A Systematic Review: Current and Future Directions of Dorsal Root Ganglion Therapeutics to Treat Chronic Pain

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Disclosures
Disclosures: Dr. Pope is a consultant for Spinal Modulation, St. Jude, Medtronic, and Jazz Pharmaceuticals. Dr. Deer is a consultant for Spinal Modulation, St. Jude, Medtronic, Nevro, Flowonix, Jazz, Vertos, and Bioness. Dr. Kramer is an employee of Spinal Modulation.

Spinal Modulation is a device company treating the Dorsal Root Ganglion.

Abstract

Objective. The purpose of the study was to systematically review the historical therapeutics for chronic pain care directed at the dorsal root ganglion (DRG) and to identify future trends and upcoming treatment strategies.

Methods. A literature search on bibliographic resources, including EMBASE, PubMed Cochrane Database of Systemic Reviews from literature published from 1966 to December 1, 2012 to identify studies and treatments directed at the DRG to treat chronic pain, and was limited to the English language. Case series, case reports, and preclinical work were excluded. Information on emerging technologies and pharmacologics were captured separately, as they did not meet the inclusion criteria.

Results. The literature review yielded three current clinical treatment strategies: ganglionectomy, conventional radiofrequency treatment of the dorsal root ganglion, and pulsed radiofrequency treatment of the DRG. Seven studies were identified utilizing ganglionectomy, 14 for conventional radiofrequency, and 16 for pulsed radiofrequency. Electrical stimulation and novel therapeutic delivery strategies have been proposed and are in development.

Conclusions. Despite a robust understanding of the DRG and its importance in acute nociception, as well as the development and maintenance of chronic pain, relatively poor evidence exists regarding current therapeutic strategies. Novel therapies like electrical and pharmacologic strategies are on the horizon, and more prospective study is required to better qualify the role of the DRG in chronic pain care.

Key Words. Spinal Cord Stimulation; Dorsal Root Ganglion; DRG; Chronic Pain

Introduction

The treatment of chronic pain has undergone a dramatic evolution since the initial introduction of the gate control theory. This has led to the identification of new treatment targets, strategies, and therapeutic options. Many of these progressive thoughts have been employed successfully, while others have been met with failure. A relatively novel neural target is the dorsal root ganglion (DRG); an appreciation for the relevant anatomy and physiology of the target structure guides our effort to understand better the historic and potential future treatment trends.

The DRG is located bilaterally on the distal end of the dorsal root in the lateral epidural space and is composed of primary afferent somatic and visceral nerve cell bodies that relay sensory information from the periphery to the
central nervous system. The primary sensory neurons are pseudo-unipolar, with a single axon hillock that bifurcates into the afferent peripheral branch and the efferent central branch, transducing information from a variety of receptors, including nociceptors, thermoreceptors, chemoreceptors, and proprioceptors, via varied nerve sizes: C-fibers, A-delta, and A-beta types, divided into the dorsal column-medial lemniscus system (touch/proprception/ vibration), the anterolateral system (somatic pain/ temperature), and the postsynaptic dorsal column system (visceral pain) [1].

This structure has been described as the “gatekeeper” for the primary afferent nerves, and accordingly, makes it a site of interest for both animal-based studies and prospective treatment evaluations. Despite this, relatively few directed treatment strategies have been employed in an attempt to manage neuropathic pain. This systematic narrative reviews current neuroablative and neuroaugmentive treatment strategies and discusses future trends and perceived needs.

Methods

We performed a literature on bibliographic resources, including EMBASE, PubMed Cochrane Database of Systemic Reviews from literature published from 1966 to December 1, 2012 to identify studies and treatments directed at the DRG to treat chronic pain. Search words included DRG, chronic pain treatment, DRG, pulsed radiofrequency (PRF), conventional radiofrequency (RF), thermal RF, surgical treatments, and ganglionectomy. The search was limited to the English language, excluding case series, case reports, or preclinical work. The literature review yielded three current clinical treatment strategies: ganglionectomy, conventional RF treatment of the DRG, and PRF treatment of the DRG. Information on emerging technologies and pharmacologics were captured separately, as they did not meet the inclusion criteria.

Results

Search results meeting the inclusion criteria yielded seven studies for DRG treatments by ganglionectomy, of which four were prospective (Table 1). Fourteen studies were identified describing conventional RF treatments to the DRG to treat chronic pain, and of these, four were randomized, prospective, controlled studies (two of which were sham controlled) (Table 2). Sixteen studies identified pulsed radiofrequency as a treatment at the DRG (only one is a randomized, double blind, sham-controlled investigation) (Table 3).

Electrical neuromodulation using conventional spinal cord stimulator technology was identified in two case reports to treat post-herpetic neuralgia and discogenic pain, along with a feasibility trial for a novel DRG stimulation device. (Table 4). The proposed pharmacologic section was compiled from the available preclinical work directed at the DRG, with key words including DRG, viral vector, DRG pharmacology in neuropathic pain (Table 5).

Discussion

Despite the growing robust literature surrounding interventional treatment strategies to treat neuropathic, chronic pain states, little is complicit in the treatment of the DRG (Tables 1–3). Background of the identified treatment strategy, along with the presented relevant data, will be reviewed.

Ganglionectomy

Background

Ganglionectomy is an irreversible neurosurgical technique that has remained relatively unchanged since its inception in the 1970s (Figure 1). It is hypothesized that removal of the primary afferent cell bodies via ganglionectomy may inhibit nociceptive signaling and reduce intractable pain, with the theoretical advantage over dorsal root entry zone (DREZ) procedures and dorsal rhizotomy as these fail to capture the ventral nociceptive afferents. Ganglionectomy has been used to treat a variety of painful disorders, from occipital neuralgia, and thoracic radicular pain, to failed back surgery syndrome. Please refer to Table 1.

Literature Review

North et al. [2] investigated efficacy of ganglionectomy for patients with failed back surgery syndrome and overwhelmingly concluded that it was not successful. Further, Taub et al. investigated ganglionectomy for patients with intractable monoradicular pain, concluding that although there may be a place for ganglionectomy to treat monoradicular pain, it must be levied against the dysthesia that commonly develops [3]. This was again echoed by Wilkisson et al. describing long-term pain relief in 38% of patients, with allodynia developing in two and complex regional pain syndrome (CRPS) developing in one patient [4]. Weigel et al. [5] described ganglionectomy for treatment of refractory segmental thoracic pain, concluding that although it may be helpful in treating dermatomal segmental pain, it may create pain in new areas. Deafferentated pain complicating the procedure is a common theme, and although sometimes transient, it can also be potentially debilitating.

