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Chronic pain patient and anaesthesia

"Pain is inevitable, suffering is optional"
(Buddhist proverb)

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Abstract

Severe chronic pain is often devastating for the affected individuals causing substantial suffering, health impairment, and a very low quality of life, including significant negative consequences for the patient and for society. Patients with complex pain disorders are seen often in relation to anaesthesia. They deserve special attention and require long time hospitalization and multiple contacts with health-care providers after discharge from hospital. A wider adoption of best perioperative and intraoperative pain management practice is required. This paper reviews current knowledge of perioperative and intraoperative pain management and anaesthetic care of the chronic pain patient. The individual topics covered include the magnitude of the problem created by chronic pain, the management of the patients taking various types of opioids, tolerance and opioid induced hyperalgesia and the multidisciplinary approach to pain management. The preventive and preemptive strategies for reducing the opioid needs and chronic pain after surgery are reviewed. The last section includes the role of acute pain services and an example of the implementation of a transitional pain service with the various benefits it offers; for example, the decrease of the opioid dose after discharge from the hospital. Patients also receive the continuity of care, with not only pain relief but also improvements in physical functioning, quality of life and emotional stress.

Keywords: pain, chronic pain, anaesthesia, perioperative pain treatment, acute pain services, transitional pain services

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Introduction

Physical pain is unavoidable but in patients with chronic pain, the levels of pain are correlated with negative thinking. Severe chronic pain is often devastating for the affected individuals and causes substantial suffering, health impairment, and a very low quality of life, including significant negative consequences for their psychological and social function. The economic consequences are often severe, since few patients with severe pain conditions manage to obtain or keep a job. For society, the chronic pain problem represents a heavy burden, including resources for sick leave, disability retirement, health care costs and productivity loss.

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The magnitude of the problem

Chronic pain is a major health problem in Europe and a challenging issue for anaesthesiologists. In a large scale computer-assisted telephone survey with 46,394 respondents from 15 European countries and Israel, Breivik et al. [1], reported that 19% of the population suffered from chronic pain, defined as pain for more

than 6 months. 61% of the patients with pain were unable to work outside their home; 19% had lost their jobs and 60% had visited their doctor about 2-9 times in the last six months. Only 2% of those patients were managed by pain specialists and nearly half received inadequate pain management. Using a large general population-based sample [2] (N = 52,095) from 19 countries including Romania (N = 2346), chronic back/neck pain affected 20 to 30% of the general adult resident population. In both studies psychiatric comorbidity was strongly associated with chronic pain. Differences between countries are observed in managing chronic pain, related to differences in cultural background and local traditions in managing chronic pain in Europe. There is also a lack of published literature evaluating chronic pain in Eastern European Countries including Romania. Looking at the consumption of analgesics, there are huge differences regarding different countries with strong opioids commonly prescribed in Western Europe whereas in the Eastern European countries the consumption is comparatively low (Figure 1).

The data from the Pain & Policy Studies Group (PPSG) regarding the consumption data for 6 principal opioids used to treat moderate to severe pain indicated an increasing consumption of opioids, mainly of fentanyl, a potent μ synthetic opioid receptor agonist known to give rapid tolerance and often rapid opioid addiction. Fentanyl stayed quietly under the radar for decades being used primarily in anaesthesiology practice i.v. but we have begun to see more use of fentanyl in the treatment of chronic pain as transdermal patches. Therefore, the recent protocols for pain treatment excluded the use of this drug from the treatment of chronic non-malignant pain. In practice it is occasionally still used by some pain management specialists due to the advantages of delivering a steady dose and improving patient compliance. However, intoxication secondary to intentional and unintentional misuse and abuse has been widely reported in the literature.

