Review Article

Perioperative Pain: Molecular Mechanisms and Future Perspectives

Zahra Talebi[1], Ali Dabbagh[1*]

Abstract

Background: Acute perioperative pain is seen in more than 80% of patients undergoing surgery, with almost 75% of them experiencing moderate, severe, or extreme pain; adequate postoperative pain management is not achieved in a satisfactory manner. This styudy was desined ana performed to assess the molecular mechanisms of acute pain management in order to find novel future perspectives.

Materials and Methods: In this narrative review, molecular mechanisms of currently available pain controlling agents were assessed based on 3 steps: preoperative, intraoperative and postoperative phases. Drugs used in each phase and potential novel agents were assessed separately.

Results: many currently available clinical agents were discussed and meanwhile, other potential drugs that could be among the future choices are discussed.

Conclusion: cellular and molecular medicine could open new windows in order to discover novel agents for management of pain; we will have possibly many new agents that will be available in future while they will be different from currently used clinical pain killers.

Keywords: cellular and molecular medicine; pain; perioperative

Please cite this article as: Talebi Z, Dabbagh A. Perioperative Pain: Molecular Mechanisms and Future Management. J Cell Mol Anesth. 2017;2(3):134-41.

1. Cardiac Anesthesiology Department, Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Ali Dabbagh, MD, Cardiac Anesthesiology Department, Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: alidabbagh@sbmu.ac.ir

Introduction

The international association for the study of pain, defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1). Acute postoperative pain is seen in more than 80% of patients undergoing surgery, with almost 75% of them experiencing moderate, severe, or extreme pain. Based on reports, adequate postoperative pain management is achieved in less than half of surgery patients (2). Effective pain management in surgery patients helps with overall recovery, increases patient satisfaction, and ultimately reduces health care cost. It can also decrease morbidity and improve surgery outcomes (3).

Although several new approaches have been introduced in the past decade as components of a multimodal approach to decrease the side effects and improve quality of analgesia, there hasn't been any major improvement in this field in the past decade. In this article, we reviewed the major mechanisms involved in this process and current clinical strategies in managing this pain in surgical patients (4).

Molecular Mechanisms

Post-operative pain has a biphasic nature,

which makes it more difficult to manage. In the first phase, great nociceptive input is produced in the surgery, where trauma to the tissue results in the production of noxious stimuli. The second phase starts after surgery, when inflammation present at the site, produces more noxious input. These processes initiate pain response in two levels. At peripheral level, the prolonged presence of noxious stimuli results in inflammation and tissue damage. Primary mediators such as prostaglandins, serotonin, leukotrienes, and bradykinins reduce the threshold of high threshold nociceptive afferents and initiate the release of pain mediators such as substance P, CGRP and cholecystokinin in the site of injury, which leads to peripheral sensitization. Hence, weaker stimuli, which normally cannot produce pain, would now be perceived as painful. Histamine, nerve growth factor and norepinephrine are also involved in peripheral sensitization (5). There is also an increased number and proportion of tetrodotoxin-resistant channels in the affected neurons, which leads to the development of spontaneous ectopic activity (6). Reducing the inflammation would be the rational approach in controlling peripheral pain and use of NSAIDs, opioids and local anesthetics is advised.

On the other level, central sensitization occurs as a result of long term potentiation of the central nerves, with NMDA and AMPA glutamate receptors and Wide Dynamic Range (WDR) neurons playing the vital role. WDR neurons receive signals from both innocuous and nociceptive sensory neurons from large areas of the body, but in the case of repeated nociceptive input, their threshold can decrease and their receptive field widen. This is due to NMDA receptor activation that ultimately leads to increased sensitivity of the WDR neurons.

A delta and C fibers bring the Impulses from the peripheral nociceptors to synapse in the lamina II and lamina V; C fibers also synapse in the lamina I of the spinal cord before projecting cranially. In lamina V, neurotransmitters such as glutamate and aspartate, activate amino-3-hydroxyl- 5-methyl-4-proprionic acid (AMPA) and Kainate (KAR) receptors and transmit the pain signal with high speed. These receptors can regulate Na^+ and K^+ ion transfer but are nearly impermeable to Ca^{2+} ions.

