

REVIEW ARTICLE

Perioperative pain therapy in opioid abuse

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Opioid addiction represents an exaggerated organic and psychological comorbidity and should be regarded as a high-risk problem. Particular features seen perioperatively are tolerance, hyperalgesia and higher analgesic requirement together with physical and psychological withdrawal symptoms. Adequate pain management should have a high priority even for these patients.

This review deals with the specific problems of addiction or opioid tolerance in this vulnerable patient group in the perioperative period. In this group are opioid-tolerant chronic pain patients on long-term therapy, addicts with long-term substitution therapy, those currently addicted and those with a previous history of addiction, mainly to heroin. This article intends to simplify the management of drug-dependent patients and offers strategies for perioperative analgesia that include

stabilisation of physical dependency by substitution with methadone or μ -agonists; avoidance of stress; use of regional techniques in combination with non-opioids or opioids with higher doses than those used in non-addicts; avoidance of inadequate analgesic dosing; effective use of the opioid-sparing effect of different co-analgesics; and psychological support wherever appropriate.

Those caring for abstinent patients should note that an inadequate dosage of analgesics can potentially reactivate addiction. After successful withdrawal of opioids and prolonged abstinence, opioid therapy can result in an exaggerated response.

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Introduction

Opioid addiction is like a chronic illness and merits a special approach to the management of perioperative pain. It is a common problem in Austria, which currently has about 30 000 addicts, and throughout the world. Opioid addicts tend to abuse a wide range of therapeutic and non-therapeutic substances giving rise to complex polytoxicities.¹ There is also a growing number who are under continuous prescribed opioid medication for pain associated with a malignant disorder, and also for pain associated with a chronic non-malignant disease.^{2,3} In the case of the latter, long-term opioid therapy is no longer routinely prescribed because psychological influences obtund the analgesic effect, which is limited.⁴ The development of abuse is enhanced by a wide range of factors.^{5–7}

The commonest source of addiction is heroin, a synthetic opioid; only 10% of addicts have an alternative dependency. It is made from morphine by acetylation and can be smoked or sniffed or injected intravenously to reach peak serum level in less than 1 min. Because of its high fat solubility, about 68% of intravenously administered heroin penetrates the blood–brain barrier, in contrast to less than 5% of intravenously administered morphine. It is more potent than morphine with a morphine equivalence of 3. Due to its rapid effect, addictive potency is high, and consequently heroin is a drug in great demand.⁸ The

purity of street heroin varies between 5 and 90% making several injections necessary to achieve a dose of 1 to 5 g per day. Other opioids taken independently or concurrently by addicts include morphine, oxycodone, buprenorphine and methadone given for the treatment of pain, or as substitution therapy.^{6,8–13}

When opioid addicts present for surgery or following trauma, effective pain management can be difficult. Even after long-lasting abstinence, a history of drug addiction is relevant, as inadequate analgesia can trigger a relapse and create a new addiction. Emphasis should be placed on personalised care with great attention to detail to avoid escalation of psychological and physical comorbidities. One example of this is the development of acute delirium or the urgent need for extremely high doses of analgesics. Anaesthesiologists need to have some understanding of the problems involved and how they might be solved. This article aims to help identify addicted patients and offers a strategy for perioperative analgesic management. A necessary starting point is a consideration of some aspects of dependency.

Psychological dependency, addiction and stress as a trigger

Opioids, alcohol, sedatives and hypnotics are depressants of the central nervous system (CNS). According to the International Classification of Diseases 10, of the World Health Organisation, dependence is diagnosed when a patient has had 3 or more of the following criteria at the same time within the last year:

- (1) A strong wish or an obsession to take psychotropic substances

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- (2) Reduced ability to control the beginning, the ending and the amount of drug consumption
- (3) Withdrawal symptoms when ending or reducing drug consumption
- (4) Signs of tolerance
- (5) Progressive disregard of other amenities or interests in favour of drug consumption
- (6) Continuing drug consumption despite knowledge of unwanted physical and psychological consequences

The central aspect of addiction is the compulsive desire for euphoria and distress reduction, and once dependent on one substance, the risk of dependence on another increases seven-fold.^{14,15} As a result, it is common for opioid addicts to abuse a range of substances. The most favoured drugs are benzodiazepines, followed by alcohol and cocaine, but the severity of psychological and physical dependence on opioids remains very high. This is important in the context of perioperative and postoperative pain therapy when the question of adequate substitution arises.

