Title
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Permalink
https://escholarship.org/uc/item/65w3h83q

Journal
Anesthesia and Analgesia, 124(1)

ISSN
0003-2999

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Publication Date
2017

DOI
10.1213/ane.000000000001581

Peer reviewed
Continuous Peripheral Nerve Blocks: An Update of the Published Evidence and Comparison with Novel, Alternative Analgesic Modalities

Brian M. Ilfeld, MD, MS

A continuous peripheral nerve block (CPNB) consists of a percutaneously inserted catheter with its tip adjacent to a target nerve/plexus through which local anesthetic may be administered. Such a “perineural local anesthetic infusion” provides a prolonged peripheral nerve block that may be titrated to the desired effect.¹ In the decades after its first report in 1946,² a plethora of data relating to CPNB was published, much of which was examined in a 2011 Anesthesia & Analgesia article. The current update is an evidence-based review of the CPNB literature published in the interim. Novel insertion sites include the adductor canal, interpectoral, quadratus lumborum, lesser palatine, ulnar, superficial, and deep peroneal nerves. Noteworthy new indications include providing analgesia after traumatic rib/femur fracture, manipulation for adhesive capsulitis, and treating abdominal wall pain during pregnancy. The preponderance of recently published evidence suggests benefits nearly exclusively in favor of catheter insertion using ultrasound guidance compared with electrical stimulation, although little new data are available to help guide practitioners regarding the specifics of ultrasound-guided catheter insertion (eg, optimal needle–nerve orientation). After some previous suggestions that automated, repeated bolus doses could provide benefits over a basal infusion, there is a dearth of supporting data published in the past few years. An increasing number of disposable infusion pumps does now allow a similar ability to adjust basal rates, bolus volume, and lockout times compared with their electronic, programmable counterparts, and a promising area of research is communicating with and controlling pumps remotely via the Internet. Large, prospective studies now document the relatively few major complications during ambulatory CPNB, although randomized, controlled studies demonstrating an actual shortening of hospitalization duration are few. Recent evidence suggests that, compared with femoral infusion, adductor canal catheters both induce less quadriceps femoris weakness and improve mobilization/ambulation, although the relative analgesia afforded by each remains in dispute. Newly published data demonstrate that the incidence and/or severity of chronic, persistent postsurgical pain may, at times, be decreased with a short-term postoperative CPNB. Few new CPNB-related complications have been identified, although large, prospective trials provide additional data regarding the incidence of adverse events. Lastly, a number of novel, alternative analgesic modalities are under development/investigation. Four such techniques are described and contrasted with CPNB, including single-injection peripheral nerve blocks with newer adjuvants, liposome bupivacaine used in wound infiltration and peripheral nerve blocks, cryoanalgesia with cryoneurolysis, and percutaneous peripheral nerve stimulation. (Anesth Analg 2016;XX:00–00)

From the Department of Anesthesiology, University of California San Diego, San Diego, California. Accepted for publication July 21, 2016. Funding: Departmental funds. Conflicts of Interest: See Disclosures at the end of the article. Parts of this report were previously presented annually since 2003 when I began giving presentations; this is a review article and therefore covers material that I have presented previously. Reprints will not be available from the authors. Address correspondence to Brian M. Ilfeld, MD, MS, University of California San Diego, 200 West Arbor Dr, MC 8770 San Diego, CA 92103. Address e-mail to bilfeld@ucsd.edu Copyright © 2016 International Anesthesia Research Society DOI: 10.1213/ANE.0000000000001581

INDICATIONS AND INSERTION LOCATIONS
The overwhelming majority of recently published CPNB data involves providing analgesia after surgical

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procedures. Noteworthy exceptions include case reports/series using CPNB to treat chronic pain such as cancer-related pain,3–8 complex regional pain syndrome,9–12 ischemia-induced pain,13,14 ulcer-derived pain,15 and phantom limb pain (Table 1).16–18 Regarding the latter, the only available randomized data come from a very small pilot study (n = 3) but does strongly suggest that further research is warranted.19 Another randomized, placebo-controlled pilot study (n = 4) provides evidence that a 3-day, continuous interscalene nerve block dramatically improves shoulder range of motion both during and up to 12 weeks after manipulation for adhesive capsulitis.20 Also noteworthy, continuous paravertebral21–23 and intercostal24–26 catheters have been used to treat pain after traumatic rib fracture; and a randomized pilot study (n = 30) detected no differences between this CPNB technique and a thoracic epidural infusion with the exception of a greater incidence and degree of hypotension using epidural anesthesia.27 Lastly, continuous transversus abdominis plane (TAP) and femoral blocks have been used to treat abdominal wall pain during pregnancy28 and femur fracture pain,29,30 respectively.

Recently, case reports and small series using CPNB to induce sympathectomy to improve transplantation success have been published.31,32 Similarly, a number of reports have been published, involving the use of continuous TAP blocks to treat postoperative pain after hernia repair,33 renal transplantation,34 and abdominal procedures.35 Unfortunately, this catheter location remains unvalidated with the only (negative) randomized, placebo-controlled trial underpowered (n = 20),33 and a different RCT comparing TAP and epidural catheters for upper abdominal surgery designed as a superiority trial yet detecting few differences between treatments (therefore, inconclusive).36 Bilateral continuous paravertebral blocks have also been used for abdominal surgery in the presence of mild coagulopathy instead of an epidural because of concern of epidural hematoma formation.37 Novel insertion sites include catheters adjacent to the lesser palatine,38 ulnar,39 superficial peroneal,40,41 and deep peroneal nerves.40 New interfascial catheter sites have also been described: interpectoral42,43 and quadratus lumborum44,45 for breast and abdominal analgesia, respectively.

However, adductor canal catheters are by far the most examined and potentially influential anatomic site described recently (Table 1).57 The adductor canal is an aponerotic tunnel in the midthird of the thigh deep to the sartorius muscle that contains multiple afferent nerves innervating the knee, yet only a single efferent nerve innervating the medial part of the quadriceps femoris muscle.48,49 Therefore, local anesthetic administered in the canal induces dramatically less quadriceps weakness compared with deposition adjacent to the femoral nerve at the inguinal crease.50 Reflecting the concern regarding the association between continuous femoral nerve blocks and both falls51–56 and physical therapy limitations,57,58 adductor canal periarterial nerve stimulation debate.86 Nonetheless, using electric current to guide the inserting needle and/or stimulating catheter failed to provide superior analgesia or decrease opioid requirements (and vice versa). In addition, using electric current with either the needle or the catheter required a longer insertion time and ultimately proved more costly. With the number of CPNB-related RCTs involving nerve stimulation appearing to fall precipitously within the past few years,14,94–99 it subjectively appears there are now some consensus emerging regarding the ultrasound-versus-stimulation debate.86 Few RCTs have been published—recently or otherwise—to help guide practitioners regarding the specifics of ultrasound-guided catheter insertion.1,101,102 For example, imagining the target nerve in the short axis (a cross-section) is far easier103 and decreases total insertion time compared with imaging the long axis103,104, and nearly all publications report this transducer-to-nerve orientation. However, catheters may be inserted through a needle introduced either parallel or perpendicular to the target nerve.105 Few RCTs compare these “in-” and “out-of-plane techniques106; and of those that do, results may agree (femoral)103,104 or conflict (interscalene).107,108 Although publication limitations of this review article preclude an in-depth discussion of these issues,109 readers are referred elsewhere for related information.105,110

Technologic innovations of the past few years offer possible improvements in CPNB application110 and include self-coiling catheters that curl immediately on exiting the
### Table 1. Catheter Locations