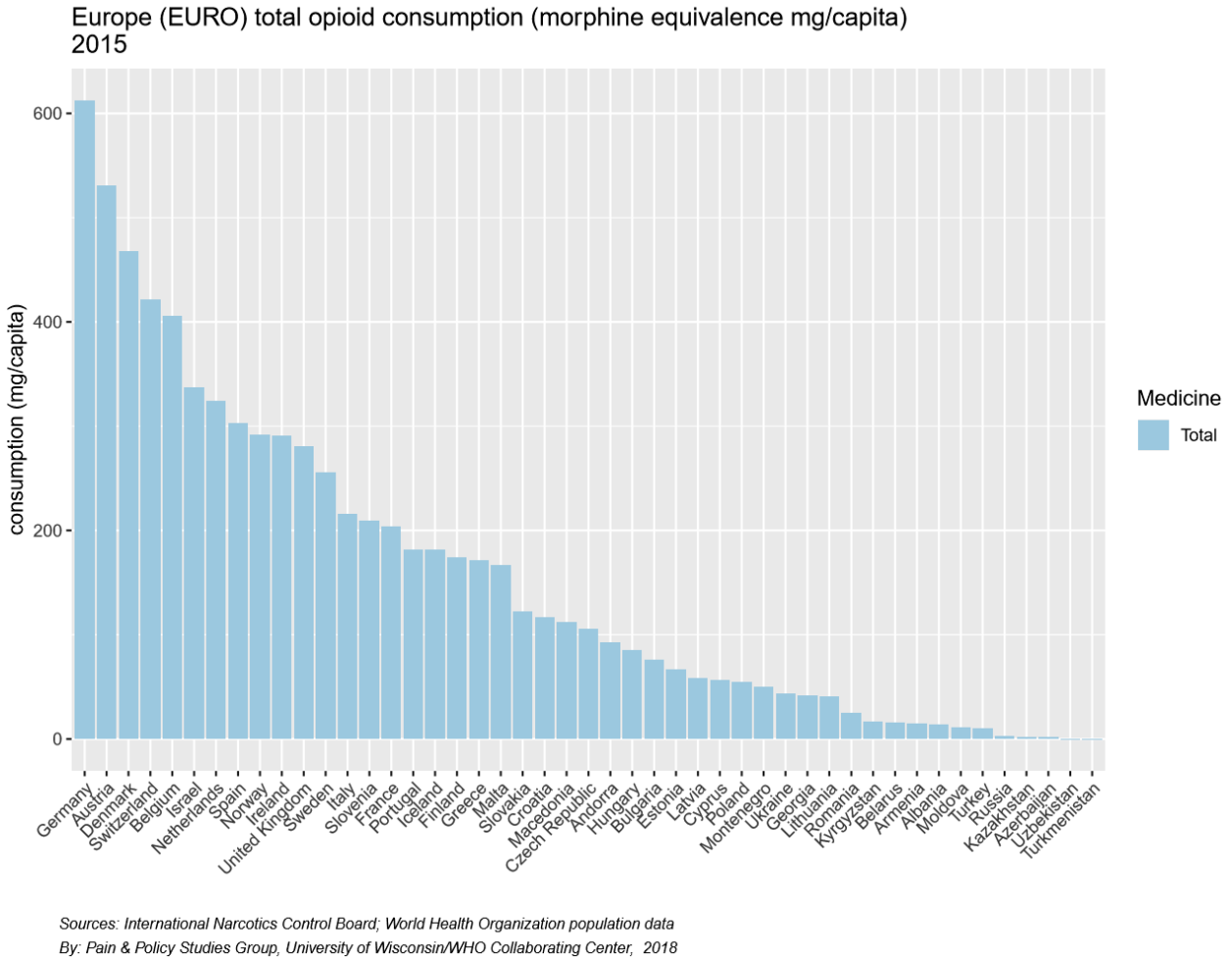

Fig. 1. Total opioid consumption in Europe (in morphine equivalence mg/capita without methadone) in 2015. Source: International Narcotics Control Board, World Health Organization (WHO) population data. Created using the Custom Consumption Graphs for Opioid Medicines [3] by: Pain and Policy Study Group, University of Wisconsin/WHO Collaborating Center, 2018

As the number of patients for whom opioids on a long-term basis has grown rapidly over the last decade, anaesthesiologists are likely to encounter with increasing probability in their clinical practice opioid users and abusers who require surgical treatment and adequate perioperative analgesia.

