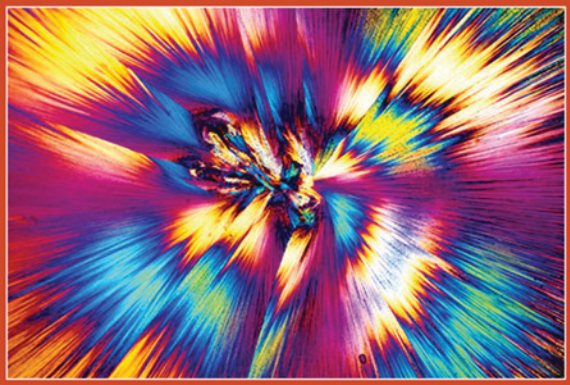
MEYLER'S

Side Effects of

Analgesics and Anti-inflammatory Drugs



J.K. Aronson

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Preface

This volume covers the adverse effects of analgesic medicines. The material has been collected from *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions* (15th edition, 2006, in six volumes), which was itself based on previous editions of *Meyler's Side Effects of Drugs*, and from the *Side Effects of Drugs Annuals* (SEDA) 28, 29, and 30. The main contributors of this material were JK Aronson, PAGM de Smet, E Ernst, and M Pittler.

A brief history of the Meyler series

Leopold Meyler was a physician who was treated for tuberculosis after the end of the Nazi occupation of The Netherlands. According to Professor Wim Lammers, writing a tribute in Volume VIII (1975), Meyler got a fever from para-aminosalicylic acid, but elsewhere Graham Dukes has written, based on information from Meyler's widow, that it was deafness from dihydrostreptomycin; perhaps it was both. Meyler discovered that there was no single text to which medical practitioners could look for information about unwanted effects of drug therapy; Louis Lewin's text "Die Nebenwirkungen der Arzneimittel" ("The Untoward Effects of Drugs") of 1881 had long been out of print (SEDA-27, xxv-xxix). Meyler therefore determined to make such information available and persuaded the Netherlands publishing firm of Van Gorcum to publish a book, in Dutch, entirely devoted to descriptions of the adverse effects that drugs could cause. He went on to agree with the Elsevier Publishing Company, as it was then called, to prepare and issue an English translation. The first edition of 192 pages (*Schadelijke Nevenwerkingen van Geneesmiddelen*) appeared in 1951 and the English version (*Side Effects of Drugs*) a year later.

The book was a great success, and a few years later Meyler started to publish what he called surveys of unwanted effects of drugs. Each survey covered a period of two to four years. They were labelled as volumes rather than editions, and after Volume IV had been published Meyler could no longer handle the task alone. For subsequent volumes he recruited collaborators, such as Andrew Herxheimer. In September 1973 Meyler died unexpectedly, and Elsevier invited Graham Dukes to take over the editing of Volume VIII.

Dukes persuaded Elsevier that the published literature was too large to be comfortably encompassed in a four-yearly cycle, and he suggested that the volumes should be produced annually instead. The four-yearly volume could then concentrate on providing a complementary critical encyclopaedic survey of the entire field. The first *Side Effects of Drugs Annual* was published in 1977. The first encyclopaedic edition of *Meyler's Side Effects of Drugs*, which appeared in 1980, was labelled the ninth edition, and since then a new encyclopaedic edition has appeared every four years. The 15th edition was published in 2006, in both hard and electronic versions.

Monograph structure

Each of the monographs on herbal products in this volume has the following structure:

- Family: each monograph is organized under a family of plants (for example Liliaceae).
- Genera: the various genera that are included under the family name are tabulated (for example the family Liliaceae contains 94 genera); the major source of information on families and genera is the Plants National Database (http://plants.usda.gov/index.html).
- Species: in each monograph some species are dealt with separately. For example, in the monograph on Liliaceae, four species are included under their Latin names and major common names—*Sassafras albidum* (sassafras), *Allium sativum* (garlic), *Colchicum autumnale* (autumn crocus), and *Ruscus aculeatus* (butcher's broom).

Each monograph includes the following information in varying amounts:

- Alternative common names; the major sources of this information are *A Modern Herbal* by Mrs M Grieve (1931; http://www.botanical.com/botanical/mgmh/mgmh.html) and *The Desktop Guide to Complementary and Alternative Medicine: an Evidence-Based Approach* by E Ernst, MH Pittler, C Stevenson, and A White (Mosby, 2001).
- Active ingredients; the major source of this information is the *Dictionary of Plants Containing Secondary Metabolites* by John S Glasby (Taylor & Francis, 1991).
- Uses, including traditional and modern uses.
- Adverse effects.

The families of plants and their species that are the subjects of monographs are listed in Table 3 (p. 000) by alphabetical order of family. The same data are listed in Table 4 (p. 000) by alphabetical order of species. Other monographs cover the Basidiomycetes (*Lentinus edodes*, shiitake) and algae. Table 5 (p. 000) gives the Latin equivalents of the common names. To locate a plant by its common name, convert the common name into the Latin name using Table 5 and then find out to which family it belongs by consulting Table 4.

Drug names

Drugs have usually been designated by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available,

chemical names have been used. In some cases brand names have been used.

Spelling

For indexing purposes, American spelling has been used, e.g. anemia, estrogen rather than anaemia, oestrogen.

Cross-references

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-l3, SED-14, etc; the *Side Effects of Drugs Annuals 1–22* are cited as SEDA-1, SEDA-2, etc.

J K Aronson
Oxford May 2008

OPIOID RECEPTOR AGONISTS AND ANTAGONISTS

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Opioid analgesics (Opioid receptor agonists)

See also individual names

General Information

Receptor nomenclature

Opioid receptors, originally called δ, κ, and μ receptors, then OP_1, OP_2, and OP_3 receptors, are now called DOR, KOR, and MOR receptors respectively

Classes of substances

Opioids are naturally occurring or synthetic substances that have morphine-like activity. The term opiate refers only to substances with morphine-like activity that are derived from opium. Substances that bind to opioid receptors but elicit little agonist activity are known as opioid antagonists. Some drugs have both agonist and antagonist effects (partial agonists). The opioids and their antagonists can be divided into three groups: (a) opioid agonists (morphine and morphine-like opioids); (b) opioid antagonists (for example naloxone and naltrexone); and (c) opioid partial agonists (for example buprenorphine and nalbuphine).

Three separate categories of endogenous substances with morphine-like activity have been identified. These families of neuropeptides are known as enkephalins, endorphins, and dynorphins. Each family is derived from a distinct precursor polypeptide (pro-enkephalin, pro-opiomelanocortin, and prodynorfin) and has a characteristic anatomical distribution. The enkephalins and dynorphins found co-exist with other neurotransmitters, such as serotonin (5-HT) and noradrenaline, but details of how the peptides modulate the activity of co-transmitters await elucidation.

Finally, several molecules with chemical structures similar to morphine have been found in mammalian brain, but it is not certain if these molecules have been derived from dietary sources or if they are synthesized in the brain.

The word narcotic was previously used to describe substances with morphine-like activity and is now largely obsolete, although it is still used in legal parlance.

Opioid receptors

There are three main types of opioid receptor: MOR (OP_3, μ), KOR (OP_2, κ), and DOR (OP_1, δ) receptors. They are mainly found within the central nervous system but also in the periphery. Subtypes of each have been identified. Opioids interact with these receptors to produce their effects, primarily by exerting presynaptic inhibition, which results in reduced release of excitatory transmitters. It is thought that analgesia is primarily mediated via activation of MOR receptors at supraspinal sites and KOR receptors within the spinal cord. The finding that morphine is ineffective as an analgesic in knock-out mice without μ receptors confirms the importance of this receptor type. However, structural studies in cloned MOR receptors have failed to support pharmacological studies that suggest the existence of separate MOR receptor subtypes that independently mediate analgesia and respiratory depression.

The identification of opioid receptors and the discovery of opioid peptides in the 1970s led to the hope that greater understanding of fundamental mechanisms would lead to the development of new drugs with all the valued properties of known opioids but without their unwanted effects. However, these hopes have remained unrealized, although a synthetic enkephalin (pentapeptide 443C81), which penetrates the blood–brain barrier poorly, produces dose-related analgesia without causing significant miosis or reducing minute volume on rebreathing carbon dioxide in healthy volunteers (SEDA-16, 86).

Understanding of nociceptive processing has progressed in recent years, and the pain mechanisms and opioid effects on various receptors and transmission systems have been elucidated (1–3), as have tolerance and physical dependence and the influence of NMDA receptors (4,5).

The peptides endomorphin 1 and 2 have been identified in human brain and show selectivity and affinity for μ receptors. In mice, endomorphin 1 and 2 produce spinal and supraspinal analgesia. They appear to act through regulation of calcium entry into the target cell via voltage-gated channels and also to inhibit cyclic AMP production in MOR receptor bearing cells. Clinically they mimic the action of other MOR opioids. Their clinical relevance and unique adverse effects profiles await further investigation. Similarly the clinical usefulness of newly discovered receptor systems, such as the orphan opioid receptor for nociceptin (ORL1), which produces analgesia, hyperalgesia, and anti-opioid effects in animals, has yet to be defined.