<table>
<thead>
<tr>
<th>Surgical Site</th>
<th>Major Approaches</th>
<th>Randomized and Controlled Study Design? (for Catheter Site)</th>
<th>Comments</th>
<th>Comparative CPNB Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head and neck</strong></td>
<td>Mandibular, maxillary, lesser palatine nerves, and cervical plexus</td>
<td>No1,38,426</td>
<td>Effectiveness of techniques unclear without RCT</td>
<td>A recent RCT demonstrated that a supraclavicular infusion is noninferior to an interscalene infusion and reduced the incidence of complete or partial hemidiaphragmatic paresis (analgesia was superior to the interscalene catheters in the recovery room)427</td>
</tr>
<tr>
<td><strong>Shoulder and proximal humerus</strong></td>
<td>Interscalene</td>
<td>Yes20,28,99,108,116,119,130,133,145-147,153,163,164,173,176,195,427</td>
<td>Recent RCT demonstrated a 2-d continuous interscalene block decreases pain 7 d after major shoulder surgery compared with a single-injection ropivacaine block178</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervical paravertebral</td>
<td>No5</td>
<td>Little published since the widespread adoption of ultrasound-guided catheter insertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intersternocleidomastoid</td>
<td>No1</td>
<td>Little published since the widespread adoption of ultrasound-guided catheter insertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supraclavicular</td>
<td>Yes627, 430</td>
<td>Relatively rare catheter site relative to the interscalene location for shoulder surgery; however, the largest series to date was recently published (n = 498)165</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suprascapular</td>
<td>No631</td>
<td>Effectiveness of technique unclear without RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Elbow, forearm, and hand</strong></td>
<td>Supraclavicular</td>
<td>Yes118, 32,77,81,159,165</td>
<td>Relatively rare catheter site relative to the infraclavicular and—historically—axillary locations; however, the largest series to date was recently published (n = 271)165</td>
<td>Infraclavicular provides superior analgesia to both supraclavicular432 and axillary433 catheters for hand, forearm, and elbow surgery; 1 new RCT detected few differences between supraclavicular and infraclavicular infusions benefits but was underpowered for these secondary endpoints, and there were trends in favor of the infraclavicular location434</td>
</tr>
<tr>
<td></td>
<td>Infraclavicular</td>
<td>Yes173,434, 436</td>
<td>A recent RCT provided 60 h of infraclavicular infusion to all participants and randomized subjects to remain hospitalized for 1 vs 3 nights173; total hospital cost of care was 15% lower in the early discharge group and no other differences between treatment groups including elbow range of motion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Axillary</td>
<td>Yes433, 35,77,79-81,127,128,436</td>
<td>Dramatic decrease in publications since the widespread adoption of ultrasound-guided catheter insertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median, ulnar nerves</td>
<td>No39,436</td>
<td>Effectiveness of techniques unclear without RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Thorax and breast</strong></td>
<td>Thoracic paravertebral</td>
<td>Yes27,130,158,167,177,204,221,437</td>
<td>For mastectomy, mixed evidence439,440 with RCTs demonstrating no infusion benefits over placebo221 and single-injection,441 yet others demonstrating benefits both during437 and after (up to 1 y) peri neural infusion177,221</td>
<td>There are no studies comparing these CNPB techniques</td>
</tr>
<tr>
<td></td>
<td>Intercostal</td>
<td>No24-26</td>
<td>Effectiveness of this technique unclear without RCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interpectoral</td>
<td>No42,43</td>
<td>Effectiveness of this relatively novel technique unclear without RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Abdomen and inguinal region</strong></td>
<td>Paravertebral</td>
<td>No37,77,83,442,443</td>
<td>New published data include pediatric patients77,83,442</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transversus abdominis plane</td>
<td>Yes23,38, 34,35,77,206,444</td>
<td>Remains unvalidated with an RCT: one RCT was negative compared with placebo but was underpowered; and a second RCT detected few differences between a continuous subcostal TAP and epidural infusion but was designed as a superiority study and the negative results should therefore be considered inconclusive and not equivalent46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quadratus lumborum</td>
<td>No64-65</td>
<td>Effectiveness of this relatively novel technique unclear without RCT</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 1. Continued

<table>
<thead>
<tr>
<th>Surgical Site (for Catheter Site)</th>
<th>Comparative CPNB Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip, thigh, and leg</strong></td>
<td></td>
</tr>
<tr>
<td>Posterior lumbar plexus</td>
<td>Published RCTs dramatically diminished in numbers within the past few years, possibly indicating a general preference for other catheter locations For hip arthroplasty, patients with femoral (vs posterior lumbar plexus) catheters: no difference in resting pain scores, but ambulation suffered; dynamic pain scores either higher or no difference; and increased opioid-related side effects and satisfaction</td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
</tr>
<tr>
<td>Yes113,206</td>
<td></td>
</tr>
<tr>
<td>No3,6,7,17,178</td>
<td></td>
</tr>
<tr>
<td>Yes39,203</td>
<td></td>
</tr>
<tr>
<td>No2,7,9,18,30,77–81,150,159,162</td>
<td></td>
</tr>
<tr>
<td>Fascia iliaca</td>
<td>First study validating this technique for hip analgesia recently published</td>
</tr>
<tr>
<td>Yes445</td>
<td></td>
</tr>
<tr>
<td>Parasacral</td>
<td>Effectiveness of this technique unclear without RCT involving hip, thigh, or leg surgery</td>
</tr>
<tr>
<td>Yes8</td>
<td></td>
</tr>
<tr>
<td>No3,7,9,18,30,77–81,150,159,162</td>
<td></td>
</tr>
<tr>
<td><strong>Knee (femoral nerve)</strong></td>
<td>Published RCTs dramatically diminished in numbers within the past few years, possibly indicating a general preference for other catheter locations Compared with femoral infusion, adductor canal CPNB induces less quadriceps femoris muscle weakness and ambulatory disability; however, the evidence is mixed regarding comparable analgesia and further research is required to draw definitive conclusions</td>
</tr>
<tr>
<td>Posterior lumbar plexus</td>
<td></td>
</tr>
<tr>
<td>Yes11</td>
<td></td>
</tr>
<tr>
<td>No77–40,96</td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>Until recently, the most commonly published catheter location for knee surgery, but concerns regarding associated falls have raised interest in alternative catheter locations such as the adductor canal</td>
</tr>
<tr>
<td>Yes50,57–59,74,86,91,93,95,101,104,121,132,138,198,216,446,447</td>
<td></td>
</tr>
<tr>
<td>No77–80,97,100,201,205,448–451</td>
<td></td>
</tr>
<tr>
<td>Adductor canal</td>
<td>Relatively recently validated with randomized, placebo-controlled trials, but multiple issues remain in dispute of unclear/unknown such as relative analgesia afforded compared with a femoral infusion</td>
</tr>
<tr>
<td>Yes47,50,57–59,61–65,73,74,144</td>
<td></td>
</tr>
<tr>
<td>No156,263,279,452–456</td>
<td></td>
</tr>
<tr>
<td>Fascia iliaca</td>
<td>Dramatic decrease in publications since the widespread adoption of ultrasound-guided catheter insertion</td>
</tr>
<tr>
<td>Yes1</td>
<td></td>
</tr>
<tr>
<td>No77</td>
<td></td>
</tr>
<tr>
<td><strong>Knee (sciatic nerve), leg, ankle, and foot</strong></td>
<td>Three recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psosas compartment) block after total knee arthroplasty; all demonstrated lower pain scores and decreased supplemental analgesic consumption, and one detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation</td>
</tr>
<tr>
<td>Subgluteal/parasacral</td>
<td>No major analgesic differences found between subgluteal and popliteal</td>
</tr>
<tr>
<td>Yes54,96,97,126,201</td>
<td></td>
</tr>
<tr>
<td>No77,78,82,128,159</td>
<td></td>
</tr>
<tr>
<td>Popliteal</td>
<td>A recent RCT provided 3 d of popliteal sciatic infusion to all participants (n = 120) and randomized subjects to remain hospitalized for 0 vs 2 nights after major orthopedic foot surgery; total costs of care were decreased 79% in the early discharge group, and no other differences between treatments were detected, including pain scores, complications, and readmission rates</td>
</tr>
<tr>
<td>Yes58,92,134,194,200</td>
<td></td>
</tr>
<tr>
<td>No58,12–15,18,19,77,81,100,128,162,165,174,457,458</td>
<td></td>
</tr>
<tr>
<td>Tibial, superficial peroneal and deep peroneal nerves</td>
<td>Effectiveness of these techniques unclear without RCT</td>
</tr>
<tr>
<td>No11,40,41</td>
<td></td>
</tr>
<tr>
<td>Femoral/saphenous</td>
<td>Femoral infusion in addition to—and not in place of—popliteal infusion for major ankle surgery</td>
</tr>
<tr>
<td>Yes1</td>
<td></td>
</tr>
</tbody>
</table>

Due to publication limitations, includes selected reports published subsequent to a previously published review article (Ilfeld) and is not intended as an exhaustive list.

CPNB, continuous peripheral nerve block; RCT, randomized controlled trial.
needle, theoretically decreasing the catheter tip-to-nerve distance;111–113; a catheter attached to a needle that is passed adjacent to the target nerve and then exited out of the body on the other side of the transducer (remaining in plane the entire trajectory);114,115; a 6-hole catheter to theoretically improve local anesthetic spread (failed in 1 RCT);116; a perineural catheter that is introduced over an insertion needle to theoretically decrease the incidence of leakage (similar to an intravenous catheter);117–120; and a novel needle-over-cannula set to also decrease leakage (successful in 1 RCT).121

Because flexible perineural catheters usually deviate from the ultrasound plane of view after exiting a rigid in-plane needle, evaluating the crucial catheter tip-to-nerve distance can be difficult.87 Various investigators have injected—under real-time ultrasound visualization—fluid, an agitated air/fluid admixture, or a small volume of air, although the relative benefits of each were previously uninvestigated.1 The “air test” was recently evaluated within a porcine–bovine model, but unfortunately there was no benefit over simply visualizing the catheter without air injection.122,123 Attempts to improve the echogenicity of perineural catheters have been somewhat equivocal124,125 with 1 RCT detecting no differences in visibility between the experimental echogenic and the standard stimulating catheters.126 Although visualizing catheter tip location using 3-dimensional ultrasound127,128 and catheter stylet “pumping” combined with color Doppler are promising techniques,129 neither has been validated.130

**INFUSATES**

Long-acting local anesthetic remains the primary analgesic infused during CPNB,1 and there is minimal new information to help guide clinical practice: data suggest that ropivacaine, bupivacaine, and levobupivacaine provide similar analgesia130 with the main differences being ropivacaine’s shorter duration of action—presumably allowing easier titration yet added expense (at least within the United States).1 New data do support previously available evidence1 that total dose and not concentration/volume is the primary determinant of clinical effects for continuous interscalene,131 femoral,132 posterior lumbar plexus (psosas compartment),133 and popliteal sciatic nerve blocks134–136; although it remains unclear whether this relationship is valid for other brachial plexus,137 adductor canal,138,139 TAP, and para-vertebral perineural infusions.140