NMDA (N-methyl-D-aspartate) glutamate receptor is a membrane protein with an ion channel that works by transferring Na^+ and Ca^{2+} into the cell and simultaneously transferring K^+ to the outside of the cell. Extracellular Mg^{2+} and Zn^{2+} ions can bind to specific sites on the receptor and block the flow of other cations through the open ion channel. Since these receptors are voltage gated, they need a positive change in the cell voltage which is brought upon by an AMPA-induced membrane depolarization, which displaces the magnesium or zinc from the channel passage and clears the way for the calcium ions to enter the neuron. Direct binding of the glutamate can further potentiate this process (5–7).

The accumulation of calcium in cell brings it to a state of excitation without stimulation where spinal neurons are "wind up" and fired rapidly in a transcription independent manner.

The transcription independent central sensitization processes such as wind up and early LTP, are heterosynaptic, and low threshold A Beta input evoke these responses after C fiber conditioning. This kind of central sensitization is reversible and with each repetitive stimulation the pain increases. In the transcription dependent central sensitization, prolonged noxious facilitation, leads to production of modified proteins as a result of activation of certain genes, therefore, Ca^{2+} influx and subsequently production of prostaglandins, nitric oxide, and superoxides increases. This process is believed to be mediated by inflammation and changes in the dorsal root ganglion, the dorsal horn, and irreversible structural modifications in the CNS (5).

This process can ultimately lead to hyperalgesia as a result of central sensitization in spinal cord as well as higher regions of CNS such as anterior cingulate gyrus, amygdale, and rostroventral medulla (5).

The neurokinin receptor (NK1) and cycloxygenase 2 (COX-2) are also involved in central sensitization; however they are not involved in hippocampal LTP. The phosphorylation of synaptic receptors and the insertion of AMPA receptors into the post-synaptic membrane is seen in both hippocampal early phase LTP and central sensitization, but in hippocampal LTP synaptic strengthening is the only mechanism, while other cellular mechanisms and neuronal network changes

are involved in central sensitization. These similarities should be noted when treating central sensitization to avoid the disturbance of memory formation and cortical function (8).

Management of pain

In order to effectively manage postoperative pain, appropriate measures should be implemented before, during and after the surgery.

During the operation

Preoperative management:

In the preoperative setting, individual assessment of the patients, patient education, preemptive, and preventive analgesia are the main examples of such measures (2-3, 17).

The analgesic plan, in respect to analgesic efficacy, potential side effects, and effects on recovery should be optimized depending on the surgical procedure. Evidence based recommendations for procedure specific pain management in the common adult surgeries has been developed by the prospect working group, which is a collaboration of surgeons and anesthesiologists, and it can be accessed freely on the website http://www.postoppain.org/.

***Intraoperative* management**

Different neuroendocrine, metabolic, and inflammatory changes are involved in the stress response from the surgery, which can harm organs and ultimately increase postoperative pain. Hypothermia and psychological stress can increase these responses, while deeper levels of anesthesia, neural blockade, and reduced surgical invasiveness can diminish them.

Intravenous Medications

- Lidocaine: Lidocaine is the safest local anesthetic; it can reduce pain and inflammation when administrated as a 100mg IV bolus followed by an infusion of 2 to 3 mg/h in surgeries. Lidocaine has weak analgesic, but potent anti-hyperalgesic effect in humans; it decreases the need for opioids and helps with the early return of bowel function.
- β-blockers: β-blockers can improve surgical stress response and inhibit sympathetic response to tracheal intubation. They also reduce the need for opioid and volatile anesthetic use (3).
- α_2 agonists: clonidine, tizanidine and dexmedetomidine are the most commonly used α_2 agonists in pain management. They can decrease opioid consumption due to their anesthetic and analgesic properties (9). Clonidine is administrated orally and can help with opioid withdrawal pains. Tizanidine acts more rapidly and is more beneficial in patients with spastic disorders. It also has less effects on blood pressure and heart rate (9). Dexmedetomidine is more selective, and it can be administrated IV. It works by hyperpolarization of neurons in locus ceruleus and therefore inhibiting the sympathetic-mediated pain at peripheral nociceptors which inhibits the release of pain mediators such as substance P and glutamate in primary afferent neurons, and the wind up effect in secondary neurons (9–11).
- NMDA inhibitors: In a prospective, randomized, double-blinded study, a 0.5 mg/kg bolus of ketamine followed by continuous intravenous infusion of 0.25 mg/kg/h during the surgery, decreased opioid consumption and reduced areas of hyperalgesia up to 72 h after surgery, compared to placebo or epidural ketamine. IV Ketamine also decreased CPOP for up to 6 months after the surgery (11). Dextromethorphan also works with this mechanism and has shown to be effective in reducing postoperative pain and opioid consumption (effect of preoperative)

