Non-narcotic Perioperative Pain Management in Prosthetic Breast Reconstruction During an Opioid Crisis: A Systematic Review of Paravertebral Blocks

Hanae K. Tokita, MD
Thais O. Polanco, MD
Meghana G. Shamsunder, MPH
Stefan Dabic, MPH
Vaidehi G. Patel
Robert J Allen, Jr, MD
Joseph H. Dayan, MD
Babak J. Mehrara, MD
Evan Matros, MD, MMSc
Jonas A. Nelson, MD

BACKGROUND

The number of implant-based postmastectomy reconstruction (PMR) procedures has steadily increased by 11% per year in the United States, being the most commonly utilized modality of PMR. Postmastectomy breast reconstruction is associated with an improved quality of life, with implant-based (IBR) or tissue expander (TE) reconstruction being a less invasive option, resulting in the shortest recovery time. Despite the cited advantages to prosthetic PMR, patients are at risk for significant postoperative acute and chronic pain. Because severe, acute postoperative pain is a major risk factor for patients to develop chronic pain, proper pain management techniques are necessary for maintaining positive quality of life following breast reconstruction.

Due to the current opioid epidemic in the United States, the use of opioid analgesics has faced intense scrutiny. Between 2010 and 2015, the estimated opioid overdose death rate increased by 156%, where 21%–29% of patients misused opioids prescribed for pain management. Surgeons routinely prescribe opioids postoperatively and are responsible for an estimated 9.8% of all opioid prescriptions in the United States. Therefore, postoperative pain management may play a role in the management of pain in patients undergoing IBR.

METHODS

A systematic search of PubMed, EMBASE, and Cochrane Library electronic database was conducted to examine PVB administration in mastectomy patients undergoing IBR. Data were abstracted regarding authors, publication year, study design, patient demographics, tumor laterality, tumor stage, type, and timing of reconstruction. The primary outcome was PVB efficacy, represented as patient-reported pain scores. Secondary outcomes of interest include narcotic consumption, postoperative nausea and vomiting, antiemetic use, and length of stay.

RESULTS

The search resulted in 1,516 unique articles. After title and abstract screening, 29 articles met the inclusion criteria for full-text review. Only 7 studies were included. Of those, 2 studies were randomized control trials and 5 were retrospective cohort studies. Heterogeneity of included studies precluded a meta-analysis. Overall, PVB patients had improved pain control, and less opioid consumption.

CONCLUSION

PVBs are a regional anesthesia technique which may aid in pain management in the breast reconstructive setting. Evidence suggests that PVBs aid in controlling acute postoperative pain, reduce opioid consumption, and improve patient length of stay. However, some conflicting findings demonstrate a need for continued research in this area of pain control.

(Plast Reconstr Surg Glob Open 2019;7:e2299; doi: 10.1097/GOX.0000000000002299; Published online 14 June 2019.)

Disclosure: The authors have no financial interest to declare in relation to the content of this article.
opioid epidemic, especially for opioid-naive patients. Opioid prescriptions to opioid-naive patients following minor surgery are increasing,\textsuperscript{17–21} with these patients having a 4.1% chance of chronic opioid use at 1 year.\textsuperscript{22–25} Furthermore, among surgical patients, female gender remains a potential factor for chronic opioid usage due to exhibiting more pain.\textsuperscript{3,26–30}

Such risk factors may contribute to opioid misuse in IBR patients with poorly controlled pain. To improve upon postoperative pain management following PMR in the context of a national, opioid epidemic, it is timely and necessary to understand alternative options. First described in the early 1900s, thoracic paravertebral blocks (PVBs) are a regional anesthetic block where local anesthesia is injected adjacent to thoracic vertebra and beneath the costotransverse ligament to block thoracic spinal nerves after they emerge from the intervertebral foramina (Figs. 1, 2). PVBs have been shown to decrease postoperative pain and opioid consumption, limit postoperative nausea and vomiting (PONV), and reduce length of stay (LOS) in patients undergoing a variety of breast cancer surgeries.\textsuperscript{31–33} However, there is little evidence and consensus on the efficacy of PVBs in breast cancer patients undergoing prosthetic PMR. The purpose of this study was to conduct a systematic review to assess the effectiveness of PVB in IBR patients with a diagnosis of breast cancer.