Outcomes are similarly mixed in the cervical region. Lozano et al. investigated refractory occipital pain treated by C2 ganglionectomy unilaterally or bilaterally, demonstrating improvement in patients with history of trauma or neuropathic pain descriptors on preoperative assessment. Seven patients had deafferentated pain symptoms at follow-up [6]. Acar et al. performed C2 and/or C3 ganglionectomy for patients with intractable occipital pain after diagnostic nerve block on 24 patients. Ninety-five percent had short-term pain reduction, pain returning on an average of 10.2 months. Further, response to diagnostic nerve block does not correlate with long-term surgical
Table 1  Selected ganglionectomy studies

<table>
<thead>
<tr>
<th>Study/Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Conclusion(s)</th>
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<tr>
<td>North et al. (1991) [2]</td>
<td>13 patients with failed back surgery syndrome over 8-year period; 9 women and 4 men, age 30–68, duration of symptoms lasted 6.3 years, patients had radicular pain pattern</td>
<td>Level of ganglionectomy was determined by small volume, diagnostic, paravertebral block, ganglionectomy performed unilaterally at S1 in three patients, L5 in six patients, one patient L5, S1 and L2, and one patient had bilateral S1</td>
<td>Success defined as at least 50% reduction of pain for 2 years and patient satisfaction, secondary outcome ADL activities and patient impressions.</td>
<td>15% success at 2 years, 7% at 5.5 years</td>
<td>Dorsal root ganglionectomy is not successful in treating failed back surgery syndrome patients</td>
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<td>Taub et al. (1995) [3]</td>
<td>61 patients, 33 men, 28 women with intractable lumbar monoradicul pain</td>
<td>Dorsal root ganglionectomy</td>
<td>VAS</td>
<td>36% of patients had reduced or eliminated pain, 60 and had dysthesia following surgery</td>
<td>Intractable monoradicular pain may respond to ganglionectomy, although dysthesia is common, it typically responds to treatment</td>
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<td>Lozano et al. (1998) [6]</td>
<td>39 patients with medically refractory occipital pain, 13 female, 26 male, duration of symptoms 1–43 years, 22 patients developed pain secondary to trauma, 17 idiopathic. 17 patients failed previous occipital neurectomy or C-2 rhizolysis.; 59% described pain as sharp, shooting, stabbing, jabbing, electric.</td>
<td>Unilateral or bilateral C2 ganglionectomy was performed, performed under general anesthesia, prone positioning, inpatient stay 2–10 days, follow-up 19–72 months.</td>
<td>VAS and questionnaire: excellent relief defined as &gt;90%, good relief 50–90%, relief &lt;50%</td>
<td>24 patients underwent unilateral ganglionectomy, 12 right, 12 left.; 15 had bilateral ganglionectom; 19 patients experienced excellent relief, seven patients had good relief, 13 failures; 82% of patients with history of trauma had &gt;50% pain reduction; seven patients had deaffrentated pain symptoms at follow-up.</td>
<td>Patients who used neuropathic terms to describe headache and had history of trauma were more likely to improve; 19 month full sample follow-up.</td>
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<td>Jansen (2000) [8]</td>
<td>102 patients with intractable cervicogenic headache; 65 female, 37 male; C2 ganglionectomy in 38 (22 males, 16 female), Decompression on 64; one sided headache w/o side shift, failed conservative medical management</td>
<td>Dorsal root ganglionectomy</td>
<td>VAS</td>
<td>26 patients reported complete relief in their pain, six reported improvement, six showed no response. Recurrence of pain occurred in 10 patients with follow-up 5–45 months.</td>
<td>Retrospectively, ganglionectomy may be helpful to treat refractory cervicogenic headache.</td>
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<td>Wilkinson et al. (2001) [4] (Retrospective)</td>
<td>19 patient with intractable radicular or segmental pain from FBSS, post herniorrhaphy, intercostal neuralgia, sciatic nerve injury, postorchiectomy neuralgia, meralgia paresthetica, brachial neuralgia, aged 27–75 years</td>
<td>Dorsal root ganglionectomy</td>
<td>VAS</td>
<td>Mean follow-up 22 months; following procedure, 74% reported pain reduction of at least 50% at short follow-up; long-term (1 year) 5/13 pts reported pain as three or less; allodynia occurred in two patients, CRPS developed one patient</td>
<td>Ganglionectomy may be a useful option in treatment of radicular pain, although long-term pain relief is poor and deafferented pain may occur.</td>
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<td>Acar et al. (2008) [7] (Retrospective)</td>
<td>24 patients with intractable occipital pain identified, 50% male, age range 18–79, etiology pain of pain motor vehicle accident 40%; or 30% unclear; underwent nerve blocks diagnostically</td>
<td>C2 and or C3 ganglionectomy, retrospective data acquisition</td>
<td>VAS, quality of pain descriptors, categorized as excellent, moderate (&gt;50% pain relief) or poor outcomes</td>
<td>95% of patients reported short-term pain relief &lt;3 months. 60% had excellent or moderate pain relief, pain returned on average 10.2 months</td>
<td>Nerve blocks not predictive of surgical efficacy, only short-term results</td>
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<td>Weigel et al. (2012) [5] (Prospective)</td>
<td>7 patients with refractory thoracic segment neuropathic pain of greater than or equal to 8/10.</td>
<td>Extraforaminal excision of spinal ganglion.</td>
<td>VAS score post-op, mean follow-up 24 months, self-reported outcome assessment</td>
<td>Preoperative pain scores dropped 7.4 from max preoperative, and 6.3 at mean of 24 months follow-up, 3/7 patients had new onset pain in a different dermatome; 3/7 ranked the operation as good/excellent</td>
<td>Selective ganglionectomy may be helpful to treat refractory pain, despite it can cause new pain and may be partially effective.</td>
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ADL, activities of daily living; CRPS, complex regional pain syndrome; VAS, visual analog scale.
### Table 2  Conventional RF ablation of DRG