Anesthesiology techniques:

Different methods of administration can be used for anesthetic drugs to ensure the optimal analgesia and minimize side effects and use of opioids. The followings are the most commonly used methods used to decrease post-operative pain:

- **Neuraxial techniques of analgesia**, in which epidural or spinal administration of local anesthetic (with a low dose opioid) blocks the nociceptive stimuli and the stress response to surgery. Administration is performed before the surgery and can be continued after the surgery. This technique can also help with postoperative mobilization and reduce the risk of ileus.
- **Transversus Abdominus Plane Blocks,** in which abdominal wall is anesthetized with peripheral nerve block for minor abdominal surgeries.
- **Peripheral Nerve Blocks,** in which afferent nociceptive pathways are blocked.
- **Wound Infiltration Anesthesia,** in which lidocaine or bupivacaine are infiltrated in the wound for local anesthesia. This method is fast acting and

epinephrine can be used to extend the duration of action. A liposomal formulation of bupivacaine has been developed to provide longer durations of action (up to 96 hours), but its clinical use is still limited due to insufficient comparative clinical data.

- **Tumescent Anesthesia,** in which local anesthetic are diluted and administrated subcutaneously in large volumes with epinephrine and other agents.
- **Topical Local Anesthesia,** in which special formulations of local anesthetics with the ability to penetrate the skin (lidocaine and prilocaine, lidocaine-epinephrine-tetracaine and tetracainephenylephrine) are used on intact skin (before surgical incision) or cuts (to facilitate suturing in pediatric patients). Topical oxymetazoline or phenylephrine and lidocaine has also been used for mucosal analgesia (3, 11).

Postoperative Management

Multimodal analgesia, is defined as the use of a combination of different analgesic medication and techniques, with different mechanisms of action in the peripheral and central nervous system to obtain additive or synergistic effects and increase the effectiveness of pain management (2). In this method individual personal and medical needs of patients are considered to obtain the best analgesia plan. Patients' response and side effects are monitored afterwards and required alterations are made depending on patient's needs. Physicians, anesthesiologists and nursing staff should all cooperate to maximize the success of pain management plan (12). Opioids are the key component in multimodal approach and other pharmacological and non-pharmacological interventions are added according to patient's individual needs, to increase their efficacy from other mechanisms, and minimize their side effects. The interventions most commonly used in multimodal analgesia are as follows (3):

- Non-pharmacologic therapies: Transcutaneous electrical nerve stimulation at incision site and cognitive modalities with guided imagery and other relaxation methods, hypnosis, intraoperative suggestions, and music.
- Acetaminophen and NSAIDs, as oral or IV injections to reduce the use of postoperative opioids. A single dose of celecoxib before major surgeries, has shown to reduce post-operative pain and opioid consumption (2).
- Opioids in IV, IM, oral, transdermal, rectal, sublingual, subcutaneous, neuroaxial administration routes, morphine, hydromorphone, fentanyl and tramadol are used more frequently. In patients with severe pain who need more frequent injections, patient controlled IV analgesia with opioids is used (3).
- Gabapentin and pregabalin which can be administrated before or after the surgery (PIIS).
- Corticosteroids (13), dexamethasone (8 mg IV) is the best option, since it can help with nausea and vomiting after the surgery.

Experimental drugs and pain control methods

With the increase in the rate of surgical operations, postoperative pain is gaining more attention in scientific studies, with the aim of finding more effective drugs and procedures with less side effects.