**METHODS**

**Data Sources and Search Strategy**

This protocol has been registered with the National Institute of Health Research: Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD42018115156). We reported in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines.

A comprehensive search was performed using PubMed, EMBASE, and Cochrane Library electronic databases with publication end date of October 2018. No language restrictions were applied. The bibliographies of selected articles were manually checked for relevant references.

![Fig. 1. Chest wall innervation. n., nerve.](image-url)
Inclusion and Exclusion Criteria
Studies were included if they described PVB use in prosthetic PMR (TE or implant) following immediate or delayed mastectomy, among women older than 18 years with a diagnosis of breast cancer. Review articles, case reports, conference or meeting abstracts, editorial comments, studies describing PVB for mastectomy only, autologous tissue-based breast reconstruction (ABR), cosmetic breast surgery, and male patients were excluded.

Abstraction
Two authors (T.P. and S.D.) independently assessed all titles and abstracts. Studies were subjected to full-text review by 2 authors (T.P. and S.D.) if at least 1 reviewer marked it for inclusion based on the above inclusion criteria. Consensus was reached when all reviewers agreed to include or exclude the study.

Data abstraction for the following were retrieved: authors, publication year, study design, patient demographics, tumor laterality, tumor stage, type and timing of reconstruction, and comorbidities. The primary outcome of interest for review was PVB efficacy at pain control. Secondary outcomes of interest included PVB-related complications, morphine consumption, PONV, antiemetic use, and LOS.

Quality Assessment
Two authors (T.P. and S.D.) performed an independent assessment of the methodological quality and risk of bias in the included studies using the Cochrane Collaboration Risk of Bias tool (randomized trials) and the methodological index for nonrandomized studies (MINORS, observational studies).

Data Synthesis
Although all of the articles included an adequate endpoint relevant to our analysis in this review, there was significant variation in the format in which outcomes were reported. As a result, meta-analysis was not conducted and comparisons among studies were made in a qualitative manner, grouped by outcomes of interest to this study.

RESULTS
The systematic search resulted in 1,516 unique articles. After screening by title and abstract, 29 articles met the inclusion criteria for full-text review. A total of 7 studies were included. (Fig. 3) Two studies were randomized control trials (RCTs) and 5 were retrospective reviews. The combined, 7 studies resulted in a total of 877 patients, of which 478 had administration of PVB (Table 1). Two studies investigated PMR with TE only, whereas 1 study focused
only IBR. The remaining 4 studies included both TE and IBR; only one of these studies reported PVB use in direct TE-to-implant exchange. PVB effectiveness was compared with general anesthesia (GA) alone in 6 studies with the seventh study comparing PVB with liposomal bupivacaine (LB) wound infiltration. All 5 of the retrospective cohort studies used ultrasound-guided administration of PVB, whereas both RCTs used anatomical landmarks to administer PVB. Regarding the administration of PVB, 5 studies reported multilevel injections, whereas the remaining 2 studies reported single-level injections. Due to heterogeneity in outcome definitions, it is unclear if level of administration impacts postoperative pain or opioid use. All 5 of the retrospective cohorts used bupivacaine in the PVB procedures, however, 1 RCT used levobupivacaine and the other RCT used ropivacaine.

Quality Assessment

Quality assessment of the cohort studies using modified MINORS score yielded a range of 18–22. The most common deficiency was lack of prospective calculation of sample size, likely due to the retrospective nature of these studies. The 2 RCTs were reviewed according to Cochrane’s Risk of Bias tool and deemed to have low bias.

Postoperative Pain Outcomes

Pain scores were reported in 3 studies (Table 2). One study used average Numeric Rating Score (NRS; 0–10 numeric pain rating scale) and 2 studies used the visual analog scale (VAS; 0–10 numeric pain rating scale). Wolf et al. reported significantly lower average NRS scores among PVB patients compared with GA-alone patients for the postoperative intervals of 0–1, 1–3, and 3–6 hours.

