Avoiding Opioids and Their Harmful Side Effects in the Postoperative Patient: Exogenous Opioids, Endogenous Endorphins, Wellness, Mood, and Their Relation to Postoperative Pain

Bradley C. Stephan MD and Fereydoun D. Parsa MD

Abstract

Prescribed opioids are routinely used for many postoperative patients. However, these medications have daunting adverse effects on the body's innate pain management system – the action of the beta-endorphins. The prescribed opioids not only severely impair the function of the mu-opioid receptors, but also inhibit the release of beta-endorphin. This is unfortunate, because beta-endorphin appears to be a much more potent agonist of the mu-opioid receptor than opioids. In addition, beta-endorphin indirectly elevates dopamine, a neurotransmitter related to feelings of euphoria. Therefore, by prescribing opioids, practitioners may inadvertently prolong and increase the overall intensity of the postoperative patients' pain as well as herald anhedonia. This article highlights the relationships between prescribed (exogenous) opioids, beta-endorphins, mu-opioid receptors, wellness, mood, and postoperative pain. The role of patient education, opioid alternatives, and additional recommendations regarding pain control in the postoperative patient are also discussed.

Introduction

Prescription opioid analgesic (hydrocodone, oxycodone, morphine, hydromorphone, etc.) use in the United States has significantly increased within the past two decades.[1] Similarly, so has the rate of opioid analgesic-related deaths.[1-3] It is estimated that the number of mortalities attributable to opioid analgesics has more than tripled since 1999.[3] This has reached near epidemic proportions with an estimated 16,651 deaths attributable to opioid analgesics in 2010[1] and an estimated 16,235 deaths due to opioid analgesic prescriptions in 2013.[4] This slight decrease in the annual death rate due to opioids is directly proportional to the number of prescriptions for these medications as physicians attempted to curtail opioid abuse.[1] However, the sheer number of deaths related to opioids remains astounding.

Opioid analgesics have other significant adverse effects including nausea, vomiting, constipation, excessive sedation, clouded sensorium, dizziness, respiratory depression, and addiction.[5,6] Unfortunately, many patients suffer with these side effects in a futile attempt to control their pain. Moreover, by using opioids, some patients experience paradoxical hyperalgesia due to a relatively poorly understood mechanism of opioid-induced neural plasticity changes in the peripheral and central nervous systems, which may lead to sensitization of the pain pathways.[7] The harmful effects of opioids have prompted much research into non-opioid modalities for pain control. However, few clinicians possess a thorough understanding of the interplay between opioid medications, endogenous beta-endorphins, wellness, mood, and postoperative pain control. The purpose of this article is to review the interplay of these factors, illustrate the importance of limiting opioids, and discuss non-opioid modalities for post-operative pain control.

Beta-Endorphins

In order to better understand the interplay between endogenous endorphins, exogenous opioids, mood, wellness, and postoperative pain, it is important to have a basic understanding of our body's production and utilization of endogenous endorphins — specifically the beta-endorphins.

The hypothalamus releases corticotrophin-releasing hormone (CRH), a peptide hormone and neurotransmitter, from the periventricular nucleus in response to stress. The "stressor" may take various forms. For the purposes of this review, we will focus on postoperative pain as the primary stressor. Once CRH is released from the periventricular nucleus of the hypothalamus, it travels through the hypothalamo-hypophyseal portal system into the anterior pituitary gland. Here, CRH stimulates basophilic cells to cleave protein proopiomelanocortin (POMC) into smaller proteins – beta-endorphin, alpha-melanocyte stimulating hormone (MSH), and adrenocorticotropin (ACTH).[8] Each one of these have specific target receptors, and therefore, different physiologic effects. If there is an over-accumulation of these POMC byproducts, feedback inhibition ensues and the hypothalamic production of CRH is halted.[8] Of note, cells of our immunologic system are also capable of producing smaller amounts of beta-endorphin.[9]

The primary action of beta-endorphin is to serve as an endogenous ligand for the mu-subtype opioid receptor. This is the same receptor site on which synthetic opioids exert their effects. In the peripheral nervous system, beta-endorphins bind to mu-opioid receptors on both pre-synaptic and post-synaptic nerve terminals.[8] Binding leads to activation of the receptors, and resultant disinhibition of the presynaptic release of gamma-Aminobutyric acid (GABA). In turn, GABA inhibits the release of substance P, a tachykinin protein involved in the transmission of pain.[8,10] In the central nervous system, beta-endorphins bind mu-opioid receptors at the presynaptic nerve terminals and inhibit the release of GABA. Since GABA normally inhibits the release of dopamine, the binding of beta-endorphin to these receptors indirectly results in an overproduction of dopamine – the neurotransmitter primarily associated with the feeling of pleasure and motivation.[8,11] Thus, the overall effect of beta-

endorphin is to decrease pain and to help produce a sense of wellbeing in response to a stressor.

