

## Preventing and Treating Chronic Disabling Pain After Surgery

Brevik, Harald <sup>(1)</sup>

### Abstract:

**Background:** Chronic postoperative pain (CPP) is an important health problem. This is a narrative review of etiologies, mechanisms, risk factors, means of reducing the risk, and treatment of chronic postoperative pain.

**Methods:** This is a topical review based on a focused literature review and personal clinical experience and research efforts on chronic pain after surgical interventions.

**Results:** CPP is defined as new pain in the area of surgery that lasts more than 3-6 months after the operation, is clearly related to tissue and nerve injuries during the operation and cannot be explained by other etiologies.

The overall prevalence is that 20-40% have some pain and discomfort for a few weeks, 10% have moderate pain that cannot be neglected for a few months, about 1% develop debilitating CPP.

CPP is caused by nerve and tissue injury and abnormal reactions to such injury. Only those who have pre- and peri-operative risk factors determined in part by genetic makeup, reinforced by abnormal pain modulating mechanisms, having chronic pain in other part(s) of the body, having psychological stress factors and catastrophizing thoughts and anxiety, having severe acute pain during and immediately after surgery, chemotherapy or radiation after cancer surgery, and being younger rather than elderly. Risks of CPP can be estimated by a simple scoring system with approximate risk prediction determined by the number and degree of preoperative risk factors.

A number of procedures and drugs can ameliorate these risk factors: Regional and local anesthetic techniques when appropriate, anti-hyperalgesic drugs with nitrous

oxide, glucocorticoids, gabapentinoids, pregabalin more than gabapentin, possibly tricyclic antidepressant, and infusions of lidocaine and ketamine. Important is that the surgeon uses nerve-sparing techniques and operates as "atraumatic" as possible.

Fast-track and vigorous mobilization and rehabilitation of functions after surgery is made possible by expert analgesic and anti-hyperalgesic drugs. Most important is to NOT do unnecessary operations such as cosmetic breast enlargement and meniscectomies for atraumatic knee-meniscus degeneration.

Acute Pain Service, extended to an Acute Pain-Follow-up Service is mandatory to make postoperative pain management optimal and to follow up and treat adequately those unfortunate patients who do develop CPP.

**Conclusions and implications:** CPP is a common complication to well indicated surgery of any type, sometimes developing into a debilitating pain condition. Therefore, evaluation of risk factors before surgery and optimal management during and after surgery is highly important for the patient's GP, his/her surgeon and anesthesiologist. Multidisciplinary pain management clinics are necessary for those unfortunate 1% of all surgical patients who develop complex, chronic postoperative pain.

**Keywords:** Chronic postoperative pain, risk factors, neuropathic pain, peripheral hyperalgesia, secondary hyperalgesia, antihyperalgesic drugs, epidural analgesic, lidocaine, pregabalin, acute pain service, acute-pain follow-up service, pain clinic.

(1) Professor em at University of Oslo, Norway and consultant at Department of Anesthesiology, Rishospitalet and Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway

### Introduction

Long-lasting new pain after an operation is a common, sometimes a debilitating consequence of surgery. We know some factors that increase the risk of developing chronic postoperative pain (CPP). The patients' GP, surgeon, and anesthesiologist must focus on these risks and prioritize efforts to reduce their effects on the postoperative course.

As Rashiq and Dick pointed out recently (1), the earliest practitioners of anesthesia could only pray that their patients survived anesthesia. Later generations, when anesthesia developed into a very safe practice, focused on reducing immediate complications after anesthesia and surgery. They established effective prophylaxis and treatment of acute pain, nausea, vomiting, and venous thromboembolism (2)]. The present generations of anesthesiologists, in collaboration with surgeons, are taking on the challenge of reducing long-term

complications of surgery: Reducing the risk of new, long-lasting, and severe pain after surgery.