Strazisar et al. and Abdelsattar et al. evaluated pain using the VAS. Strazisar et al. studied changes in postoperative pain stratified by activity levels. Resting PVB patients had a significantly lower median VAS score compared with GA-alone patients only in the recovery room. However, “on activity” (activity with the upper extremity), PVB patients had significantly lower median pain scores than GA-alone patients at all postoperative time periods (from recovery room to 9 hours, at 3-hour intervals). On activity, median VAS scores on the day of surgery were significantly lower for PVB patients than for GA-alone patients; there was no significant difference in median scores for the first postoperative day between these groups. Abdelsattar et al. compared a PVB treatment group to a LB control group, reporting a significantly lower, average VAS pain score only at day 0 among the LB group versus the PVB group. The pain scores were not significantly different for the other postoperative assessment days.

Opioid Use Outcomes

Opioid use was reported as consumption of narcotics or morphine equivalents (MEs) in 6 of the 7 studies (Table 3). Both RCT studies showed that PVB patients received less postoperative opioids compared with GA-alone patients. Specifically, Strazisar et al. reported that on average, patients who received PVB with levobupivacaine consumed significantly less piritramide in the first 24 hours after surgery compared with GA-alone patients. Wolf et al. reported average, total fentanyl administered preoperatively and intraoperatively, noting that PVB patients were administered less fentanyl compared to patients with GA alone.

Additionally, 2 retrospective studies showed that PVB patients received less postoperative narcotics compared with the comparator. For patients undergoing bilateral PMR, Fahy et al. reported on average, PVB patients consumed significantly less ME than those given GA alone; however, this difference was not observed in patients undergoing unilateral mastectomy with PMR. Aufforth et al. also reported that PVB patients who underwent immediate TE PMR consumed less ME than GA-alone patients during the first postoperative day; however, this difference was not seen between the 2 groups in the recovery room or 0 days following surgery.

Glissmeyer et al. reported that PVB patients received less ME compared to non-PVB patients; however, no statistical analysis was conducted. Lastly, Abdelsattar et al. found that PVB patients consumed a significantly higher average of ME compared to LB-only patients in the postanesthesia care unit (PACU) but had no significant difference in postoperative opioid consumption days 0–2.

Length Of Stay

Two studies reported LOS as proportion of patients with a LOS less than 36 hours. Abdelsattar et al. reported no significant difference in LOS between the LB group versus the PVB group. Similarly, Fahy et al. reported no significant difference in LOS between patients with PVB.
compared to GA alone/non-PVB patients, following a multivariate analysis.41

One study reported LOS in hours while 2 studies measured LOS in days. Coopey et al. reported that, on average, patients undergoing prosthetic PMR with PVB had a significantly shorter LOS compared to the non-PVB group, regardless of laterality (unilateral versus bilateral) or type (TE versus immediate implant placement) of PMR.33 Strazisar et al. reported that there was no significant difference in LOS between the local PVB group and the standard treatment group.37 Glissmeyer et al. reported PVB patients had shorter LOS (1.3 days) compared to those without PVB (2 days); however, this study did not perform a statistical analysis to determine significance.59

Lastly, Wolf et al. reported that on general LOS, no significant difference in length of hospital stay was found between the PVB treatment and control groups.36

**PONV and Antiemetic Medication**

Wolf et al. investigated postoperative nausea scores (reported as NRS ranging from 0 to 10), reporting no significant difference in average scores between the PVB group and the GA-alone group at various intervals (immediately following surgery and up to 22 hours postoperatively). Additionally, they reported no significant difference in the average number of vomiting episodes in the PACU or at time of discharge between the 2 groups.36

Fahy et al. used postoperative antiemetic administration as a proxy for postoperative nausea. Analyses showed the PVB group receiving significantly less antiemetics than the GA-alone group, even after controlling for laterality of PMR.41 Coopey et al. reported a significantly lower proportion of patients with postoperative nausea in the PVB group compared to the non-PVB group, but found no significant difference in the proportion of patients with postoperative vomiting. However, this study did not quantify antiemetic use between the 2 groups.36