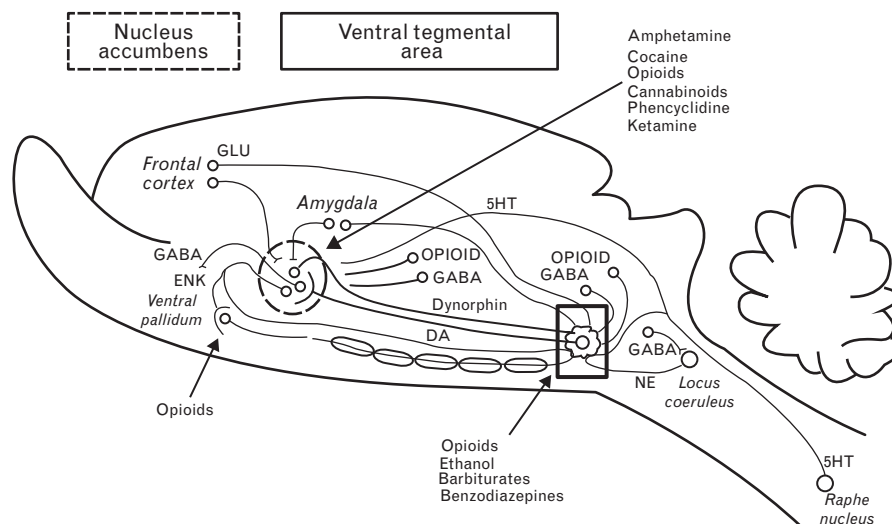
So far it is unclear whether addiction is a feature of the toxicity of substances abused or aggravation of various genetic and other influential factors, or a combination of all of these. According to the vulnerability theory, it is believed that biological and environmental factors lead into the vicious cycle of addiction. Addictive behaviour can be explained neuropsychologically through the effect of psychoactive substances on parts of the mesocortico-limbic systems,^{16,17} involving the ventral tegmental area, the locus coeruleus and the limbic system with the nucleus accumbens and the amygdala (Fig. 1).^{16,18,19}

Here the main effects of opioids take place, producing euphoria and addiction, but also dysphoria.

Euphoria is created through the μ -agonists by repeated activation of the dopaminergic reward system. The outcome of this is sensitisation and conditioning processes, which are involved in the development of psychological dependence and drug hunger (craving). Repeated substance exposure leads to neuroplastic processes that change the structure and function of different receptor systems. This sets up typical addictive behaviour and also establishes the long-lasting memory of addiction.^{15,16} Even following periods of abstinence, certain situations with a sensory physiological context can reawaken the addiction memory at any time. Two such situations are provided by anaesthesia and postoperative pain therapy.

Addicts are highly vulnerable to physical stress, such as surgery and trauma, and psychological stress such as anxiety or work pressure. When exposed, the activity of the limbic and the autonomic systems is increased. This activation of the endogenous stress system is considered significant for the development of the vulnerability to stress and also for a negative mood during abstinence. Koob *et al.*¹⁶ postulate that it is dysregulation in the cerebral stress and anti-stress system, which permanently alters the feeling of distress and creates the desire for distress-reducing substances. It must be assumed that even after many years of drug abstinence, the neuroplastic changes are not fully reversible, which explains the high relapse rate of addicts.

Fig. 1



The mesocorticolimbic dopamine system as the centre of action of psychoactive substances. Schematic representation of neural networks of nociceptive, affective-emotional and vegetative influencing nucleus areas in the brain (selection of major centres; for explanation see text) [from Koob *et al.*,¹⁶ Nestler,¹⁸ Treede¹⁹].

Physical dependency, tolerance and opioid-induced hyperalgesia

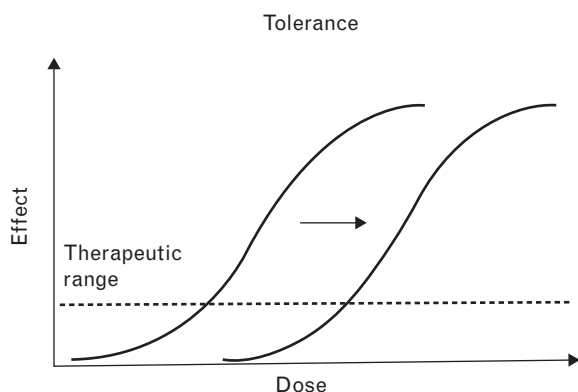
Dependency and tolerance are linked by the same adaptive neuroplastic changes in neurotransmitter systems that follow repeated opioid consumption. Dependency is revealed only when a reduction in opioid use occurs, and if this is sufficiently abrupt, severe physical withdrawal symptoms become evident.¹⁷ One abrupt cause of withdrawal is the specific antidote naloxone, and its use in addicts is contraindicated.