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<tr>
<td>Sluijter et al. (1980) [22]</td>
<td>20 patients with cervicobrachial pain</td>
<td>RF at 75% for 60 seconds</td>
<td>At 3 months and 9 months, &gt;70% pain reduction reported in 65% of pts</td>
<td>RF may be helpful in treating cervical radicular pain</td>
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<td>Sluijter (1981) [23] (Prospective)</td>
<td>60 patients with lumbar and cervical complaints</td>
<td>DRG RF at 70°C for 60 seconds</td>
<td>40% of patients had &quot;good results&quot; by patient opinion score. At 3–21 month follow-up</td>
<td>RF may be helpful in treating cervical and lumbar radicular pain</td>
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<td>Nash (1986) [24] (Retrospective)</td>
<td>26 patients with intractable pain in cervical, thoracic and lumbar area after failed CMM</td>
<td>RF of DRG at 70–80°C for 120 seconds or 22 V for 120 seconds</td>
<td>Perceived benefit by self reported pain scale: excellent = no pain; good = some measurable decline in pain and significant reduction in oral analgesics</td>
<td>10/26 had excellent relief, 5 had good relief; f/u 6–72 months</td>
<td>DRG RF may be helpful in relieving intractable pain</td>
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<td>Vervest et al. (1991) [25]</td>
<td>24 patients with cervico-brachialgia</td>
<td>RF of DRG at 67°C for 90 seconds</td>
<td>At 2 months and 1.5 years, respectively, 80% and 85% of patients &quot;pain free&quot;</td>
<td>RF is safe and may provide long term treatment options for patients with cervicobrachial pain</td>
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<td>Niv et al. (1992) [21] (Prospective)</td>
<td>50 patients with malignant and nonmalignant pain; thoracic and lumbar pain</td>
<td>RF of DRG at 70°C for 90 seconds</td>
<td>62% of patients “pain free” at 3 months, 48% of patient “pain free” at 12 months</td>
<td>Option for treatment for malignant and nonmalignant pain</td>
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<td>Van Kleef, et al. (1993) [19]</td>
<td>20 consecutive patients with pain radiating to the head/shoulder/arm and failed conservative strategies, pain duration &gt;1 year; 6 male/14 female; diagnostic segmental nerve blocks</td>
<td>RF at 67°C for 60 seconds</td>
<td>NRS at baseline, 3 weeks post-op, 6 weeks post-op and 3 months, telephone interview in 17/20 pts at 9 months; EMG/SEP</td>
<td>Subtle burning paresthesia in 12/20 patients resolved at 6 weeks; 10 had at least 50% pain reduction at 3 months, 6 at 6 months, and 4 at 9 months</td>
<td>RF safe and effective in treating pain in cervical spine, although it may need to be repeated often</td>
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<td>Stolker et al. (1994) [20]</td>
<td>45 patients (12 men/33 women) median age 52 years, &lt; 6 months segmental pain pattern, nonresponsive to conservative treatment,</td>
<td>Posterior thoracic rhizotomy using common dorsolateral technique. In upper thoracic region dorsal approach via drill hole, 67°C for 90 seconds. 45 patients underwent 53 RF procedures, 37 patients underwent a single rhizotomy. 7 patients treated at two levels, 1 patient was bilateral.</td>
<td>5-grade oral analog scale. At baseline and 2 months following the procedure.</td>
<td>At 2 months after treatment, 66.7 percent of 30 patients were pain free, 11 patients obtained more than 50% pain relief, 4 patients obtained no relief</td>
<td>Thoracic rhizotomy may be safe and effective in treating segmental thoracic pain</td>
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<td>Van Kleef et al. (1995) [26]</td>
<td>Chronic thoracic pain; 43 patients; 37 patients presented with 1–2 segmental pain, 16 with &gt; 2; 22 male/21 female; age mean 52.45, pain duration &gt; 6 months</td>
<td>DRG RF at 67°C for 60 seconds.</td>
<td>4-step verbal rating scale; 8 weeks post procedure, then &gt; 36 weeks following procedure</td>
<td>17/43 patients had &gt; 50% reduction in pain at 8 weeks; 13 at mean follow-up of 113.35 weeks</td>
<td>Thoracic pain treated with RF lesioning of DRG is safe and effective, improved outcomes for &lt;2 thoracic segmental levels</td>
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<td>Van Kleef et al. (1996) [15]</td>
<td>20 patients with cervicobraчialgia, unilateral pain, duration of at least 12 months, positive response to diagnostic nerve blocks; 8 men, 12 women; mean age 43.32 years</td>
<td>Double blinded randomization into RF-DRG at 67°C or no RF-DRG lesion for 60 seconds.</td>
<td>Data collection at week 1 and 8 weeks post treatment: VAS, McGill Pain Questionnaire, MPI, side effects</td>
<td>11 sham patients: two successful and 9 unsuccessful; in lesion group 1 not successful and 8 successful.; all side effects abated prior to 3 months</td>
<td>DRG lesioning adjacent to the DRG can reduce cervicobraчial pain and appears to be safe</td>
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<td>Slappendel et al. (1997) [16]</td>
<td>Patients with intractable cervicobraчialgia, successful diagnostic blockade; 61 patients analyzed (32 in treatment, 29 in control) demographics comparable in each</td>
<td>Randomized to treatment group 67°C for 90 seconds; control received 40°C for 90 seconds, double blinded period limited to three months</td>
<td>VAS, subjective changes, side effects before RF treatment, at 6 weeks and 3 months; side effects</td>
<td>VAS reduction from 6.7 to 4.8 to 5.0 for treatment; 6.3 to 4.9 to 4.4 for control; subjective measure whether equal to or better at 3 months 27/29; 51% control success at 3 months, 47% treatment group</td>
<td>RFA with 40 degrees may yield the same efficacy as RFA with 67°C, with improved side effect profile</td>
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<td>Study</td>
<td>Population</td>
<td>Treatment Details</td>
<td>Outcomes</td>
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<td>Van Wijk et al. (2001) [27] (Retrospective)</td>
<td>279 evaluated undergoing first treatment to DRG (92 men, 187 women; mean age 47.8, mean duration of symptoms 7.2 years.)</td>
<td>DRG RF 67°C for 90 seconds&lt;br&gt;4 point pain perception scale, follow-up 2 months</td>
<td>59% of patients reported satisfactory pain reduction at 2 months; outcome no influenced by surgical history</td>
<td>DRG RF appears to be a safe in intractable lumbar radicular pain</td>
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<td>Geurts et al. (2003) [17] (Prospective Controlled)</td>
<td>1,001 patients screened, 83 patients randomized; lumbosacral pain, diagnostic nerve block conformation, mean age 46 RF group, 45 control group. Male/female ratio 18/27 RF group, 15/23 control</td>
<td>45 in RF group, 38 control treatment; RF at 67°C, iohexol and mepivacaine injected prior to lesioning</td>
<td>VAS for leg and back pain, physical impairment, medication use in a diary, SF-36 questionnaire, Zung self-rating depression, MPI at 3, 6, 9, and 12 months</td>
<td>Success with RF group was 7/44 (16%) and for control 9/36 (25%); no differences in side effects between groups</td>
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<td>Haspeslagh et al. (2006) [18] (Prospective Controlled)</td>
<td>30 patients with unilateral, cervicogenic headache, mean age 47.5, control 49.1, male to female ratio 4/11; duration of pain 9.7 RF, 6.6 control</td>
<td>15 randomized to RF group (facets and DRG), 15 randomized to injection therapy and TENS unit</td>
<td>VAS, headache days, GPE, headache days, medicine use, headache intensity, RAND-36, MPI, SCL-90 at 4 weeks before, 8 weeks after, and then 4, 6, 8, 10, and 12 months</td>
<td>Primary endpoint was percentage if relief at 8 weeks. No statistically difference between the 2 treatments at any point in the trial</td>
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<td>Nagda et al. (2011) [28] (Retrospective)</td>
<td>50 patients (24 men and 26 women), mean age 62, had relief with segmental nerve block, MRI evidence of nerve root involvement; mean age 62.</td>
<td>Pulsed and continuous RFA of the lumbar dorsal root and segmental nerves; 26 received one level of therapy, 15 received 2 levels, 9 patients received three levels, 8 received bilateral</td>
<td>Initial and subsequent RF compared by NRS; success is at least 50% reduction in pain, failure defined as less than 50% improvement in pain;</td>
<td>Mean relief for patients with 2 treatments was 4.7 months; 28 patients had 3 treatments with duration of 4.5 months; 20 patients with 4 treatments had average of 4.4 months; 18 patients with 5 treatments of 4.3 months</td>