Since various complex mechanisms are involved in the spinal pain amplification caused by surgical insult, numerous therapeutic targets can interfere with this process. Therapies may target neuronal or non-neuronal processes of sensitization. Sensitization is also dependent on calcium influx and inflammation processes. Some therapeutics modulates neuronal activity or by blocking receptor proteins such as NMDA and AMPA receptor, which increase intracellular calcium levels during neuronal activation. Other therapies may target CNS inflammation (11). An overview of the main experimental approaches for management of postoperative pain is presented here.

Acupuncture: auricular acupuncture, in which needles are placed in various parts of the earlobe has been shown to be beneficial in post-operative pain control, but larger studies with improved quality are needed to obtain a definitive conclusion in this matter and justify the routine use of this method (5).

Probiotics: Probiotics has shown beneficial effects on inflammatory pain, by inhibiting pro-inflammatory mediators and increasing the production of anti-inflammatory cytokines in animal models. The adjuvant use of probiotics should be considered in the postoperative period, due to their nonexistent side effects (14).

Magnesium: Administration of IV magnesium

after major GI surgery has shown to reduce postoperative ileus, postoperative severe pain and perioperative analgesic requirements in a randomized clinical trial. Magnesium has no side effects in these doses and its routine administration can be advised for major GI surgeries (15).

Pulsed electromagnetic fields: PEMF improves calmodulin-dependent nitric oxide and/or cyclic guanosine monophosphate signaling, but it can also increase phosphodiesterase activity which inhibits cyclic guanosine monophosphate activity. At certain intervals, this method has demonstrated beneficial effects in postoperative pain in breast reduction patients (16).

Glutamate receptor antagonism: as mentioned before, glutamate plays a key role in central sensitization and pain, and different glutamatergic receptors and pathways have been investigated for their potential in treatment of neuropathic and postoperative pain. Currently ketamine, dextromethorphan, amantadine, and memantine, are clinically available as NMDA receptor antagonists (17). Other drugs such as MK-801 (i.e. dizocilpine), AP5, traxoprodil and norketamine, works with the same mechanism and has been introduced in the literature as treatments for postoperative pain (11). Other than inhibition of the NMDA receptor itself, other molecules involved in the phosphorylation of these receptors can also be considered as therapeutic targets. Examples of such molecules are protein kinase A (PKA) which has a role in phosphorylation of NR1 subunit and the Src. family of protein which are involved in NR2B phosphorylation (11). Although IV administration of ketamine is associated with side effects such as hallucination, combined use of these agents with opioids, while reducing the need for opioids, does not bare any additional side effects when compare to opioids alone (17). AMPA receptors (18) and G protein-coupled metabotropic glutamatenreceptors, mGluR 1 and 5, are other interesting targets in these pathways and several substances has been introduced as antagonists for this receptors (19), but although animal studies were promising, more clinical studies are needed to find the best molecule for human use.

Opioids- New substances and new administrations

Tapentadol is a novel opioid analgesic with potency between tramadol and morphine but with less abuse potential than all other opioid analgesic drugs. It has a unique ability to inhibit norepinephrine reuptake as well as its agonistic effect on μ receptors. Incidence of nausea and vomiting is also lower with this drug compared to oxycodone (5,20,21). It can be used both in preemptive treatment and postoperative period to manage the pain (22). Since the risk for addiction is one of the most important challenges when using opioids, there's an increasing interest focused on development of abuse-deterrent formulations of opioids. Such formulations are based on technologies such as physical or mechanical barriers or the addition of a noxious component (e.g. niacin) or an antagonist (e.g. naloxone, naltrexone) (23). A typical example is slow-release oxycodone formulation that combines a mechanical and a physical barrier effect which prevents crushing or drawing out drug for injection (23). Although these preparations require further evaluation, it has been suggested that they may well become the standard of care in the future (24).