Analgesic tolerance is the phenomenon that occurs after repeated use of opioids when their analgesic effect decreases. This can develop even within a week from first consumption, and an increase in dose will be required to achieve adequate analgesia.

With dependency and tolerance, at the molecular level, in the area of the limbic system and the locus coeruleus, increased activity occurs in the adenylate cyclase system together with a permanent increase in activity of the excitatory receptor systems. As a consequence, more *N*-methyl-D-aspartate (NMDA) receptors are expressed.^{15,16} This triggers a downregulation of opioid receptors and leads to a decreased effect of opioids.^{18,20} This shifts the dose–response curve to the right, and higher opioid doses are needed to achieve a comparable analgesic effect (Fig. 2).²¹

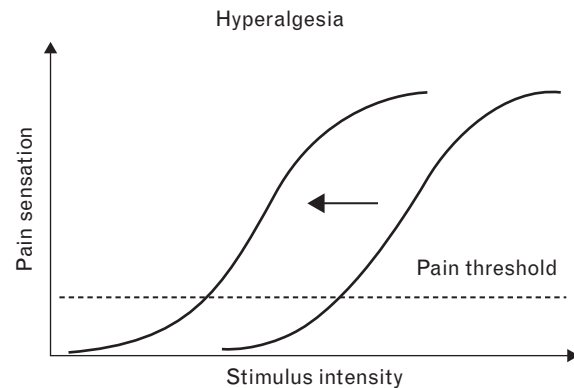
Tolerance with morphine is considerable, resulting in 30 to 100% higher opioid requirement.^{22–24} Perioperative cross-tolerance must be expected with a markedly increased need for analgesics, the dose of which can only be decided by clinical assessment. Associated with reduced opioid analgesic activity is the problem of opioid-induced hyperalgesia, recognised by an increased perception of pain after opioid consumption. Opioid administration will activate anti-nociceptive mechanisms, but with repeated exposure, a variety of pain-enhancing countermechanisms develop (Fig. 3).^{10,21,25}

Fig. 2



Tolerance. Rightward shift of the dose–response curve, i.e. the potency of the drug decreases (from Koppert *et al.*)²¹.

Fig. 3



Hyperalgesia. Leftward shift of the stimulus–perception curve, i.e. an originally non-painful stimulus is then perceived as painful (allodynia), whereas an originally painful stimulus increases in intensity (from Koppert *et al.*)²¹.

The hyperalgesia results from activation of the NMDA system and an increase in the spinal dynorphin concentration.²⁶ The increased release of excitatory neurotransmitters and the effect of activating descending efferents over the dorsolateral funiculus lead to a more intensive spinal synaptic transmission, which can cause severe intraoperative and postoperative pain.^{10,25,27}

All opioids used in daily clinical practice lead to a dose-dependent reduction of the pain threshold. Remifentanyl has been subject to particular investigation of opioid-induced hyperalgesia in clinical and experimental use.^{28–31} Although remifentanyl can be finely controlled, following discontinuation it can cause clinically significant destabilisation of the nociceptive system and provoke withdrawal symptoms with increased signs of hyperalgesia. Remifentanyl's short duration induces acute tolerance³¹ and also hyperalgesia evident in clinical practice and in healthy volunteers.^{25,28,31} Following its administration, catecholamine values in the blood increase greatly, in response to depression of sympathetic tone. These problems of opioid-induced hyperalgesia are much more pronounced in patients with opioid addiction and methadone substitution than in non-addicts.^{29,30,32} Heroin compared to methadone has a much stronger hyperalgesic effect. For that reason, poorly managed postoperative pain can trigger an escalating problem, exacerbated by a heightened perception of distress. More controlled studies of this phenomenon are needed.

Instead of remifentanyl, other opioids such as sufentanil, fentanyl or alfentanil can be given without problems. Their subcellular, acute pronociceptive NMDA activation seems to be less important probably because their analgesic efficacy tapers off slowly, and the gradual recurrence of pain is more remediable than after remifentanyl use.

In all studies, hyperalgesia was reduced by the administration of S-(+)-ketamine.³³ The α^2 -agonists also have a preventive effect.¹⁶ COX inhibitors reduce the spinal release of excitatory neurotransmitters and act synergistically with NMDA receptor antagonists.³⁴

Problems in dealing with dependent and abstinent patients

The problems that arise in regard to adequate pain management of opioid-dependent patients result from a lack of knowledge about addiction by the therapists themselves, from social prejudice, from an opioid phobia and from fear of triggering renewed addictive behaviour. Opioid-dependent patients usually provide inadequate information about their addiction, fearing that opioids might be withheld. The abstinent patient fears another relapse and so compliance with pain therapy often is inadequate. Not surprisingly, addicts are time-consuming patients, who usually require a complex perioperative and postoperative analgesic approach.