Abdelnsattar et al. reported a significantly lower proportion of LB patients using antiemetic medication one day following PMR compared to PVB patients.40 Strazisar et al. also reported that PVB patients on average consumed significantly less metoclopramide than GA patients.57 Lastly, Wolf et al. found no significant difference in average consumption of antiemetics among PVB patients compared to GA-alone patients.36

**DISCUSSION**

In light of the US opioid epidemic, there is an intense focus on finding alternatives to effective postoperative pain control following surgery.5,6,50 In 2016, the CDC released clinical guidelines for chronic pain management, aiming to decrease misuse, abuse, and overdose from opioids. However, there remains minimal guidance for physicians on the management of acute pain, specifically in the perioperative and acute postoperative setting.47,48 Regional anesthetic techniques, such as PVBs, are an example of a possible method to reducing postoperative pain and initial narcotic utilization with well described, minimal complications.49 This review demonstrates that this technique not only may favor positive postoperative outcomes, but also displays the heterogeneity of existing studies and their slightly conflicting results.

PVB was shown to positively reduce acute postoperative pain and reduce PONV/antiemetic medication consumption in IBR patients. However, there is not enough evidence to draw strong conclusions regarding PVB’s impact on opioid consumption and LOS. Two of 3 studies reporting pain show PVB reduces acute postoperative pain (during the recovery room and within the first postoperative day following PMR) compared to GA alone.36,57 Furthermore, 4 of 5 studies indicate significant decreases in postoperative nausea and antiemetic consumption. There is positive evidence of PVB’s impact on opioid consumption. Lastly, there is not enough evidence to state PVB significantly reduces LOS with 4 of 6 studies showing no significant difference between PVB and non-PVB groups.36,37,40,41

The 2 RCTs show an overall significant decrease in acute postoperative opioid consumption,37,58 a finding supported by 2 retrospective studies also indicating significant decreases in opioid consumption among the PVB group.38,41 However, 1 study showed a decrease in opioid consumption but lacked statistical analysis,39 while another study conversely reports significantly higher consumption of opioids in the PVB group versus the control group receiving LB in the PACU.40 Abdelnsattar et al did not use contemporary groups for comparison and found no difference in opioid consumption at later postoperative time points. Due to the strength of evidence from the included RCTs in addition to some evidence from observational studies, PVB does seem to reduce acute postoperative opioid consumption.

Several studies have shown that IBR patients are at risk for significant, postoperative pain compared to ABR patients.6,8,50 As such, these patients require more narcotics and other analgesics for their pain management.7,8 Suboptimal pain management is associated with further negative effects: slowed recovery, increased morbidity, prolonged opioid use during and after hospitalization, impaired physical function, and lowered quality of life.8,51,52 Increased acute postoperative pain is a significant predictor of chronic pain syndromes, which negatively impact quality of life and affects nearly 50% of patients with breast cancer.9,12,53,54 One study reviewed long-term chronic pain, reporting PVB patients had less pain compared to GA alone at 3 months following PMR;7 however, the mechanism for developing chronic pain among breast cancer patients following PMR is poorly understood.

Possible factors contributing to the development of chronic pain in this patient population may include: pain due to surgical scars, chest wall pain, upper-arm pain, shoulder discomfort, and/or a neuropathic component that develops into a complex, regional pain syndrome.55 Surgical technique is another possible mechanism for the development of chronic pain in IBR patients. The predominant technique, placement of the implant under the pectoralis muscle, has been associated with increased pain compared to the prepectoral method.57 Manipulation of the muscle could lead to higher rates of referred pain7 or
found no significant difference in average pain scores on all postoperative days between the PVB and non-PVB groups, whereas Fahy et al. reported no significant difference in average pain scores between their experimental groups, on the day of surgery. However, Aufforth et al. did not specifically distinguish patients who only underwent IBR.