Although there is recently published preclinical evidence involving perineural pregabalin infusion141 as well as the addition of clonidine, dexamethasone, and buprenorphine to perineural bupivacaine in a rat model,142 these data are preliminary and there remains no medication other than local anesthetic approved for continuous perineural administration by the US Food and Drug Administration (FDA).1 Randomized, controlled clinical trials have failed to detect benefits of adding clonidine or epinephrine to perineural infusions.1 There are sporadic RCTs reporting benefits of various opioids in a perineural infusion143,144–146; however, all but 1146 lacked an active systemic control group, precluding any determination on the importance of perineural (vs intravenous) administration. Unsurprisingly, the addition of opioids often resulted in an increased incidence of opioid-related side effects.14,139 Regardless, considering the absence of safety data,142 a dearth of evidence of perineural efficacy, reports of unacceptable side effects,14,139 and lack of Federal regulatory approval,143 no adjuvants can be recommended at this time; and CPNB with solely local anesthetic remains the infusate by general consensus as judged by published reports of the past 2 decades.1

**LOCAL ANESTHETIC DELIVERY REGIMENS**

The RCTs published in the past few years have done little to clarify the optimal mode of delivering perineural local anesthetic: as exclusively a basal infusion, solely repeated bolus doses, or a combination of the 2.1 A large body of relatively older evidence suggests that providing a basal infusion improves baseline analgesia, decreases the incidence and severity of breakthrough pain, and decreases sleep disturbances and supplemental analgesic requirements for interscalene, infraclavicular, subgluteal, and popliteal sciatic infusions.1 In contrast, recently published data indicate that few benefits—if any—are afforded with a basal infusion, as opposed to repeated boluses for catheters in these anatomic locations (Table 2).84,144–147 Contrary new data also exist for femoral CPNB: although previous data suggested that the delivery mode is irrelevant for femoral infusions,1 a recent RCT suggests that including a basal infusion improves analgesia for this catheter site.85

The conflicting results are most likely due to the heterogeneity of catheter designs (eg, nonstimulating vs stimulating), catheter insertion techniques (eg, ultrasound vs stimulating vs a combination), local anesthetic type (eg, ropivacaine vs bupivacaine) and concentration, basal infusion rates, bolus volumes, lockout times, surgical procedures, outcome measures evaluated, measurement sensitivity, and a multitude of other factors. Consequently, there is no evidence-based “ideal” delivery regimen,148 although investigators have provided clinical recommendations.143,149

Nevertheless, there are some clinical situations in which including bolus doses are theoretically beneficial such as to enable block reinforcement before potentially painful dressing changes150 or physical therapy.20 Virtually all RCTs providing patient-controlled boluses to 1 treatment group report a lower local anesthetic requirement, suggesting 3 possible benefits: (1) theoretically decreasing motor block by decreasing the required basal infusion rate (inadequately investigated to date)31,151,152; (2) decreasing the incidence of an insensitive extremity153; and (3) increasing infusion/analgesia duration for outpatients discharged with a fixed local anesthetic reservoir volume.154,155

One technique variation has recently garnered increased interest: the use of mandatory/automatic bolus doses based on the theory that increasing the volume of local anesthetic introduced at a single time point might improve perineural spread compared with an equivalent volume/dose provided as a basal infusion.156 Continuous adductor canal blocks appear to require a higher basal rate of local anesthetic than their femoral counterparts; and a recent study demonstrated that even with a relatively high rate of 8 mL/h, local anesthetic spread remains somewhat limited.156 A subsequent investigation involving healthy volunteers found sensory perception and quadriceps femoris...
strength equivalent when administering ropivacaine 0.2% at 8 mL/h as either a continuous basal or hourly bolus doses. 144

Similar results were reported for interscalene, 145 femoral, 152 and popliteal catheters. 157 It would therefore be understandable to discount the concept of repeated bolus doses, except a new RCT did find analgesic benefit after thoracotomy in administering a relatively large volume of levobupivacaine (15 mL) via paravertebral catheters once every 6 hours compared with a continuous infusion. 158 Although this study was somewhat confounded by the use of 2 different concentrations of levobupivacaine, it does raise the possibility that the strategy previously used—a repeated hourly bolus

<table>
<thead>
<tr>
<th>Catheter Location</th>
<th>Infusate(s)</th>
<th>Treatment Groups</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interscalene</strong></td>
<td>Ropivacaine 0.2%</td>
<td>Two groups receiving ropivacaine had lower pain scores and consumed less supplemental analgesics than the control group. No differences between the basal and bolus treatment groups.</td>
<td></td>
</tr>
<tr>
<td>- Arthroscopic rotator cuff repair</td>
<td>- Ultrasound in-plane</td>
<td>- Nonstimulating needle</td>
<td>- Nonstimulating catheter</td>
</tr>
<tr>
<td>- Arthroscopic rotator cuff repair</td>
<td>- Ultrasound in-plane</td>
<td>- Stimulating needle</td>
<td>- Stimulating catheter</td>
</tr>
<tr>
<td><strong>Interscalene</strong></td>
<td>Ropivacaine 0.2%</td>
<td>Bolus group used a lower total volume of local anesthetic and experienced less motor block. No other differences between the basal and the bolus treatment groups noted.</td>
<td></td>
</tr>
<tr>
<td>- Arthroscopic or open rotator cuff repair</td>
<td>- Ultrasound out-of-plane</td>
<td>- Nonstimulating needle</td>
<td>- Nonstimulating catheter</td>
</tr>
<tr>
<td><strong>Interscalene</strong></td>
<td>Ropivacaine 0.2%</td>
<td>No differences detected between treatments with one exception: higher basal rate group required a temporary infusion cessation because of side effects (predominantly hand numbness).</td>
<td></td>
</tr>
<tr>
<td>- Major shoulder surgery</td>
<td>- Ultrasound, out-of-plane</td>
<td>- Stimulating needle</td>
<td>- Nonstimulating catheter</td>
</tr>
<tr>
<td><strong>Paravertebral</strong></td>
<td>Bupivacaine 0.5%</td>
<td>Pain scores lower in bolus group, although statistically significant only at 48 and 72 h. Higher total volume of local anesthetic consumed by the basal group.</td>
<td></td>
</tr>
<tr>
<td>- Thoracotomy</td>
<td>- Nonstimulating catheter</td>
<td>Inserted by surgeon under direct vision</td>
<td></td>
</tr>
<tr>
<td><strong>Adductor canal</strong></td>
<td>Ropivacaine 0.2%</td>
<td>Equivalence between treatments to tolerance to cutaneous electrical current and quadriceps femoris maximum voluntary isometric contraction strength.</td>
<td></td>
</tr>
<tr>
<td>- Healthy volunteers</td>
<td>- Ultrasound, in plane</td>
<td>- Nonstimulating needle</td>
<td>- Nonstimulating catheter</td>
</tr>
<tr>
<td><strong>Femoral</strong></td>
<td>Ropivacaine 0.1%</td>
<td>Analgesia superior in basal + bolus group at rest and during mobilization.</td>
<td></td>
</tr>
<tr>
<td>- Anterior cruciate ligament repair</td>
<td>- Stimulating needle</td>
<td>- Nonstimulating catheter</td>
<td></td>
</tr>
<tr>
<td><strong>Sciatic</strong></td>
<td>Ropivacaine 0.2%</td>
<td>Few differences between groups, other than the basal + bolus group consumed a higher total volume of local anesthetic.</td>
<td></td>
</tr>
<tr>
<td>- Total knee arthroplasty</td>
<td>- Anterior approach</td>
<td>- Stimulating needle</td>
<td>- Nonstimulating catheter</td>
</tr>
<tr>
<td>- Femoral catheter and continuous infusion also used for both groups</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Due to publication limitations, includes selected randomized, controlled trials specifically investigating varying local anesthetic delivery method completed subsequent to a previously-published review article (Ilfeld1), and is not intended as an exhaustive list.

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Mandatory bolus doses administered (not as needed).
equivalent to the volume from 1 hour of a basal infusion comparator—could be improved by scheduling larger bolus volumes over a longer period of time. Additional investigation at other catheter sites and administering a higher volume of local anesthetic is required (ClinicalTrials.gov, NCT02662023 and NCT02539628).

Lastly, evidence accumulates that prolonged ropivacaine infusions—even at relatively high doses >40 mg/h—have an extraordinarily low incidence of inducing toxicity signs, symptoms, or plasma levels.159

**PORTABLE INFUSION PUMPS**

Little has changed regarding portable infusion pumps since they were last reviewed,1,149,160 with 3 exceptions. First, more disposable pumps now allow a similar ability to adjust basal rates, bolus volume, and lockout times compared with their electronic, programmable counterparts.161 Second, a number of portable pumps now have the capability of delivering repeated bolus doses at intervals set by the provider.144 How useful this capability will prove to be remains under investigation (see the previous section).13 However, the development with potentially the most influence on clinical care is the new ability of health care providers to remotely communicate directly with electronic infusion pumps via the Internet.162 In a prospective cohort study of 59 hospitalized subjects undergoing CPNB over approximately 3 days, investigators were alerted by text message when the need for pump changes arose because of an insensate extremity, muscle weakness, or difficulty during physical therapy. The infusion pumps would query subjects and, based on the responses, then communicate directly with health care providers who could remotely control the device. The mean (standard deviation) time for pump setting adjustment from the initial alert was 15 (2) minutes with no associated adverse events, demonstrating at least the feasibility of this technique.