Differences between individual agents

Morphine remains the gold standard against which all other opioids are compared. Most opioids are used as analgesics, although some are used primarily as antitussives, despite the fact that the cough-suppressing effect of codeine and dextromethorphan has not been demonstrated in children (SEDA-22, 98); others, such as loperamide and diphenoxylate, are used exclusively in the treatment of diarrhea; fentanyl and its congeners are primarily used in anesthesia. Fentanyl, the oldest of the anesthetic opioid agonists, and its derivatives alfentanil and sufentanil, are used either as anesthetic supplements or in appropriate doses as complete anesthetics. Butorphanol and nalbuphine have largely replaced pentazocine in analgesia, because they are less likely to have dysphoric effects and, in contrast to the pure agonists, any respiratory depression that follows their use is not dose-related and reaches a ceiling as the dose increases.

The main characteristics and use of opioid drugs are listed in Table 1. Drugs in widespread clinical use each have a separate monograph.

some opioid drugs

e	Route of administration	Half-life (hours)	Usual indication	Main adverse effects
pwards y	Oral, subcutaneous, intravenous, intramuscular, intrathecal	2–4	Severe pain, anesthesia	Sedation, constipation, nausea, vomiting, itching, respiratory depression, tolerance and dependence, euphoria
	Epidural, intravenous	1.6–4	Analgesia, anesthesia	As morphine
hourly	Oral	3–4	Cough, diarrhea, moderate pain	As morphine; lack of effect in poor metabolizers by CYP2D6
y	Oral	2.7–3.3	Dry cough	
y	Oral	6–32 (norpropoxyphene 24–42)	Moderate pain	As morphine; cardiotoxicity, not reversible by naloxone; convulsions possible, due to norpropoxyphene
	Epidural, intravenous, transdermal patch	2–7	Acute pain, anesthesia	As morphine
hourly; /day	Oral, intravenous, intramuscular	15–60	Severe pain; opioid dependence	As morphine
3-hourly	Oral, intramuscular	3.2	Moderate/severe pain	As morphine; excitement and convulsions
g	Epidural, intravenous	2.7–6	Severe pain, anesthesia	As morphine
y;	Sublingual, intravenous Sublingual	5–12	Moderate/severe pain Opioid dependence	As morphine, but less pronounced; less well reversed by naloxone
y	Oral, intravenous, intramuscular	2–4	Acute pain	As morphine; dysphoria
repeated to	Intravenous	1.1	Reversal of opioid-induced respiratory depression	Nausea, vomiting, hypertension, cardiac dysrhythmias, rarely seizures
epeated to	Intravenous	10	Reversal of opioid-induced respiratory depression	Nausea, vomiting, tachycardia, hypertension, fever, dizziness
ay	Oral	2.7	Adjunct to prevent relapse in formerly opioid-dependent patients	Nausea, vomiting, abdominal pain, dysphoria, joint and muscle pains, dizziness

The use of opioid drugs is continuing to increase, mainly because of the development of alternative routes of administration and increasing use in the very young. Pharmacological maneuvres have been made in order to improve analgesic potency and reduce adverse effects. Benzodiazepines have been used to improve analgesic effects (SEDA-17, 78), and methylphenidate has been given to patients in order to reduce drowsiness (SEDA-17, 78). Combinations of opioids with non-steroidal anti-inflammatory drugs have been used to provide analgesia postoperatively, with the aim of reducing the amounts of opioid required, with consequent reduction in adverse effects (SEDA-18, 79).

The more novel routes of administration of opioids, including oral, nasal, rectal, transdermal, spinal, and by patient-controlled methods, have been outlined (SEDA-17, 78). Oral transmucosal fentanyl administration, avoiding first-pass metabolism, produces analgesia and sedation in both adults and children undergoing short, painful outpatient procedures. The quality of analgesia is good, and the adverse effects are those typical of the opioids.

Degrees of risk

When the opioids are used correctly, their adverse effects are usually minimal. However, when they are used illicitly, they are often adulterated with other substances, which can cause adverse effects.

A strategy for controlling pain caused by malignant disease has been outlined and the classic effects that can be associated with opioid administration have been reviewed (6). These include constipation, nausea, sedation, pruritus, urinary retention, myoclonus, and respiratory depression. The latter can be life-threatening. Particular care is needed in opioid-naive individuals, those with compromised respiratory function, and elderly patients.

The use of opioids in very young patients is increasing. In a review of pain management in children, various routes of administration of opioids and their associated adverse effects have been discussed (SEDA-17, 78). Attention has been drawn to the adverse effects of intravenous codeine in children and to the risk of convulsions with pethidine in neonates, because of accumulation of its metabolite norpethidine. The risk of respiratory depression with morphine was also highlighted, and morphine is recommended for use only in neonates who are being ventilated or intensively nursed. Routine use of pulse oximetry has been recommended in all children receiving opioids (SEDA-21, 86).

The use of patient-controlled analgesia (PCA) (SEDA-15, 68) highlights the importance of adequate monitoring, in order to avoid potentially catastrophic adverse effects, such as respiratory depression. With PCA, patients generally use less morphine but still achieve the same degree of pain control (7). This supports the view that self-administration of opioids does not put patients at risk of over-medication or drug dependence.

It has been suggested that the risk of producing opioid dependence in the medical setting is greater in those who prescribe and administer them than in those who receive them (8). The likelihood of dependence in patients treated with opioids has been examined. In the treatment of cancer pain, tolerance and physical dependence occur but psychological dependence (addiction) is rare (9,10). In 11 882 patients who had received at least one opioid, addiction was reasonably well documented only in four (11).

Of 130 patients with chronic malignant and chronic benign pain attending a pain relief unit over 3 years, 9 (18%) were considered to be addicted to analgesics on subjective evaluation (12). Of 71 patients with chronic pain referred to a pain relief center, 86% were taking analgesics, 58% opioids, and 68% psychotropic agents; 49% of those taking opioids were considered to be dependent (13).

These studies emphasize the need to define the meaning of terms such as addiction and dependence correctly and to distinguish between psychological and physical dependence. Failure to do so could lead to unwitting deprivation of opioids in patients for whom they provide undisputed benefit with minimal harm. These results also suggest that patients receiving opioids for less well-defined pain conditions, quite often for longer periods and sometimes along with other drugs with abuse potential, may be at special risk of dependence and abuse. Thus, withdrawal may be important, but may become extremely difficult. The adverse effects encountered during long-term opioid therapy have been reviewed, as well as the evidence that opioids can cause seizures or seizure-like activity (SEDA-22, 97).

Opioid therapy and chronic non-cancer pain has been reviewed by the Canadian Pain Society in a consensus document that states that there is no recorded risk in the medical literature of direct permanent organ damage (including cognitive and psychomotor deficits) due to the appropriate therapeutic use of opioids and that problems are more often due to concurrent use of sedatives, such as benzodiazepines (14,15). Respiratory depression caused by opioid analgesics occurs largely in opioid-naïve patients and is short-lived. Constipation is a common initial adverse effect and is usually more difficult to treat than to prevent. It is therefore important to manage constipation prophylactically, using a stepped approach involving adequate dietary fiber, stool softeners, osmotic agents, and if necessary intermittent stimulant laxatives. Nausea is also a common adverse effect and usually resolves with continued use within days. Patients with a history of addiction should not necessarily be denied a trial of opioid therapy but will require more careful prescribing, closer follow up, and joint clinics between chronic pain and addiction specialists (16,17).

Finally, it must be borne in mind that some of the problems with opioids are treatable: for example, naloxone can reverse respiratory depression, but care must be taken in opioid-dependent individuals, as it may precipitate opioid withdrawal.

General adverse effects

Opioid agonists

Although opioids share many adverse effects, in some respects they are qualitatively and quantitatively different. They all cause constipation by reducing gastrointestinal

motility. Respiratory depression, cough suppression, nausea, vomiting, and urinary retention also occur. With the exception of constipation, tolerance to these effects develops. Physical and psychological dependence is also possible. Interaction with monoamine oxidase inhibitors leads to central nervous excitation and hypertension. Hypersusceptibility reactions are rare, although anaphylactic reactions have occurred after intravenous use and skin phenomena can occur. Tumor-inducing effects have not been described in man, but in vitro experiments have suggested a mutagenic effect of papaveretum in mammalian cell lines apparently related to the noscapine content.

The role of opioids in chronic non-malignant pain has been reviewed (18,19), and reports of randomized, double-blind, controlled studies of opioids in chronic non-malignant pain have been identified (19). Opioids appear to be more effective in patients with well-defined nociceptive pain (that is pain associated with clear evidence of tissue damage) than in patients with chronic non-malignant pain of neuropathic origin (i.e. pain associated with injury, disease, or section of the peripheral or central nervous system in the absence of tissue damage) or psychogenic causes (no organic pathology present). Gastrointestinal and CNS adverse effects (sedation, dizziness, cognitive impairment, respiratory depression, myoclonus) were frequent and distressing in most of the studies.

Clinical observations suggest that patients often find adverse effects, particularly nausea and vomiting, more distressing than the postoperative pain for which they are prescribed. Some are even willing to endure pain rather than suffer unpleasant adverse effects. This important aspect of opioid-induced analgesia has been investigated in a randomized, double blind, three-way, crossover study of between- and within-patient variability in response to equianalgesic doses of morphine, pethidine, and fentanyl during postoperative PCA (20). In 82 patients undergoing a variety of surgical procedures, the three opioids were equally efficacious from objective measurements in relieving pain and the subsequent incidence and intensity of adverse effects. However, the responses to the three opioids were highly individual, and there were three types of response. One group of patients tolerated all three opioids, another tolerated none, and a third group was sensitive to one or more of the opioids with no preference for any of the opioids used. The authors suggested that it would be good clinical practice to change from one opioid to another in patients who have intolerable adverse effects during PCA, since there is wide variation in subjective interpretation of pain and adverse effects.