<td>Repeated pulsed RF of the lumbar DRG may be a safe and effective management strategy to treat lumbosacral radicular pain</td>
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DRG, dorsal root ganglion; GPE, global perceived effect; NRS, numerical rating scale; MRI, magnetic resonance imaging; RFA, radiofrequency ablation; RF, radiofrequency; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.
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<tbody>
<tr>
<td>Sluijter et al. (1998) [29]</td>
<td>60 patients; lumbar radicular pain and or FBSS, diagnostic nerve root blocks; 15 patients with FBSS</td>
<td>PRF 120 seconds and RF at 42°C for 60 seconds.</td>
<td>GPE, VAS</td>
<td>6 weeks GPE &gt;50% in 86% of PRF group, 12% in RF group, VAS more than two point difference in 53% of FBSS pts in PRF group at 6 months, 40% at 12 months</td>
<td>PRF is safe superior to RF at 42°C and PRF may provide long term relief of monoradicular pain in patients</td>
</tr>
<tr>
<td>Van Zundert et al. (2003) [30]</td>
<td>18 patients with cervicobrachial pain</td>
<td>DRG PRF at single level at 42°C</td>
<td>GPE at 8 weeks, then &gt;6 follow-up, mean 19.4 months, maximum 30 months</td>
<td>72% of patients had GPE &gt;50% relief at 2 months, 33% at 1 year,</td>
<td>PRF treatment may provide long term relief for patients suffering from refractory cervicobrachial neuralgia</td>
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<td>Munglani et al. (2003) [31]</td>
<td>Chronic pain with neuropathic features of at least 18 months duration, diagnostic block 29 patients lumbar (14 previous back surgery), 6 patients cervical pain/headache (5 with whiplash injury)</td>
<td>PRF for 180 seconds at 42°C, corticosteroid and LA</td>
<td>VAS, week duration of relief, medication use,</td>
<td>14/29 “long term” responders for lumbar DRG, 4/6 “long term” responders in cervical DRG group</td>
<td>PRF of the cervical and lumbar DRG may be helpful in the treatment of segmental radicular pain</td>
</tr>
<tr>
<td>Erdine et al. (2004) [32]</td>
<td>15 patients with FBSS</td>
<td>DRG PRF</td>
<td>VAS, SF-36 physical function and body pain</td>
<td>60% have decrease of VAS at least 2 points and decrease in SF-36 bodily pain, 66.6% in SF-36 physical function</td>
<td>PRF of the DRG may be helpful in treatment of patients with FBSS</td>
</tr>
<tr>
<td>Abejon et al. (2004) [33]</td>
<td>61 pts with lumbar radicular pain for pts with FBSS, hemiated disc, or FBSS</td>
<td>DRG PRF</td>
<td></td>
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<td>PRF DRG helpful in managing lumbar radicular pain from spinal stenosis or hemiated disk, not FBSS</td>
</tr>
<tr>
<td>Teixeira et al. (2005) [34]</td>
<td>13 patients; subacute or chronic radicular pain, HNP with CT/MRI</td>
<td>PRF DRG for 180 seconds involved levels</td>
<td>NRS at 12 months</td>
<td>92% of patients had &gt;5 point improvement on NRS at 12 months</td>
<td>PRF alternative to ESI in the treatment of hemiated discs.</td>
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<td>Study</td>
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<td>Pevzner et al. (2005)[35]</td>
<td>28 patients with radicular pain both cervicobrachial or lumbar</td>
<td>PRF DRG after corticosteroid and LA injection</td>
<td>GPE at 3, 6, 12 months</td>
<td>&gt;50% relief achieved in 14/28 pts at 3 months, 9/28 at 6 months, 8/28 at 12 months</td>
<td>DRG PRF helpful in treatment of radicular pain</td>
</tr>
<tr>
<td>Shabat et al. (2006)[36]</td>
<td>28 patients with spinal and radicular pain</td>
<td>PRF DRG after corticosteroid injection and LA injection</td>
<td>1, 3, 6, 12 months GPE and VAS</td>
<td>&gt;50% relief achieved in 14/28 pts at 3 months, 9/28 at 6 months, 8/28 at 12 months</td>
<td>PRF may be safe and effective in treating spinal pain</td>
</tr>
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<td>Cohen et al. (2006) [37]</td>
<td>49 Pts with thoracic segmental pain</td>
<td>13/49 pts had PRF of DRG, 28 had PRF to intercostal nerve, 21 had CMM</td>
<td>VAS</td>
<td>62% of the DRG treated pts had &gt;50% relief at 6 months, 54% at 3 months</td>
<td>PRF superior to CMM or intercostal nerve PRF for thoracic segmental pain.</td>
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<td>Van Zundert et al. (2007)</td>
<td>256 patients with cervicobrachialgia randomly screened, 23 patients met inclusion criteria, double blinded; pain &gt;6 months; treatment group N = 11; sham N = 12.</td>
<td>PRF of DGR for 120 seconds</td>
<td>Baseline, 4 weeks, 3 month (primary outcome), 6 months, VAS 3 day average, GPE, pain medication, SF-36 and Euroqol, QoL</td>
<td>&gt;50% relief in 9/11 patients in treatment group, 4/12 in the sham group. VAS improved 2 points in 9/11 RF patients, 3/12 sham patients, no significant difference in pain medication intake</td>
<td>PRF may provide pain relief for carefully selected patients with chronic radicular pain.</td>
</tr>
<tr>
<td>Abejon et al. (2007) [39]</td>
<td>54 patients, 75 procedures</td>
<td>PRF at one or more adjacent levels for 120 seconds</td>
<td>NRS and GPE at 1, 2, 3 and 6 months</td>
<td>GPE &gt; 50% at 3 months, no complications</td>
<td>PRF of the DRG was more efficacious in hemiated disc and spinal stenosis than in FBSS</td>
</tr>
<tr>
<td>Chao et al. (2008)[40]</td>
<td>116 patients with chronic cervical or lumbar radicular pain. Mean age 53.2 and 62.42, respectively mean VAS was approximately 66 mm; 75 male, 90 female</td>
<td>DRG PRF at 42°C for 120 seconds</td>
<td>Follow-up period was one week to 1 year, VAS score (symptom free or better ≥50% improvement)</td>
<td>26/49 and 59/116 after cervical and lumbar PRF, respectively, had at least 50% improvement in first week.; 27/49 and 52/116 at 3 months, no complications</td>
<td>Pulsed RF safe and reliable in providing pain reduction for cervical and lumbar radicular pain, long term efficacy requires more study</td>
</tr>
<tr>
<td>Study/Methods</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Conclusion(s)</td>
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<tr>
<td>Simopoulos et al. (2008) [41] (Prospective)</td>
<td>76 patients with chronic lumbosacral radicular pain; 45 males, 31 female, &gt;3-year duration of symptoms</td>
<td>PRF of the DRG at 42°C for 120 seconds versus PRF and RF (approximately 54°C for 60 seconds)</td>
<td>VAS at baseline and 8 weeks post procedure</td>
<td>Average duration of action for PRF (at least two point reduction in VAS) was 3.18 months; for PRF + RF 4.39 months</td>
<td>PRF is safe and no advantage to histological lesion creation was observed</td>
</tr>
<tr>
<td>Tsou et al. (2010) [17] (Prospective)</td>
<td>127 patients with low back and leg pain secondary to HNP or FBSS</td>
<td>DRG PRF at 45 V for 120 seconds, not exceeding 42°C at L2 for LBP, and L2-S1 for leg pain.</td>
<td>VAS, success is &gt;50 percent pain reduction at 1 week to 3 yrs.</td>
<td>25/49 pts with isolated back pain had &gt;50% pain reduction at 1 week s/p L2 PRF and 20/45 pt at one year. 34/78 patients with LBP/leg pain had &gt;50% relief of back pain at 1 week and 34/74 at 1 year; leg pain relief &gt;50% 37/38 at one week, 35/74 at one year.</td>
<td>L2 DRG PRF is safe and provides intermediate-term relief of low back pain. No complications reported.</td>
</tr>
<tr>
<td>Van Boxem et al. (2011) [43] (Retrospective)</td>
<td>60 consecutive patients s/p PRF of lumbar DRG; 29 men and 31 women mean age 58 years, duration of complaints 8.9 months</td>
<td>PRF at 45 V for 120 seconds, temperature no more than 42°C at L4 or L5 or S1</td>
<td>GPE by 7-point Likert scale, primary endpoint was at least 50% improvement in pain at 2 months, Medication Quantification Scale III</td>
<td>18/60 patients had success at 2 months; at 6 months 14/60; at 12 months 8/60.</td>
<td>PRF of DRG safe and beneficial in short term to treat lumbosacral radicular pain</td>
</tr>
<tr>
<td>Choi et al. (2012) [44] (Prospective)</td>
<td>21 patients with cervical pain unresponsive to TFESI, 16 males, 5 females, mean age 60, mean duration of symptoms 14.6 months, mean TFESI failed 3</td>
<td>DRG pulsed RF at 45 V for 120 seconds, not exceeding 42°C</td>
<td>NRS for arm pain at baseline, then 1, 3, 6, 12 months, success is &gt;50% reduction in pain, at 12 months GPE 7 point Likert scale, adverse events</td>
<td>14/21 pts had &gt;50% pain reduction at 3, 6 and 12 months.; GPE 14/21 with very good/good on Likert at 12 months, no adverse events long term</td>
<td>PRF of DRG effective and safe for treatment of patients with failed TFESI and continued cervical pain</td>
</tr>
</tbody>
</table>