**AMBULATORY PERINEURAL INFUSION**

In contrast to the topic of portable infusion pumps, research involving ambulatory CPNB has been relatively prolific in recent years.4,5,7,19,23,33,78,79,116,153,163–175 Originally, the objective of ambulatory perineural infusion was to simply improve analgesia for patients who were never intended to be hospitalized overnight.149,155 Because enhanced pain control and its many derived benefits have been well documented in earlier RCTs (reviewed previously),1 nearly all recent investigation has centered on describing new applications or complications.4,6–8,19,23,171,174,175 optimizing perineural techniques (few major revelations).34,168,169 and reporting large series of cases (including over 1600 pediatric patients).78,79,165,168,169,177 Although most series were retrospective in design, 1 large multicenter effort prospectively enrolled over 1500 patients receiving ambulatory continuous interscalene nerve blocks at home.168 This study documented relatively few CPNB-related complications after discharge with a 1.5% catheter dislodgement rate and no catastrophic incidents. Whereas major problems outside the hospital are very rare,174 they can prove more challenging to treat than in hospitalized patients.171,174,179,180

However, with the collective experience and thousands of published cases in the past 15 years, the main arguments against ambulatory CPNB has shifted from a lack of validation and the risks of complications181 to instead the challenges of setting up and running an effective ambulatory service (“perineural catheter analgesia as a routine method after ambulatory surgery: effective but unrealistic”).182,183 This view is countered by others who contend that “rather than dismissing these techniques as too difficult, and settling for an unsubstantiated (but probably ineffective) alternative [wound infusion], future research should focus on facilitating the uptake of perineural infusions….”184 Indeed, there are published accounts specifically addressing practitioners’ successes185 and challenges186 in developing and implementing ambulatory infusion programs.172,187

A second goal of ambulatory infusion eventually developed: using improved pain control to allow patients— who would be expected to remain in the hospital—to be instead discharged earlier than otherwise possible.188,20,175 Theoretical benefits include improved patient satisfaction, decreased risk of nosocomial infection and health care provider error, and decreasing health care-related costs.170,189,190 Although multiple RCTs demonstrate that ambulatory CPNB reduces the time until discharge readiness,1 only 2 have demonstrated a shortening of actual hospitalization duration.191,192

Nevertheless, with interest growing in the “perioperative surgical home,” ambulatory CPNB is being viewed as a possible enabling intervention.193 One recent example is an investigation that randomized subjects (n = 38) undergoing complex arthroscopic elbow surgery accompanied by a 60-hour continuous intra-articular (brachial plexus) nerve block to either remain hospitalized for the 3-day standard of care or be allowed discharge as early as the morning after surgery (Table 3).173 Both groups underwent continuous passive motion of the elbow for 14 days, and subjects discharged early had similar elbow range of motion after 2 weeks and 3 months compared with patients remaining hospitalized for at least 3 days. Furthermore, there were no statistically significant differences in pain scores, opioid requirements, patient satisfaction, and function-related questionnaires. Importantly, the cost of care for subjects remaining hospitalized was greater than for those allowed early discharge. Although there remains debate as to the significance of the degree of savings (15%),193 these data are supported by an additional clinical trial that permitted a total avoidance of hospital admission.194 This second investigation randomized subjects (n = 120) with a continuous poulpeal nerve block having major orthopedic foot surgery to be discharged either after surgery or remain hospitalized for 2 nights (Table 3).194 Total costs of care were decreased 79% in the early discharge group, and no other differences between treatments were detected, including pain scores, complications, and readmission rates. These savings are not applicable to practices within the United States because the surgical procedures under investigation—ostotomies and hallux valgus corrections—are already nearly exclusively performed as outpatients procedures, regardless of the presence of CPNB. However, the strong interest in these investigations may be an indication of the direction ambulatory infusion research—and practice worldwide—will take over the coming decade.
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<tr>
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<tr>
<td><strong>Interscalene catheters</strong></td>
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<tr>
<td>Fredrickson et al(^{[163]}) (2010)</td>
<td>Minor arthroscopic shoulder</td>
<td>Ropivacaine 0.2% (n = 31) 2 mL/h + 5 mL PCB [60]</td>
<td>Catheters removed in recovery room (n = 30)</td>
<td>Lower resting and dynamic pain scores; less supplemental analgesic requirements</td>
</tr>
<tr>
<td>Malhotra et al(^{[20]}) (2013)</td>
<td>Adhesive capsulitis manipulation</td>
<td>Ropivacaine 0.2% (n = 2) 8 mL/h + 4 mL PCB [30]</td>
<td>Normal saline (n = 2) 8 mL/h + 4 mL PCB [30]</td>
<td>Lower average and dynamic pain scores; lower opioid analgesics; fewer awakenings because of pain; greater shoulder range of motion on day 1, as well as weeks 6 and 12 (preliminary data from a pilot study—underpowered for definitive conclusions)</td>
</tr>
<tr>
<td><strong>Infraclavicular catheters</strong></td>
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<tr>
<td>Salviz et al(^{[176]}) (2013)</td>
<td>Arthroscopic rotator cuff repair</td>
<td>Ropivacaine 0.2% (n = 20) 5 mL/h + 5 mL PCB [60]</td>
<td>• Single injection only (n = 23) • No block or catheter (n = 20)</td>
<td>Catheter group with less pain, opioid requirements, and sleep disturbances; at 7 d (2-d infusion) only 26% of catheter group reported NRS ≥4 compared with 83% and 58% of single-injection and no block groups, respectively</td>
</tr>
<tr>
<td><strong>Paravertebral catheters</strong></td>
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<tr>
<td>Ilfeld et al(^{[167,177]}) (2014) and (2015)</td>
<td>Mastectomy</td>
<td>Ropivacaine 0.4% (n = 30) 5 mL/h basal only</td>
<td>Normal saline (n = 30) 5 mL/h basal only</td>
<td>Lower resting and breakthrough pain scores; less pain-induced physical and emotional dysfunction during infusion; less chronic pain at 1 y</td>
</tr>
<tr>
<td>Karmakar et al(^{[221]}) (2014)</td>
<td>Modified radical mastectomy</td>
<td>Ropivacaine 0.25% (n = 60) 0.1 mL/kg/h basal only</td>
<td>• Single injection only (n = 57) • No block or catheter (n = 60)</td>
<td>No differences among groups during infusion period nor chronic pain incidence at 3 or 6 mo, but at 3 and 6 mo, both infusion and single-injection group had less severe pain, exhibited fewer symptoms and signs of chronic pain, and experienced better physical and mental health-related quality of life</td>
</tr>
<tr>
<td>Pintaric et al(^{[204]}) (2011)</td>
<td>Thoracotomy (open lung surgery)</td>
<td>Levobupivacaine 0.125% and morphine 30 μg/mL (n = 16) 0.1 mL/kg/h + 0.1 mL/kg PCB [60]</td>
<td>Epidural levobupivacaine and morphine at same concentration and rate/bolus as paravertebral catheters</td>
<td>Similar analgesia but greater hemodynamic stability than epidural analgesia with less required colloid volume and vasopressors to maintain target oxygen delivery index</td>
</tr>
<tr>
<td><strong>Transversus abdominis plane (TAP) catheters</strong></td>
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<tr>
<td>Heil et al(^{[33]}) (2014)</td>
<td>Abdominal or inguinal hernia repair</td>
<td>Ropivacaine 0.2% (n = 10) 10 mL/h basal only</td>
<td>Normal saline (n = 10) 10 mL/h basal only</td>
<td>No statistically significant difference in pain scores or supplemental analgesics (underpowered study because of curtailment of enrollment)</td>
</tr>
<tr>
<td>Niraj et al(^{[36]}) (2011)</td>
<td>Open renal or hepatobiliary</td>
<td>Bupivacaine 0.375% (n = 29) 1 mg/kg each of bilateral catheters every 8 h</td>
<td>Epidural bupivacaine 0.125% with fentanyl 2 μg/mL (n = 33) 6–12 mL/h + 2 mL PCB [30]</td>
<td>No statistically significant differences in any outcomes between treatments except that the TAP group required a higher dose of rescue analgesics</td>
</tr>
<tr>
<td><strong>Adductor canal catheters (placebo controlled)</strong></td>
<td></td>
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</tr>
<tr>
<td>Andersen et al(^{[34]}) (2013)</td>
<td>Total knee arthroplasty</td>
<td>Ropivacaine 0.75% (n = 20) 15 mL “twice daily”</td>
<td>Normal saline (n = 20) 15 mL “twice daily”</td>
<td>Lower average resting and breakthrough (maximum) pain scores and fewer sleep disturbances; ambulation possible in 100% vs 65% of subjects in the ropivacaine vs saline groups, respectively</td>
</tr>
<tr>
<td>Grevstad et al(^{[35]}) (2015)</td>
<td>Severe pain on flexion after total knee arthroplasty</td>
<td>Ropivacaine 0.75% (n = 24) 30 mL single injection</td>
<td>Normal saline (n = 25) 30 mL single injection</td>
<td>Reduced pain during active flexion of the knee, but a large proportion (78%) still had at least moderate pain on flexion</td>
</tr>
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<thead>
<tr>
<th>First Author, Year</th>
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</thead>
<tbody>
<tr>
<td>Hanson et al (2014)</td>
<td>Total knee arthroplasty</td>
<td>Ropivacaine 0.2% (n = 36) 8 mL/h basal only</td>
<td>Sham catheter (n = 40)</td>
<td>Decreased resting and dynamic pain scores, lower required supplemental analgesics, greater quadriceps strength, greater ambulation distance, and higher satisfaction</td>
</tr>
<tr>
<td>Jaeger et al (2012)</td>
<td>Total knee arthroplasty</td>
<td>Ropivacaine 0.75% (n = 21) 30 mL single injection</td>
<td>Normal saline (n = 20) 30 mL single injection</td>
<td>Decreased pain during hours 1–6 and less nausea</td>
</tr>
<tr>
<td>Jaeger et al (2013)</td>
<td>Total knee arthroplasty</td>
<td>Ropivacaine 0.75% (n = 14) 30 mL bolus; 6 h later 0.2% 15 mL bolus; then ropivacaine 0.2% 8 mL/h</td>
<td>Normal saline (n = 13) administered at the same time points and volumes as the ropivacaine group</td>
<td>Lower pain on knee flexion at 4 h (underpowered study for remainder of endpoints)</td>
</tr>
<tr>
<td>Jenstrup et al (2012)</td>
<td>Total knee arthroplasty</td>
<td>Ropivacaine 0.75% (n = 34) 30 mL bolus; then 15 mL bolus at 6, 12, 18, and 24 h</td>
<td>Normal saline (n = 37) administered at the same time points and volumes as the ropivacaine group</td>
<td>Lower dynamic pain on flexion and supplemental analgesic requirements, superior ambulation, and mobilization at 24 h</td>
</tr>
<tr>
<td>Fisker et al (2015)</td>
<td>Major ankle surgery</td>
<td>Continuous popliteal sciatic blocks for all subjects Ropivacaine 0.2% (n = 20) 5 mL/h basal only</td>
<td>Normal saline (n = 24) 5 mL/h basal only</td>
<td>No differences between treatment groups detected</td>
</tr>
</tbody>
</table>