Limitations to the use of opioids in cardiac surgery have been reviewed, highlighting the fact that μ receptor agonists cause dose-related respiratory depression through a reduction in carbon dioxide sensitivity in the respiratory centre (21). This depression, with a reduced respiratory rate and hypoxia, outlasts the analgesic effect of μ receptor agonists. Thoracic muscle rigidity on anesthetic induction with high doses of opioids has also been reported and can further compromise respiration. Hypotension through reduced peripheral vascular resistance occurs, while a negative inotropic effect of opioids acting directly on the heart via κ receptors is proposed, based on evidence from in vitro studies. The above effects have limited the role of opiates in patients with coronary artery disease, although they are of less importance in cardiopulmonary bypass surgery, when the heart is quiescent. In such surgery fentanyl partially blocks the expected tachycardia, hypertension, and release of inflammatory mediators that constitute the stress response, although the block is incomplete, owing to a lack of anesthetic effect.

Opioid partial agonists

There is evidence that in the case of partial opioid agonists, such as buprenorphine, the relative clinical activity of agonist and antagonist actions can differ, depending, among other things, on the dose.

The prevention of opioid-induced adverse effects

Prevention of sedation

The use and possible mechanism of amphetamines to counteract opioid-induced sedation has been reviewed (22). Most studies had methodological problems, including small numbers of patients completing short-term trials (under 1 week) and the small number of randomized, placebo-controlled, crossover trials. The quantitative measure of sedation was highly subjective and no uniform cognitive tests were performed to help compare the results of using amphetamines to reduce opioid-induced sedation. The overall conclusion was that more research is needed to determine the exact role of amphetamines. The use of amphetamine and amphetamine derivatives for the treatment of opioid-induced sedation is not recommended.

Prevention of emesis

Another excellent review has focused on the use of prophylactic antiemetics during PCA (23). A systematic search for relevant randomized controlled trails identified 14 studies involving 1117 adults published between 1992 and 1998. Without antiemetic drugs the incidence of opioid-induced nausea was on average 48% and of vomiting 55%, with a 67% chance of having an emetic episode. The most frequently studied antiemetic was droperidol, which was added to morphine PCA in six placebo-controlled trials in 642 adults and to tramadol in another trial. A wide range of doses of droperidol was used, with a constant degree of antiemetic efficacy. Based on this review, the optimal dose of droperidol is said to be less than 0.1 mg of droperidol per mg of morphine or less than 4 mg/day of droperidol. There were few adverse reactions: 56 in 10 000 patients had extrapyramidal adverse effects when droperidol was added to morphine PCA.

The next most frequently used drugs in the prevention of opioid-induced emesis are the 5-HT_3 receptor antagonists (ondansetron and tropisetron). There is no evidence that they prevent nausea, but the effect on vomiting is satisfactory enough for them to be regarded as second-line choices after droperidol. However, in 109 patients undergoing day-case oral surgery there was a higher incidence of nausea with tramadol plus ondansetron compared with three other treatments (fentanyl plus metoclopramide, tramadol plus metoclopramide, and

fentanyl plus ondansetron) (24). There was no difference between the groups in analgesic efficacy.

Other prophylactic antiemetic agents include clonidine, promethazine, hyoscine, propofol, and metoclopramide. However, the data on these drugs are either insufficient or non-existent.

In a randomized, double-blind, placebo-controlled study of 80 patients who required epidural morphine after abdominal hysterectomy, 40 received intravenous dexamethasone (8 mg) (25). The incidence of vomiting with dexamethasone group was 5% compared with 25% with placebo; the total incidence of nausea and vomiting was 16% compared with 56%.

Prevention of pruritus

The incidence of opioid-induced pruritus varies widely, and depends on the opioid used and its mode of administration. The highest incidence (up to 80%) is associated with intrathecal morphine. The pruritus is usually localized to the area of the face that is innervated by the trigeminal nerve. A central encephalinergic mechanism has been proposed to explain this localization. The pruritus is often difficult to treat and responds poorly to conventional treatments, except for naloxone and propofol; 10–15% remain unresponsive. Naloxone reversibility of opioid-induced pruritus supports the existence of an opioid-medicated central mechanism. However, naloxone will reverse the analgesic effects of the opioids.

Three studies have suggested the use of ondansetron, a 5-HT_3 receptor antagonist, for the treatment of opioid-induced pruritus (26–28). The articles suggested a possible interaction between the opioid and the serotonergic systems. In one prospective, randomized, double-blind, placebo-controlled study, 80 patients undergoing any type of surgery were given intravenous ondansetron 4 mg or 0.9% saline over 1 minute, with alfentanil as the opioid used in the anesthetic technique (26). The study was inconclusive; there was a significant reduction in the incidence of scratching in patients who received ondansetron compared with placebo but a non-significant incidence of itching in the ondansetron group.

In a prospective randomized, double-blind, placebo-controlled study in 100 patients scheduled for elective orthopedic surgery and presenting with pruritus induced by epidural or intrathecal morphine, intravenous ondansetron 8 mg was effective in 70% of cases and placebo in 30% (27). Ondansetron was well tolerated, did not change the degree of analgesia, and was not associated with adverse effects usually associated with ondansetron, such as headache, abdominal pain, and cardiac dysrhythmias.

In a double-blind randomized study of 130 patients given subarachnoid bupivacaine 0.5% with morphine 0.3 mg for surgical and postoperative analgesia, repeated-dose and single-dose ondansetron were compared (28). The overall incidence of pruritus was 73% in the group not given ondansetron, 63% in those who received intravenous ondansetron 4 mg 20 minutes before the spinal analgesia and 2 ml of saline at 12, 24, 26, and 48 hours after surgery, and only 49% in those who received ondansetron 4 mg 20 minutes before the spinal and 12, 24, 36, and 48 hours after surgery. There were methodological problems—the small number of subjects studied and the lack of an objective scoring system—but these results add to the current discussion of pursuing further studies to determine the effective dose of ondansetron in the treatment of opioid-induced pruritus. Further neurobiological research is needed to determine a "human" model of explaining the role and interactions of the central serotonergic system with the opioid system.

In a prospective, randomized, controlled study, 90 women with moderate to severe pruritus due to intrathecal morphine after cesarean section were given intravenous nalbuphine 2 mg, 3 mg, or 4 mg (29). Nalbuphine 2–3 mg relieved morphine-induced pruritus without increasing pain scores or causing other adverse effects.

Observational studies

Drug-related emergency department visits have been studied in a district hospital in Finland (30). Adverse drug reactions were responsible for 2.3% (n = 167) of all visits over a 6-month period; 102 visits were related to adverse drug reactions without intentional overdoses, and 65 were related to overdose. Opioids were responsible for only four adverse drug reactions; three patients complained of nausea and one of constipation. The opioids involved were fentanyl, oxycodone and tramadol. Two of these patients required admission to hospital.

Systematic reviews

The administration of opioids has been compared with continuous peripheral nerve block for pain control (31). Peripheral nerve catheter analgesia resulted in superior pain control and was associated with fewer adverse effects. Peripheral nerve block was associated with motor block, whereas nausea, vomiting, pruritus, and sedation were associated with opioid administration.

Organs and Systems

Cardiovascular

Orthostatic hypotension can occur and is common after intravenous administration. Histamine release sometimes contributes to this.

Respiratory

Opioids cause respiratory depression by virtue of a direct effect on brain-stem respiratory centers (32). The nadir depends on the route of administration, and occurs at about 7 minutes after intravenous opioids, but not until about 30 minutes after intramuscular and 90 minutes after subcutaneous injection. The mechanisms of the respiratory effects of opioids (with special reference to their postoperative use) have been reviewed (SEDA-20, 76) (SEDA-21, 85). Pulmonary granulomatosis has occurred (33), and asthma after opioid inhalation has been described (34).

Nervous system

Opioids produce analgesia without loss of consciousness, although drowsiness, changes in mood, and mental clouding occur. Responses to painful stimuli are blocked at several locations in the brain, resulting in both an alteration in the sensation of pain and a change in the affective response. The ability of a patient to perceive pain can remain the same while tolerance to pain is markedly increased (35).

Opioids cause nausea and vomiting by stimulating the chemoreceptor trigger zone in the medulla, although tolerance to this effect usually develops within a few days (36).

Patients using chronic opioids tend to have more pain when attempts are made at managing pain by giving larger doses, and pain is probably best managed by withdrawing the opioid medication. In one study higher degrees of pain were experienced with high potency bolus release medications, such as oxycodone modified-release, than with less potent immediate-release medications, such as hydrocodone (37). On the other hand, a study of opiate addicts undergoing detoxification with methadone and/or heroin provided evidence of hyperalgesia (38). Patients and controls were subjected to a cold pressor test and reactions were monitored. Reactions were suggestive of hyperalgesia; however, they also indicated increased pain latency and reduced pain intensity. These phenomena are contradictory and require further research.

Morphine and most opioids cause pupillary constriction, which may be due to an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. Tolerance to this miotic effect is not usual.

Single therapeutic doses of opioids produce a shift toward increased voltage and lower frequencies in the encephalogram, such as occurs in natural sleep or after very low doses of barbiturates. High doses of morphine can cause sleep disturbances in some children (SEDA-17, 78).

