable for the patient. This is especially true when the pain is due to injury to an isolated nerve [81, 82]. For example, Fig. 2.10c shows the electrode configuration in a patient receiving sacral nerve stimulation for persistent focal neuropathic pain in the pelvic floor after cystectomy and hysterectomy for chronic pelvic pain. Spinal cord stimulation failed to provide adequate analgesia whereas she continues to receive good analgesic benefit from sacral nerve stimulation 3 years after implantation.

1st Line	• Morphine • Hydromorphone • Ziconotide
2nd Line	• Fentanyl • Morphine/hydromorphone + ziconotide • Morphine/hydromorphone + bupivacaine/clonidine
3rd Line	• Clonidine • Morphine/hydromorphone/fentanyl/bupivacaine + clonidine + ziconotide
4th Line	• Sufentanil • Sufentanil + bupivacaine + clonidine + ziconotide
5th Line	• Ropivacaine, buprenorphine, midazolam, meperidine, ketorolac
6th Line	• Experimental agents: gabapentin, octreotide, conpeptide, neostigmine, adenosine, XEN2174, AM336, XEN, ZGX 160

Fig. 2.8 Polyanalgesic algorithm for intrathecal therapy for cancer pain. With permission from Deer et al. [71])
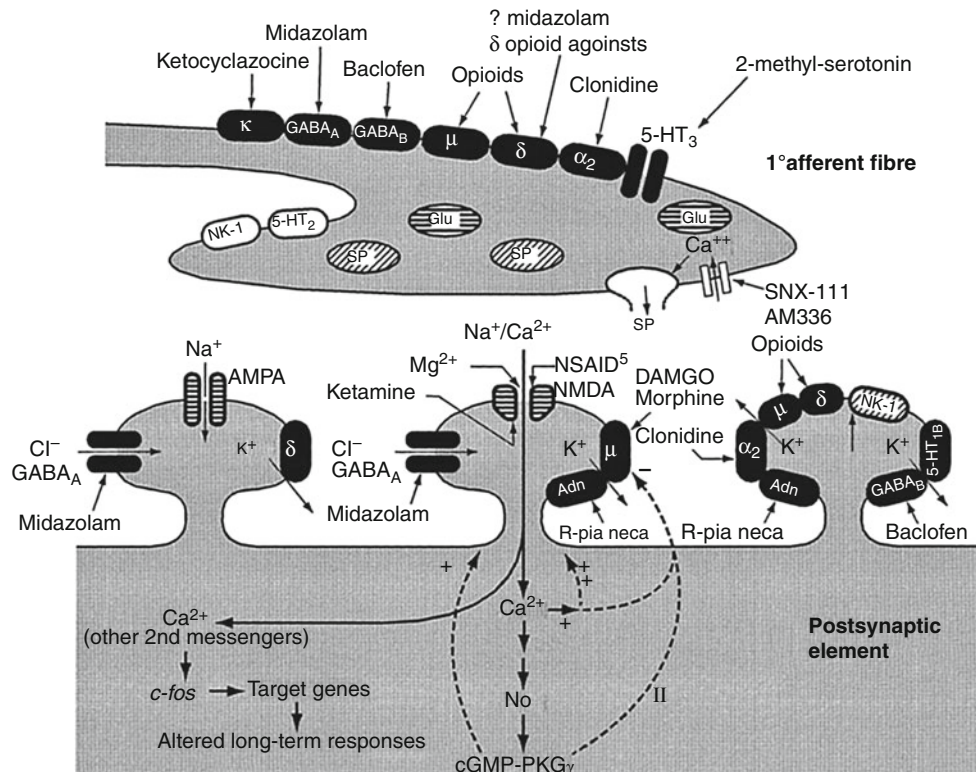
Fig. 2.9 Possible arrangement of pre- and postsynaptic receptors on structures in the dorsal horn of the spinal cord and potential sites of action of opioid and non-opioid spinal analgesics. Presynaptic release of the neurotransmitter glutamate (*Glu*) results in activation of the postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (*AMPA*) receptor, which controls a rapid-response sodium (Na^+) channel. Substance P (*SP*) interacts with the neurokinin (*NK-1*) receptor and results in activation of second messengers. With prolonged activation, the *N*-methyl-D-ASPARTATE (*NMDA*) receptor is primed, Glu activates the receptor, the magnesium (Mg^{2+}) plug is removed, and the ion channel allows entry of Na^+ and calcium (Ca^{2+}) ions. The increase in intracellular Ca^{2+} then triggers a number of second-messenger cascades. Production of nitric oxide (*NO*) increases via the Ca^{2+}/calmodulin-dependent enzyme NO synthase. NO may diffuse out of the neuron to have a retrograde action on primary afferents and also activates guanylyl cyclase, leading to increases in intracellular cyclic guanosine monophosphate (*cGMP*) and activation of cGMP-dependent protein kinases. Activation of the Ca^{2+}-dependent protein kinase C γ isoform (*PKCγ*) leads to phosphorylation of the NMDA receptor, which reduces the Mg^{2+} block (dotted line II) relating to the development of opioid tolerance. The increase in intracellular Ca^{2+} also results in the induction of proto-oncogenes such as c-*fos*, with a presumed action on target genes of altering long-term responses of the cell to further stimuli. κ, μ, and δ opioid receptors, *GABA* γ-aminobutyric acid, $α_2$ $α_2$ adrenoceptor, *5-HT* serotonin. Details of the potential analgesics are outlined in the text. *NSAID* nonsteroidal anti-inflammatory drug, *SNX-111* and *AM336* omega conopeptides that block neuronal Ca^{2+} channels. *DAMGO* [D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin, *R-Pia* R-phenyl-isopropyl-adenosine, *Neca* N-ethylcarboxamide-adenosine (With permission from Walker et al. [69])