Perioperative considerations for patients with chronic opioid use

The treatment of chronic pain with opioids carries risks of side effects and possible drug interactions that need to be monitored in the perioperative settings. Underlying central sensitization, increased nociception and opioid-induced hyperalgesia are some of the pathogenic mechanisms which interact with the preoperative chronic opioid use and acute postoperative pain. Chronic pain patients are more sensitive to painful conditions, making it more challenging to treat them postoperatively [4]. Patients taking opioid medication are more sensitive to pain and the opioid induced vulnerability may persist long time after opioid withdrawal [5]. While mechanisms are not fully understood, chronic opioid use may enhance pain by increased DNA methylation [5]. Chronic pain patients treated with low doses of opioid had an increased risk for postoperative pain at rest and walking after total knee arthroplasty (TKA) [6, 7] and hyperalgesia before surgery [7]. Preoperative opioid use is the strongest predictor of persistent postoperative opioid use [8]. Preoperative opioid dependency is also a risk factor for uncontrolled and problematic pain after surgery, requiring multiple follow-ups by acute pain services in an academic hospital [9]. Cozowicz et al. [10], demonstrated that higher opioid prescription was associated with a dose-response increase in most postoperative complications with the strongest effect observed in thromboembolic, infectious and gastrointestinal complications. Chronic opioid use is a risk factor for outcome after surgery: chronic opioid users who taper their dose before surgery achieved significantly improved outcomes compared with those who did not taper [11]. These results highlight the need to decrease opioids before surgery in patients with chronic opioid use. Even a small decrease of opioids preoperatively for at least a month before surgery may result in a reduced intake of intra- and postoperative opioids and may improve pain after surgery. Therefore, these patients should be assessed well in advance of surgery.

Preoperative assessment of opioid tolerant patients

As opioid medication use for treatment of chronic non malignant pain has increased, there has been increasing evidence for unintended pronociceptive consequences of long-term use of opioids such as opioid-induced hyperalgesia (OIH) and opioid tolerance. The paradoxical worsening of pain sensitivity without a new injury or exacerbation of an old injury is called opioid-induced hyperalgesia-OIH [12]. Tolerance is characterized by a progressive lack of response to opioids that can be overcome by increasing the dose [13]. Both mechanisms lead to the decreased efficacy of opioid analgesic effects. Opioid tolerance may be suspected in all patients treated with opioids for a long time. Opioid tolerance may be assumed to be present with a daily intake per oral opioid equivalent over 72 mg for one month (Table 1) or morphine intravenously 1 mg/h for one week [14, 15]. "As-needed" dosing is usually not associated with tolerance. Opioid-tolerant patients may have significantly higher opioid requirements than opioid naive patients, but the risk of adverse events increase proportionally with the opioid dose. Patients receiving more than 50 mg per day equivalents of morphine have a 3.7 fold increase in the risk of an overdose and the patients using 100 mg per day morphine equivalents have a 8.9 fold increased risk of an overdose, compared with patients receiving doses under 20 mg morphine equivalent a day [16].

Patients on long-term opioid therapy should take their usual opioid dose in the morning of surgery (including methadone and buprenorphine) or as a premedication before surgery [17]. The patient's preoperative opioid dose continues through the day of surgery by intra- and postoperative opioid administration. Besides the prescription of the patient's preoperative opioid dose, at least 30-100% more opioid than the preoperative daily dose may be required additionally per day for chronic opioid users and based on the patient's pain estimation. Bolus doses of one-sixth of the total daily dose are given to treat acute pain breakthroughs. However, assessment of the exact opioid dose is difficult and requires adjustment after

Table 1. Minimum opioid tolerant daily doses (revised after *Shands at the University of Florida. Drugs & Therapy Bulletin*)

Codeine oral – 150 mg per day	Fentanyl patch – 25 mcg transdermal/day	Equianalgesic daily doses of another opioid
Hydromorphone oral – 8 mg per day	Pethidine i.m. – 75 mg per day	Oxymorphone oral – 25 mg per day
Methadone oral – 20 mg per day	Methadone i.m. – 10 mg per day	Tapentadol (Palexia) oral – 150 mg per day
Morphine oral – 60 mg per day	Oxycodone oral – 30 mg per day	Buprenorphine patch – 30 mcg transdermal/day

the patient's pain according to pain rating scales. Intraoperatively the opioid-tolerant patients may have much higher than expected additional intraoperative opioid requirements and are at an increased risk of awareness [18]. Transdermal opioid administration continues during surgery but the patch should be moved from the surgical area and from warming devices, as the heat may accelerate drug release. When this is not possible, the same morphine equivalents as in the transdermal patch may be given as long acting opioids or be replaced with an infusion [19].

Methadone is the leading opioid in death related to opioid administration due to prolonged QT time, arrhythmias and interaction with different drugs. Special attention should be given to older patients (> 70 years of age), those with sleep apnea, patients on drugs that may influence methadone metabolism (induce or inhibit cytochrome CYP2B6 such as for example, ondansetron, some antidepressants and antimycotic antibiotics), and patients with significant underlying diseases (pulmonary, cardiac). Methadone should not be increased preoperatively and the ECG and, if possible, methadone blood concentration should be checked preoperatively. If the patients cannot take methadone orally, half of their daily dose should be administrated intravenously (Conversion rate 1:2) [20]. The methadone dose i.v. is given from a one time daily dose used for addiction maintenance divided into three times dosing schedule that would benefit pain control.