The results of this systematic review support PVB’s value as an alternative to opioids for controlling postoperative pain among IBR patients. However, this review was limited by the quantity and quality of the available literature. The significant heterogeneity in the results prevented the conduct of a meta-analysis. Aufforth et al.

---

**Table 1. Study Characteristics**

| Reference      | Study Design | Patient Population and Type of Prosthetic PMR | Laterality (n) | PVB Group (n) Description |
|----------------|--------------|-----------------------------------------------|----------------|----------------------------|
| Abdelsattar et al. 38 | Retrospective cohort (N = 337) | Women with BC who underwent PMR with/without axillary surgery (SLB and ALND) | NA | (Overall n = 241) Immediate TE n = 45 US guidance and anatomically landmarked multilevel T1–T6 injections with local lidocaine (1%) and 4 mL of bupivacaine at each level |
| Wolf et al. 36 | RCT (N = 74) | Women who underwent immediate TE or implant PMR with/without axillary surgery (SLB and ALND) | Unilateral (n = 21) and bilateral (n = 76) | US guidance multilevel T3–T5 single injections with 6–10 mL of bupivacaine (n = 44; unilateral: 0.5%, bilateral: 0.25%) plus 1:400,000 epinephrine |

---

ALND, axillary lymph node dissection; BC, breast conserving; IV, intravenous; NA, not available; PO, postoperative; RR, recovery room; SLB, sentinel lymph node biopsy; US, ultrasound. Bold values indicate significant p values (p < 0.05)

muscle spasming. Lastly, psychological factors and psychological vulnerability to pain perception are significantly associated with greater postoperative pain intensity.

---
Table 1. Study Characteristics

| Control Group (n) Description | Pain Outcomes | Opioid Use Outcomes | LOS Outcomes | PONV/Antiemetic Use Outcomes | Bias MINORS Score (Observational Studies)/Cochrane Risk of Bias (RCT) |
|-------------------------------|---------------|---------------------|--------------|------------------------------|---------------------------------------------------------------|
| LB analgesic: 20 mL, LB diluted with 120 mL NS (n = 53; unilateral, total 140 mL) or with 260 mL NS (bilateral, total 260 mL; 130 mL/breast) (Overall n = 96) (Immediate TE n = 14) GA only | VAS (ranging from 0 to 10) for PACU and PO days 0, 1, 2 (mean ± SD) | Intraoperative and PO oral (oxycodone and morphine) and IV (fentanyl, meperidine, morphine, and hydromorphone) collected and converted to oral ME (mean ± SD) | Proportion of patients with LOS < 36 h (%) | Need for antiemetic use PO day 1 (%) | 22 |
| (n = 154) GA only | NA | NA | Hours (mean ± SD) | Nausea defined as patient requiring PO antiemetics (%) and episodes of vomiting (n) | 20 |
| (n = 294) GA only | Scale not reported (mean ± SD) | Oral (oxycodone and morphine) and IV (morphine, fentanyl, and meperidine) collected and converted to oral ME (mean ± SD) | Proportion of patients with LOS >36 h, % | Nausea defined as patients requiring PO antiemetic consumption, % | 21 |
| (n = 7) GA only | NA | All narcotics converted to IV ME (mean) | Days (mean) | NA | 18 |
| (n = 30) GA only | On activity and rest VAS (ranging from 0 to 10) for RR, PO 0–3, 6, and 9 h on day of surgery, PO days 1–4 (median) patients with chronic pain 3 mo follow ing PMR (n) | Piritramide consumption during first 24 h (mean), mg | Days (mean) | Metoclopramide consumption during first 24 h (mean), mg | Low |
| (n = 39) GA only | NRS (ranging from 0 to 10) at immediately following surgery, PO 0–1, 1–3, 3–6 h, worst in PACU, PO 18–22 h, worst in PO 24 h, and PO 1 wk (mean ± SD) | Total preoperative and intraoperative fentanyl (mean ± SD), μg | Scale not reported | Nausea NRS (ranging from 0 to 10) immediately following surgery, PO 0–1, 1–3, 3–6 h, worst in PACU, PO 18–22 h, and worst in PO 24 h (mean ± SD) Episodes of vomiting in PACU and since discharge (mean ± SD) Consumption of antiemetics (mean ± SD) | Low |

used.\(^{41}\) For LOS, Aufforth et al. displayed a significantly lower LOS for the PVB group versus the non-PVB group and no significant difference in the proportion of patients with PONV. However, these results refer to all included patients, not simply IBR patients.\(^{38}\)