Fentanyl and sufentanil can cause epileptiform activity in patients undergoing coronary artery bypass grafting (SEDA-18, 79).

Catatonia is a rare complication of prolonged epidural opioid administration in cancer pain (SEDA-16, 78). Patients with advanced cancer who were taking opioids had significant but transient cognitive impairment when opioid doses were increased (39). This correlates well with studies of the effects of psychotropic medications on ability to drive (40).

Opioids and hypnotic drugs are often used to prevent increased intracranial pressure and the subsequent reduction in cerebral perfusion pressure. However, it is still uncertain whether opioids can cause increased intracranial pressure. The effects of a bolus injection and infusion of sufentanil, alfentanil, and fentanyl on cerebral hemodynamics and electroencephalographic activity have been studied in a randomized crossover study in six patients with increased intracranial pressure after severe head trauma (41). All three infusions were associated with a significant increase in intracranial pressure (9, 8, and 5.5 mmHg respectively) 3–5 minutes after the bolus opioid injection. Intracranial pressure gradually fell and returned to baseline after 15 minutes. This increase was associated with significant falls in mean arterial pressure and cerebral perfusion pressure throughout the study period. The electroencephalogram changed from a fast to a reduced activity pattern, with an improvement in background activity. It is therefore advisable to avoid using bolus injections of opioids in patients with head injury and to use continuous infusion for sedation.

Psychological

The neuropsychiatric syndrome that results from opioid toxicity consists of cognitive impairment, severe sedation, hallucinations, myoclonic seizures, and hyperalgesia (42). Opioid-induced neurotoxicity is most often seen in patients receiving high doses of opioids for prolonged periods, often in association with psychoactive medications (for example benzodiazepines and tricyclic antidepressants), and in older patients with associated dehydration and renal insufficiency. Strategies for reducing the occurrence of opioid-induced neurotoxicity primarily include opioid rotation and dosage reduction and circadian modulation techniques. Drugs such as amphetamines, amphetamine-like derivatives, and neuroleptic drugs like haloperidol can be used to treat hallucinations and delirium as a result of opioid-induced neurotoxicity and when the minimal dose of opioid that can cause sufficient analgesia also causes excess sedation. Proper assessment of the potential risk factors of opioid-induced neurotoxicity with careful monitoring of early signs is the fundamental principle in prevention.

Delirium and cognitive impairment are common postoperative adverse events, especially in elderly patients. Susceptibility factors and intraoperative and postoperative factors influence the development of postoperative delirium and/or cognitive impairment and are associated with poor functional recovery and increased morbidity. A systematic review including clinical trials and observational studies explored the use of opioids postoperatively in elderly patients and the risk of development of postoperative cognitive impairment and/or delirium (43). Opioids more commonly used postoperatively include morphine, fentanyl, and hydromorphone. When comparing the postoperative use of these opioids with postoperative pethidine, the latter was significantly associated with an increased risk of delirium or cognitive impairment. These studies did not provide sufficient evidence to establish whether there were any differences in the risks of morphine, fentanyl, or hydromorphone. The authors also explored whether the route of administration of opioids made a contribution to the risk of cognitive impairment; there was no significant difference between epidural and parenteral analgesia. They recognized that delirium and/or cognitive impairment are common adverse events that affect morbidity and postoperative recovery, the limitations of the papers reviewed (e.g. small sample sizes and non-standardized measurement of cognitive impairment), and recommended future

studies of both the and postoperative cognitive impairment in patients given postoperative opioids.

In another study postoperative cognitive function was assessed after patient controlled analgesia in 30 patients undergoing lower abdominal surgery, who received either fentanyl (n = 17) or tramadol (n = 13) intraoperatively and postoperatively (44). Cognitive function was assessed on days 1 and 2 using the Mini Mental State Examination and the Benton Visual Retention Test. Although the patients in the two groups had similar cognitive abilities, those who received tramadol were motivated to accomplish cognitively demanding tasks.

Dependent drug users, current and former, have impairment of executive and memory function. Executive and memory function has been explored in 25 chronic amphetamine users and 42 chronic opiate users (45). Compared with controls, drug users had impairment of spatial planning, paired associate learning, and visual pattern recognition. Amphetamine users had greater impairment of spatial planning, pattern recognition memory, and attentional set-shifting.

Endocrine

Morphine reduces the response of the hypothalamus to afferent stimulation (46). In many species, opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanisms.

In patients undergoing surgery, opioids inhibit the stress-induced release of ACTH (47).

Secretion of luteinizing hormone (LH) and thyrotropin is suppressed by opioids, whereas the release of prolactin and, in some cases, growth hormone is enhanced (48).

Gastrointestinal

Opioids reduce the secretion of hydrochloric acid and have a marked effect on gastrointestinal motility. Gastric emptying is prolonged and the likelihood of esophageal reflux is increased (49). Tone in the antral part of the stomach and first part of the duodenum is increased. The passage of gastric contents through the duodenum can be delayed by as much as 12 hours, retarding the absorption of orally administered drugs (50). In 260 patients with malignant disease, 23–40% vomited and 8–10% felt nauseated (SEDA-17, 79). Transdermal hyoscine (scopolamine) can reduce these problems (SEDA-17, 79).

Biliary and pancreatic and intestinal secretions are reduced by morphine, and digestion in the small intestine is delayed.

Opioid-induced gastrointestinal dysfunction contributes to patient dissatisfaction and affects quality of life. The pathophysiological mechanisms underlying gastrointestinal dysfunction following opioid use have been reviewed (51). Nausea and vomiting, experienced by a large number of patients who take opioids, are believed to be triggered by both peripheral and central mechanisms. Constipation, experienced by 40–50% of patients, is induced by doses of opioids lower than the doses required for analgesia.

The tone of the anal sphincter is increased and the usual reflex relaxation response to rectal distension is reduced.

Tolerance to constipation does not tend to develop. The authors suggested several options to reduce the incidence of constipation: e.g. administering newer opioid compounds (such as dihydroetorphine hydrochloride); using the transdermal route; opioid-sparing through adjunctive treatment.

Another gastrointestinal effect is ileus, with several potential underlying pathophysiological mechanisms (52).

- A woman on chronic narcotics (oxycodone 5 mg, 2–3 times per week) underwent colonoscopy, during which she was given midazolam 7 mg, pethidine 100 mg, and fentanyl 125 micrograms. She later developed acute colonic pseudo-obstruction necessitating hospital admission.

Ileus is postulated to result from motor inhibition of the gastrointestinal tract by narcotics.

Biliary tract

Therapeutic doses of opioids constrict the sphincter of Oddi, and biliary tract pressure rises ten-fold. Patients with biliary colic can have exacerbation of pain after morphine. Likewise, opioids such as fentanyl, morphine, and dextropropoxyphene can cause bile duct spasm (SEDA-21, 85).

"It is standard teaching that morphine should not be used to treat patients with pancreatitis because it causes a rise in biliary and pancreatic pressure" (53). From this starting point, this comprehensive review discusses current approaches to opioid analgesia in pancreatitis, pointing out that morphine has been reported to cause biliary colic in individuals without biliary tract disease and that pethidine (meperidine) has become the analgesic of choice. Constriction of the sphincter of Oddi and the basal tone of the sphincter and the frequency of phasic contractions have been measured using endoscopic retrograde cholangiopancreatography (ERCP); an increase in basal tone is believed to be the best indication of sphincter dysfunction. Morphine sulfate in intravenous doses of 2.5–5 micrograms/kg caused increased contractions but no change in basal pressure, while doses of 10 micrograms/kg and over caused a rise in basal pressure. Pethidine increased contractions but not basal tone, while tramadol had no effect on basal pressure in a small study. Among mixed opiate agonist/antagonists, pentazocine increased basal pressure. Buprenorphine, a partial opiate agonist, resulted in no pressure changes, while the antagonist naloxone 0.4 mg intravenously had no effect alone on the sphincter basal pressure and did not stop the increase in pressure caused by morphine. However, case reports have suggested that naloxone reduces sphincter spasm in clinical situations.

Urinary tract

The urinary voiding reflex is inhibited by opioids, and both the tone of the external sphincter and the volume of the bladder increase; urinary retention is therefore common.

Skin

Flushing of the face, neck, and upper thorax can follow therapeutic doses of opioids. These effects may be partly due to release of histamine, which is also implicated in the sweating and pruritus seen after opioid administration. Opioid effects on neurons may partly be involved in the pruritus, as pruritus is provoked by opioids that do not release histamine and is abolished by small doses of naloxone.

Urticaria at the site of injection is due to histamine release. It is seen with pethidine and morphine, but not with oxymorphone, methadone, fentanyl, or sufentanil. Wheal and flare responses to various opioids differ (54).

Musculoskeletal

Opioid use results in reduced bone mineral density, probably mediated by suppression of endogenous production of sex hormones. In a large sample of the US population opioid users had a reduced bone mineral density compared with non-users, when adjusting for all co-variates (55). This effect was more evident in long-term users. Owing to lack of data on testosterone and estradiol, the investigators could not prove causality.

A report of bilateral femoral neck stress fractures in a heroin addict has highlighted the importance of early identification of osteopenia (56).