Buprenorphine is a partial agonist at the μ-opioid receptor (MOR) and an antagonist at k receptors [21, 22]. Conflicting recommendations exist as to whether buprenorphine should be continued or ceased in the perioperative period. Continuation of buprenorphine throughout the perioperative period is recommended in day case surgery with additional opioids given as required for the management of acute pain [17]. At higher doses, buprenorphine is able to displace full opioid agonists, such as morphine and methadone, from the receptor [23]. Due to buprenorphine's relatively long half-life (25 to 45 hours), slow elimination from body (2-3 days) and slow dissociation rate (166 minutes), some protocols recommended to decrease buprenorphine gradually over 2 to 4 weeks prior to surgery, allowing buprenorphine to be fully cleared from the body well before surgery [24]. The use of a buprenorphine patch (up to 70 μg h^{-1}) and also buprenorphine sublingual in lower doses than 10 mg (divided in two to three equal doses) is unlikely to interfere with the use of full opioid agonists for acute pain management and these should also be continued in the perioperative period with additional opioids given as required.

Opioid-sparing techniques

"The greatest evil is physical pain. Saint Augustine"

Woolf and Chong [25] demonstrated that "simple changes in the timing of treatment can have profound effects on postoperative pain". Despite highly effective in relieving postoperative pain, opioids often do not contribute to postoperative recovery and rehabilitation but cause opioid related adverse effects [26]. During the last 20 years there has been an increasing use of a wide range of analgesic interventions in acute pain initiated before and during surgical procedures in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure and reduced opioid use and opioid side effects such are hyperalgesia and tolerance [26]. These observations have led to the concept of "multimodal" or "balanced" analgesia [27] (a combination of analgesic medication and techniques with different sites or mechanisms of actions in order to improve analgesia, while reducing the requirements for opioids and thereby lessening adverse effects) [27].

Long before the surgery, a clear multi-disciplinary management plan has to be created with the involvement of the chronic pain patient. Opioid-sparing techniques may be of particular importance in patients taking strong opioids (Table 2). The most important components of multimodal analgesia are regional anaesthesia and local anaesthetic pain relief which can be applied wherever possible to reduce opioid needs. The efficacy and safety of peripheral regional anaesthesia has been increased by the use of ultrasound guidance. Although previous studies demonstrated no analgesic benefit for pre-emptive compared with post-incisional administration of NSAIDs [28], acetaminophen remains an important non-opioid analgesic in postoperative analgesia for preventing nausea and vomiting when used preoperatively [29, 30] and has a synergistic effect with NSAIDs and Coxibs [31]. Perioperative ketamine decreases postoperative pain scores, reduces postoperative opioid requirements and reduces postoperative nausea and/or vomiting [32]. It also reduces the risk of chronic pain in the first 3-6 months after operation [33]. The benefit of gabapentinoids, pregabalin in the treatment of opioid-naive patients without neuropathic pain for routine acute pain management is uncertain. However, gabapentinoids may have a role in opioid-tolerant patients as an opioid-sparing adjunct [34, 35]. Lidocaine has been demonstrated to decrease pain scores and opioid analgesic consumption in patients with poorly controlled pain, previous substance abuse or when an epidural is contraindicated or failed, as in laparoscopic surgery or trauma [36].