**Adductor canal catheters (versus femoral catheters)**

<table>
<thead>
<tr>
<th>First Author, Year</th>
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</thead>
<tbody>
<tr>
<td>Elkassabany et al (2016)</td>
<td>Total knee arthroplasty</td>
<td>Adductor ropivacaine 0.2% (n = 31) 8 mL/h basal only</td>
<td>Femoral ropivacaine 0.2% (n = 31) 8 mL/h basal only</td>
<td>Greater quadriceps femoris strength*</td>
</tr>
<tr>
<td>Jaeger et al (2013)</td>
<td>Total knee arthroplasty</td>
<td>Adductor ropivacaine 0.2% (n = 22) 8 mL/h basal only</td>
<td>Femoral ropivacaine 0.2% (n = 26) 8 mL/h basal only</td>
<td>Greater quadriceps femoris strength (52% vs 18% of baseline)</td>
</tr>
<tr>
<td>Machi et al (2015)</td>
<td>Total knee arthroplasty</td>
<td>Adductor ropivacaine 0.2% (n = 39) 6–8 mL/h + 4 mL PCB [30]</td>
<td>Femoral ropivacaine 0.2% (n = 39) 4–8 mL/h + 4 mL PCB [30]</td>
<td>Improved ability to stand, sit, and ambulate, but higher dynamic pain scores than femoral infusion</td>
</tr>
<tr>
<td>Shah and Jain (2014)</td>
<td>Total knee arthroplasty</td>
<td>Adductor ropivacaine 0.75% (n = 48) 30 mL, then ropivacaine 0.25% 30 mL every 4 h until postoperative day 2</td>
<td>Femoral ropivacaine 0.75% (n = 50) 30 mL, then ropivacaine 0.25% 30 mL every 4 h until postoperative day 2</td>
<td>Improved ability to stand, sit, and ambulate, as well as climb stairs; decreased time until actual discharge (3.1 vs 3.9 d)</td>
</tr>
<tr>
<td>Sztain et al (2015)</td>
<td>Unicompartment knee arthroplasty</td>
<td>Adductor ropivacaine 0.2% (n = 15) 6–8 mL/h + 4 mL PCB [30]</td>
<td>Femoral ropivacaine 0.2% (n = 15) 2–6 mL/h + 4 mL PCB [30]</td>
<td>Fewer days until discharge readiness; improved ability to sit, stand, and ambulate; but higher resting pain scores than femoral infusion</td>
</tr>
<tr>
<td>Zhang et al (2014)</td>
<td>Total knee arthroplasty</td>
<td>Adductor ropivacaine 0.2% (n = xx) 5 mL/h + 5 mL PCB [30]</td>
<td>Femoral ropivacaine 0.2% (n = x) 5 mL/h + 5 mL PCB [30]</td>
<td>Greater quadriceps femoris strength (52% vs 18% of baseline)</td>
</tr>
</tbody>
</table>

**Femoral catheters**

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<thead>
<tr>
<th>First Author, Year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Al-Zahrani et al (2015)</td>
<td>Total knee arthroplasty</td>
<td>Femoral bupivacaine 0.2% (n = 25) 5 mL/h basal only (single-injection sciatic block 15 mL bupivacaine 0.25%)</td>
<td>Epidural bupivacaine 0.0625% + fentanyl 2 μg/mL (n = 25) 5–10 mL/h basal only</td>
<td>No differences between treatment groups detected</td>
</tr>
<tr>
<td>Sakai et al (2013)</td>
<td>Total knee arthroplasty</td>
<td>Femoral ropivacaine 0.15% (n = 30) 4 mL/h basal only</td>
<td>Epidural ropivacaine 0.15% (n = 30) 4 mL/h basal only</td>
<td>Shorter time to achieve 120° knee flexion (8 vs 15 d), improved dynamic analgesia, and lower supplemental analgesic requirements</td>
</tr>
<tr>
<td>Baranović et al (2011)</td>
<td>Total knee arthroplasty</td>
<td>Femoral levobupivacaine 0.25% (n = 35) 5–6 mL/h basal only</td>
<td>No catheter (n = 36)</td>
<td>Improved analgesia, improved knee flexion on postoperative day 2, lower intravenous morphine requirements, and dramatically lower opioid-related adverse events such as urinary retention, sedation, and nausea/vomiting</td>
</tr>
</tbody>
</table>

(Continued)
Ebers supplemental analgesic requirements. Compared with vertebral, adductor canal, femoral, and sciatic analgesic requirements) using interscalene, para-tive analgesia (and in most cases decreases supplemental single-injection peripheral nerve block improves postoperative provided evidence that adding a perineural infusion after a blocks provide similar analgesia with lower supplemental intrathecal morphine, continuous posterior lumbar plexus the past few years, suggesting benefits for an even wider array of morbidities. New RCTs have published solely a fixed basal infusion (8 mL/h) Novel indications for CPNB have been published within the past few years, suggesting benefits for an even wider array of morbidities. New RCTs have provided evidence that adding a perineural infusion after a single-injection peripheral nerve block improves postoperative analgesia (and in most cases decreases supplemental analgesic requirements) using interscalene, para-tive analgesia (and in most cases decreases supplemental single-injection peripheral nerve block improves postoperative provided evidence that adding a perineural infusion after a blocks provide similar analgesia with lower supplemental intrathecal morphine, continuous posterior lumbar plexus blocks provide similar analgesia with lower supplemental opioid requirements and incidence of pruritis. Data continue to accumulate, demonstrating that CPNB provides superior analgesia compared with continuous wound infusions. Because of the association between continuous femoral nerve blocks and falling after knee arthroplasty, the past 5 years have seen a plethora of research validating adductor canal catheter effectiveness after major knee surgery based on the theory that any risk of falling will be decreased because of less induced quadriceps weakness compared with femoral infusion (Table 3). Of the 6 RCTs directly comparing continuous adductor canal and femoral nerve blocks, 50,57–59,74,209 3 demonstrated dramatic improvements for subjects with adductor catheters in the ability to stand, sit, ambulate, and climb stairs. One study did not investigate ambulation209, but the 2 remaining RCTs failed to detect mobilization improvements using an adductor infusion—although they did document and quantify improved quadriceps femoris strength (52% vs 18% of baseline in one).50,59 It is noteworthy that these 2 latter studies provided solely a fixed basal infusion (8 mL/h)