CMM, conservative medical management; CT MRI, computed tomography magnetic resonance imaging; DRG, dorsal root ganglion; ESI, epidural steroid injection; FBSS, failed back surgery syndrome; GPE, global perceived effect; HNP, herniated nucleus pulposus; LBP, low back pain; QoL, quality of life; RF, radiofrequency; TFESI, transforaminal epidural steroid injection; VAS, visual analog scale.
efficacy [7]. Jansen et al. [8] similarly noted after a retrospective review that ganglionectomy may be helpful in treating refractory occipital and cervicogenic headache in appropriately selected patients.

The bulk of the literature surrounding ganglionectomy to treat chronic, intractable pain is limited by quality of evidence, as it is dominated by limited prospective, observational, and retrospective strategies. Randomized prospective, controlled studies are ominously absent [9]. Although many case reports and small case series suggested promising outcomes, larger prospective controlled studies are needed.

Subsequently, limited by the aforementioned poor evidence, procedure invasiveness, and the potential for deafferentation and other complications, ganglionectomy to treat chronic intractable pain has been relegated to the end of the treatment algorithm. Further, hypothesized failure may be secondary to the inability to arrest afferent signaling, either because of intersegmental connections, ventral afferent nociceptive afferent fibers, or central neural plasticity.

### Conventional and PRF Treatments

#### Background

Radiofrequency of the DRG (Figure 2) was suggested as an alternative to ganglionectomy to destroy the primary afferents’ soma. There is robust literature surrounding RF strategies to treat chronic pain, including treatment of the DRG. As only conventional and PRF strategies have been described with the DRG as a target, these will be reviewed in succession.

Histologically detected, thermal lesions are dependent on the amplitude of the current, electrode size, and distance from the target tissue [10]. Conventional (or thermal RF) uses high frequency electrical current, creating ionic oscillation of the tissue and frictional dissipation of the ionic current, producing heat. Evidence suggests that cellular damage occurs at temperatures above 42°C; commonly 60–65°C is required. When applied immediately adjacent to a DRG, temperatures of 45, 55, 65, 75, and 85°C produce complete destruction of unmyelinated and near complete destruction of myelinated fibers [10,11].

PRF was introduced in 1998 with the intention of providing analgesia without creation of a histological lesion, and is commonly thought of as a neuromodulation technique [12]. Typical treatment employs a current of 50,000 Hz in 20 ms pulses, at a frequency of 2 per second, minimizing temperature increases above 42°C. Cellular studies have shown little to no destructive effects of PRF on cells in the DRG, although expression of sodium channels can be altered [13,14]. In animal models, PRF reduces mechanical allodynia and enhances the bulbospinal descending pain inhibitory pathways (noradrenergic and serotonergic) [14]. PRF appears to be selective in targeting small...
diameter axons composed of the C and A delta class, as evidenced by the lack of ATF3 upregulation, a common marker for cellular stress [14].

**Conventional RF Literature Review**

Conventional RF treatments to the DRG have been described to treat a variety of pain conditions. We review the available literature here, excluding case reports, case series, or preclinical studies. Four randomized, prospective, controlled studies were identified [15–18], two of which were sham controlled [15,17]. Table 2.

Van Kleef et al. [15] performed a randomized, sham controlled, double blind study with cervicobrachialgia unresponsive to conventional therapy of 12 months duration and response to diagnostic selective nerve root blocks. In a double-blinded fashion, subjects were randomization to the RF group with conventional lesioning of the DRG at 67% for 60 seconds versus needle placement and no lesioning in the control group. At 8 weeks post operation, eight out of nine RF patients reported success, while two of 11 in the control group, defined as greater than 2-point reduction on the visual analog scale (VAS) scale. This suggested short-term success where dysthesia and hypoesthesia side effects were short lived (lasting <3 months).