It is perhaps surprising that there are no guidelines to help with managing anaesthesia or analgesia for drug addicts. There are mainly recommendations from review articles containing personal experiences.^{35,36} An overview of the most important perioperative principles is given below.

In the presence of dependence, withdrawal of the source triggers a physical syndrome, the basis of which is sympathoadrenergic overactivity. This, together with associated cardiovascular stress,³⁷ can result in an intensification of the perioperative stress response (Table 1).¹⁵ The administration of the α_2 -adrenergic agonist clonidine can be useful in reducing these symptoms. It activates presynaptic noradrenergic receptors and so reduces the release of noradrenaline in the CNS, calming the excitatory sympathoadrenergic withdrawal syndrome. Through neuronal pathways to the mesolimbic dopamine systems, clonidine inhibits the addiction-activating process. Its unwanted side-effects are sedation, hypotension and bradycardia.

Unrestrained activity of the NMDA system, which is caused by the acute withdrawal of the dependent substance, also contributes to pain intensification. The stress generated triggers further activity in the limbic and the autonomic systems, building to a crisis in the already vulnerable addict. An additional effect is reduction of the pain threshold. Bound in with this are psychological factors. Affective-emotional centres are closely linked with nociceptive centres^{38,39,19} explaining why nociception is further enhanced by distress and anxiety.^{28,30} The aim of management is to curb physical and emotional distress, because these are potential triggers for the craving for drugs or the relapse into addiction.⁴⁰ The reduced stress tolerance of these patients continues even in abstinence.

Table 1 Scheme of acute opioid effects and withdrawal syndrome with opposing symptoms

| Acute opioid effects (dominated by acetylcholine) | Withdrawal syndrome (dominated by noradrenaline) |
|-------------------------------------------------------|--------------------------------------------------|
| Respiratory depression | Hyperventilation, yawn |
| Analgesia | Hyperalgesia |
| Euphoria | Dysphoria |
| Relaxation | Restlessness |
| Sleep induction | Insomnia |
| Sedation | Hypervigilance |
| Anxiety | Fear |
| Antiemesis | Emesis |
| Hypothermia | Cold shivering, fever |
| Hypomotric movement | Hypermotric movement |
| Miosis | Mydriasis |
| Urinary retention | Urinary urge |
| Intestinal atony | Abdominal cramps, diarrhoea |
| Suppression of exocrine glands (dry skin, nose, eyes) | Hyperhidrosis, rhinorrhoea, sneezing, tears |
| Satisfaction | Craving |

The variety of the opioid withdrawal syndrome reflects the diverse symptoms of the acute effect according to Bonnet and Gaspar.¹⁵

Questionnaires can be used to gather subjective and objective information for measuring symptoms of withdrawal (Table 2).^{41,42} They are useful for the quantitative assessment of the intensity of the withdrawal syndrome, and assist the development of rational prophylaxis and treatment of withdrawal symptoms.^{41,42}

Anaesthesia management

The addicts are chronically ill. Their numerous comorbidities make them at high-risk, especially when needing major surgery.⁴³ They are also more exposed to psychological disorders than the general population (Table 3),^{44,45} and a higher incidence of both physical and psychological complications must be expected.^{46–48} Anxiety, depression, lack of motivation, a lack of insight toward disease and 'coping' strategies as well as a high therapeutic demand can turn the perioperative phase into a challenge. The problems are best managed by the establishment of an interdisciplinary team that includes surgeons, anaesthesiologists and a psychiatrist or

Table 2 Self-administered scale for opioid withdrawal symptoms: Subjective Opiate Withdrawal Scale

| | |
|------------------------------------------|-----------|
| I feel anxious | 0 1 2 3 4 |
| I yawn frequently | 0 1 2 3 4 |
| I am sweating | 0 1 2 3 4 |
| My eyes are weeping | 0 1 2 3 4 |
| My nose is running | 0 1 2 3 4 |
| I have goose-skin | 0 1 2 3 4 |
| I have the shivers | 0 1 2 3 4 |
| I have heat flashes | 0 1 2 3 4 |
| I have limb and muscle pain | 0 1 2 3 4 |
| I feel nervous | 0 1 2 3 4 |
| I feel dizzy | 0 1 2 3 4 |
| I feel nauseous | 0 1 2 3 4 |
| My muscles twinge | 0 1 2 3 4 |
| I have abdominal cramps | 0 1 2 3 4 |
| I feel as if I would explode in a second | 0 1 2 3 4 |