Exogenous opioids halt production of beta-endorphins as well as down-regulate and impair the function of mu-opioid receptors.[8,12-14] The profound effect of exogenous opioids on the production of beta-endorphins and the expression/alteration of mu-opioid receptors leads to tachyphylaxis. Interestingly, studies have suggested that beta-endorphins are 18 to 33 times more potent analgesics than morphine.[15] Therefore, counterintuitively, the administration of exogenous opioids may lead to the prolongation and overall increased intensity of postoperative pain. In addition, these opioids do not target the inflammatory response, the usual underlying cause of patients' discomfort.[16]

Wellness

The definition of the term "wellness" is controversial. The general consensus is that wellness does not solely entail the absence of disease, but rather the full realization of an individual's potential as related to social, occupational, spiritual, physical, intellectual, and emotional aspects of their life.[17] Regarding emotional wellness, dopamine levels are inversely proportional to depressive behavior.[18] Activation of the mu-opioid receptors in the central nervous system leads to a dopamine excess, and a feeling of relative euphoria.[8,19] The acute administration of exogenous opioids *can* produce a short-term feeling of euphoria due to the indirect overexpression of dopamine. However, at the same time, exogenous opioids inhibit the production of beta endorphins (via down-regulation of POMC), as well as downregulate mu-opioid receptors.[8,12,20] This leads to a relative paucity of dopamine resulting in a depressive mood and lack of "wellness". Additionally, exogenous opioid administration often leads to poor physical wellness due to the numerous side effects of opioids.

The Role of Patient Education

Exogenous opioids can have incredibly deleterious effects on an individual's physical and mental state via derangements of beta-endorphin production and mu-opioid receptor function. Therefore, it behooves practitioners to discuss manners to limit exogenous opioid use with their patients.

In 2013, Sugai, Deptula, Parsa, and Parsa demonstrated how effective communication in the preoperative setting can significantly reduce postoperative opioid use. The authors demonstrated that 90% of patients who received preoperative oral and written education concerning the body's response to pain (and how endogenous endorphins cause natural analgesia) declined a hydrocodone prescription preoperatively, and did not request opioids postoperatively. Moreover, it was demonstrated that the patients who received this education reported lower postoperative pain scores. The authors concluded: "By empowering the patient with a sense of control and proper education, it is possible to minimize and in many instances eliminate the use of opioid analgesics."[21]

Opioid Alternatives

Due to the harmful side-effects of opioids, many practitioners have decided to forgo the excessive use of these medications and pursue non-opioid modalities for postoperative pain control—often acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS)/cyclooxygenase-2 (COX-2) inhibitors, gabapentin, local anesthetic infusion pumps, paravertebral or transverse adominis plane nerve blocks, long-acting local anesthetics, botulinum toxin, as well as various combinations of these non-opioid modalities. Numerous articles regarding non-opioid methods of pain control for various patient populations or patients undergoing various procedures have been published. General consciousness supports the use of these non-opioid alternatives in light of the potential side effects of the opioids. However, the practitioner must be careful to not generalize one modality of pain control for all of their postoperative patients. The practitioner must also be aware of the potential adverse effects of these non-opioid analgesics, and weigh the risks and benefits for individual patients.

Acetaminophen is believed to raise the pain threshold via inhibition of isoforms of cyclooxygenase, primarily in the central nervous system.[22-24] The IV form of acetaminophen provides the most predictable bioavailability in comparison to the oral and rectal forms.[24,25] Studies have demonstrated decreased opioid use in patients treated with both acetaminophen and morphine; however, literature has often been unable to demonstrate a decreased incidence in opioid-related adverse effects in these patients.[26-28] Numerous studies have been conducted which depict the efficacy of acetaminophen for pain control. A meta-analysis performed by De Olivera et al showed that a single preventative dose of systemic acetaminophen significantly decreased postoperative opioid consumption as well as postoperative nausea and vomiting.[29] Acetaminophen has minimal adverse side effects when used as recommended by the Food and Drug Administration (FDA),[30,31] and therefore, has been a common modality for postoperative pain management.