A nationwide case-control study in Denmark established that opiates were associated with an increased risk of fractures (57). The study included all individuals who had sustained a fracture in the year 2000 (n = 124 655). For each case, three controls matched for age and sex were randomly drawn from the general population. A number of opioids (morphine, methadone, fentanyl, ketobemidone, nicomorphine, oxycodone, codeine, and tramadol) were associated with an increased risk of fractures. However, dextropropoxyphene, pethidine, acetylsalicylic acid + codeine combination, and buprenorphine were not associated with an increased risk. With most of the opioids mentioned there was an increased risk at all doses. Fentanyl increased the risk at higher doses, while nicomorphine and ketobemidone increased the risk at lower doses. The increased fracture risk, even at lower doses and even when the opioids had only been taken for a short time, suggested that the most probable underlying primary reason for fractures was falls due to the central nervous system effects of the opioids, as opposed to weakening of the bone structure. The use of alcohol was a significant risk factor in all cases. Although the study had significant limitations and potential confounding factors, the large numbers made the results more reliable.

Sexual function

Although long-term administration of low-dose opioids, especially intrathecally, improves quality of life through improved pain control, it can compromise it by causing impaired sexual function. Low testosterone concentrations have been reported in heroin addicts (58) and subjects in a methadone maintenance program (59).

In prospective non-randomized non-blinded evaluation of the effects of a 12-week course of intrathecal opioids for the control of chronic non-cancer pain on the hypothalamic–pituitary–gonadal axis in 12 men, it was suppressed and serum testosterone concentrations fell (60). This effect not only reduces quality of life through sexual dysfunction but can also increase the risk of spinal osteoporosis in men, with an increased risk of vertebral and hip fractures. Patients receiving long-term intrathecal opioid therapy need to be informed of potential hypothalamic–pituitary–gonadal axis suppression as a result of the treatment, and testosterone replacement after hypothalamic–pituitary–gonadal axis surveillance during treatment should be considered if indicated.

Immunologic

The immunosuppressive effects of morphine, tramadol, and the combination of tramadol + lornoxicam for pain management after elective gastric cancer surgery (n = 45) have been compared (61). Immunosuppression was measured by observing expressions of T lymphocyte subsets, natural-killer cells, and activated T lymphocytes. The combination of tramadol + lornoxicam provided equivalent analgesia but caused less immunosuppression than morphine or tramadol alone.

Infection risk

The immunomodulatory effects of opioids contribute to altered immune responses to injury. In a case-control study patients with burns who developed infections were more likely to be taking high doses of opioids (62). Both burns and opioids induce immunosuppression, and the authors suggested that they act synergistically, increasing the risk of infection, especially in mild to moderate injuries. In those with large burns, opioids had no effect, possibly because of maximal immunosuppression by the burns.

Death

Opiates are widely used all over the world, but recently concerns about opiate use (and deaths from such use) have increased in Australia and the UK (63). The rate of opiate overdose deaths in these countries increased dramatically between 1985 and 1995. Throughout that period, it was four to ten times higher in Australia than the UK, but the rate of increase may have been greater in the UK in the latter half of the period, since the difference in rate narrowed substantially during that time. Methadone maintenance treatment, established in Australia in 1969 and in the UK in 1970, has become the main treatment for opiate dependence in both countries. About half of the opiate deaths in the UK were attributed at least in part to methadone. By contrast, considerably fewer (18%) opiate overdose deaths in Australia were attributed to methadone. The authors suggested that the discrepancy in the rates between the two countries could be artefacts of the differences in (a) the documentation of these deaths, (b) the rate of opiate dependence, (c) the

route of opiate administration, (d) opiate purity, and, most importantly, (e) the method of delivery of methadone maintenance treatment.

Methadone-related fatalities have been reported from all countries in which methadone has been used for either detoxification or maintenance treatment of opiate users. These fatalities are often defined as cases of poisoning due to methadone or as polydrug intoxication with methadone as the leading cause of death. Methadone maintenance treatment was introduced in Germany in 1989, and 1396 drug-related deaths were reported from 1990 to 1999 in Hamburg (64). While the absolute numbers of drug-related deaths by poisoning did not change over this period, the rise in methadone-associated deaths paralleled a fall in the number of heroin-associated deaths. From 1990 to 1998, the rate of monovalent heroin intoxication in cases of poisoning fell from 60% to 11%, while the rate of polydrug intoxication increased. Poisoning caused by methadone combined with other substances first gained significance 4 years after methadone maintenance treatment was introduced in Hamburg. Since 1994, methadone-related deaths have increased steadily, and by 1997–1998 the numbers had increased exponentially. In the first 6 months of 1999, 60% of all cases of poisoning among drug addicts showed the presence of methadone. When strict guidelines for describing such poisonings were used, 39 poisonings in 1998 (40%) were predominantly caused by methadone, six of them being monovalent methadone intoxication. About two-thirds of all methadone-related poisonings concerned drug addicts who never stayed in methadone maintenance treatment, implying that they obtained methadone from outside of regular treatment. Almost 10 years after the introduction of methadone maintenance treatment in Hamburg, methadone replaced heroin as the leading cause of death due to poisoning. At the same time, however, the absolute number of drug-related deaths and poisonings fell slightly. While methadone maintenance treatment has clearly reduced overall morbidity and mortality in addicts globally, some issues remain unresolved. There are significant differences in the delivery of methadone maintenance treatment from one country to another. The authors reported that in some patients the starting doses of methadone are quite high and potentially lethal. This is especially so when the patients are also using other drugs and attempting to wean off them. Thus, continued polydrug use in treatment is an important risk factor for mortality. Many patients receive take-home doses for a week at a time. While this is useful in a select group of patients, it is not useful in those who sell methadone to buy heroin and combine the two drugs without knowledge of their half-lives and potential complications. The authors suggested changes in methadone maintenance treatment policy, in order to reduce the chances of accidental overdose/poisoning. Specifically, they recommended: a substantial improvement in quality assurance; a more restrictive methadone take-home policy (at least for patients with evidence for concomitant opiate use); and evaluating heroin or long-acting acetylmethadol as alternatives.

Another report from Australia reviewed all the accidental illicit drug deaths that occurred in the Sydney area in 1995–1997 (65). There were 3559 autopsies, of which 4% were considered accidental illicit drug deaths; of these deaths, 121 were men and 22 were women. While the highest number of male deaths occurred in the 25–35 year age group, female deaths were evenly spread from ages 20–35. Almost half (49%) of the deaths occurred from morphine poisoning, 27% from multiple drug toxicity, and 21% from heroin toxicity combined with alcohol. Methadone was detected in 19 cases (13%); 12 of these people were enrolled in a methadone maintenance program. Methadone intoxication alone was responsible for two deaths (1%) only. Methadone was present in the blood in a potentially fatal concentration in 13 cases, while 113 people (80%) had a heroin concentration in the fatal range and 91% had detectable concentrations of heroin. There were no significant neurological findings in the 143 cases studied. More than 50% of those with methadone detected also had heroin in their blood. Unfortunately, this appears to show that some people who participate in a methadone program may still die from accidental heroin overdose. Thus, the authors emphasized the importance of education of heroin users about the risk of accidental overdose.

There is excess mortality in heroin users compared with the general population. The prevalence and experience of heroin overdose in drug users in a general practice in Ireland were examined during 5 months (66). Of the 33 patients identified, 24 agreed to participate. They had had their first overdose on average 5 years after starting to use heroin. Ten had taken an overdose themselves, 23 had witnessed an overdose, 22 knew a victim of fatal overdose, and 4 had been present at a fatal overdose. However, they reported poor understanding of how to deal with an overdose. Despite maintenance treatment with methadone, a significant proportion continued to inject heroin; 17% admitted to the use of illicit methadone, but methadone was not implicated in overdose in any case. The authors suggested that overdose prevention and management should become a priority for general practitioners who care for opiate-dependent patients. Factors implicated in overdose include too high a dose, use after a period of abstinence, and mixing with other drugs.

Clostridium novyi type A, a bacterium that was associated with serious infection during the two World Wars, killed 35 injecting heroin users in Britain and Ireland (67). *Clostridium novyi* type A is present in soil and dust and is a well-recognized cause of infection in sheep, cattle, and other animals. Contaminated batches of heroin from a common source were believed to be responsible for the recent outbreak. The bacteria were able to survive the process of preparation for injection. All recent cases occurred after intramuscular injection, which provides the requisite anerobic conditions for infection. This was the first time that this organism caused an outbreak of infection in drug injectors. In all, 74 cases with the same clinical features were reported.

An increase in the number of deaths of all body packers in New York has been associated with an increase in

deaths among opiate body packers: of 50 deaths among body packers from 1990 to 2001, 42 were due to opiates (68). Four were related to cocaine and four to both opiates and cocaine. In 37 cases, open or leaking drug packets in the gastrointestinal tract resulted in acute intoxication and death. Five cases involved intestinal obstruction or perforation, one a gunshot wound, one an intracerebral hemorrhage due to hypertensive disease, and one was undetermined. The number of packets recovered was 1–111 (average 46).

An unbound morphine blood concentration of 100 ng/ml or more is considered potentially fatal. However, fatal cases of heroin intoxication occur in patients with blood morphine concentrations below 100 ng/ml. In 62 cases of heroin intoxication, death was associated with unbound morphine heart blood concentrations below 100 ng/ml in 21 cases and 100 ng/ml or over in 41 cases (69). In the 21 with low concentrations, respiratory tract infections occurred more often, and plausible causes of death were identified in 19.