In spite of over 40 years of clinical experience and success, routine implementation of spinal cord stimulation in clinical practice has been stifled, in part due to limited well-controlled clinical studies, a trend that has reversed in recent years. In a randomized prospective crossover design study comparing spinal cord stimulation versus reoperation for persistent leg pain after spinal decompression, North et al. found that patients initially randomized to SCS were significantly less likely to cross over than were those randomized to reoperation. Patients randomized to reoperation required increased opiate analgesics significantly more often than those randomized to SCS [83]. Kumar et al. followed shortly thereafter with a multicenter randomized prospective clinical study comparing spinal cord stimulation with conventional medical management (CMM) [84, 85]. This study found that compared with the CMM group, the SCS group experienced improved leg and back pain relief, quality of life, and functional capacity, as well as greater treatment satisfaction for over 2 years. More recently, a multicenter randomized study of SCS versus sham treatment demonstrated that spinal cord stimulation but not sham treatment decreased the frequency of angina attacks [86]. These pivotal studies have opened the door to even more investigations of SCS for an even greater number of disease states including intractable angina, peripheral vascular disease, chronic pancreatitis, and chronic pelvic pain to name just a few [87–89]. As the clinical evidence grows in support of spinal cord stimulation for a wide range of chronic pain states, so does the resistance to approve this therapy by third-party payors due to concerns about initial cost. To address these concerns, Krames et al. proposed that
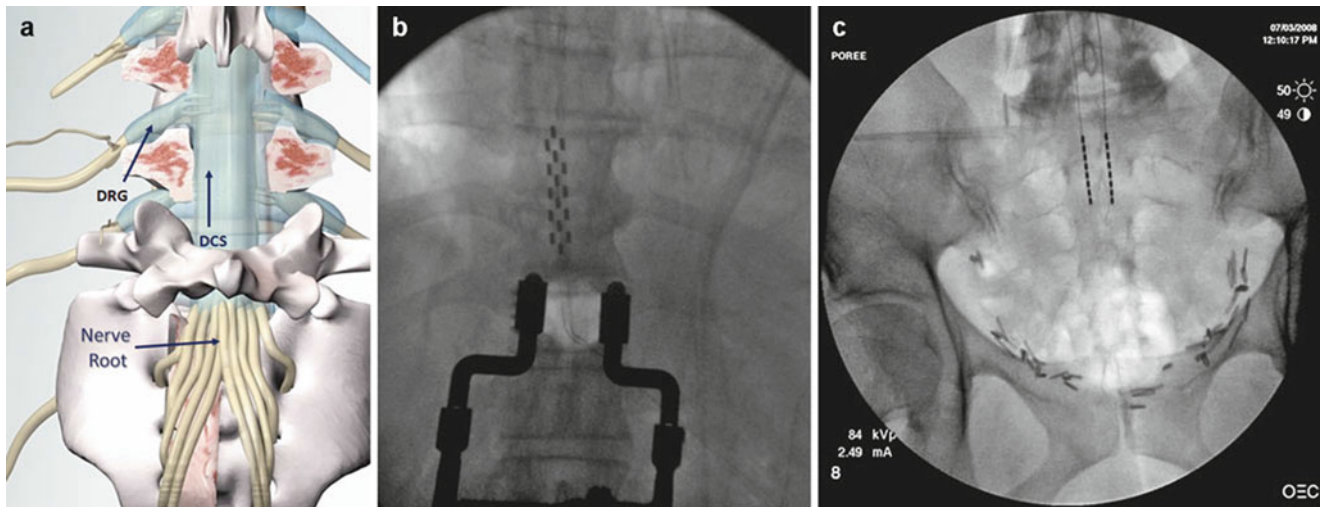
Fig. 2.10 (**a**) Illustration of intraspinal targets for electrical stimulation includes the dorsal columns (*DC*) of the spinal cord, the intraspinal nerve roots, and the dorsal root ganglia (*DRG*) (Courtesy of Jeff Kramer, Ph.D. Spinal Modulation, Menlo Park, CA) (**b**) Fluoroscopic image of intraoperative placement of 16 contact tripole paddle lead. Tripole configuration allows for greater maneuverability of the electric field. (**c**) Fluoroscopic image of retrograde placement of electrodes allows for stimulation of sacral nerve roots for patient with pelvic pain (Fluoroscopic images courtesy of Lawrence Poree MD PhD)

spinal cord stimulation, as with other advanced therapies, be subject to a more comprehensive evaluation process whereby the initial cost is balanced with long-term health-care cost, safety, efficacy, and appropriateness of other therapies. They termed this new algorithm the SAFE (safety, appropriateness, fiscal neutrality, and effectiveness) principle [65, 90]. The authors went on to use this algorithm to assess when SCS should be used in the treatment of failed back surgery syndrome (FBSS). They concluded that SCS should be considered before submitting a patient to either long-term systemic opioid therapy or repeat spinal surgery for chronic pain resulting from FBSS [91].

As health-care costs continue to rise and advanced technologies rapidly emerge, employing the SAFE principle may provide a more rational approach to making individual as well as intuitional decisions regarding appropriate selection of therapies and allocation of resources.

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