Nonsteroidal anti-inflammatory drugs (NSAIDS) act primarily by inhibiting the activity of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 enzymes (COX-2), and thereby produce analgesic, antipyretic, and anti-inflammatory effects by inhibiting prostaglandin synthesis.[24,32] NSAIDS have proven to be efficacious and associated with significantly decreased opioid use in postoperative patients.[33-35] However, the nonselective NSAIDS have been associated with significant gastrointestinal, cardiovascular, renal, and coagulopathy adverse effects.[36,37] Selective COX-2 inhibitors have been developed to reduce gastrointestinal bleeding associated with the nonselective NSAIDS and have been shown to reduce, but not eliminate, the risk for gastrointestinal bleeding.[38] This is in part due to an almost negligible effect on platelet function (in contrast to the nonselective NSAIDS).[39] However, the COX-2 inhibitors are associated with an increased risk for myocardial infarction, stroke, and renal failure.[40,41] Given the strong correlation be-

tween the administration of NSAIDS and the reduction of opioid use, combined with the decreased incidence of gastrointestinal bleeding associated with the COX-2 inhibitors, we have added celecoxib to our multi-modality non-opioid management of postoperative pain in the majority of our patients. However, caution must be used to not administer COX-2 inhibitors to patients at higher risk for myocardial infarction, stroke, or renal failure.

Gabapentin is a widely used antiepileptic drug which has been shown to have analgesic effects, possibly related to regulation of arachidonic acid, nitrergic, and serotonergic systems.[42] This medication has been used extensively for the treatment of neuropathic pain, epilepsy, and restless leg syndrome, with the majority of literature citing dizziness and somnolence as the primary side effects.[43,44] Regarding perioperative opioid consumption, a meta-analysis of 12 randomized controlled trials consisting of 896 patients undergoing a variety of surgical procedures was performed by Hurley, et al. Their findings demonstrated a significant decrease in opioid use in patients who received between 300 and 1200 mg of gabapentin within one to two hours prior to the operation.[45] However, the study failed to show a significant decrease in postoperative nausea, vomiting, or lightheadedness in these patients, and a significant increase in postoperative sedation was observed in the gabapentin group.[45]

The efficacy of local anesthetic infusion pumps ("pain pumps") appears to vary greatly with location of placement. For example, the use of pain pumps has not been shown to significantly decrease the amount of postoperative opioid use, or opioid-related side effects in patients undergoing abdominoplasty, open acrominoplasty, or rotator cuff repair.[46,47] However, these pain pumps have been shown to be extremely efficacious in lowering the overall opioid consumption in patients undergoing other procedures such as breast reconstruction after mastectomy, thoracotomy, open-heart surgery (when 0.5% bupivicane was used), and open inguinal hernia repair.[48-51] Overall, pain pumps have been associated with a relatively low complication rate, with pump failure being the primary complication.[52]

Thoracic and lumbar paravertebral nerve blocks have often been demonstrated to be efficacious in the immediate postoperative period regarding pain control for various procedures, resulting in decreased opioid use and decreased postoperative nausea and vomiting.[53] However, in a study of 620 adults and 42 children, Naja and Lonnqvist reported a 6.1% failure rate in adults (none in the children), 6.8% rate of vascular puncture, 4% experienced hypotension, 1% had epidural or intrathecal spread of the anesthetic, 0.8% had pleural puncture, and 0.5% suffered from a post procedural pneumothorax.[54,55] Thus far, transversus abdominis plane block has shown promise; however, additional evidence is necessary in order to determine its true efficacy and complication rates. Similarly, the use of long-acting liposomal bupivacaine local aesthetic and botulinum toxin for postoperative pain relief require additional research.

The authors of this article have extensive experience involving pre-operative administration of gabapentin and celecoxib as well as pre-operative and intra-operative administration of long-acting local anesthetic for patients undergoing various plastic surgery procedures.[5,56,57] These non-opioid modalities of postoperative pain control have resulted in significant limitation of post-operative opioid administration for patients undergoing extensive abdominal wall reconstruction, sub-pectoral breast augmentation, and other aesthetic operations. One of the authors has been able to forgo the use of opioids in almost all of his patients undergoing various plastic surgery procedures—for approximately the last 10 years.