Unintentional fatal poisoning in the USA increased by 18% per year from 1990 to 2002, and the majority were attributed to 'narcotics' and 'unspecified drugs' (70). From 1999 to 2002 opioid analgesic poisoning increased by 91% and heroin poisoning increased by 12%, making licit drugs the most common cause of fatal drug poisoning in the USA, replacing illicit drugs. Of the opioid analgesic fatalities 54% were from semisynthetic opioids (e.g. oxycodone and hydrocodone), 32% from methadone, and 13% from other synthetic opioids (for example fentanyl). This increase in fatalities has coincided with a change in prescribing practices amongst physicians. Since 1990, they have increased prescribing of opioids for pain management. This epidemiological study has suggested that the increase in prescribing may have contributed to the increase in opioid-related deaths.

In an epidemiological study in the USA the trends in opioid-related deaths in 1990–2003 were analysed (71). Fatalities increased by 529%, from 1.4 per 100 000 in 1990 to 8.8 per 100 000 in 2003, among both sexes, all age groups, and all racial/ethnic groups. These trends in Massachusetts are consistent with trends of opioid-related deaths elsewhere in the USA.

Epidemiological data from the UK from 1993 to 2004 give the number of heroin/methadone deaths as 7072 and methadone deaths as 3298 (72). Age-standardized mortality rates increased from 5 to 15 per million from 1993 to 1997. Methadone deaths fell from 1997 to 2004. During this period there was an increase in the use of methadone, but the data suggest that this was not associated with an increased number of deaths.

Opiate overdose deaths in England fell by 21% from 2002 to 2003; Brighton had the highest drug-related death rate (73). In 75% of the deaths that involved methadone there was also polydrug use, and in 30% there were toxic concentrations of other substances. The authors highlighted the fact that buprenorphine also carries a significant risk of respiratory depression, is easier to inject, and carries a risk of pulmonary edema. This finding was confirmed in study in Germany (74). One buprenorphine death was reported in 2002–2003, resulting from injection of crushed buprenorphine. Of note is the higher numbers of incidents reported with methadone (35%) and heroin (62%). Buprenorphine appears to be associated with a lower risk of fatal overdoses.

Benzodiazepines, identified through toxicology screening at autopsy, were found in a significant number of buprenorphine-related deaths in Singapore (75). Between September 2003 and 2004 there were 21 cases of buprenorphine-related deaths, in 19 of which benzodiazepines had also been used.

The risk of accidental overdose in those found to be positive for methadone is increased by the concomitant use of tricyclic antidepressants, benzodiazepines, and both (76). In a retrospective epidemiological study in New York City in 2003, there were 500 (8.6%) methadone positive deaths, of which 493 were analysed; tricyclic antidepressants were also found in 19% and benzodiazepine in 32%. The authors advised increased awareness of the risk of such combinations.

In a review of the literature the three main factors that predicted fatal opioid overdoses were injecting heroin, chronic alcohol misuse, and having been arrested more than three times (77).

Long-Term Effects

Drug abuse

The abuse potential and importance of identifying and managing the risks of opioids has been reviewed (78). Abuse of opioids is highly prevalent globally, and the authors discussed strategies for reducing it, such as making tablets 'tamper resistant', providing controlled-release dosage forms, partial agonists, and drug combinations that precipitate withdrawal if misused. Such strategies are linked to a risk of overdose. They suggested a standard procedure for evaluating the abuse potential of substances at various stages of drug development.

Drug tolerance

The clinical significance of opioid tolerance has been extensively reviewed (4) and the evidence for tolerance in acute and prolonged opioid administration has been presented. The former remains controversial while the latter has been adequately demonstrated. Different patterns of opioid use in chronic cancer-related pain are described, these being essentially escalating prescribing, steady-dose prescribing, and opioid withdrawal. The particular pattern followed by any individual is the result of the balance between physical changes in the level of nociceptive activity, psychological processes, such as increased anxiety and depression, and the degree of tolerance itself. While tolerance to an opiate reduces its clinical effectiveness, the tolerance may be beneficial if it mitigates drug adverse effects. Tolerance to respiratory depression and nausea occurs swiftly, sedation takes longer to resolve, and constipation is relatively resistant to the development of tolerance. Cross-tolerance is partial; hence switching from one opioid to another can relieve particular adverse effects without loss of clinical effect.

Physical dependence on opioids appears to occur in patients who use opioids for long-term pain relief, and cases of addiction have been reported. However, rates of addiction are low and occur mainly in individuals who have a history of substance misuse. The role of long-term opioid medication in non-cancer-related chronic pain remains controversial. "Opiophobia," a fear of the legitimate use of opioid analgesics because of the potential for addiction, remains a significant issue for physicians, patients, and relatives alike. The review is illustrated with a report of a 52-year-old man with multiple myeloma who displayed tolerance to oral morphine over 2 years.

Opioid tolerance in neonates

Tolerance to opioids in neonates has been reviewed (79). There are two forms of neonatal opioid exposure. First, in-utero exposure to opioids of neonates with opiate-addicted mothers; secondly, preterm infants requiring prolonged support in intensive care when opioid administration is used to reduce the stress response. The adverse effects of opioids on neonates are similar to those described in adults (sedation, dysphoria, seizures, nausea and vomiting, urinary retention, reduced intestinal motility, biliary tract spasm, histamine release, and chest wall rigidity), but it has been proposed that differences in the densities of the different opioid receptor subtypes lead to an increased theoretical propensity for respiratory depression with given opioid doses compared with older people. However, clinical studies have not confirmed increased sensitivity to respiratory depression in neonates or young infants. Tolerance may occur more swiftly in neonates due to slower opioid metabolism and a more permeable blood–brain barrier. Opioid withdrawal symptoms in neonates are similar to those for other age groups but can be mimicked by hypoxia, hypercarbia, hypoglycemia, hypocalcemia, or hypomagnesemia. Assessment of tolerance and withdrawal is made using the neonatal abstinence score rating scale and the neonatal withdrawal index.

Management of neonatal opioid withdrawal relies on gradually reducing doses of opioids to reduce the severity of withdrawal symptoms. Paregoric was formerly used as a withdrawal aid but is little used now owing to toxic effects. Tincture of opium (10% solution), consisting of 1 ml in 24 ml of sterile water, 0.05 ml/kg 4-hourly is proposed as the most suitable replacement. Speed of reduction depends on the length of neonatal exposure to opioids and a short reducing regimen (over 2–3 days) can be sufficient. A methadone replacement withdrawal regimen is also discussed, while benzodiazepines, phenobarbital, chlorpromazine, and clonidine are all reviewed as having a potential role in symptomatic relief during withdrawal; however, each has its own associated adverse effects, which limit their usefulness.

Mechanism

At micromolar concentrations opioids cause an increase in the cell membrane threshold, shortened action potentials, and inhibition of neurotransmitter release. At nanomolar concentrations opioid agonists are excitatory and prolong the action potential via the stimulatory G proteins, which act on the adenylate cyclase/cAMP system and on protein kinase A-dependent ion channels. Tolerance is proposed to be the result of an increase in the association of opioid receptors to stimulatory G proteins, to an activation of *N*-methyl-D-aspartate receptors via protein kinase C, and calmodulin-dependent increases in cytosolic calcium, resulting in cellular hyperexcitability.

Drug withdrawal

Chronic administration of opioids produces physical and psychological dependence. A characteristic withdrawal syndrome occurs when the opioid is stopped abruptly or an opioid antagonist is given. In the case of morphine and other OP_3 receptor agonists with a similar duration of action, lacrimation, rhinorrhea, yawning, and sweating occur about 8–12 hours after the last dose. Symptoms peak at about 24–48 hours after withdrawal, with restlessness, irritability, and insomnia, as well as severe sneezing, weakness, anxiety, and depression. Other symptoms include dilated pupils, anorexia, piloerection, nausea, vomiting, diarrhea, pyrexia, hypertension, muscle cramps, dehydration, and weight loss (80).

Treatment of opioid withdrawal

Various regimens were used in the past in an attempt to withdraw patients from opioid addiction (81). The modern scientific basis for the evaluation of opioid withdrawal regimens was established by Kolb and Himmelsbach (82), who concluded that the methods that produced the least discomfort and the best results were either abrupt or rapid withdrawal of the opioid. Rapid withdrawal consisted of gradually reducing doses of morphine over 4–10 days. Such methods were in regular use until the advent of methadone as a heroin substitute in the 1950s.

Antidepressant, anxiolytic, and neuroleptic drugs can allow some patients to participate in treatment programs, especially when drug abuse is associated with psychiatric disorders such as depression, chronic anxiety, or schizophrenia.

Methadone

A widely used technique, pioneered by Isbell and Vogel (83), involves the substitution of methadone for the illicit opioid, followed by a gradual reduction in the amount of methadone taken. Methadone is used to substitute for a variety of opioid drugs. It is well absorbed after oral ingestion, with peak blood concentrations after about 4 hours. Steady-state concentrations are reached after about 5 days. By virtue of its long duration of action (the half-life with regular dosing is about 22 hours), methadone suppresses opioid withdrawal symptoms for 24–36 hours. In the early stages of treatment, patients may report problems such as drowsiness, insomnia, nausea, euphoria, difficulty in micturition, and excessive sweating. With the exception of chronic constipation and excessive sweating, these effects do not generally persist.