### Table 3. Continued

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<tr>
<td>Peng et al218 (2014)</td>
<td>Total knee arthroplasty</td>
<td>Femoral ropivacaine 0.15% (n = 127) 5 mL/h + 5 mL [30]</td>
<td>No catheter (n = 123)</td>
<td>Less supplemental analgesics required and improved knee flexion during infusion, and lower incidence of chronic pain and improved knee flexion at 3 and 6 mo after surgery</td>
</tr>
<tr>
<td>Wu and Wong237 (2014)</td>
<td>Total knee arthroplasty</td>
<td>Femoral levobupivacaine 0.08% (n = 30) 8–12 mL/h basal only</td>
<td>No catheter (n = 30)</td>
<td>Lower intravenous opioid requirements, fewer opioid-related side effects, improved satisfaction with analgesia, and increased ambulation ability</td>
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</table>
|### Sciotic catheters

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<tr>
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<tr>
<td>Elliot et al230 (2010)</td>
<td>Hind foot or ankle surgery</td>
<td>Bupivacaine 0.25% (n = 27) 4 mL/h + 1 mL [60]</td>
<td>Normal saline (n = 27) 4 mL/h + 1 mL [60]</td>
<td>Lower pain scores and less supplemental analgesic requirements</td>
</tr>
<tr>
<td>Saporito et al134 (2014)</td>
<td>Toes 2–5 osteotomy or hallux valgus correction</td>
<td>Ropivacaine 0.2% 5 mL/h + 5 mL PCB [60]</td>
<td>Required to remain hospitalized 2 nights (n = 60)</td>
<td>Total costs of care were 79% lower in the early discharge group; no other differences between treatment groups including pain scores, complications, and readmission rates</td>
</tr>
<tr>
<td>Cappelletti et al96 (2011)</td>
<td>Total knee arthroplasty</td>
<td>Continuous posterior lumbar plexus blocks for all subjects Subgluteal levobupivacaine 0.06% (n = 19) 0.1 mL/kg/h</td>
<td>Subgluteal normal saline (n = 19) 0.1 mL/kg/h</td>
<td>Lower resting and dynamic pain scores, less supplemental opioids, lower incidence of nausea and vomiting, improved knee flexion and ambulation</td>
</tr>
<tr>
<td>Sato et al275 (2014)</td>
<td>Total knee arthroplasty</td>
<td>Continuous femoral nerve blocks for all subjects Subgluteal ropivacaine 0.2% (n = 30) 5 mL/h</td>
<td>Subgluteal normal saline (n = 30) 5 mL/h</td>
<td>Lower resting pain scores and less supplemental opioids</td>
</tr>
<tr>
<td>Wegener et al97,220 (2011 and 2013)</td>
<td>Total knee arthroplasty</td>
<td>Continuous femoral nerve blocks for all subjects Parasacral levobupivacaine 0.125% (n = 30) 10 mL/h</td>
<td>Parasacral single injection only (n = 30) • No block or catheter (n = 30)</td>
<td>Catheter group with lower dynamic pain scores compared with the other 2 treatment groups on postoperative days 1 and 2 during the infusion; and in a subset of the most initially disabled subjects preoperatively, joint stiffness was reduced at 3 and 12 mo, and dynamic pain reduced at 3 mo compared with the no block or catheter group</td>
</tr>
</tbody>
</table>

Due to publication limitations, includes selected reports published subsequent to a previously-published review article (lifetile), and is not intended as an exhaustive list. In addition, investigations included in Table 2 are excluded. NRS, numeric rating scale for pain (0–10; 0: no pain, 10: worst imaginable); PCB, patient-controlled bolus volume (lockout period in minutes).

*Infusions were discontinued morning of postoperative day 1 before endpoint evaluation.

**BENEFITS**

Novel indications for CPNB have been published within the past few years, suggesting benefits for an even wider array of morbidities. New RCTs have provided evidence that adding a perineural infusion after a single-injection peripheral nerve block improves postoperative analgesia (and in most cases decreases supplemental analgesic requirements) using interscalene, para-vertebral, adductor canal, femoral, and sciatic catheters (Table 3). Compared with epidual infusions, CPNB provides similar analgesia but improves hemodynamic stability (presumably by inducing less sympathetic stimulation) and after knee arthroplasty shortens the time to achieve flexion goals, improves analgesia, and lowers supplemental analgesic requirements. Compared with intrathecal morphine, continuous posterior lumbar plexus blocks provide similar analgesia with lower supplemental opioid requirements and incidence of pruritis. Data continue to accumulate, demonstrating that CPNB provides superior analgesia compared with continuous wound infusions.
without either patient-controlled or repeated provider-administered bolus doses, which may have decreased adductor infusion effectiveness. In addition, 2 of the RCTs detected improved analgesia for subjects with femoral infusions at either rest (unicompartiment arthroplasty) or with movement (tricompartment arthroplasty), whereas others failed to detect differences between the 2 catheter locations.

Lastly, 1 of the investigations reported a decreased time until discharge favoring the adductor catheters (3.1 vs 3.9 days), although there were issues raised regarding its protocol/findings and a similar RCT detected no decrease in time until discharge readiness or actual discharge, albeit with slightly different criteria. What does appear likely is that continuous adductor canal blocks are associated with greater mobilization ability while providing similar analgesia compared with their femoral counterparts. What remains unclear is the ideal catheter insertion location/protocol, optimal method of local anesthetic delivery (eg, basal infusion vs repeated bolus doses, basal rate, bolus volume), and if an optimized delivery regimen can shorten hospitalization duration.

In an effort to further improve analgesia after total knee arthroplasty, 3 recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psosas compartment) block. All demonstrated lower pain scores and decreased supplemental analgesic consumption, and 1 detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation. As has been previously opined, there are potential drawbacks to providing a continuous sciatic nerve block such as the extra time required to place a second catheter, an inability to fully evaluate sciatic nerve function postoperatively, and interference with physical therapy goals (eg, foot drop, leg weakness).

Although there are relatively few demonstrated benefits of CPNB after catheter removal, there are significant additions to our knowledge base within recently published data. Two RCTs found that a 2- to 3-day postoperative continuous interscalene or femoral nerve block resulted in less pain, opioid requirements, and sleep disturbances compared with postoperative day 7 compared with a control group after shoulder and knee procedures, respectively. Similarly, 2 RCTs add to the previous evidence that a continuous femoral nerve block after total knee arthroplasty improves joint flexion for up to 6 months.

However, it is the possibility of decreasing persistent postsurgical pain that has perhaps garnered the most attention and optimism. Four new RCTs add data to the single previous positive study that involved the addition of a femoral catheter to a popliteal infusion for major ankle surgery. One study reported that providing a continuous femoral nerve block after total knee arthroplasty reduced chronic pain at 3 and 6 months, and another involving the same surgical procedure found that providing a continuous sciatic nerve block in addition to a femoral infusion resulted in a reduction of dynamic pain at 3 months (no difference at 12 months for either trial). Finally, 2 RCTs investigating continuous paravertebral blocks after mastectomy detected improvements in analgesia up to a full year after surgery, including superior physical and mental health-related quality of life and decreased pain-related physical and emotional dysfunction.

**COMPLICATIONS**

Probably the largest change in the CPNB literature of the past 5 to 6 years is the proportion of reports involving ultrasound guidance versus nerve stimulation with the former now eclipsing the latter to an overwhelming degree. This is undoubtedly multifactorial; but a predominant reason is probably that the risk of inaccurate and/or difficult catheter insertion is, on average, decreased with the use of ultrasound guidance. However, the incidence for all CPNB-related complications can vary dramatically, most likely because of heterogeneous catheter insertion equipment, techniques, anatomic locations, and infusion protocols. For example, the reported frequency of catheter failure over the past few years varies between 0.5% and 26%, accordingly, precise complication rates will not necessarily be widely applicable. This section reviews reports of adverse events published since the previous review article, and readers are directed to that report for a complete examination of all possible complications.

Relatively few complications during insertion have been reported in recent years, perhaps because of the widespread adoption of ultrasound guidance (or possibly because all the adverse events had been previously published). However, new cases do include the inadvertent penetration of the epidural space and a catastrophic incident involving an unidentified intrathecal placement bolused on the wards. In addition, a single report describes the potential contamination of the surgical site caused by leakage from an interscalene catheter with the patient in a seated position. In contrast, reports of adverse events occurring during infusion are more common, including those reported previously such as hoarseness, dyspnea, and respiratory distress associated with continuous interscalene nerve blocks. Although 1 healthy-volunteer study reported a catheter dislocation rate of 25% and 5% for femoral and interscalene catheters, respectively, over a period of 5 hours, the incidence of dislodgement reported in both RCTs and large series is dramatically lower, even for ambulatory pediatric patients. Leakage at the catheter site continues to be an issue in a small minority of cases, but 2-octyl cyanoacrylate glue can decrease this problem by a factor of 10.