Discussion

Exogenous opioids are commonly, almost routinely, provided in the immediate postoperative period after numerous types of surgeries. Unfortunately, these medications are not without significant adverse effects. Per our ongoing studies and literature review, opioids appear to increase the overall intensity and duration of post-operative pain by inhibiting the body's production of endogenous beta-endorphins, as well as down-regulating the expression of and inhibiting the function of mu-opioid receptors. These opioids also indirectly limit the action of dopamine in the central nervous system, leading to a feeling of anhedonia.

Exogenous opioids effectively inhibit the body's innate pain management system—a system which has been postulated to be more potent than prescribed opioids. Therefore, escalating doses of opioids are often used for pain control. This further impairs the action of beta-endorphin. Unfortunately, additional research is needed to fully understand how we may promote the body's production and response to endogenous beta endorphin.

The many adverse effects of opioids has prompted numerous practitioners to seek alternatives for pain control in the postoperative patient. Additional research into non-opioid manners of pain control is needed and forthcoming. Tremendous results regarding postoperative pain control while eliminating opioid use in patients after various plastic surgery procedures have been experienced by the authors of this article.[5,21,56] It has been shown that postoperative opioid use may be significantly reduced, and often completely eliminated, for procedures that historically require a substantial amount of postoperative opioid analgesia (i.e. subpectoral breast augmentation).

The primary advantage of eliminating the use of opioids for postoperative pain control appears to be avoidance of the common negative side effects of opioid analgesics. In addition, patients who do not use opioids are often more pleased with their overall postsurgical wellness in our experience. We believe that the profound impacts of beta-endorphin are often underscored in literature. Based on our research, the following guidelines should be implemented to achieve adequate opioid-free postoperative pain control:

(1) The patient must be provided adequate preoperative verbal and written education concerning the rational for eliminating the use of opioids in the perioperative period.
(2) The preoperative and intraoperative use of local anesthetic is strongly recommended.

(3) Preoperative use of gabapentin and celecoxib (in appropriate-risk patients) is advised.

(4) The practitioner should avoid intraoperative use of opioids in order to preserve the effects of endogenous beta-endorphins.

(5) Avoidance of postoperative opioid use is strongly recommended.

Limitations

A limitation of this article includes a lack of case-control analysis. This article's principal focus is expert opinion and literature review. The purpose of this article is to acquaint the reader with the relationship between opioid analgesics, beta endorphins, mu-opioid receptors, postoperative pain, and patients' sense of wellness, as well as describe various opioid alternatives for the operative patient. Another limitation of this article is that our research focuses primarily on non-opioid reduction of postoperative pain in patients undergoing plastic surgery procedures, which may limit the generalizability of our study. Also, additional research regarding opioid-free modalities of postoperative pain management are needed.

Conflict of Interest

The authors report no conflict of interest.

Authors' Affiliation:
- University of Hawai'i John A. Burns School of Medicine, Honolulu, HI

Correspondence to:
Bradley C. Stephan MD; 1356 Lusitana Street, 6th Fl., Honolulu, HI 96813;
Email: bstephan@hawaii.edu