0 = not at all, 1 = a little bit, 2 = moderate, 3 = quite, 4 = high (maximum score = 60). Score: mild = 4 to 20, moderate = 21 to 40, high = 41 to 60 (according to Bradley *et al.*⁴¹ and Wesson and Ling⁴²)

Table 3 Prevalence rates of comorbidities in substance dependence (according to International Classification of Diseases 10)

| | |
|---------------------------------|------------|
| F0 organic disorders | 1 to 6% |
| F2 schizophrenia | 7 to 25% |
| F3 affective disorders | 7 to 74% |
| F4 anxiety disorders | 5 to 46% |
| F5 eating disorders | 2.7 to 10% |
| F6 personality disorders | 25 to 90% |

psychologist experienced in the field of addiction. Perioperative therapy is not intended to treat the underlying disease and must accept the characteristics and special needs of chronic addiction.

Evaluating dependence

An attempt must be made to obtain as much information about an individual's dependence as possible. Answers should be sought as to which opioids and other substances are and have been abused, the forms of administration and the amounts consumed. The duration of consumption should be established and the time and nature of last drug use. Any history of episodes of abstinence and withdrawal should be sought together with experience of complications resulting from intoxication and withdrawal. If the addict is unhelpful or unreliable, these questions should be addressed to family and friends. Analysis of blood and urine can also be helpful.

Premedication

A reassuring conversation with addicts, to create a situation of confidence, is essential in reducing stress and fear of pain during the perioperative period. Patients' concerns have to be addressed and the treatment discussed. It may seem appropriate to explain the proposed plan to a partner or friend. Consent for the use of psychotropic substances must be obtained. This approach is conducive to transparency and might improve compliance of dependent and abstinent patients. Hopefully, the involvement of the addicts in their management will reduce self-medication with unprescribed drugs.

Table 4 Equivalent doses on the basis of clinical experience

| Substance | Dose | Methadone equivalent | Conversion factor |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|----------------------|-------------------|
| Street heroin | (1g) | (40 to 80 mg) | |
| This is a rough estimate because the purity of street heroin is uncertain | | | |
| Morphine | 40 to 80 mg | 10 mg | (4 to 8): 1 |
| There is a clear 'dependence of direction': the conversion of morphine to methadone is rarely problematic; often lower doses than mentioned here are possible (possibly 10:1); however, the conversion of methadone to morphine is often a problem and may require an increase in dose for a few days | | | |
| Dihydrocodeine | 100 to 120 mg | 10 mg | (10 to 12): 1 |
| Can be used for treatment of acute withdrawal symptoms or for short interval substitution | | | |
| Buprenorphine | 2 mg | 10 mg | 1: (5 to 6) |
| Is especially used for lower dose ranges up to about 60 to 80 mg of methadone; however, there is often no satisfactory conversion possible or very high doses are required | | | |

Modified according to Werner.⁵⁰

Because opioid addicts frequently abuse a number of drugs, including benzodiazepines, the first choice for premedication should be antipsychotics or neuroleptics.

A withdrawal episode during the perioperative period must be avoided and a maintenance plan is required to ensure that physical and psychological dependence are stable throughout.^{49,50} How this is achieved will differ according to whether the dependence is based on recreational use or on a chronic pain regimen. For the latter, the daily oral, transdermal or intravenous opioid dose must be continued as prescribed up to and including the day of surgery.

Numerous patients with chronic pain are treated with highly potent opioids through transdermal application. In Austria, matrix systems containing fentanyl or buprenorphine are approved. These application systems are even slower than the effects of slow-release formulations such as that of morphine. Therefore, one should leave patches containing fentanyl or buprenorphine on during small procedures that are unlikely to interfere with normothermia. After major procedures, hypothermia can occur and the peripheral circulation can be further reduced by loss of volume. In these circumstances, the stability of transcutaneous opioid resorption cannot be guaranteed, and it has proven effective to remove the opioid patch shortly after inducing anaesthesia, continuing with intravenous opioid. The dose can be calculated based on the morphine equivalent.