British studies have shown that, using methadone, about 80% of inpatients but only 17% of outpatients were

successfully withdrawn (84,85). However, the technique is not without problems, one being that the methadone reduces but does not eliminate withdrawal symptoms. The withdrawal response has been described as being akin to a mild case of influenza, objectively mild but subjectively severe (86). The fear of withdrawal symptoms expressed by those dependent on drugs should not be underestimated: these factors are associated with the subsequent severity of withdrawal symptoms, and they are more closely related to symptom severity than drug dosage (87). Methadone substitution can result in a protracted withdrawal response, with patients still experiencing significantly more symptoms than controls 2 weeks after withdrawal (88).

In a study of methadone withdrawal, patients who were withdrawn over 10 days had a withdrawal syndrome that began to increase in severity from day 3, with peak severity of symptoms on day 13; in those who were withdrawn over 21 days, symptoms began to increase about day 10 with a peak on day 20 and abated thereafter, although some patients did not recover fully until 40 days after starting withdrawal (89). Thus, the duration of the withdrawal syndrome is much the same for both treatments in terms of symptom severity. It is possible that an exponential rather than a linear reduction in dosage may improve the withdrawal response. These results may be of clinical significance, in that patients may feel it important that they recover from withdrawal as quickly as possible, in order to participate fully in other aspects of drug withdrawal programs. However, although there was no difference between the 10-day and the 21-day programs regarding completion rates for detoxification (70 and 79% respectively), the dropout rates after detoxification were significantly different. During the 10 days after the last dose of methadone, the dropout rate in the 21-day group was 18% compared with 30% in the 10-day group. These results may also have financial implications in respect of the number of subjects who can be admitted to treatment programs.

In some treatment programs total abstinence is not considered to be a practical objective and treatment may involve the use of drugs such as methadone as maintenance therapy with the expectation of reducing illicit drug consumption (90). Well-organized methadone maintenance treatment can reduce the intake of illicit opioids in many injecting drug users (91,92).

The methadone maintenance treatment was established in 1964 in New York City by Vincent Dole and Marie Nyswander (see the monograph on Methadone). In the initial studies, subjects who were heavily addicted to heroin were evaluated and stabilized on daily methadone doses as inpatients before transfer to an outpatient clinic for continued treatment. With further experience, it was feasible to drop the inpatient phase.

Outcome studies of methadone maintenance treatment have reported favorable results, with high rates of patient retention, reduced criminality, and improved social rehabilitation. However, despite its proved effectiveness, it remains a controversial approach among substance abuse treatment providers, public officials, policy makers, the medical profession, and the public at large. Nevertheless, almost every nation with a significant narcotic addiction problem has established a methadone maintenance treatment program.

For patients entering treatment from an institution where they have been drug-free, initial daily methadone doses should be no more than 20 mg. Otherwise initial daily doses of 30–40 mg should be sufficient to obtain the necessary balance between withdrawal and narcotic symptoms. Thereafter, stabilization is achieved by gradually increasing the dose. When methadone is given in adequate oral doses (usually 60 mg/day or more), a single dose in a stabilized patient lasts 24–36 hours, without creating euphoria and sedation. Tolerance to methadone seems to remain steady, and patients can be maintained on the same dose, in some cases for more than 20 years.

The methadone dose must be determined individually, because of individual variability in pharmacokinetics and pharmacodynamics. Maintenance of appropriate methadone blood concentrations is recommended.

Tolerance to the narcotic properties of methadone develops within 4–6 weeks, but tolerance to the autonomic effects (for example constipation and sweating) develops more slowly.

The major adverse effects during treatment occur during the initial stabilization phase. In addition to constipation and sweating, the most frequently reported adverse effects are transient skin rash, weight gain, and fluid retention. Since the main metabolic pathway of methadone is CYP3A4 numerous drug interactions can be expected. Drugs that interact with methadone and other opioid analgesics are listed in Table 2.

Methadone maintenance treatment is considered to be a medically safe treatment with relatively few and minimal adverse effects. However the danger of serious adverse effects and death with the increasing use of methadone as maintenance therapy in drug addicts has been highlighted. It must be emphasized that a daily maintenance dose of 50–100 mg is toxic in a non-tolerant adult, and as little as 10 mg can be fatal in a child. There is an increasing number of reports of the deaths of children of mothers on maintenance therapy from inadvertent ingestion.

Clonidine

Clonidine appears to ameliorate the opioid withdrawal syndrome by reducing central noradrenergic activity. It has been hypothesized that the opioid withdrawal syndrome is due to increased noradrenergic neuronal activity in areas such as the locus ceruleus, which are regulated by both opioid receptors and α_2-adrenoceptors (93). Opioids and clonidine both act at the locus ceruleus, reducing central noradrenergic function. This common pathway hypothesis is supported by the similarity of clonidine and opioid withdrawal in respect to their effects on vital signs, mood, and noradrenergic hyperactivity (94). Since the actions of clonidine are mediated by α-adrenoceptors they are not antagonized by opioid antagonists.

There have been many reports of the use of clonidine in the treatment of acute opioid withdrawal (95). A dose of 500 micrograms/day for 10 days reduced but did not completely abolish withdrawal symptoms in 50 patients

Table 2 Some drug interactions involving opioid analgesics

Object drug	Precipitant drug	Clinical consequences	Proposed mechanism(s)
Carbamazepine	Dextropropoxyphene	Increased effect of carbamazepine	Reduced metabolism
Codeine	Quinidine	Reduced analgesic effect	Reduced liver metabolism of codeine to morphine
Dextropropoxyphene	Ethanol	Increased effect of dextropropoxyphene	Reduced metabolism
Methadone	Carbamazepine	Reduced effect of methadone	Increased metabolism
Methadone	Cimetidine	Increased effect of methadone	Reduced metabolism
Methadone	Phenobarbital	Reduced effect of methadone	Increased metabolism
Methadone	Fluvoxamine	Increased effect of methadone	Reduced metabolism
Methadone	Phenytoin	Reduced effect of methadone	Increased metabolism
Methadone	Rifampicin	Reduced effect of methadone	Increased metabolism
Morphine	Cimetidine	Increased effect of morphine	Reduced metabolism
Morphine	Amitriptyline	Increased effect of morphine	Increased systemic availability
Morphine	Clomipramine	Increased effect of morphine	Increased systemic availability
Nortriptyline	Dextropropoxyphene	Increased effect of nortriptyline	Reduced metabolism
Pethidine	Cimetidine	Increased effect of pethidine	Reduced metabolism
Pethidine	Chlorpromazine	Increased toxicity of pethidine	Altered metabolism
Pethidine	Moclobemide	Increased effect of pethidine	Serotonin syndrome reported
Pethidine	Selegiline	Increased effect of pethidine	Serotonin syndrome reported
Phenobarbital	Dextropropoxyphene	Increased effect of phenobarbital	Reduced metabolism
Phenytoin	Dextropropoxyphene	Increased effect of phenytoin	Reduced metabolism

dependent on methadone or heroin. The patients still complained of sluggishness, insomnia, and bone pain, but there were none of the usual complaints associated with opioid withdrawal, such as anxiety, abdominal cramps, chills, muscle spasms, irritability, and anger.

Others have reported good results from the use of clonidine (96,97). Of 25 inpatients physically dependent on methadone, 20 were able to withdraw completely from methadone at the end of 2 weeks. In most patients, 10–11 days of clonidine, in a peak dose of 16 micrograms/kg/day, produced a perceived reduction in symptoms compared with previous attempts to become opioid-free. In these dosages, clonidine significantly reduced standing blood pressure without producing clinical problems. Withdrawal symptoms of anxiety, restlessness, insomnia, and muscle aching were still evident.

In a randomized double-blind, placebo-controlled comparison of clonidine with a reducing dose of methadone, there was no difference in success rate: 42% abstinence with clonidine and 39% with methadone (98). However, patients who received clonidine had more self-rated withdrawal symptoms and a higher percentage of days on which symptoms were severe.

Clonidine has been reported to reduce both diastolic and systolic blood pressure by 10–15 mmHg during treatment for opioid withdrawal. Sedation and insomnia have also been noted. However, it is often difficult to distinguish which symptoms are due to the treatment and which are caused by opioid withdrawal. In a comparison of clonidine and methadone, seven of 14 patients in the clonidine group were withdrawn from the study because they had unacceptable adverse effects, compared with one of 11 in the methadone group. Two of those taking clonidine had severe immediate adverse effects that prevented them from continuing beyond 2 days (99).

One of the limitations of clonidine treatment is that it does not appear to reduce the duration of the opioid withdrawal syndrome. In one study, 10 days of clonidine therapy were required to suppress the symptoms of opioid withdrawal from long-acting opioids such as methadone (97).

The effect of clonidine in the management of opioid-dependent individuals undergoing gradual methadone detoxification over 14 days has been studied (100). In those who completed the course, clonidine did not significantly reduce either the symptoms or objective signs of opioid withdrawal. There was a substantial dropout rate, and several subjects were withdrawn from the study because of symptoms related to hypotension. In those who completed detoxification, clonidine did not reduce either the symptoms or the signs of opioid withdrawal. Clonidine therefore seems to have no place as an adjunct to a program of gradual methadone detoxification.