Capsaicin: (8-methyl-N-vanillyl-6-nonenamide) is a TRPV-1 (transient receptor potential vanilloid 1) agonist which can be found in chili pepper seeds, it is non-narcotic and acts peripherally (24). TRPV1 receptors are present on unmyelinated C fiber endings in the periphery, and they tend to be significantly reduced in inflammatory conditions. The activation of the TRPV receptors produces high intensity impulses which lead to the release of substance P, and a burning sensation. C fiber activation is ultimately reduced when substance P is depleted. The A delta and A alpha fibers are not significantly affected by capsaicin. It is available in injection and topical forms. It is thought to have opioid sparing effects and can be used as an adjuvant in a variety of pain disorders, especially in age groups more sensitive to opioid adverse effects. The initial burning sensation with this molecule can be managed with pre-administration of neural blockade before injection of capsaicin. Capsaicin's favorable safety profile makes it an interesting choice in the management of postoperative pain and there are more attempts to identify therapeutically useful agonists and antagonists for the TRPV1 receptor (25, 26).

Immune modulation with glial modulators

According to recent findings astrocytes and microglia, central and peripheral, participate in neuronal hyper excitability and chronic pain (27). These resulted in an increased focus on these cells as targets in pain management. However, although animal studies demonstrate an overall beneficial effect from glial modulators in treatment of pain and central sensitization, and brain glial activation in chronic pain patients has been established, human studies have so far yielded diverse results (28). An example of these modulators is propentofylline, which proved to be beneficial in a variety of rodent pain models in reducing pain hypersensitivity but failed to indicate a beneficial effect in postherpetic neuralgia, in a Phase IIa clinical trial. It seems that different aspects of pain and differences between humans and animal models should be determined carefully to ensure successful translation of use of glia modulators in human (29).

Immune modulation with anti-cytokines agents

Cytokines have also been directly targeted in order to modulate inflammatory processes in pain (30). Intrathecal etanercept as a TNF inhibitor was found effective in preventing phosphorylation of the AMPA-subunit GluR1 in the spinal dorsal horn, and also SNL pain models, with optimal effect achieved when the drug was administrated early after nerve injury (11). Intrathecal IL-1ra was not found beneficial in the SNT model of peripheral nerve injury, but it was found effective in attenuating established mechanical hypersensitivity at 7 days after induction of CCI of the sciatic nerve and reversing mechanical pain hypersensitivity at 96 h after intraplantar CFA injection (31). Interference with IL-1b signaling was also effective in reducing established inflammatory pain. As a biological inhibitor of TNF-a signaling, intraperitoneal injection of Erythropoietin (EPO) and the synthetic peptide ARA290 which mimicks its effects, has demonstrated beneficial effects in SNT nerve injury with reduced SNT-induced inflammation and attenuation of SNT-induced increases in the levels of GFAP, TNF-a, and IL-1b (32). Although these data are highly impressive, the clinical use of these drugs and their risk benefit profile are yet to be determined in larger scale clinical trials.

Antidepressants : Although the efficacy of antidepressants in acute postsurgical pain has been suggested in numerous clinical trials, most of these trials are old and their results are limited by not specifying primary outcomes, disregarding movement-evoked pain, small size and insufficient safety assessment (33,34). Data on use of antidepressants in prevention of chronic postsurgical pain is inclusive with only one of three trials in this indication suggesting any efficacy. Therefore, current evidence does not yet support routine use of any one specific antidepressant for treatment of acute, or prevention of chronic, postsurgical pain and further larger trials are needed to determine optimal dosing and duration of antidepressant treatment, procedure specificity, safety profile, and assessment of movement-evoked pain (35).

Cannabinoids are a group of proteins including endocannabinoids such as anandamide (produced naturally in the body by humans and animal), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured chemically) which act on cannabinoid receptors (36). Since cannabinoid receptors are thought to be involved in analgesic, euphoric and anticonvulsive processes (CB1) and also demonstrate anti-inflammatory and immunosuppressive effects (CB2), cannabinoids represent an interesting target for neuropathic pain management. However the overall clinical data available is still limited and confusing, and suggests limited efficacy from drugs on this category in some neurologic disorders, such as chronic neuropathic pain conditions, in MS and AIDS (24).

Resolvins: A large number of evidence supports the potent anti-inflammatory and pro-resolution actions of omega-3 polyunsaturated fatty acids-derived lipid mediators, such as resolvins, lipoxins, and neuroprotectins in various animal models of inflammation (37). Resolvin E1 (RvE1) is an eicosapentaenoic acid (EPA) derivative that with peripheral spinal, or systemic administration at very low doses, has shown to reduce inflammatory pain, via transient receptor potential ion channel (TRPV1) and modulating microglial signalin (38). Mechanism of RvE1 activates the G-protein-coupled receptor ChemR23, widely expressed in immune cells

(macrophages), neurons (primary sensory neurons and spinal cord neurons), and microglia (39).