Addicts with uncontrolled use of street heroin present a problem of substitution because the purity varies greatly and finding the appropriate dose is difficult. The available equivalence scales are based on animal studies or on clinical experience, and are subject to unpredictable fluctuation.⁴⁹ Estimates of equivalence drawn from clinical practice are not necessarily good guides and doses must be immediately adjusted if withdrawal symptoms occur (Table 4).⁵⁰

Substitution

There are approximately 30 000 addicts in Austria with problematic opioid use and about 10 000 are in a

substitution treatment regimen.¹ Of these, about 46% are managed as outpatients and about 65% are inpatients until stabilised with extended release morphine. Methadone is used in about 20 to 25%, and buprenorphine in about 10 to 21% of cases. Other substances, such as codeine, are used by only about 1% of patients.

Methadone, a synthetic opioid agonist and NMDA receptor antagonist, is used mainly in cases of acute substitution.⁵¹ The elimination half-life is highly variable and averages 24 to 36 h. If a patient is already substituted with methadone, the once-daily dose should be continued through the perioperative period. The initial dose tends to be in the region of 30 to 40 mg methadone equivalent per day. It is possible to titrate the substitution dose using 10 mg orally every 30 to 45 min, while being on the alert for the development of withdrawal symptoms. If these occur, the dose or the time interval should be increased from once-daily to twice-daily. Intravenous titration is carried out with 0.5 to 1 mg every 10 min. Each day, the effectiveness must be reviewed. Because of the long and variable half-life, the cumulative dose may overtake the development of tolerance, especially on the second or third day, which could lead to an overdose.

Other pure μ -opioid agonists (morphine, fentanyl, sufentanil, hydromorphone) can be used for substitution in the form of an intravenous infusion. An essential feature of substitution therapy is the concept of the morphine equivalent for measuring the potency of an analgesic. Equivalence tables offer choices for different routes of administration but provide only a rough guide, not an exact estimation, especially in chronic administration.^{52,53}

Buprenorphine, a partial μ -agonist and κ -antagonist with a limited maximum effect, is used sublingually for long-term substitution.^{8,54} Its high affinity for opioid receptors requires a time interval of at least 6 h after the last consumption of heroin, and at least 24 h after the last dose of methadone or slow-release morphine, so as not to cause withdrawal. The duration of effect is estimated at up to 72 h, so dosing once a day or three times a week at a higher dose is needed. The initial dose is 2 to 4 mg and the daily dose 2 to 8 mg.

For minor procedures, buprenorphine can be continued as a substitute, and sublingual administration is appropriate for postoperative analgesia. For planned major procedures, buprenorphine should be substituted with methadone or a pure μ -opioid agonist to ensure adequate intraoperative and postoperative pain relief.^{55,56}

The same doses and procedures also relate to the combination of buprenorphine and naloxone. The latter, orally or sublingually, does not block the central analgesic opioid effect; only the intravenous form will trigger withdrawal. This buprenorphine–naloxone combination is

also used for substitution therapy because it blocks the potential effect of an illicit intravenous drug.

Substitution with slow-release morphine is carried out once a day. The initial dose is 200 mg and the daily dose 600 to 800 mg.

Dihydrocodeine has a duration of about 12 h and requires multiple daily administrations. It is not recommended as a substitute.

Tramadol, due to its analgesic ceiling effect and its potential to lower the seizure threshold, is also unsuitable as a substitute.

The aim of substitution is to maintain dependence in a stable form. Additional analgesic drugs are needed to provide pain relief.

Addicted patients

Therapeutic strategies

The choice of drugs and options for a multimodal perioperative analgesia plan depends on clinical criteria and the nature of the procedure.³⁵ Opioids and non-opioids should be included. The choice of anaesthesia is unlikely to influence the addiction, and both inhalational and total intravenous techniques can be used. Pure μ -opioid agonists, especially sufentanil, due to its high intrinsic activity, are highly rated.⁵⁷ Large fluctuations in the plasma level of opioids selected for substitution are undesirable if withdrawal is to be avoided. Continuous intravenous infusion ensures constant plasma concentrations. Should tachycardia, hypertension and profuse perspiration occur intraoperatively, one has to differentiate between insufficient anaesthesia and the beginning of withdrawal symptoms. Remifentanil should be avoided to prevent acute development of tolerance and of hyperalgesia.^{25,28,31}

Regional anaesthesia

Preference for regional anaesthesia seems to be high in addicts,^{35,58,59} although there are no large prospective studies to confirm this. Because regional anaesthesia has a failure rate, and cooperation in this group of patients cannot be guaranteed, rescue general anaesthesia should be discussed in advance. Relative contraindications for the use of regional anaesthesia are systemic infections, blood clotting disorders and unstable neurological disorders. When possible, a regional analgesia catheter should be used. An acceptable alternative could be wound or joint infiltration, shortly before the end of the operation. Thresholds for local anaesthetic cardiotoxicity might be reduced in addicts who are also consuming cocaine, so care must be taken with dosing.