### **What is chronic postoperative pain (CPP)?**

CPP is pain in the area of surgery that was not there before the operation, and it lasts more than 3-6 months after surgery. CPP is not a continuation of pain that the patient had in that area before surgery. About ¼ of chronic postoperative pain is nerve-injury pain, i.e. neuropathic pain (3).

### **Etiology and mechanisms of pathogenesis of chronic postoperative pain.**

The pain is caused by nerve and tissue injury. However, nerve injury alone is not sufficient for new pain after surgery to become chronic postoperative pain – other contributing factors and abnormal reactions to the injury are necessary (4). This is clearly demonstrated by the fact that there are many with evidence of nerve damage (hypo- and/or hyper-aesthesia around the scar) who do not have chronic postoperative pain (4,5).

A series of events and reactions to the tissue and nerve injury occurs at many levels of the CNS:

1. Peripheral nociceptive nerve endings become hypersensitive and “silent nociceptors” wake up due to the many pronociceptive components, e.g. prostaglandins and cytokines, in the “inflammatory soup” in the injured tissue. This causes primary hyperalgesia.
2. Secondary hyperalgesia is due to central hypersensitivity reactions in the dorsal horn of the spinal cord and at the brain stem.
3. In the mid-brain – thalamic area negative emotional reactions to incoming nociceptive signals occur.
4. In the cortex cerebri, cognitive modulation or cognitive misinterpretations of the tissue injury occurs, dampening or aggravating the conscious experience of pain.
5. In addition, there are descending inhibiting and facilitating signals from the brain and brainstem to the dorsal horn of the spinal cord. These can again reduce or increase transmission to higher centres in the CNS of incoming nociceptive signals from the injured nerves and tissues (4).

This series of events happens always in all patients having surgery. However, it is only persons with additional risk factors and those who have a genetic makeup that allows or facilitates exaggerated and pathological reactions to nerve and tissue injuries, who will eventually end up with a painful condition that lasts for a long time: i.e. only these unfortunate few patients develop chronic, severe and debilitating postoperative pain (4,6).

### **Prevalence of chronic pain after surgery**

There are several cross-sectional prevalence studies estimating occurrence of long lasting pain after different types of surgery. CPP can follow any type of surgery, but it is more frequent after surgery where tissue trauma is large and where the surgeon cannot avoid injuring nerves (3,4). In the large Tromsø-health survey in Norway, ongoing for more than two decades, pain-issues were included in 2007-8 (5). 13 000 respondents were examined for aspects of pain sensitivity and interviewed about their past health history.

3000 had had surgery during the last 3 years, and 2045 of these persons could be examined in detail: 60% had not had any new pain after their surgery, 40% answered that they did have persistent pain in the area of surgery, 7% had severe pain, 20% had moderate pain, and 13% had only mild pain (5). The round numbers from cross-sectional and prospective studies are approximately like this:

1. Among 100 patients who have had surgery 20-40 will have some (new) pain and discomfort in the area of surgery that lasts for several weeks-months after surgery.
2. About 10 will have moderately intense pain that lasts for several months, and the pain is severe enough that the patient cannot neglect the symptoms, but they are usually able to perform the activities of normal life.
3. However, 1 of 100 surgical patients will unfortunately have severe, disabling pain in the area of surgery that becomes a major problem for every aspects of the patient's life.

### **Known preoperative risk factors for having chronic postoperative pain**

1. Pain in the area of surgery before the operation (4).
2. Chronic pain outside the surgical area before surgery are well-documented risk factors, e.g. low-back pain, migraine, neck pain, and any type of widespread pain (4).
3. Patients who have had a stressful life situation during the months before surgery are at higher risk, and so are patients who have catastrophizing thoughts about the surgery they are about to undergo (7).
4. Younger women have higher risk than older women who have surgery for cancer of the breast (10). Younger men having inguinal hernia repair are at higher risk than elderly men (28). Women are at higher risk than men.
5. Several genetic variants appear to confer higher risks than the general population (6). It is well documented in twin-studies that tendency to have chronic wide-spread pain, headache, low-back pain, migraine, neck pain, and other types of chronic pain have 30-50% heritable causes (8).