Calcitonin: Calcitonin is a polypeptide hormone produced naturally in humans by the parafollicular cells of the thyroid gland (40). It is commonly used in treatment of osteoporosis and Paget's disease. Calcitonin's use in acute and chronic pain states has been examined in different studies. A more recent network meta-analysis supports short-term use of calcitonin in later stages of complex regional pain syndrome (24). There is also limited evidence that calcitonin can be used in acute, but not chronic, phantom limb pain after amputation (41).

Vitamin C: Several trials have been conducted on use of vitamin C in postoperative pain. A meta-analysis of the available references in 2016 concluded that there is moderate-level evidence supporting that preoperative dose of 2 g vitamin C can be used as an adjunct for its opioid spring abilities, and high-level evidence is available that supplementation of 1 g/d vitamin C for 50 days is useful in prevention of complex regional pain syndrome type I after extremity surgery (42). Additional studies can be useful in determining overall effectiveness and optimum dosage of vitamin C.

Conclusion

Postoperative pain is a complex phenomenon which depends on several factors, from type of the surgery and the skill of the surgeon to patient's characteristics and background history. Effective management of postoperative pain requires identification of these factors and their underlying molecular mechanisms, and planning an individual approach for each patient accordingly using multimodal analgesia. Pain prevention should be considered in all stages of surgery, preoperative and postoperative period, and each member of the medical team should play their parts optimally to minimize patient's harm and improve surgical outcomes.

Acknowledgment

The authors acknowledge the kind help of Anesthesiology Research Center in administrative issues.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Bonica JJ. The need of a taxonomy. Pain. 1979;6(3):247.
2. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Commi. J Pain. 2016;17(2):131–57.
3. Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. Surg Clin North Am. 2015;95(2):301–18.
4. Kang S, Brennan TJ. Mechanisms of postoperative pain. Anesth Pain Med. 2016;11(3):236–48.
5. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale J Biol Med. 2010;83(1):11.
6. Neil MJE, Macrae WA. Post surgical pain-the transition from acute to chronic pain. Rev pain. 2009;3(2):6.
7. Paoletti P, Neyton J. NMDA receptor subunits: function and pharmacology. Curr Opin Pharmacol. 2007;7(1):39–47.
8. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696–705.
9. Giovannitti Jr JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015;62(1):31–8.
10. Kamibayashi T, Maze M. Clinical uses of α2-adrenergic agonists. J Am Soc Anesthesiol. 2000;93(5):1345–9.
11. Deumens R, Steyaert A, Forget P, Schubert M, Lavand'homme P, Hermans E, et al. Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. Prog Neurobiol. 2013;104:1–37.
12. Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. Anesthesiol Clin. 2010;28(2):217–24.
13. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2012;aes431.
14. Nazemian V, Shadnoush M, Manaheji H, Zaringhalam J. Probiotics and Inflammatory Pain: A Literature Review Study. Middle East J Rehabil Heal. 2016;3(2).
15. Moharari RS, Motalebi M, Najafi A, Zamani MM, Imani F, Etezadi F, et al. Magnesium can decrease postoperative physiological ileus and postoperative pain in major non laparoscopic gastrointestinal surgeries: a randomized controlled trial. Anesthesiol