One case report describes a patient with an ambulatory popliteal sciatic block who fractured a metatarsal 2 days into the infusion, which was recognized only after the catheter was removed the next day. In contrast, it is reassuring that there is 1 case of limb ischemia because of a surgically induced axillary artery injury and 3 reports of compartment syndrome all identified in a timely fashion by breakthrough pain not masked by the presence of a CPNB. Catheters have been accidentally cut during tunneling, suture removal, and for unknown reasons (most likely catheter withdrawal into the needle). Although it is common to leave a fractured epidural catheter remnant in situ, health care providers should be cognizant that many perineural catheters contain coiled wire, which is...
at risk for heating during subsequent magnetic resonance imaging.\textsuperscript{289} Catheter retention during withdrawal can also occur caused by a perineural loop,\textsuperscript{165} knot,\textsuperscript{240} kink,\textsuperscript{241,242} or adherence.\textsuperscript{171,179,243–247} Although multiple catheter designs have been involved with retained catheter reports,\textsuperscript{240,242} it is notable that within the past few years, 1 specific stimulating catheter (StimuCath; Teleflex, Morrisville, NC) has been overwhelmingly the predominant model described: 9 publications reporting a total of 18 separate cases.\textsuperscript{165,171,179,243–247} One investigator opined referring to these case reports, “While stimulating peripheral nerve catheters do have clinical utility, the expanding body of literature describing catheter entrapment is worrisome.”\textsuperscript{248} Regarding infusion-induced local anesthetic toxicity, both older\textsuperscript{1} and more recent evidence suggest that peripheral infusion-induced local anesthetic toxicity is very rare.\textsuperscript{199,249} Similarly, major hematoma formation is extraordinarily infrequent and usually occurs in the presence of anticoagulation and/or comorbidity such as myeloproliferative thrombocytosis.\textsuperscript{250} There is limited new information regarding the concurrent use of anticoagulants and perineural catheters.\textsuperscript{251–253} and no new recommendations from the American Society of Regional Anesthesia and Pain Medicine have been published since the previous review article.\textsuperscript{254,255} Of note, some investigators have advocated replacing epidural with paravertebral or TAP catheters in certain situations\textsuperscript{256} based on the theoretical premise that a hematoma in the peripheral nervous system carries less risk of catastrophic nerve injury.\textsuperscript{35,37} Minimal information regarding CPNB-related infection has been published in recent years.\textsuperscript{77,79,268} other than the identification of diabetes and obesity as risk factors for catheter-associated infection\textsuperscript{257,258} and a few new cases of previously described related complications such as abscess formation.\textsuperscript{259–262} Of note, although the incidence of infection increases with infusion duration, there remains no “maximum” time period for a perineural catheter (although there are various regulations regarding the maximum duration of local anesthetic contained within a reservoir); and the longest reported infusion of 88 days was recently published.\textsuperscript{7} In contrast, there has been a significant amount of data published in the past few years involving neurologic risk in the presence of a CPNB.\textsuperscript{260} In most cases of postoperative neurologic symptoms (PONS), it is problematic assigning causality to the surgical procedure, CPNB, or simply perioperative injuries (eg, tourniquet or positioning injuries) causality to the surgical procedure, CPNB, or simply perioperative injuries (eg, tourniquet or positioning injuries).\textsuperscript{51,54,274} although some investigators have questioned this correlation.\textsuperscript{275,276} Regardless of the relationship between CPNB and falls, this complication continues to occur even with the implementation of specific, intensive fall prevention programs.\textsuperscript{52,56,277,278} Although replacing continuous femoral nerve blocks with adductor canal infusions have been proposed as a method to decrease the risk of falling because of decreases induced quadriceps weakness,\textsuperscript{59} such an association has yet to be demonstrated.\textsuperscript{59,279} ALTERNATIVE MODALITIES While perineural infusion has become accepted and now routine within anesthesiology, there are a number of novel, alternative analgesic modalities either currently available or under development/investigation. Although numerous analgesic possibilities are available,\textsuperscript{99,207,280–282} publication limitations prohibit inclusion of every option.\textsuperscript{182} The current article compares and contrasts 4 of the most novel analgesic alternatives to CPNB. LOCAL ANESTHETIC ADJUVANTS Single-injection peripheral nerve blocks have multiple benefits over their continuous infusion counterparts, including less time required for administration, management, follow-up; lower risk of infection; no risk of leakage, catheter dislodgement, or pump malfunction; and simply cost. Of course, the reason that CPNB is used despite these relative disadvantages is that the duration of treatment effects may be prolonged beyond the duration of a single-injection peripheral nerve block.\textsuperscript{1} However, a single-injection block with a similar duration to what is possible with CPNB
would provide the benefits of a 1-shot block without the drawbacks of a perineural catheter and infusion. Toward this end, multiple medications—some in just the past few years—have been combined with (and without) local anesthetic, including opioids, clonidine, dexmedetomidine, dexamethasone, epinephrine, magnesium, midazolam, and tramadol.

Unfortunately, most reported adjuvants prolong analgesia by fewer than 12 hours with even the most effective—buprenorphine and dexamethasone—reliably providing <24 hours of pain control. Many of the additives may increase the incidence of side effects such as pruritis, nausea/vomiting, hypotension, bradycardia, and sedation. Optimal doses remain unknown, and the risk of neurotoxicity remains a concern for multiple agents. Importantly, because systemic administration may result in similar or even superior prolongation of analgesic benefits versus perineural administration—although there are exceptions—and there is no adjuvant currently approved by the US FDA for perineural administration, the risk–benefit ratio of perineural administration remains in question at the time of this writing.

While there are no direct comparisons of CPNB and single-injection blocks including an adjuvant, it is unlikely that such studies will be conducted because most perineural catheters are inserted for use of at least 2 days, and no adjuvant given by any route of administration has been shown to reliably extend analgesia even 1 full day. The 2 techniques do not, in fact, “compete” but are instead complementary, depending on the desired duration of block effects.

LIPOSOME LOCAL ANESTHETIC

Liposomes consist of 2 hydrophobic tails and a hydrophilic head and can form vesicles to act as a medication “depot” (Figure 1). After administration, the liposomes gradually break down, resulting in an extended release of medication. Combining liposomes and a local anesthetic (lidocaine) was first proposed in 1979, initially used in humans in 1988, and first reported for postoperative analgesia in 1994. Although multiple subsequent reports were published, a liposomem local anesthetic was not approved by the US FDA until 2011 (Exparel liposome bupivacaine; Pacira Pharmaceuticals, Parsippany, NJ) for administration at the surgical site to provide postoperative analgesia in adults.

Two multicenter RCTs demonstrated superior postoperative analgesia of this approved medication compared with placebo wound infiltration after hemorrhoidectomy and bunionectomy. In contrast, when compared with bupivacaine HCl (“standard” bupivacaine), 10 of the 12 currently published RCTs were negative for their primary (and most secondary) analgesic end points. Of the 2 positive RCTs versus bupivacaine HCl, 1 involved hemorrhoidectomy, although another similar trial had negative results. The second positive RCT involved submuscular augmentation mammoplasty in which mean pain scores were reduced by <1 on the 0 to 10 numeric rating scale and the investigators concluded, “...it is our assertion that the additional cost of liposomal bupivacaine is unjustified for this particular use.” Some of these 14 RCTs were dose–response studies, not powered to be a conclusive test of efficacy; and when combined with the placebo-controlled trials, there were some detected positive associations for secondary endpoints such as pain scores at individual time points, opioid use (although differences were minimal), and duration until first use of opioid analgesics. However, considering the new medication costs an estimated 100 times that of bupivacaine HCl, it is incumbent on those proposing the conversion to produce data conclusively demonstrating superiority. Various large RCTs currently ongoing should provide much-needed data to help practitioners make evidence-based decisions involving this analgesic modality (ClinicalTrials.gov NCT02713490, NCT02111746, NCT02197273).

There are no RCTs directly comparing CPNB with liposome bupivacaine wound infiltration. The only direct comparison to a single-injection femoral nerve block after total knee arthroplasty suggests that liposome bupivacaine

Figure 1. Liposome local anesthetic: (A) electron micrograph of a replica showing the outer surface of a multivesicular liposome. The abrupt change in the gray scale near the center of the multivesicular liposome is because of the shadowing effect of the freeze-fracture replica. The white region near the bottom is a crack in the replica, and (B and C) electron micrographs of freeze-fracture replicas showing cross sections through 2 multivesicular liposomes. The multivesicular liposomes are, on average, approximately 10 μm in diameter. The polyhedral interior compartments range from approximately 100 nm to several micrometers. The bars represent 2 μm. Reprinted with permission from Spector MS, Zasadzinski JA. Topology of multivesicular liposomes, a model biliquid foam. Langmuir. 1996;12:4704–4708. Copyright 1996 American Chemical Society.
infiltration provides inferior analgesia during the duration of the peripheral nerve block without subsequent analgesic differences between the 2 treatments. Considering that there are now 4 negative published RCTs comparing liposome bupivacaine with bupivacaine HCl infiltration after total knee arthroplasty, and the literature is replete with positive studies involving CPNB, the evidence certainly does not suggest even equivalence between these 2 modalities.

In contrast to wound infiltration, recently published data from 1 RCT strongly suggest that liposome bupivacaine within a single-injection subcostal TAP block provides statistically and clinically superior analgesia to bupivacaine HCl up to 3 days after robotic-assisted hysterectomy. Of note, the US FDA recently revised the label for the single approved liposome bupivacaine formulation explicitly including, “infiltration into the transversus abdominis plane (TAP) which is a field block technique is covered by the approved indication for EXPAREL.”