### **Known risk factors during surgery**

Clearly, the degree of tissue and nerve injury is important. Nerve-sparing techniques, e.g. laparoscopy compared with open inguinal hernia operations decrease the risk (9). Lymph node dissection has threefold higher risk than sentinel biopsy for chronic pain after breast cancer surgery (10).

### **Known factors immediately after surgery**

1. Inadequate acute pain management and severe postoperative acute pain during the first few days after surgery markedly increases the risk (4, 11).
2. Chemotherapy and radiation therapy after cancer surgery doubles the risk (10).
3. Immobilization aggravates the risk of CPP (4).

### **What can we do to reduce the risk of chronic pain after surgery?**

During anesthesia, the following procedures and drugs are documented to reduce the risk of chronic pain after surgery, as documented in some studies and some types of surgery.

They should be considered in patients who have high risk of developing chronic postoperative pain (see below):

1. Thoracic epidural analgesia during and after thoracotomy and major abdominal surgery (11, 12).
2. Paravertebral nerve blocks during breast cancer surgery (12). Paravertebral block is in fact an epidural plus intercostal nerve, or nerve-roots block (13). It is important to note that paravertebral blocks may have at least as high risk of complications as standard epidural analgesia (13).
3. Intravenous lidocaine at induction (1.5 mg/kg bolus) and as an i.v. infusion (1.5 mg/kg/h) during surgery is likely to reduce risk of prolonged chronic pain after surgery (14).
4. Nitrous oxide (70%) inhalation during general anesthesia reduces the risk (15), possibly because nitrous oxide has an NMDA glutamate receptor antagonist effect (like ketamine).
5. Ketamine i.v. in a low bolus dose and infusion during and after surgery reduces secondary hyperalgesia after surgery (17), and there is some evidence that it may reduce the risk of chronic pain after surgery (16).
6. Glucocorticoids, such as dexamethasone and methylprednisolone have potent and prolonged relieving effect on acute pain after surgery (18, 24), and there is some evidence that the risk of chronic pain is reduced as well (18, 19).
7. Pregabalin, and possibly gabapentin, given before surgery and for several days after surgery are documented to reduce the risk of chronic pain (16, 20). Pregabalin is rapidly and completely absorbed when taken orally and need to be taken only twice daily. Compared with gabapentin, pregabalin has a rapid onset of relieving effect on neuropathic pain – seen already after a few days in many patients (21). Gabapentin is slowly absorbed from the gastrointestinal tract, and when using gabapentin to relieve neuropathic pain, it can take up to two months before any effect is evident, while side-effects like sedation and dizziness often appear after the first dose (21). Therefore, whereas the mechanisms of action are similar for the two gabapentinoids, the pharmacokinetics of pregabalin are superior to those of gabapentin. But gabapentin is cheaper than pregabalin.

### Immediate postoperative drugs and procedures

Acute postoperative pain must be relieved effectively for fast track mobilization and rehabilitation of functions to be possible. No doubt epidural analgesia and peripheral nerve blocks are the most effective for relieving pain during movement and mobilization of the patient after major surgery (22). Immobilization, also when due to unrelieved pain on movement, increases the risk of abnormal pain modulation in the CNS (23). Glucocorticoids have a very marked effect on acute pain after surgery (18, 22, 24), and they should be used routinely because there are almost no adverse effects from one or two boluses of dexamethasone, betamethasone, or methylprednisolone. There may be a transient increase in blood glucose concentration, and also in the patients' mood, but there is no increased risk of wound-infection, and the healing process goes on unhindered (22, 24).