Slappendel et al. [16] followed with a second critique of conventional RF to the DRG in a randomized double-blinded fashion, but at two different temperatures, 67°C and 40°C, in a similar population of patient (cervicobraichalgia) and follow-up to 3 months. Fifty-one percent of

### Table 5  Proposed novel pharmacologic therapeutics for the dorsal root ganglion (DRG)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pharmacologic Agent</th>
<th>Reasons for Interest</th>
<th>Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al.</td>
<td>GDNF</td>
<td>Intrathecal infusion of GDNF prevents and reduces the expression of experimentally induced neuropathic pain</td>
<td>GDNF can be administered exogenously and may have a neuroprotective role to the injured primary afferent</td>
</tr>
<tr>
<td>Averill et al.</td>
<td>NGF and GDNF</td>
<td>Exogenous trophic factors reduce pro-nociceptive inflammatory and neuropathic changes in the DRG</td>
<td>Intrathecally administered NGF or GDNF modulate gene induction in the injured DRG</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Gene transfer into rat DRG with sonoporation</td>
<td>Delivery vehicle to alter gene expression in DRG neurons</td>
<td>U.S.-mediated gene transfer may provide means to alter pro-neuropathic gene expression</td>
</tr>
<tr>
<td>Yu H et al.</td>
<td>Lentiviral gene transfer</td>
<td>Delivery vehicle to alter gene expression in DRG neurons</td>
<td>U.S.-mediated gene transfer may provide means to alter pro-neuropathic gene expression</td>
</tr>
<tr>
<td>Milligan</td>
<td>IL-10 gene therapy</td>
<td>Prevents pro-inflammatory mediators and cytokines from activated glia that typically enhance pain transmission</td>
<td>Reduction of nociceptive and neuropathic pain, potential for IT or epidural infusion.</td>
</tr>
<tr>
<td>Jin et al.</td>
<td>Nitric oxide</td>
<td>Decrease production of TRPV1</td>
<td>May be target for neuropathic pain treatment</td>
</tr>
<tr>
<td>Kwak et al.</td>
<td>Capsaicin</td>
<td>Blocks TRPV1 hyperpolarization</td>
<td>Reduces firing threshold, improving pain in neuropathic models</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>Gastrodin</td>
<td>Reduces diabetic induced membrane current alterations</td>
<td>May improve peripheral neuropathy pain</td>
</tr>
<tr>
<td>Samad et al.</td>
<td>AAV vector against NA1,3, direct injection</td>
<td>Na1,3 up regulation is known to contribute to neuropathic pain</td>
<td>Knockout of Na1,3 reduced mechanical allodynia in segmental injectable delivery, feasibility of peripheral delivery of gene transfer constructs</td>
</tr>
<tr>
<td>Xu et al.</td>
<td>AAV5, anti-RNA, intrathecal administration</td>
<td>Delivery vehicle to alter gene expression in DRG neurons</td>
<td>Intrathecal delivery of AAV5 anti-RNA is capable of DRG knock out</td>
</tr>
</tbody>
</table>

AAV, adeno-associated viral vector; IT, intrathecal; GDNF, glial derived neurotrophic factor; NGF, nerve growth factor; RNA, ribonucleic acid.
the 40°C group had success (>2-point reduction in VAS) at 3 months, compared with 47% of the 67°C group. Interestingly, the group lesioned at the lower temperature developed less side effects, although at 3 months the symptoms abated, and had longer duration of reduction in VAS, suggesting 40-degree lesioning may as good as, with lower neuritis incidence, than the conventional 67°C methodology.

Geurts et al. [17] performed a prospective, randomized, double blind, sham-controlled study on patients with lumbar radicular pain, identified from 1,001 screened patients and confirmed with diagnostic injection(s). The treatment group received iohexol and mepivacaine injection prior to lesioning, with the control group having identical needle placement and preparation without the thermal lesioning. The primary “success” endpoint was defined using a multidimensional decision rule, with changes in VAS, physical activities, and analgesic use: 50% of median VAS leg, without a drop in daily physical activities or a rise in analgesic use (from baseline) or 25% reduction in VAS leg, rise in activity of 25%, and 25% reduction in analgesics (from baseline). Seven out of 44 patients met the “success criteria,” with 25 of 44 having moderate or severe treatment-related pain at 3-month follow-up. This data demonstrated that traditional RF of the lumbar DRG was no better than local anesthetic injection alone, suggesting lumbar dorsal root lesioning with conventional RF should not be performed. Similarly, Haspeslagh et al. [18] demonstrated poor response to RF treatment for cervicogenic headache, as compared with conservative therapy, although only three of 15 patients in the treatment group underwent DRG RF.

**Figure 1** Dorsal root ganglionectomy at C3 [7].

**Figure 2** Radiofrequency probes in the cervical (A) and lumbar (B) region [50].
Pope et al.

Van Kleef et al. [19] performed a prospective study on 20 consecutive patients with refractory cervicobrachial neuralgia and subsequent diagnostic selective nerve root block. RF was performed at 67°C for 60 seconds and numerical rating scale (NRS) tracked at 3, 6, and 9 months. Ten out of 20 patients had at least 50% reduction in NRS at 3 months, six out of 20 at 6 months, and four out of 20 at 4 months. The authors concluded that conventional RF of the DRG may be helpful in treating refractory cases, although it may also need to be repeated often. Stolker et al. investigated [20] DRG RF lesioning at 67°C for 90 seconds for treatment of thoracic segmental pain; and despite creating a drill hole to access the thoracic DRG at times, 66.7% at 2 months were pain free, and 11 patients obtained more than 50% relief again suggesting clinical utility for dorsal root lesioning for segmental pain treatment. Niv and Chayen demonstrated long-term relief of a year with thoracic and lumbar DRG lesioning at 70°C for 90 seconds [21]. This was echoed by Stolker et al. [20], describing long-term efficacy to treat thoracic segmental pain for up to 2 years following RF of the DRG at 67°C for 90 seconds.

Although prospective observational and retrospective studies have yielded consistent support for DRG treatment in the cervical, thoracic, lumbar, and sacral regions [15–28], controlled studies are less compelling, complicated by the challenge of the lurking deafferentated pain potential. Further, patient selection appears to be vague in predicting treatment outcomes. Larger, sham-controlled, prospective studies are required to elucidate the place of conventional RF treatment of the DRG for treatment of chronic pain.

PRF Literature Review

The literature for PRF of the DRG is sizeable, with again a paucity of randomized controlled trials [29–49]. Of the 16 studies identified describing PRF treatment to the DRG, only one is a randomized, double-blind, sham-controlled investigation (Table 3).

Van Zundert et al. [38] investigated PRF of the DRG for patients with cervicobrachial neuralgia unresponsive to conservative treatment, with pain duration of at least 6 months and diagnostic selective block success. Two hundred fifty-six patients were screened, 23 enrolled (11 treatment, 12 sham). The treatment arm received PRF of the DRG for 120 seconds, while the sham treatment was identical, excluding the passage of current for the PRF. Greater than 50% pain reduction in the global perceived effect (on the Likert scale) was achieved in the PRF group in nine of 11 patients, and in four of 12 in the sham group at 3-month follow-up. Further, a 20-point reduction in VAS was achieved at 3 months in nine of 11 PRF patients and three of 12 sham patients. These were both statistically significant. The third primary outcome measure of pain medicine intake was not statistically significant between the groups, although six of 11 of the PRF group and four of 12 of the sham group had reduced analgesic medicines from baseline. The authors concluded that PRF of the cervical root DRG might be helpful in treating patients carefully selected with cervical radicular pain.