Although no liposome local anesthetic is currently approved for use within the epidural space or peripheral nerve blocks, a great deal of related research has been completed (if not all published). Both preclinical toxicology and clinical data indicate that liposome bupivacaine has a safety profile at least as favorable as bupivacaine HCl. Although phase 1 to 3 clinical trials involving the use of liposome bupivacaine have been reported for intercostal and ankle blocks, the most published data may be found for femoral nerve blocks. No direct comparisons with CPNB are available, but liposome bupivacaine in a femoral nerve block produced over 72 hours of analgesia with an incomplete motor block in healthy volunteers and demonstrated analgesic activity for up to 72 hours versus placebo in subjects after total knee arthroplasty (albeit extraordinarily minimal analgesic differences after 24 hours). Further sizable RCTs involving adductor canal, brachial plexus, and femoral nerve blocks with liposome bupivacaine are ongoing (ClinicalTrials.gov NCT02607579, NCT02713230, NCT02713178).

Theoretical benefits over CPNB include the avoidance of catheter insertion (eg, less procedure time, no catheter management/removal), the lack of an infusion pump and anesthetic reservoir to purchase/carry, a lower risk of infection, and no risk of catheter dislodgement or leakage. It is emphasized that at the time of this writing, there are no liposome bupivacaine local anesthetics approved for use in the epidural space or peripheral nerve blocks (other than the possible exception of TAP blocks, depending on how this block is categorized).

CRYOANALGESIA

Cryoneurolysis is the application of exceptionally low temperatures to reversibly ablate peripheral nerves, resulting in temporary analgesia termed “cryoanalgesia.” The first cryosurgical apparatus was described in 1961, and modern cryoprobes transmit a gas (usually nitrous oxide or carbon dioxide) at high pressure down their length, through a minute opening, and into the sealed distal tip at a lower pressure (Figure 2A). Explained by the Joule-Thomson effect, a large drop in temperature occurs when the gas moves from a high to low pressure inducing brisk expansion and absorption of heat. The gas is returned out of the body through a larger diameter (low pressure) cylinder in the middle of the shaft. This closed circuit ensures that all gas exits the body. The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. However, because the temperature resulting in irreversible degeneration is colder than the boiling point of the gas (carbon dioxide: –79°C;
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Nitrous oxide: −88°C, the remaining endoneurium, perineurium, and epineurium remain intact and the axon regenerates at a rate of approximately 1 to 2 mm/d.356 Cryoneurolysis has been used via the surgical incision to treat acute pain after thoracotomy,358–374 tonsillectomy,375 and herniorrhaphy.376,377 Alternatively, ultrasound may be used to guide378,379 a percutaneously inserted probe to a peripheral nerve to provide analgesia and has been described for various chronic pain conditions.380–385 The combination of ultrasound and newly designed, FDA-approved handheld cryoneurolysis devices386,387 may now make percutaneous cryoanalgesia a valuable postoperative analgesic alternative to CPNB (Figure 2B).354 The largest limiting factors when applying this technique to acute pain states are (1) the inhibition of efferent signals effectively paralyzing innervated muscles; and (2) the relatively unpredictable duration of action measured in multiple weeks and often months. Therefore, the modality has historically been used to target sensory-only nerves,388 although mixed motor–sensory nerves have been cryoablated to treat spasticity,389 and preclinical studies found no lasting changes to the structure or function of motor nerves after remyelination.386,387

Surgical procedures possibly amenable to cryoneurolysis include iliac crest bone harvesting (superficial superior cluneal nerves), total knee arthroplasty (anterior femoral cutaneous and infrapatellar saphenous nerves), various thumb surgeries (superficial branch of the radial nerve), rotator cuff repair (suprascapular nerve), and digit/limb amputations, among others.354,356 Although there are available cryoneurolysis devices currently approved by the US FDA for relief of pain, the use of cryoanalgesia to treat acute pain requires a great deal of further investigation with both RCTs and large series. It remains undetermined whether the duration of denervation can be shortened (eg, decreasing the freezing interval or number of cycles) and the incidence of adverse events such as neuralgias after thoracotomy.372–374 Direct comparisons with CPNB are unavailable, but some theoretical benefits of cryoneurolysis include an ultralong duration of action, no catheter management/removal, the lack of an infusion pump and anesthetic reservoir to carry, a lower risk of infection, and no risk of local anesthetic toxicity, catheter dislodgement, or leakage.

**Percutaneous Peripheral Nerve Stimulation**

Electric current applied in both the central and the peripheral nervous systems induces analgesia. There are numerous theories regarding the mechanism of action,390 but most are usually based on “gate control theory” by Melzack and Wall:391 current activates large-diameter myelinated afferent peripheral nerves which then—within the spinal cord—impede pain signal transmission from small-diameter pain fibers to the central nervous system.392,393 Implanted spinal cord and peripheral nerve stimulators have since been used to treat multiple chronic pain states.394–398 In contrast, the use of peripheral nerve stimulation to treat acute/postoperative pain is extraordinarily rare,399–401 in no small part because of cutaneous pain fiber activation with transcutaneous electrical nerve stimulation392 and the invasive requirement of surgically implanting/removing peripheral nerve electrodes/leads.402,403

Electrical leads are now available with a diameter small enough to allow passage through a needle, allowing percutaneous insertion (Figure 3A).404–409 Precise placement is possible using ultrasound guidance410,411 and has been reported to treat chronic pain.412–415 More recently, postoperative pain was treated using ultrasound-guided percutaneous peripheral nerve stimulation.416–418 In one report, femoral—and in 2 cases sciatic—leads were inserted in subjects (n = 5) 8 to 58 days after total knee arthroplasty.417 Percutaneous peripheral nerve stimulation decreased pain an average of 93% at

![Figure 3. Percutaneous peripheral nerve stimulation: (A) a preloaded, small-diameter (0.2 mm), open-coiled, helical electrical lead with an anchoring wire preloaded within the 12.5-cm, 20-g insertion needle (MicroLead; SPR Therapeutics, Cleveland, OH) and (inset) a small-diameter (0.2 mm), open-coiled, helical electrical lead with an anchoring wire (MicroLead; SPR Therapeutics); and (B) a stimulator small enough to be simply adhered to the skin during use (SPR Therapeutics) (both used with permission from B.M.I.).](image-url)
rest (reduced from a mean of 5.0 to 0.2 on a 0–10 numeric rating scale) with 4 of 5 subjects experiencing complete resolution of pain. During passive and active knee motion, pain decreased an average of 27% and 30%, respectively. Neither maximum passive nor active knee range of motion was consistently affected in this small cohort of subjects.

There are no direct comparisons with CPNB, but theoretical benefits of percutaneous peripheral nerve stimulation are numerous.416c Leads function optimally when inserted 0.5 to 3.0 cm from a target peripheral nerve, negating the importance of location within a particular facial plane. Electrical generators are now so minute that their footprint is smaller than a business card and may be literally adhered to a patient’s limb, so there is no large portable infusion pump or local anesthetic reservoir to carry (Figure 3B). Helically coiled leads are designed to minimize the risks of migration and fracture and decrease the infection risk to the pump or local anesthetic reservoir to carry (Figure 3B).

Electrical generators are now so minute that their footprint was consistently affected in this small cohort of subjects. Neither maximum passive nor active knee range of motion was affected in this small cohort of subjects. Pain decreased an average of 27% and 30%, respectively.

resolution of pain. During passive and active knee motion, pain decreased an average of 27% and 30%, respectively. The possibility of preoperative insertion and continued postoperative stimulation for the entire interval of surgically related pain.417–421 There are theoretically no induced sensory, proprioception, or motor deficits, enabling full engagement in physical therapy and likely lacking any association with an increased falling risk. Obviously, there is no risk of local anesthetic toxicity or leakage. Conversely, practical implementation of percutaneous peripheral nerve stimulation to treat acute pain states is dependent on multiple factors that are currently undetermined: the time required for lead insertion, clinical efficacy and applicability, adverse event rate, the cost of leads and electrical generators, the maximum provided analgesia, and the future commercial availability of US FDA-approved equipment specifically approved for the treatment of acute pain.415,422

CONCLUSIONS
Although the recently published evidence presented in this review helps to clarify questions previously unanswered, many unknown aspects of CPNB persist. Although the data demonstrating perineural local anesthetic infusion’s many benefits continue to grow in quality, breadth, and depth, both older280,282,298,423 and novel307,352,354,424 analgesic alternatives must be considered and investigated. Only through persistent, unbiased investigation will we be able to optimize analgesia for patients, whether from CPNB or an alternative modality.425

ACKNOWLEDGMENTS
The author thanks Elan Ilfeld for his rendering of Figure 2A, Haley Chung for her rendering of Figure 3B, and Anya Morgan, MA, research coordinator extraordinaire (University of California San Diego, San Diego, California) for her assistance with the myriad of articles used in this review.

DISCLOSURES
Name: Brian M. Ilfeld, MD, MS.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Brian M. Ilfeld approved the final manuscript.

Conflicts of Interest: Brian M. Ilfeld’s university has received research funding from Smiths Medical, Telesof Medical, Summit Medical, Pacira Pharmaceuticals, Myoscience, SPR Therapeutics, and Infronics. In addition, he was a consultant to Pacira Pharmaceuticals through March 2015.

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