Remember that methadone is an effective and very safe

opioid for routine postoperative pain management, with the additional advantage of having NMDA-antagonist effects (like ketamine) (25). An i.v. bolus of 15-20 mg will be sufficient for pain relief for about 48 hours, in most patients, with a few additional bolus doses of 1-3 mg i.v., as required in the early post-anesthesia recovery period (25).

Those patients, who have one or more of the now well-documented risk factor for developing chronic pain after surgery, are candidates for one or more of the antihyperalgesic drugs mentioned above, also in the immediate postoperative period. Pregabalin, a very safe drug, should be considered to high-risk patients whenever oral drug administration is possible – see above. Other drugs with few side effects and possible beneficial effects on the risk of chronic pain, such as Vitamin C, should also be considered in the patients who have a high-risk of CPP.

For acute pain management to be available and optimal for all patients after surgery, an acute pain service (APS) is needed in all hospitals doing surgery (22). The value of an APS cannot be overestimated in view of the importance of reducing the risk of CPP which can occur after any type of surgery causing severe acute pain.

### Predicting the risk of developing chronic pain after surgery

Two scoring systems have been developed, one for surgery in general (26), and one for women to undergo surgery for breast cancer (27). The latter takes into account most risk factors for chronic pain that are known for breast cancer patients, a special high-risk group of patients.

The Althaus et al (26) score is based on the five risk factors with the best evidence base:

Estimating risk of chronic pain after surgery based on 5 known risk factors:

Risk factors	Score
1. Stressful life-conditions 6 months prior to surgery	= (1)
2. Preoperative pain in surgical area	= (1)
3. Preoperative pain distant from surgical area	= (1)
4. Signs of stress reaction right before surgery	= (1)
5. Average pain score >5/10 on days 1-5 postoperative	= (1)

Maximum Sum score is 5 = 70% risk of chronic pain after surgery

Sum score 0	=	12% risk of chronic pain after surgery
Sum score 1	=	30% risk of chronic pain after surgery
Sum score 2	=	40% risk of chronic pain after surgery
Sum score 3	=	50% risk of chronic pain after surgery
Sum score 4	=	60% risk of chronic pain after surgery
Sum score 5	=	70% risk of chronic pain after surgery

Using this simple scoring system, the anesthesiologist and the surgeon in charge of the patient should be able to select patients who are at considerable risk of developing long-lasting and severe pain after an operation. These patients must receive special attention and all the abovementioned procedures and drugs that can be applied without decreasing safety of anesthesia and surgery should be considered. These

patients must be given special attention and monitoring for up to several weeks after surgery. Patients who have abnormal pain intensities and clearly have components of neuropathic pain 6 weeks after surgery, have a much increased risk of having such pain also 3 and 6 months after surgery (18).

### **Acute Pain Service (APS) and Acute Pain Follow-up Service (or Sub-acute Pain Service)**

All hospitals doing surgery should have an Acute Pain Service team (APS) as described by Breivik et al (22). Recently these APS teams are being extending into Acute Pain-follow-up teams [Michele Curatolo and Eija Kalso, personal communications]. They continue to have special attention on patients who have the recognized risk factors and keep on having abnormal pain and sensory findings: Hypo-phenomena (hypo-aesthesia for pinprick, cold or warm stimuli, cotton or brush-stimuli) as well as hyper-phenomena (mechanical, dynamic allodynia, or cold- and/ or warm-allodynia, temporal summation) in the weeks following surgery (18, 29). Those who have clear symptoms and signs of neuropathic pain at 6 weeks, frequently have such pain also 3 and 6 months after surgery (18).

It is more likely that we can influence the long-term outcome if we treat and manage the pain conditions of these patients aggressively early on with drugs and procedures that are documented to have beneficial effects on neuropathic pain. If patients have been neglected, or they may even have been told by ignorant health care providers that the pain will soon subside naturally, they may have a high risk of suffering for many months and years after surgery, from a treatment-resistant pain that they did not have before that operation.