For epidural analgesia, to intensify the analgesic effect, either an epidural opioid (sufentanil 0.5 to 0.75 $\mu\text{g ml}^{-1}$ and fentanyl 0.5 $\mu\text{g ml}^{-1}$) or the addition of an α_2 -agonist (clonidine 0.5 $\mu\text{g kg}^{-1}$ as a single-shot or 0.25 $\mu\text{g kg}^{-1} \text{ h}^{-1}$ as a continuous infusion) is suitable.^{60,61}

Local anaesthetic by continuous infusion or in combination as part of a regional patient-controlled technique has an advantage over intermittent administration. At the same time, systemic administration of non-opioids should be fully exploited.

Postoperative phase

The same strategies should be continued throughout the postoperative period, with emphasis on maintaining substitution to stabilise dependence and prevent withdrawal, supplemented by an approach to analgesia that meets the needs of the procedure and the patient. The emergence phase should be stress-free and so antidotes such as naloxone, flumazenil and prostigmine should not be given. A common failing is to underestimate the degree of postoperative pain in this group, and a plan for supplementation and adjustment is advisable. This is made simpler if continuous infusion or intravenous patient-controlled analgesia (PCA) with background infusion is used. Opioid bolus doses should be increased and lockout intervals shortened, for example beginning with a bolus dose of 2 to 3 mg piritramide and a lockout time of 10 min.^{35,56,59,62} Short infusions outside PCA with higher doses of opioid are undesirable. They produce high concentrations in the blood and brain with the potential to cause unwanted psychotropic effects.

Once the immediate postoperative phase is passed, oral slow-release opioids may be used to advantage, titrating the dose against the pain intensity. To assess this, and because of possible psychotropic effects, close monitoring should be continued.

Co-analgesics

Co-analgesics are important as part of multimodal analgesia and play an important role in the treatment of opioid-addicted patients. A wide variety of drugs can be considered.

The α_2 -adrenergic agonist clonidine (0.1 to 0.2 $\mu\text{g kg}^{-1} \text{h}^{-1}$ intravenously or 75 (150) μg two to three times a day orally and on demand) is a logical choice because of its opioid-sparing property as well as its anti-hyperalgesic effect. It also suppresses the symptoms of adrenergic withdrawal through activation of presynaptic noradrenergic receptors.⁶³

Several studies show the positive effect of S-(+)-ketamine on postoperative pain when given during simultaneous opioid use.^{60,64} Benefit comes from the reduction of tolerance and hyperalgesia together with an opioid-sparing effect.³³ In one report, the continuous administration of S-(+)-ketamine (2.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$) reduced the daily morphine consumption by one third and analgesia was improved. It can be given in bolus doses (0.25 to 0.5 mg kg^{-1}) or as a continuous infusion (1 to 2 $\mu\text{g kg}^{-1} \text{min}^{-1}$) during the procedure and may be continued postoperatively.⁶⁵ When the demand for opioid

analgesia is high, it can be given as a one-off infusion of 5 to 10 mg to achieve better pain control.

Tricyclic antidepressants (amitriptyline 10 to 25 mg at night, doxepin 10 to 25 mg at night) can be a useful supplement because of their smooth sedating effect.⁶⁶

The anticonvulsants gabapentin and pregabalin may have a role in both perioperative pain treatment and the prevention of chronic persistent pain. Both substances have an anxiolytic effect, which can be useful. Premedication with gabapentin 1200 mg lowered rest pain intensity and opioid consumption on the first postoperative day, and reduced chronic persistent pain. Freedman and O'Hara⁶⁷ showed that premedication with 75 mg of pregabalin, and a subsequent dose of 75 mg twice daily for 7 days postoperatively, led to significant opioid-sparing. In a recent and extensive randomised, placebo-controlled trial, Buvanendran *et al.*⁶⁸ gave a pre-emptive dose of pregabalin 300 mg 1 h preoperatively as well as 150 mg twice daily for the postoperative period of 14 days. They found a significant reduction in postoperative oral opioid consumption, more rapid mobilisation and a significantly decreased incidence of chronic neuropathic pain after 3 and 6 months. The optimal dose and evidence of safe administration have yet to be resolved, and so currently there is insufficient information to formulate an evidence-based recommendation on its place in postoperative pain therapy.

Benzodiazepines should be avoided wherever possible because of their high potential for addiction.