Of the 15 remaining PRF DRG investigations, six are prospective and nine are retrospective, with auspicious support for therapeutic efficacy [29–34,36–44,46]. Prospectively, Sluijter et al. [29] treated 60 patients with lumbar radicular pain from a variety of etiologies, with PRF for 120 seconds or RF at 42°C for 60 seconds. Eighty-six percent of the PRF group had >50% improvement at 6 weeks, as compared with 12% in the RF group, suggesting PRF is safer and more effective than conventional RF at 42°C. Of the 15 patients with failed back surgery syndrome (FBSS) with PRF of DRG, 53% had >2-point VAS reduction at 6 months and 40% of patients at 1 year. Study limitations include limited follow-up, lack of clinical utility of RF at 42°C, nonrandomization, non-blinded, and not placebo or sham controlled.

PRF has been demonstrated to be an alternative to, or rescue treatment for, traditional therapy. Teixeira et al. [34] retrospectively compared PRF versus epidural injections in the treatment of subacute or chronic radicular pain, with results suggesting a role for PRF. This was reinforced by Choi et al. [44], describing 21 patients unresponsive to transforaminal epidural steroid injection (TFESI) for cervical pain, and after PRF of the DRG at 45 V for 120 seconds, 14 out of 21 patients had >50% pain reduction at 12 months. These findings were further supported by Chao et al. [40]. Cohen et al. [37] retrospectively determined DRG PRF was superior to conservative medical management or peripheral nerve PRF for patients with thoracic segmental pain. Tsou et al. [42] described benefit of pulsed DRG of the L2 DRG at 45 V for 120 seconds. Twenty of 49 patients with axial back pain from herniated nucleus pulposus (HNP) or FBSS had >50% pain reduction by VAS at 1 year. In patients with axial low back and radicular pain, 34 out of 74 had back pain relief at 1 year, while 35 out of 74 had leg pain relief at 1 year.

Combination therapy of PRF and RF treatment of the DRG has been investigated. Simopoulos et al. [41] prospectively analyzed 76 patients with chronic lumbosacral radicular pain randomized to either PRF of DRG at 42°C for 120 seconds or PRF and RF at 54°C for 60 seconds. At 2 months, VAS score with at least 2-point reduction was 70% for PRF group and 82% for the PRF + RF group. The average duration of relief with maintained 2-point difference in VAS was 3.18 for RF group and 4.39 months in the RF + RF group. No statistically significant difference was observed. Nagda et al. [28] retrospectively reviewed PRF and RF of DRG to treat lumbar radicular pain. After identification of patients with >50% pain reduction with PRF at 42°C for 120 seconds and RF at 56°C for 60 seconds, examination of serial treatments was performed: the mean duration of relief was 4.7 months for two treatments, 4.5 months for three treatments, 4.4 months for four treatments, and 4.3 months for five or more.
treatments. This suggests that repeated PRF + RF of the DRG is helpful and provides consistent duration of relief and repeatability for long-term management.

In summary, lumbar radicular pain treatment strategies directed to the DRG have intriguing results. North et al. [2] reported exclusively on lumbar radicular pain treatment failure in patients with FBSS with ganglionectomy, while Geurts [17] described similar dismal results with RF lesioning in the same population (21 of 45 patients in treatment group had at least one back surgery). PRF for radicular pain following FBSS is equivocal, as multiple studies provide conflicting results. Namely, Abejon et al. [39] retrospectively evaluated the efficacy of pulsed RF on 54 consecutive patients with pain from herniated disc (HD), from spinal stenosis (SS) or from FBSS ($N = 13$). Therapeutic success was defined as global perceived effect (GPE) >5 (Likert scale) or NRS reduction of 2 points at 60 days. The NRS was significantly higher, while the GPE was lower after PRF of the DRG for FBSS patients as compared with HD or SS patients, suggesting treatment failure for the FBSS group. Meanwhile, Erdine [32] retrospectively described treatment in 15 patients with FBSS with PRF. At 6 months, 60% had 2–3 point drop in VAS, 66.6% had an improvement in SF-36 physical function, and 60% reported a decrease in SF-36 bodily pain. Further study with larger powered, prospective, randomized, sham-controlled studies needed to elucidate this treatment strategy for FBSS patients, and studies are already forthcoming [49].

Malik and colleagues [50] performed the most recent literature review dedicated to RF treatments of the dorsal root ganglia in 2008 commenting on quality of evidence at the time. Cervicobrachial pain, level C evidence exists for RF and PRF, as one relevant, high-quality RCT or more than one relevant low-quality RCT exists. Cervicogenic headache treatment with RF of the DRG is class D and class C evidence against RF treatment of the DRG for lumbar radicular pain [50,51]. Given the importance of the DRG in the maintenance and development of chronic pain, and with the aforementioned limited evidence for our current treatment strategies, focus has directed to emerging therapeutics.

**Emerging DRG Therapeutics**

**Electrical Neuromodulation**

Understanding the importance of the primary afferent in the transduction and translation of nociceptive and neuropathic pain, interest has focused on electrical stimulation strategies directed at the DRG. Case reports have described successes with cervicogenic headache, postherpetic neuralgia, and discogenic pain [52,53]. Equipment specifically designed to target the DRG may improve efficacy and safety, as common practice requires manipulation of dorsal column stimulating equipment, with inherent challenges [52–54]. Further, the sheer bulk, rigidity and contact spacing of the traditional dorsal column lead may compress the DRG and recruit unwanted neuromodulatory targets, including DREZ and motor fibers.

New equipment design and delivery mechanism has remedied the aforementioned challenges (Figure 3). Prospective studies are ongoing.

In an initial short-term feasibility trial [55–56], 10 subjects underwent DRG stimulation and followed prospectively, where seven of nine completed the study with >50% pain reduction with concurrent reduction in oral analgesic medication. Of note, position effects, which hinder the therapeutic tolerability of the paresthesia elicited by traditional spinal cord stimulation, were absent. Further, steerable and segmental stimulation, with both discrete and broad coverage was observed commonly in patients where therapeutic stimulation is difficult to achieve with traditional spinal cord stimulation. Ongoing trials of DRG stimulation employing this novel delivery strategy suggest that statistically significant pain reduction is present at 6 months [55,57] Further, larger powered observational studies are warranted, as are controlled randomized trials to evaluate it role in chronic pain care.

**Figure 3** Sequential fluoroscopy views of the use of a novel dorsal root ganglion (DRG) stimulation system to deploy a DRG directed lead. (A) Epidural needle entry. (B) Lead exiting needle. (C) Delivery system used to steer lead toward lateral epidural space. (D) Final position of lead in lateral epidural space near the DRG. (Used with permission from Spinal Modulation.)
Pharmacologic Neuromodulation

As one can appreciate in the proceeding section, chronic neuroaugmentative strategies are overwhelmingly more popular than neuroablative therapies, as poor evidence and deafferentation pain plague the latter. Electrical neurostimulation of the DRG has been reported with excellent prospective data to date. However, this should not overshadow, but rather encourage, the development of novel DRG infusion strategies to treat intractable pain employing local application of pharmalogic agents.