The majority of the included studies were retrospective and observational. Other limitations of reviewed studies include: studies with small sample sizes, use of varying anesthetic agents for PVB injection along with different anesthetics for the control group, the lack of standard postoperative protocols for pain management, lack of controlling for the impact of sentinel lymph node biopsy or axillary lymph node dissection on pain, and different measurement scales for each outcome of interest. An additional limitation is lack of reported costs incurred from using PVB. From a policy perspective, understanding the costs of introducing an intervention is an important factor in considering its overall benefits and should be included in future studies.
In multiple meta-analyses that included patients undergoing an array of breast surgery procedures (from breast-conserving surgery to cosmetic), PVB has been shown to be a superior and effective treatment for postoperative pain management, limiting opioid consumption, and reducing LOS and PONV compared to GA alone. However, to draw strong conclusions about PVB’s effectiveness in IBR patients is dependent on further research. A systematic review conducted by Offodie et al. assessing the effectiveness of PVB in PMR (both IBR and ABR) patients was overall consistent with our findings. The review of Offodie et al. was limited by number and quality of included studies (9 studies were included, of which 7 were observational while 2 were RCTs) and heterogeneity of results. Therefore, they reported on the trends of PVB’s efficacy showing some positive impact in improving pain management, decreasing opioid consumption, and reducing LOS while not impacting PONV.

Despite the limitations, this review is a rigorous synthesis of current literature. Overall, the limited number of studies and heterogeneity of results necessitates further research in examining PVB as an alternative to narcotic, postoperative pain control in the prosthetic PMR patient.
CONCLUSIONS

Given the current opioid crisis, there is a growing emphasis on non-narcotic alternatives in the perioperative setting. In prosthetic PMR, PVBs may provide an alternative analgesic approach to improve postoperative pain and enhance recovery. Evidence suggests that PVB reduces acute, postoperative pain, improves PONV, and may have a positive impact on reducing opioid consumption. There is not enough evidence to support that PVB is associated with a decreased LOS. More high-quality studies are needed to assess the effects of PVB on perioperative opioid consumption, quality of recovery, and chronic pain in IBR patients.

Jonas A. Nelson, MD
Section of Plastic and Reconstructive Surgery
Memorial Sloan Kettering Cancer Center
1275 York Ave
New York, NY 10065
E-mail: nelsonj1@mskcc.org