Table 2. Opioid-sparing techniques

Intervention	Type/Dose	Effects	Side effects
Local anaesthetic techniques	• Peripheral plexus catheter should be used in extremity surgery • Epidural anaesthesia (EDA) can be used in bilateral extremity surgery or thoracotomy/ laparotomy • Transversous abdominal plane block can be used in laparotomy if the patient is not suitable for EDA • Wound catheters can be used when EDA is not possible	Local anaesthesia is advantageous in opioid dependent patients, potentially obviating the need for additional opioids EDA decreases with 50% the need of continuously infusion opioids	Peripheral nerve blocks may induce nerve injury and/or neuropathy due to potential toxicity of local anaesthetics or due to a nerve lesion for needle trauma or infection The risks of epidural anaesthesia in unexperienced hands are already known
Acetaminophen (Paracetamol)	1 g × 4 for adults 1 g × 3 for older patients	Reduces opioid [29] requirement by 20-30% Beneficial effect on postoperative nausea and vomiting as used pre-operatively, synergistic effect with NSAIDs [30] and Coxibs [31]	Minimal adverse effects Care has to be taken in patients with severe liver insufficiency
NSAIDs Coxibs	Ketorolac 30 mg Celecoxib 400 mg	Have opioid-lowering effect and good pain relieving effect, especially in combination with paracetamol	Care has to be taken regarding renal, hepatic and gastro-intestinal side-effects
Gabapentin Pregabalin	• 100-300 mg once daily p.o. or via gastro-intestinal tube, then increases with 100-300 mg each day to 600 mg × 3 • 50-75 mg p.o. once daily or via gastro-intestinal tube, then increases with 50-75 mg each day to 150 mg × 2	Indicated in patients with neuropathic pain No benefit in enhanced recovery [34] The benefits of using gabapentin and pregabalin is uncertain in opioid sparing techniques	Both increase risk of postoperative sedation
Ketamine	• After induction, bolus dose is given 0.25-0.5 $mg \cdot kg^{-1}$ • Continuous infusion 0.25 $mg \cdot kg^{-1} h^{-1}$ (at expected moderate pain) • Continuous infusion 0.5 $mg \cdot kg^{-1} h^{-1}$ (at expected moderate pain) • Stop infusion 30 minutes before extubation • Postoperative continuous infusion 0.08-0.16 $mg \cdot kg^{-1} h^{-1}$ (for the patients who can be monitored on the ward)	Ketamine reduces opioid need and inhibits the development of OIH (opioid induced hyperalgesia) Reduces postoperative nausea and vomiting	Psychotomimetic effects (hallucinations, agitation, anxiety, dysphoria, and euphoria)
Magnesium	Bolus dose at induction or during maintenance Infusion 40-50 $mg \cdot kg^{-1}$	Reduces opioid dose and pain estimation up to 24 hours postoperatively	Bradycardia May prolong the duration of non-depolarizing muscle relaxants, therefore TOF measurement is recommended
Lidocaine	The dose of i.v. lidocaine [36] necessary for analgesia in the perioperative period is 1-2 $mg \cdot kg^{-1}$ as an initial bolus given slow in 2-4 min followed by a continuous infusion of 1.5 $mg \cdot kg^{-1} h^{-1}$	Potent anti-inflammatory, anti-hyperalgesic, and gastrointestinal pro-peristaltic drug Decreased pain scores, opioid analgesic consumption, and side-effects	Symptoms and signs of toxicity Adverse effects on cardiac conductivity, myocardial contractility, and precipitate partial or grand mal seizures
Clonidine	Recommended as premedication 75 µg p.o. or continuously i.v. postoperative 0.1-0.3 µg $kg^{-1} h^{-1}$	Reduces withdrawal Potentiates morphine effects	Hypotension Bradycardia Sedation
Dexmedetomidine	Continuously postoperative 0.3-0.8 mg $kg^{-1} h^{-1}$	Reduces opioid use up to 24 hours postoperatively	Hypotension Bradycardia Sedation
Dexamethazone	8 mg i.v. preoperatively	Reduces postoperative pain and opioid needs up to 24 hours postoperatively Less fatigue after operation	Elevated blood sugar

Postoperative phase

Current evidence supports the use of multimodal analgesia in the setting of postoperative pain for chronic pain patients. Thus the recommendations for perioperative pain continue in the postoperative period. For some patients with a risk of increased postoperative pain after major operations it is important to take control over their treatment with the help of patient-controlled analgesia (PCA) or patient-controlled epidural anal-

gesia (PCEA). Patient-controlled analgesia is recommended postoperatively being a useful way of delivering opioids as it allows self-titration and minimizes the risk of under-dosing. PCA permits a patient to self-deliver a small bolus of opioid to achieve prompt relief without over sedation. Unfortunately, PCA is a difficult method since predicting the total dose in opioid-tolerant patients is difficult and also it is an inappropriate method in patients with evidence of cognitive dysfunction or physical disabilities which make the use of the patient-controlled device impossible. The disadvantage with PCA is that the patient with anxiety uses this technique as a way of distraction, pressing the button even in the absence of pain. Transcutaneous electrical stimulation, acupressure, or acupuncture and other non-pharmacological interventions such as hypnosis, psychotherapy, can be utilized in some patients.