References

1. Dart RC, Surratt HL, Cicero TJ, et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. *New England Journal of Medicine.* 2015;372(3):241-248.
2. Chen LH, Hedegaard H, Warner M. Drug-poisoning Deaths Involving Opioid Analgesics: United States, 1999-2011. *NCHS data brief.* 2014(166):1-8.
3. Nelson LS, Juurlink DN, Perrone J. ADdressing the opioid epidemic. *JAMA.* 2015;314(14):1453-1454.
4. Rates of deaths from drug poisoning and drug poisoning involving opioid analgesics-United States, 1999-2013. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6401a10.htm. Accessed November 16, 2015.
5. Parsa AA, Soon CW, Parsa FD. The use of celecoxib for reduction of pain after subpectoral breast augmentation. *Aesthetic Plast Surg.* 2005;29(6):441-444; discussion 445.
6. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician.* 2008;11(2 Suppl):S105-120.
7. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011;14(2):145-161.
8. Sprouse-Blum AS, Smith G, Sugai D, Parsa FD. Understanding endorphins and their importance in pain management. *Hawaii Med J.* 2010;69(3):70-71.
9. Mousa SA, Shakibaei M, Sitte N, Schafer M, Stein C. Subcellular pathways of beta-endorphin synthesis, processing, and release from immunocytes in inflammatory pain. *Endocrinology.* 2004;145(3):1331-1341.
10. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med.* 1995;332(25):1685-1690.
11. Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behaviour--review of data from preclinical research. *Acta Psychiatr Scand Suppl.* 2005(427):14-21.
12. Przewlocki R. Opioid abuse and brain gene expression. *Eur J Pharmacol.* 2004;500(1-3):331-349.
13. Wardlaw SL, Kim J, Sobieszczyk S. Effect of morphine on proopiomelanocortin gene expression and peptide levels in the hypothalamus. *Brain Res Mol Brain Res.* 1996;41(1-2):140-147.
14. Christie MJ, Williams JT, North RA. Cellular mechanisms of opioid tolerance: studies in single brain neurons. *Mol Pharmacol.* 1987;32(5):633-638.
15. Loh HH, Tseng LF, Wei E, Li CH. beta-endorphin is a potent analgesic agent. *Proc Natl Acad Sci U S A.* 1976;73(8):2895-2898.
16. Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin.* 2007;45(2):27-37.
17. Hettler B. The six dimensions of wellness. 1976.
18. Lee M, Ryu YH, Cho WG, Kang YW, Lee SJ, Jeon TJ, Lyoo CH, Kim CH, Kim DG, Lee K, Choi, TH, Choi JY. Relationship between dopamine deficit and the expression of depressive behavior resulted from alteration of serotonin system. *Synapse.* 2015;69(9):453-460.
19. Wise RA, Bozarth MA. Brain mechanisms of drug reward and euphoria. *Psychiatr Med.* 1985;3(4):445-460.
20. Zhang G, Lagrange AH, Ronnekleiv OK, Kelly MJ. Tolerance of hypothalamic beta-endorphin neurons to mu-opioid receptor activation after chronic morphine. *J Pharmacol Exp Ther.* 1996;277(1):551-558.
21. Sugai DY, Deptula PL, Parsa AA, Don Parsa F. The importance of communication in the management of postoperative pain. *Hawaii J Med Public Health.* 2013;72(6):180-184.
22. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology.* 2013;21(3):201-232.
23. Liu J, Reid AR, Sawynok J. Antinociception by systemically-administered acetaminophen (paracetamol) involves spinal serotonin 5-HT7 and adenosine A1 receptors, as well as peripheral adenosine A1 receptors. *Neurosci Lett.* 2013;536:64-68.
24. Gupta A, Jakobsson J. Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs, and Cyclooxygenase-2 Selective Inhibitors: An Update. *Plastic and Reconstructive Surgery.* 2014;134(4S-2):24S-31S.
25. Brett CN, Barnett SG, Pearson J. Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomised controlled trial. *Anaesth Intensive Care.* 2012;40(1):166-171.
26. McNicol ED, Tzortzopoulou A, Cepeda MS, Francia MB, Farhat T, Schumann R. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth.* 2011;106(6):764-775.
27. Tzortzopoulou A, McNicol ED, Cepeda MS, Francia MBD, Farhat T, Schumann R. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. *The Cochrane database of systematic reviews.* 2011(10):CD007126.
28. Marel CDvd, Peters JWB, Bouwmeester NJ, Jacqz-Aigrain E, Anker JNvd, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *British Journal of Anaesthesia.* 2007;98(3):372-379.
29. De Oliveira GS, Jr., Castro-Alves LJ, McCarthy RJ. Single-dose systemic acetaminophen to prevent postoperative pain: a meta-analysis of randomized controlled trials. *Clin J Pain.* 2015;31(1):86-93.
30. Acetaminophen Information. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm. Accessed Nov 21, 2015.
31. Gupta A, Jakobsson J. Acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 selective inhibitors: an update. *Plastic And Reconstructive Surgery.* 2014;134(4):24S-31S.
32. *NSAIDs : Non-Steroidal Anti-Inflammatory Drugs : An Overview.* Global Media; 2008.
33. Sultan A, McQuay HJ, Moore RA, Derry S. Single dose oral flurbiprofen for acute postoperative pain in adults. *The Cochrane database of systematic reviews.* 2009(3):CD007358.
34. Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *The Cochrane database of systematic reviews.* 2009(3):CD001548.
35. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clinical Therapeutics.* 2009;31(9):1922-1935.
36. James DS. The multisystem adverse effects of NSAID therapy. *The Journal of the American Osteopathic Association.* 1999;99(11 Suppl):S1.
37. *NSAIDs : a profile of adverse effects.* Philadelphia, PA : St. Louis, MO: Philadelphia, PA : Hanley & Belfus St. Louis, MO : North American and worldwide sales and distribution, Mosby-Year Book; 1992.
38. Jarupongprapa S, Ussavasodhi P, Katchamart W. Comparison of gastrointestinal adverse effects between cyclooxygenase-2 inhibitors and non-selective, non-steroidal anti-inflammatory drugs plus proton pump inhibitors: a systematic review and meta-analysis. *Journal of Gastroenterology.* 2013;48(7):830-838.
39. Scharbert G, Gebhardt K, Sow Z, Duris M, Deusch E, Kozek-Langenecker S. Point-of-care platelet function tests: detection of platelet inhibition induced by nonopioid analgesic drugs. *Blood Coagulation & Fibrinolysis: an international journal in haemostasis and thrombosis.* 2007;18(8):775.
40. Lader E. ACP Journal Club. Review: NSAIDs increase GI and CV events; coxibs increase mortality. *Annals of Internal Medicine.* 2013;159(8):JC12.
41. Demaria AN, Weir MR. Coxibs—Beyond the GI Tract. *Journal of Pain and Symptom Management.* 2003;25(2):41-49.
42. Kilic FS, Sirmagul B, Yildirim E, Oner S, Erol K. Antinociceptive effects of gabapentin & its mechanism of action in experimental animal studies. *The Indian journal of medical research.* 2012;135(5):630.
43. Ramsay RE. Clinical efficacy and safety of gabapentin. *Neurology.* 1994;44(6 Suppl 5):S23.
44. Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. *Progress in Neuropsychopharmacology & Biological Psychiatry.*
45. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The Analgesic Effects of Perioperative Gabapentin on Postoperative Pain: A Meta-Analysis. *Regional Anesthesia and Pain Medicine.* 2006;31(3):237-247.
46. Bray DAJ, Nguyen J, Craig J, Cohen BE, Collins DRJ. Efficacy of a Local Anesthetic Pain Pump in Abdominoplasty. *Plastic and Reconstructive Surgery.* 2007;119(3):1054-1059.
47. Boss AP, Maurer T, Seiler S, Aeschbach A, Hintermann B, Strebel S. Continuous subacromial bupivacaine infusion for postoperative analgesia after open acromioplasty and rotator cuff repair: Preliminary results. *Journal of Shoulder and Elbow Surgery.* 2004;13(6):630-634.
48. Baroody M, Tameo MN, Dabb RW. Efficacy of the Pain Pump Catheter in Immediate Autologous Breast Reconstruction. *Plastic and Reconstructive Surgery.* 2004;114(4):895-898.