### **What is the long-term prognosis of chronic postoperative pain?**

There is one long-term follow-up study of a large number of patients with chronic pain after inguinal hernia repair (28): In a national registry of inguinal hernia repair in Sweden comprising more than 140.000 patients since 1992, a survey was undertaken by Professor Torsten Gord's Pain Centre at Uppsala University Hospital. They surveyed patients living in the Uppsala County in Sweden. From data of 2834 hernia repairs (in 2583 patients), they were able to estimate a decline by 50% in pain during a bit more than 6 years. These are important observations, and we can tell the patients with some confidence that with time, their pain will gradually decrease. However, if re-operations are done, in order to explore and "look for a cause of the pain" in the scar, chances are that the patient will have even worse pain after such a re-operation (28). There are occasional indications for surgery, when there are convincing signs that a localized peripheral nerve entrapment in scar tissue contribute to the pain. However, expert surgeons in collaboration with clinical neurophysiologists [Henrik Kehlet, personal information] should do such re-operations.

### **Most important is to avoid all unnecessary surgery.**

This may seem like an unnecessary statement. However, there are many cases reported in the literature of patients ending up with a disabling chronic postoperative pain condition after surgery that was not indicated. A striking example is the large numbers of cosmetic breast augmentation operations being done in affluent societies: In Norway about 5% of young

women have silicone implants into their breast – for purely self-esteem-increasing purposes. That effect is at best only short lasting. Unfortunately, 20-40% have pain and discomfort 3 years later, 1-2% have severe and disabling pain after this completely unnecessary type of surgery (18, 29). If rumors are correct, in Brazil parents give their teenage daughters the price of such a cosmetic operation as a birthday gift!

A similar situations occurs with patients without osteoarthritis but with symptoms of a degenerative medial meniscus tear: In a double blind trial in Finland published in 2013 the outcomes after arthroscopic partial meniscectomy were no better than those after a sham surgical procedure (30).

### **Conclusions and implications**

About 10% patients having surgery will suffer from prolonged pain and discomfort, about 1% will suffer severe disabling persistent pain after surgery.

We must screen patients before surgery for the well-known risk factors of chronic pain after surgery and those we find are at risk of developing CPP we must treat appropriately with drugs and procedures that are safe and at least somewhat effective in reducing the risk for chronic pain after surgery.

Those who still end up with severe neuropathic pain after surgery should receive treatment with drugs and procedures that have some proven effect on neuropathic pain (21).

There are many complications and negative consequences of suffering from persistent pain with no specific and universally effective treatment. These patients receive the best help from a multidisciplinary pain management team (31). A medical doctor who is a pain specialist is the most important member of such a pain clinic, but (s)he will need the assistance of an expert and experienced pain physiotherapist, a psychologist or psychiatrist, a social worker, an occupation therapist, and a family-therapist. Even in the best of hands, not more than about half of the patients are helped back to better quality of life (31). This fact underscores the importance of focusing on preventing chronic postoperative pain.

**Autor(es) no declaran conflictos de interés en el presente trabajo.**

Correspondencia:  
Harald Breivik  
Professor em at University of Oslo, Norway  
and consultant at  
Department of Anesthesiology, Rishospitalet  
and Department of Pain Management and  
Research, Oslo University Hospital, Oslo,  
Norway