Targeted drug therapy has become an underutilized treatment strategy to treat mixed, neuropathic, or nociceptive somatic pain, likely secondarily to a poor understanding and misinterpretation of the publicized, iatrogenic patient morbidity and mortality in patients with intrathecal therapy [58], poor physician training, practice troubleshooting algorithms and management, along with misconceptions regarding reimbursement.

Despite these challenges, chronic infusion therapy directed at the DRG is a promising modality. Glutamate is the primary neurotransmitter of the primary sensory afferent nociceptors, with its action shaped by neuropeptides released at the terminal endings, such as substance P, neurokinin A, adenosine triphosphate, adenosine, somatotin, cytokines, and calcitonin gene-related peptide [59]. Further, cytokines, catecholamines and prostaglandins can change the chemical sensitivity and gene expression of membrane channels of the DRG [60,61]. The fact that many of the membrane neurophysiologic changes occur in the soma and not in the projection axons, and many of the neurotransmitter alterations involve neurochemical synthesis changes within the parykaria, point to the DRG as a potential site for directed therapy, as this may be a source of chronic pain development and maintenance.

Anatomically, the DRG is outside the blood brain barrier. As the dorsal and ventral roots course away from the spinal cord, the arachnoid and dura mater accompanies them. A dural root sleeve extends distal to the DRG and then becomes adherent to the nerve, forming the epineurium [62]. Cerebrospinal fluid (CSF) does not extend beyond the intervertebral foramen (Figure 4).

The presence of the dural sleeve suggests the pharmacokinetics of infusion therapy directed to the DRG is likely more epidural-like in nature than intrathecal-like, providing inherent advantages, including reduced or eliminated concern for granuloma, the ability to target pain segmentally, and avoidance of the poorly understood CSF flow dynamics and intrathecal drug pharmacokinetics. If early successes with electrical neuromodulation of the DRG are an indication, infusion therapy may also be rewarding. Moreover, the renewed interest in analgesic drug development is important, as avoidance of the sequella of chronic treatment with opioid and non-steroidal anti-inflammatory drugs classes. Prescription opioid misuse and diversion is in epidemic proportions and has gained national attention.

Surprisingly to date, the Food and Drug Administration (FDA) has approved only two intrathecally administered analgesics to treat pain: morphine and ziconotide. In clinical practice, however, a variety of local anesthetic, alternative opioids, and non-opioid analgesics are used in a variety of combinations, with clinical justifications for each, and include clonidine, bupivacaine to name a few. As these medications can surely be translated to epidural infusion for DRG treatment, attention has refocused on new potential anti-nociceptive and neuropathic opportunities within the primary afferent (Table 5).

Neurotrophin TrkA is a receptor that promotes nociception and sensitizes the neuron to painful stimuli, activated by nerve growth factor (NGF). NGF also negatively regulates injury-associated molecules [63]. Activating transcription factor 3 (ATF3), a member of the activating transcription factor/cAMP responsive binding protein, is induced after nerve injury, and is subsequently used a marker for DRG injury [63]. Averill et al. [63] placed an intrathecal lumbar catheter in Wister rats to deliver NGF or glial derived neurotrophic factor (GDNF) in a controlled, unilateral sciatic nerve injury model treatment arm, to determine effect on ATF3 upregulation. Using immunochemistry methods, GDNF reduced the percentage of ATF3 upregulation of neurotransmission-related molecules from 70 to 4% P2X3 and NGF-CGRP (calcitonin gene-related peptide) from 10% to <1%. This suggests exogenous application of specific trophic factors can modulate the expression of pro-nociceptive mediators in the DRG [63]. This is of particular importance since the FDA recently lifted the restriction on anti-NGF studies after fears of accelerated joint destruction halted phase III trials [64]. Wang et al. [65] further described the neuroprotective effects of GDNF, as it appears to have broad neuroprotective properties given intrathecally at high doses [65].

![Figure 4 Dural sleeve surrounding the dorsal root ganglion (DRG) [73].](http://painmedicine.oxfordjournals.org/)
Gastrodin (isolated from Gastrodia elata Blume) has been used clinically in China as an analgesic, antiepileptic, and sedative for many years [48]. Sun et al. investigated its effects on streptozocin induced peripheral neuropathy in rats by peritoneal infusion. Gastrodin reduced mechanical allodynia and thermal hyperalgesia by ameliorating the diabetic-induced enhancement of inward transient sodium currents and reduction in slowly inactivating potassium currents [68].

Interleukin 10 (IL 10) gene therapy may reduce glial cell activation, reducing pain by IL 10 production will suppress pro-nociceptive mediators, including tumor necrosis factor (TNF) interleukin 1 m and interleukin 6, further downregulates receptors for proinflammatory cytokines and upregulates antagonists to proinflammatory cytokines [69].

Different strategies of post-meiotic transfection have been trialed, including liposomal, lentiviral, microinjection, cationic polymers, and electroporation. Ultrasound can be employed to increase the permeability of cellular intake to facilitate cellular uptake. Lin et al. evaluated sonoporation mediated gene transfer in the rat DRG, concluding optimization of ultrasound frequency was 5 W for 2 seconds, yielding gene transfection rate of 31% and survival rate of 35%. Yu et al. demonstrated lentiviral gene transfer into the rat DRG is a useful strategy in delivering target genes [70].

Upregulation of voltage-gated sodium channels has been suggested in neuropathic pain models and hyperexcitability [71]. Samad et al. constructed an adeno-associated viral vector expressing small hairpin ribonucleic acid (RNA) against rat Na,1.3 and injected it into rat DRG with spared nerve injury (SNI) and demonstrated attenuation of mechanical allodynia in the SNI model [71]. This suggests peripheral delivery route of gene delivery products is feasible and validates Na,1.3 as a target.

Xu et al. [72] investigated intrathecal delivery and transduction efficacy of an adenovirus vector in the rat DRG, and the efficacy of gene expression knockdown in rat DRG by a small interfering RNA (siRNA), specifically the mTOR gene, a commonly upregulated gene in peripheral nociception. Indeed, the intrathecal route was effective at delivering the adenovirus-associated virus serotype 5 and small interfering RNA into the target mTOR DRG neurons, providing validation of this vehicle in altering nociceptive and neuropathic disease process [72].

Conclusions

Despite a robust understanding of the DRG and its importance in acute nociception, as well as the development and maintenance of chronic pain, relatively poor evidence exists regarding current therapeutic strategies. Although auspiciously suggested by prospective observational and retrospective investigations, randomized, placebo/sham/conventional-therapy controlled studies are warranted to determine where DRG targeted therapeutics fit in chronic pain care algorithms. Novel DRG neuroaugmentative therapies hold promise, as advancement in the field of neuromodulation to treat intractable pain continues to evolve.

References


Dorsal Root Ganglion, Therapeutics, Review