49. Barron DJ, Tolan MJ, Lea RE. A randomized controlled trial of continuous extra-pleural analgesia post-thoracotomy: efficacy and choice of local anaesthetic. *Eur J Anaesthesiol.* 1999;16(4):236-245.
50. White PF, Rawal S, Latham P, et al. Use of a continuous local anesthetic infusion for pain management after median sternotomy. *Anesthesiology.* 2003;99(4):918.
51. LeBlanc KA, Bellanger D, Rhynes VK, Hausmann M. Evaluation of continuous infusion of 0.5% bupivacaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. *Journal of the American College of Surgeons.* 2005;200(2):198-202.
52. Pu LLQ, Committee PSEFD. The Use of a Pain Pump for Optimal Postoperative Pain Management. *Plastic and Reconstructive Surgery.* 2006;117(6):2066-2069.
53. Thavaneswaran P, Rudkin GE, Cooter RD, Moyes DG, Perera CL, Maddern GJ. Brief reports: paravertebral block for anesthesia: a systematic review. *Anesthesia and Aanalgesia.* 2010;110(6):1740.
54. Batra R, Krishnan K, Agarwal A. Paravertebral block. *Journal of Anaesthesiology Clinical Pharmacology.* 2011;27(1):5-11.
55. Naja Z, Lonnqvist PA. Somatic paravertebral nerve blockade. Incidence of failed block and complications. *Anaesthesia.* 2001;56(12):1184-1188.
56. Parsa AA, Sprouse-Blum AS, Jackowe DJ, Lee M, Oyama J, Parsa FD. Combined preoperative use of celecoxib and gabapentin in the management of postoperative pain. *Aesthetic Plast Surg.* 2009;33(1):98-103.
57. Stephan B, Ramshaw B, Forman B. Value-Based Clinical Quality Improvement (CQI) for Patients Undergoing Abdominal Wall Reconstruction. *Surg Technol Int.* 2015;26:135-142.