Former addicts

Stress reduction: pseudoaddiction

Again, interdisciplinary management with the aim of minimising perioperative stress is desirable. As addiction is a chronic disease, relapse can occur even after many years of abstinence, though the longer the interval of abstinence, the lower the risk of relapse. Fear and pain remain potential triggers for drug craving and the relapse into addiction.³⁶ Even in abstinence, stress is poorly tolerated.

Inadequate analgesia in this group can lead to pseudo-addictive behaviour.⁶⁹ Because of insufficient analgesia, the patient calls for more pain relief, and this is misinterpreted as addictive behaviour. The same mechanism is also seen in non-addicted patients. The reluctance of staff to prescribe opioids triggers major fears in addicts, which can lead, as a result of comorbid personality disorders, to a complicated pattern of interaction. The risk of relapse into active addiction due to restrictive treatment of severe pain is great.²²

Premedication

The high degree of motivation of drug-free patients may help involve them in the management plan, creating a basis of trust. Psychological support during the hospital

stay has a high priority because mental and physical complications relating to their earlier addiction can complicate management significantly. The choice of premedication must be based on individual needs.

Abstinence syndrome

In ex-addicts whose abstinence is a relatively new event, attendants must be alert to the development of abstinence syndrome,^{32,70} which is characterised by persistent instability, hyperalgesia and reduced pain threshold, together with sedation and respiratory depression after administration of opioids. The duration of this syndrome can last from months to years.⁹ The first 6 months of abstinence are critical, because complications or an overdose can occur even after small amounts of opioid and careful monitoring is advisable.

Regional anaesthesia

If the procedure is suitable, regional block in combination with non-opioids is a preferred option,^{36,58} unless there are contraindications or problems with consent,³⁵ but there is no evidence to suggest that it can reduce the relapse rate. The use of opioids in abstinent patients is best avoided and so epidural opioid cocktails should be used only when severe pain is anticipated.^{35,59}

Nevertheless, epidural clonidine ($0.5 \mu\text{g kg}^{-1}$ as a single-shot or $0.25 \mu\text{g kg}^{-1} \text{h}^{-1}$ as a continuous infusion) is recommended. Indwelling analgesia catheters are useful for postoperative management.

Systemic balanced analgesia

There are no specific recommendations for general anaesthesia. Patients in the early phase after termination of drug consumption may require increased anaesthetic and analgesic use. An important factor for anaesthesia in drug-free patients is to first inject the hypnotic and only then the opioid, to avoid the psychotropic effects of the latter. Remifentanyl should be used cautiously because of the possible acute development of tolerance and of hyperalgesia.^{28,31} μ -Opioid agonists such as fentanyl and sufentanyl should be given because of the possible existence of a protracted abstinence syndrome, but the initial dose should be 50% of that calculated for non-addicts. Analgesic administration should be started during the operation in high enough doses. Also, intravenous loading doses, of piritramide for example, should be given at this time.

An opioid hangover in immediate postoperative emergence must be avoided. Concerns about re-activating addiction should not be allowed to interfere with effective control of pain,³⁶ and dose titration can help to get this right. Effective monitoring and swift and proficient pain management will limit unnecessary interruptions in treatment.

Although management with non-opioids is desirable, this is only going to be possible after minor procedures.^{36,58} With major procedures, their limitations will be all too apparent, and strong opioids in low single doses should be prescribed. For moderate postoperative pain that cannot be controlled with non-opioids, weak opioids with low addictive potential should be used. If tramadol is considered, it must be remembered that a tendency to epileptic seizures is a contraindication. PCA with an initial reduced bolus, piritramide 1 mg for example, and a lock out of 10 min, can be titrated against pain intensity, with adjustments as required.^{35,59} Whereas short-lived infusions are undesirable, longer-term, continuous infusions are beneficial because peaks and troughs can be avoided. Later, oral slow-release opioids and non-opioids can be used. Sustained release oxycodone in this group should be used with caution due to its two-phase galenic structure, which contains 25% rapid release oxycodone. Recommendations for co-analgesics are the same as those for addicts. Details of suitable drugs and their doses can be found above.

Conclusion

Addiction is a chronic disease that demands special management in the perioperative period.

Opioid-dependent patients should be classified as high-risk patients.

Any management plan requires the following:

- (1) Treatment by an interdisciplinary team with a psychological element that aims for perioperative stabilisation
- (2) A history of drugs and dependence
- (3) Substitution therapy to stabilise physical dependence
- (4) Avoidance of distress and drug craving
- (5) Intraoperative and postoperative stress shielding
- (6) Avoidance of inadequate analgesia
- (7) Postoperative optimisation of regional or systemic analgesia with non-opioids or administration of co-analgesics
- (8) Consideration of the complex physical and psychological comorbidities

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