Email: harald.breivik@medisin.uio.no  
Fax: +47 23073690  
Tele: +47 95865323

## References

- (1) Rashiq S, Dick BD. Post-surgical pain syndromes: a review for the non-pain specialist. *Can J Anaesth* 2013; Nov 2. (Epub ahead of print). PMID:24185829
- (2) Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand* 2010; 54:16–41.
- (3) Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent post-surgical pain: a systematic literature review. *Pain* 2013;154:95-102.
- (4) Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006;367:1618-25.
- (5) Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study. *Pain* 2012;153:1390-6.
- (6) Costigan M, Belfer I, Griffin RS, et al. Multiple chronic pain states are associated with one amino acid-changing allele in KCNS-1. *Brain* 2010;133:2519-27
- (7) Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain*. 2012;28:819-41
- (8) Nielsen CS, Knudsen GP, Steingrimsdóttir ÓA. Twin studies of pain. *Clin Genet* 2012;82:331-40.
- (9) Aasvang EK, Gmähle E, Hansen JB, Gmähle B, Bittner R, Kehlet H. Predictive factors for persistent postoperative pain – the Copenhagen – Stuttgart hernia study. *Anesthesiology* 2010;112:957-69.
- (10) Mejdahl MK, Andersen KG, Gärtner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. *BMJ Open* access 2013 April 11;346:f1865.
- (11) Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain* 1996;12:50-5
- (12) Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. *Br J Anaesth* 2013;111:711-20.
- (13) Norum H, Breivik H. A systematic review of comparative studies indicates that paravertebral block is neither superior nor safer than epidural analgesia for pain after thoracotomy. *Scand J Pain* 2010;1: 12–23.
- (14) Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. *Clin J Pain*. 2012;28:567-72.
- (15) Chan MT, Wan AC, Gin T, Leslie K, Myles PS. Chronic postsurgical pain after nitrous oxide anesthesia. *Pain* 2011;152:2514-20.
- (16) Caparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *The Cochrane Library* 2013, Issue 7;1-110.
- (17) Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand*. 1997;41:1124-32.
- (18) Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty: Long term effects of preincisional administration of methylprednisolone. *Pain*. 2006;124:92-9.
- (19) Rasmussen S, Krum-Møller DS, Lauridsen LR, Jensen SEH, Mandøe H, Gerlif C, Kehlet H. Epidural steroid following discectomy for herniated lumbar disc reduces neurological impairment and enhances recovery. A randomized study with two year follow-up. *Spine* 2008;33:2028-33.
- (20) Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110:199-207.
- (21) Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2010;85(suppl):S3-S14.
- (22) Breivik H, Curatolo M, Niemi G. How to implementing an acute postoperative pain service: an update. In: Breivik H, Shipley M, eds. *Pain Best Practice and Research Compendium*. London: Elsevier, 2007; 255–70.
- (23) Terkelsen AJ, Bach FW, Jensen TS. Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia. *Anesthesiology*. 2008;109:297-307.
- (24) Romundstad L, Breivik H, Niemi G, Helle A, Stubhaug A. Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. *Acta Anaesthesiol Scand*. 2004;48:1223-31.
- (25) Kharasch ED. Intra- and post-operative methadone: Rediscovery, reappraisal, and reinvigoration. *Anesthesiology* 2011;112:13-6.
- (26) Althaus A, Hinrichs-Rocker A, Chapman R, Arránz Becker O, Lefering R, Simanski C, Weber F, Moser KH, Joppich R, Trojan S, Gutzeit N, Neugebauer E. Development of a risk index for the prediction of chronic post-surgical pain. *Eur J Pain*. 2012;16:901-10.
- (27) Sipilä R, Estlander A-M, Tasmuth T, Kataja M, Kalso E. Development of a screening instrument for risk factors of persistent pain after breast cancer surgery. *Brit J Cancer* 2012;107:1459-99.
- (28) Sandblom G, Kalliomäki M-L, Gunnarsson U, Gordh T. Natural course of long-term postherniorrhaphy pain in a population-based cohort. *Scand J Pain* 2010;1:55–9.
- (29) von Sperling ML, Høimyr H, Finnerup K, Jensen TS, Finnerup NB. Persistent pain and sensory changes following cosmetic breast augmentation. *Eur J Pain* 2011;15:328-32.
- (30) Sihvonen R, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TLN. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515-24.
- (31) Heiskanen T, Roine RP, Kalso E. Multidisciplinary pain treatment—Which patients do benefit? *Scand J Pain* 2012;3:201–7.