The aim of multimodal analgesia is not only to improve analgesia but also to reduce opioid dose and opioid side effects [26]. Recent evidence suggests that opioids produce long-lasting effects on neural circuits, such as pain exacerbation and hypersensitivity that last for years after methadone withdrawal and the contribution of opioids to chronification [37]. Patients with a high opioid dose postoperatively are at a greater risk of developing opioid induced hyperalgesia (OIH) in which the pain is worse with escalations in the dose of an opioid. The treatment of OIH is to reduce the opioids and should be differentiated from opioid tolerance in which the increase of the dose of the opioids would attenuate pain. Opioid rotation is a clinically useful technique that involves switching from one opioid preparation to another to utilize incomplete cross tolerance. The "new" opioid dose should be reduced by 25-50%. Useful preparations for opioid rotation in these cases are buprenorphine transdermally or sublingually with moderate opioid doses. Tapentadol can be another option [22]. In high dose opioid use, which means > 200 morphine equivalents/day, buprenorphine dosing may be 2-8 mg/day. Another option is methadone, but here the dose is individual and careful dose and titration necessary. All measures to reduce opioid doses postoperatively should be taken, including the use of ketamine with and without dexmedetomidine, a selective centrally acting alpha 2 agonist, which could reduce morphine consumption [38].

For extreme cases with severe pain and very high doses of opioid, more than 500-1,000 morphine equivalents, an anaesthesia assisted rapid detoxification can be performed using ultra low dose naloxone 0.5 μg/kg/h in infusion for 12-24 hours in combination with an alpha 2 agonist in the form of clonidine or dexmedetomidine. For this, routine sedation with propofol and intensive care monitoring of vital functions is often required [39].

For opioid-tolerant patients the doses of opioids may need to be increased by 30-50% over baseline preoperative levels administered orally or as a continuous infusion.

Organization of acute pain services (APS) and the transitional pain services

The effective relief of pain is of the utmost importance to anyone treating patients. The treatment of the complicated pain patient with chronic pain is not possible without the contribution of acute pain services (APS). These services were introduced by Brian Ready in 1988 and called anaesthesiology-based acute pain services [40]. Although the initial target of APS was to improve postoperative pain, the role of this service includes today not only the treatment of acute pain, but also the treatment of acute and chronic pain attributed to both medical and surgical patients and the follow-up of the patient's pain at home [9]. The pain treatment instituted by the acute pain services induced reduction in pain intensity in both medical and surgical patients [9]. APS still vary greatly between countries. In Uppsala University Hospital pharmacological pain therapy is followed-up on a daily basis by physicians and all the staff members on the wards are educated by APS pain nurses in the management of systemic PCA. In special cases, such as patients with unsuccessful pain management (with intensity over 6 NRS despite treatment instituted by the ward, chronic pain patients on high doses of opioids or substance abuse patients), the patients are referred to a pain specialist. To address the problem of chronic pain after major surgery through multidisciplinary, integrated care beginning preoperatively, extending postoperatively and continuing after hospital discharge, so called transitional pain services were developed [41]. Their mission is to offer effective treatment to patients at a high risk of developing chronic postsurgical pain after undergoing a variety of surgical procedures. The early identification of these complex patients (Table 3) by surgeons and preoperative pain assessment staff is highly recommended and includes multimodal medication optimization before surgery and can facilitate forward planning and ample time to involve the experience of others (e.g. anaesthetists, pain specialists, psychologist, GP, occupational therapists, psychologists and physiotherapists etc.).

Conclusion

Patients with chronic pain deserve special attention and require long time hospitalization and multiple contacts with health-care providers after discharge from hospital. In summary, this review supports the

Table 3. Transitional Pain Service referral criteria (*revised from Katz et al 2015*)

Preoperative criteria	Postoperative criteria
• Chronic pain in patients with or without opioid use • High preoperative opioid consumption • Patients who consume more than 100 mg/day of oral morphine equivalents given high requirement for opioid weaning assistance after discharge • Patients admitted to the hospital with methadone or buprenorphine • Psychiatric comorbidities	• Patients with intense pain, who continue to be seen by the APS beyond the expected trajectory • Patients with complex pain situation and severe postoperative pain unable to be discharged • Patients discharged with high opioid consumption • New neuropathic pain • Prolonged postoperative pain disturbing ADL or sleep • Postoperative pain is severe and patient has risk factors for chronification (preop. pain, anxiety, new nerve lesion, severe acute pain, certain operations e.g. TOS, thoracotomy, amputation etc.)

need for a close follow-up of chronic pain patients in relation to anaesthesia offering them a coordinated care by a multidisciplinary team.

Conflict of interest

Nothing to declare

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