pain Med. 2013;4(1).
16. Taylor EM, Hardy KL, Alonso A, Pilla AA, Rohde CH. Pulsed electromagnetic fields dosing impacts postoperative pain in breast reduction patients. J Surg Res. 2015;193(1):504–10.
17. Vorobeychik Y, Willoughby CD, Mao J. NMDA Receptor Antagonists in the Treatment of Pain. In: Treatment of Chronic Pain by Medical Approaches. Springer; 2015. p. 59–65.
18. Gomez-Mancilla B, Brand R, Jürgens TP, Göbel H, Sommer C, Straube A, et al. Randomized, multicenter trial to assess the efficacy, safety and tolerability of a single dose of a novel AMPA receptor antagonist BGG492 for the treatment of acute migraine attacks. Cephalalgia. 2014;34(2):103–13.
19. Vincent K, Cornea VM, Jong Y-JI, Laferrière A, Kumar N, Mickeviciute A, et al. Intracellular mGluR5 plays a critical role in neuropathic pain. Nat Commun. 2016;7.
20. Tzschentke TM, De Vry J, Terlinden R, Hennies H-H, Lange C, Strassburger W, et al. Tapentadol hydrochloride. Drugs Future. 2006;31(12):1053–61.
21. Fidman B, Nogid A. Role of Tapentadol Immediate Release (Nucynta) in the Management Of Moderate-to-Severe Pain. Pharm Ther. 2010;35(6):330.
22. Yadav G, Jain G, Samprathi A, Baghel A, Singh DK. Role of preemptive tapentadol in reduction of postoperative analgesic requirements after laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2016;32(4):492.
23. Schaeffer T. Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics. J Med Toxicol. 2012;8(4):400–7.
24. Schug SA, Goddard C. Recent advances in the pharmacological management of acute and chronic pain. Ann Palliat Med. 2014;3(4):263–75.
25. Szallasi A, Sheta M. Targeting TRPV1 for pain relief: limits, losers and laurels. Expert Opin Investig Drugs. 2012;21(9):1351–69.
26. Uchytilova E, Spicarova D, Palecek J. TRPV1 antagonist attenuates postoperative hypersensitivity by central and peripheral mechanisms. Mol Pain. 2014;10(1):67.
27. Ji R-R, Xu Z-Z, Gao Y-J. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13(7):533–48.
28. Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, et al. Evidence for brain glial activation in chronic pain patients. Brain. 2015;138(3):604–15.
29. Gazerani P. Targeting glia in human pain: challenges and opportunities. Future Medicine; 2016.
30. Clark AK, Old EA, Malcangio M. Neuropathic pain and cytokines: current perspectives. J Pain Res. 2013;6:803–14.
31. Mika J, Korostynski M, Kaminska D, Wawrzczak-Bargiela A, Osikowicz M, Makuch W, et al. Interleukin-1alpha has antiallodynic and antihyperalgesic activities in a rat neuropathic pain model. Pain. 2008;138(3):587–97.
32. Jia H, Feng X, Li W, Hu Y, Zeng Q, Liu J, et al. Recombinant human erythropoietin attenuates spinal neuroimmune activation of neuropathic pain in rats. Ann Clin Lab Sci. 2009;39(1):84–91.
33. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med. 2000;32(5):305–16.
34. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, Raja S, et al. Antidepressant Drugs for Prevention of Acute and Chronic Postsurgical PainEarly Evidence and Recommended Future Directions. J Am Soc Anesthesiol. 2014;121(3):591–608.
35. Gilron I. Antidepressant Drugs for Postsurgical Pain: Current Status and Future Directions. Drugs. 2016;76(2):159–67.
36. Russo EB, Hohmann AG. Role of cannabinoids in pain management. In: Treatment of Chronic Pain by Medical Approaches. Springer; 2015. p. 179–95.
37. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8(5):349–61.
38. Xu Z-Z, Berta T, Ji R-R. Resolvin E1 inhibits neuropathic pain and spinal cord microglial activation following peripheral nerve injury. J Neuroimmune Pharmacol. 2013;8(1):37–41.
39. Ji R-R, Xu Z-Z, Strichartz G, Serhan CN. Emerging roles of resolvins in the resolution of inflammation and pain. Trends Neurosci. 2011;34(11):599–609.
40. Visser EJ. A review of calcitonin and its use in the treatment of acute pain. Acute Pain. 2005;7(4):185–9.
41. McCormick Z, Chang-Chien G, Marshall B, Huang M, Harden RN. Phantom Limb Pain: A Systematic Neuroanatomical-Based Review of Pharmacologic Treatment. Pain Med. 2014;15(2):292–305.
42. Chen S, Roffey DM, Dion C-A, Arab A, Wai EK. Effect of perioperative vitamin C supplementation on postoperative pain and the incidence of chronic regional pain syndrome: a systematic review and meta-analysis. Clin J Pain. 2016;32(2):179–85.