REFERENCES
1. Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in U.S. Breast reconstruction: increasing implant rates. Plast Reconstr Surg. 2013;131:15–25.
2. Wilkins EG, Cederna FS, Lowery JC, et al. Prospective analysis of psychosocial outcomes in breast reconstruction: one-year postoperative results from the Michigan Breast Reconstruction Outcome Study. Plast Reconstr Surg. 2006;110:104–25; discussion 1026.
3. Al-Ghazal SK, Sully L, Fallowfield L, et al. The psychological impact of immediate rather than delayed breast reconstruction. Eur J Surg Oncol. 2004;29:17–19.
4. Chao LF, Patel KM, Chen SC, et al. Monitoring patient-centered outcomes through the progression of breast reconstruction: a multicentered prospective longitudinal evaluation. Breast Cancer Res Treat. 2014;146:299–308.
5. Teo I, Reece GP, Christie IC, et al. Body image and quality of life of breast cancer patients: influence of timing and stage of breast reconstruction. Psychooncology. 2016;25:1106–1112.
6. Wallace MS, Wallace AM, Lee J, et al. Pain after breast surgery: a survey of 282 women. Pain. 1996;66:195–205.
7. Gassman AA, Yoon AP, Maxhimer JB, et al. Comparison of postoperative pain control in autologous abdominal free flap versus implant-based breast reconstructions. Plast Reconstr Surg. 2015;135:356–367.
8. Kulkarni AR, Pusic AL, Hamill JB, et al. Factors associated with acute postoperative pain following breast reconstruction. JPRAS Open. 2017;11:1–13.
9. Vadivelu N, Schreck M, Lopez J, et al. Pain after mastectomy and breast reconstruction. Am Surg. 2008;74:285–296.
10. Gärtner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA. 2009;302:1985–1992.
11. Hickey OT, Burke SM, Haefee P, et al. Severity of acute pain after breast surgery is associated with the likelihood of subsequently developing persistent pain. Clin J Pain. 2010;26:556–560.
12. Macdonald L, Bruce J, Scott NW, et al. Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. Br J Cancer. 2002;92:225–230.
13. Baigian J, Cohen M, Barnsteiner J, et al.; The Joint Commission; Patient Safety Advisory Group. Sentinel Event Alert. Safe use of opioids in hospitals. Available at http://www.masimo.com/sitesassets/us/documents/pdf/sea_49_opioids_8_2_12.pdf. Accessed September 5, 2017.
14. Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths—United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65:1445–1452.
15. Vowles KE, McIntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156:569–576.
16. Levy B, Paulozzi L, Mack KA, et al. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med. 2015;49:409–413.
17. Demsey D, Carr NJ, Clarke H, et al. Managing opioid addiction risk in plastic surgery during the perioperative period. Plast Reconstr Surg. 2017;140:613e–619e.
18. Wunsch H, Wijeyasurya DN, Passarella MA, et al. Opioids prescribed after low-risk surgical procedures in the United States, 2004-2012. JAMA. 2016;315:1654–1657.
19. Johnson SP, Chung KC, Zhong L, et al. Risk of prolonged opioid use among opioid-naïve patients following common hand surgery procedures. J Hand Surg Am. 2016;41:947–957.e3.
20. Sun EC, Darnall BD, Baker LC, et al. Incidence of and risk factors for chronic opioid use among opioid-naïve patients in the postoperative period. JAMA Intern Med. 2016;176:1286–1293.
21. Brummett CM, Waljee JF, Goings J, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152:e170564.
22. Calcaterra SL, Yamashita TE, Min SJ, et al. Opioid prescribing at hospital discharge contributes to chronic opioid use. J Gen Intern Med. 2016;31:478–485.
23. Clarke H, Soneji N, Ko DT, et al. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348:g1251.
24. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372:241–248.
25. Waljee JF, Li L, Brummett CM, et al. Iatrogenic opioid dependence in the United States: are surgeons the gatekeepers? Ann Surg. 2017;265:728–730.
26. Parsells Kelly J, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. Pain. 2008;138:507–513.
27. Johansen A, Rornunstad L, Nielsen CS, et al. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. Pain. 2012;153:1390–1396.
28. Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain. 2010;151:61–68.
29. Wijnhoven HA, de Vet HC, Picavet HS. Prevalence of musculoskeletal disorders is systematically higher in women than in men. Clin J Pain. 2006;22:717–724.
30. Barry DT, Fizler C, Potenza MN, et al. Prevalence and psychiatric correlates of pain interference among men and women in the general population. J Psychiatr Res. 2012;46:118–127.
31. Schnabel A, Reichl SU, Kranke P, et al. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. Br J Anaesth. 2010;105:842–852.
32. Terkawi AS, Tsang S, Sessler DI, et al. Improving analgesic efficacy and safety of thoracic paravertebral block for breast surgery: a mixed-effects meta-analysis. Pain Physician. 2015;18:E757–E780.
33. Coopey SB, Specht MC, Warren L, et al. Use of preemptive paravertebral block decreases length of stay in patients undergoing mastectomy plus immediate reconstruction. Ann Surg Oncol. 2013;20:1282–1286.
34. Silverman SR, Schertz LA, Yuen HK, et al. Systematic review of the methodological quality and outcome measures utilized in exercise interventions for adults with spinal cord injury. Spinal Cord. 2012;50:718–727.