Clonidine plus an opioid antagonist

In a double-blind study using titrated doses of clonidine and naltrexone, combined clonidine and naltrexone treatment allowed 38 out of 40 patients physically dependent on methadone to withdraw completely in 4–5 days (101). For most patients naltrexone was gradually increased from 1 to 50 mg/day over 4 days. The dose of clonidine was 200–600 micrograms every 4 hours. After the first 48 hours the dose was rapidly tapered without recurrence of withdrawal symptoms. Flurazepam was used for night sedation. Although clonidine reduced the intensity of naltrexone-induced withdrawal symptoms, it did not eliminate them completely. On the first day after withdrawal of methadone and initiation of naltrexone and clonidine the frequencies of craving, anxiety, restlessness, insomnia, muscular aching, anorexia, hot and cold flushes, and diarrhea were significantly higher than whilst taking methadone. However, after 4 days of naltrexone, the patients

were considerably less symptomatic. Compared with their feelings whilst taking methadone, they complained of significant increases in irritability, unpleasantness, and lethargy during the first 3 days.

The combined use of clonidine and naltrexone appears to allow successful withdrawal from long-term methadone therapy within 4–5 days of its abrupt withdrawal. Although patient selection may be an important consideration, the apparent success rate compares favorably with other methods and is achieved in a much shorter time (97).

Buprenorphine

In a study designed to assess the safety of buprenorphine for the treatment of cocaine and opiate dependence there were no adverse effects or serious interactions with a single dose of intravenous morphine or cocaine during daily maintenance on buprenorphine (SEDA-18, 85).

Second-Generation Effects

Pregnancy

A major review of the problems of drug dependence in pregnancy and the clinical management of mother and child was published in 1979, and its findings remain valid today (SED-11, 138) (102).

Opioids taken in pregnancy by a drug-dependent mother, or administered to the parturient, can cause respiratory depression in the newborn. Abstinence symptoms have been reported in the infants of mothers who are opioid-dependent at term (103).

The adverse consequences for the neonate of drug abuse in pregnancy can be dramatically reduced by comprehensive medical and psychosocial care for the mothers during pregnancy and delivery (SED-11, 138) (104,105). However, without due care during pregnancy problems are likely.

The long-term consequences of maternal opioid dependency on the child have been examined in detail in 89 infants born to mothers addicted to heroin, morphine, and methadone (SED-11, 138) (106); 20% were preterm and 31% were light for gestational age; 85% of the infants had withdrawal symptoms and 12% had convulsions. The somatic and neurobehavioral findings in children in their first 18 months of life, born to methadone-maintained mothers and to a matched drug-free comparison group of mothers, have been reported (SED-11, 138) (107). At 18 months the methadone children had: (a) a significantly higher incidence of otitis media; (b) a significant incidence of head circumference below the third percentile; (c) neurological findings of tone discrepancies, developmental delays, and poor motor co-ordination; (d) a high incidence of abnormal eye findings; and (e) significantly lower scores on the Bayley mental and motor developmental indices. In a study of 72 such children investigated 1–10 years after birth, only 25% were physically, mentally, and behaviorally normal (106).

In 41 children born to methadone-maintained mothers and 23 children from matched controls at 6 months of age, there was delayed motor development in methadone-exposed infants and greater vulnerability of males to adverse environmental conditions; in adult male rats there was a correlation between early methadone exposure and behavioral abnormalities (SED-11, 138) (108).

Opioid analgesia during the first stage of labor

The 50% and 95% effective doses (ED_{50} and ED_{95}) of intrathecal sufentanil for analgesia in labor have been characterized in several studies (109,110). The same criteria have been applied to fentanyl in 90 women in active early labor (at least 5 cm dilatation), who received a range of doses of intrathecal fentanyl (5–25 micrograms) in a double-blind, randomized study (111). Fentanyl induced rapid and effective dose-dependent analgesia in early labor. Pruritus occurred in 66% of patients and falls in ventilation were dose-related. The ED_{50} and ED_{95} values were 5.5 and 17.4 micrograms respectively.

In 60 women who requested epidural analgesia during labor randomized to sufentanil 10 micrograms, fentanyl 10 μg, or saline in addition to intrathecal bupivacaine 2.5 mg, the combination of sufentanil plus bupivacaine gave a significantly longer duration of analgesia (112). Pruritus was more common in women given sufentanil (80%) and fentanyl (47%) than in those given plain bupivacaine. However, there were no differences in the incidences of gastrointestinal effects, hypotension, or motor blockade between the groups. Adding sufentanil 10 micrograms to intrathecal bupivacaine 2.5 mg provided fast onset, better analgesia for a longer duration than the other treatments.

In another similar study, the adverse effects profile, especially in regard to pruritus, improved if intrathecal sufentanil 2.5 micrograms was added to bupivacaine 1.25 mg and adrenaline 2.5 micrograms, without compromising analgesia in women in the first stage of labor (113).

In 30 women randomized to receive either sufentanil 7.5 micrograms plus bupivacaine 2.5 micrograms, with or without clonidine 50 micrograms, using a combined spinal-epidural technique, analgesia was prolonged in those given clonidine without an increased incidence of adverse effects or worse pain scores (114).

In a prospective, randomized, double-blind comparison of nalbuphine with pethidine in 310 women requiring analgesia during labor, nalbuphine produced a lower incidence of nausea and vomiting (115). There were no differences between the two groups in the other adverse effects of the opioids, and nalbuphine did not afford major analgesic benefits.

Use of opioids in cesarean section

The use of intrathecal or epidural opioids has been recommended for the relief of pain after cesarean section, and there have been several comparisons of intrathecal and epidural opioid use.

In 50 women randomized to intrathecal diamorphine 0.25 mg or epidural diamorphine 5 mg in addition to intrathecal bupivacaine 10 mg, there was no significant difference in the duration or quality of analgesia (116). The incidence of nausea and vomiting was higher in the epidural group (24 versus 4%). There was no difference in

the incidence of pruritus, but the incidence was as high as 88% of patients, and it was severe enough to require treatment in 20%.

In a double-blind, randomized study, 55 women undergoing elective cesarean section were allocated to either epidural diamorphine 3 mg or intrathecal morphine 0.2 mg (117). There were no significant differences between the two groups in pain assessed by visual analogue scale or in the incidence of pruritus, sedation, or respiratory depression measured by pulse oximetry during the 28-hour postoperative period. Nausea and vomiting were significantly more common in the intrathecal morphine group (73 versus 41%).

Patient-controlled analgesia with epidural pethidine or a single bolus of epidural morphine 4 mg during the 24 hours after cesarean section has been studied in 78 women (118). There were no differences in the degree of analgesia or opioid adverse effects profiles.

In 66 cesarean section patients the effects of sufentanil (2 micrograms/ml), tramadol (10 mg/ml), or a mixture of the two were compared using patient-controlled extradural analgesia (119). Nausea and vomiting were closely related to the use of tramadol, while pruritus was associated with sufentanil. The combined regimen reduced the dosage requirements of both opioids by 20%. Extradural tramadol cannot be recommended, because of the increased incidence of severe gastrointestinal adverse effects, the high dose required, and inferior analgesia.

Patient-controlled epidural fentanyl (20 micrograms with 10 minute lock-out) has been compared with patient-controlled intravenous morphine (1 mg with a 5-minute lock-out) in 48 women after cesarean section (120). Fentanyl was more efficacious in controlling postoperative pain, with a lower incidence of nausea and drowsiness.

Finally, 60 women undergoing cesarean section were randomly given epidural tramadol 100 mg, epidural tramadol 200 mg, or saline (121). Pain scores and adverse effects were evaluated for 24 hours after surgery. In all three groups there were no opioid-related adverse effects and epidural tramadol 100 mg provided adequate postoperative analgesia.

Fetotoxicity

The pharmacokinetics and effects of various systemically administered analgesics on the uterus, fetus, and neonate have been reviewed (SED-11, 137). Fetal bradycardia lasting up to 7 minutes was reported in 53 of 1910 fetuses (2.7%) after the administration of pethidine (meperidine) 75 mg and promethazine 25 mg intravenously to the mothers during labor (SED-11, 137) (122).

The relation between maternal morphine administration during labor and the Apgar score of the baby at birth has been studied (SED-11, 137) (123). The authors concluded that morphine alone did not seem to cause asphyxia at birth, but that morphine together with other fetal and/or obstetric factors would definitely be a cause for concern with regard to birth asphyxia.

The effect of maternal analgesia on neonatal behavior has been assessed (SED-11, 137) (124). The authors suggested that neonates respond to pethidine in the same way as adults, but the changes observed were relatively subtle, and comparison of these infants with a control group whose mothers had received no drugs showed no differences in behavior.

Opioid analgesia can cause prolonged reductions in the baseline variability of the fetus during monitoring in labor (SEDA-17, 85). This is thought to occur by a direct effect on the cardiac centers or fetal myocardium. The danger of this is the risk of misinterpretation of the cardiotocogram as being indicative of fetal distress.

Intramuscular tramadol (50 or 100 mg) during labor is associated with fewer adverse effects than pethidine 75 mg (SEDA-18, 83). Pethidine and the higher dose of tramadol had similar analgesic efficacy, but pethidine was associated with a significantly lower neonatal respiratory rate at birth.

Susceptibility Factors

Age

Neonates, infants, and children are at risk of adverse effects of opioids, owing to pharmacokinetic and pharmacodynamic changes (SEDA-17, 78). Routine use of pulse oximetry is recommended in all children receiving opioids (SEDA-21, 85).

Elderly patients are particularly at risk, as a number of other susceptibility factors can co-exist.

Sex

Accumulating evidence suggests that there are sex differences in analgesic responses to opioid agonists (125,126), and there is increasing evidence from both laboratory and clinical studies that women may experience greater MOR (OP_3, μ) opioid receptor analgesia than men (127,128,129).The type of pain receptors, pharmacokinetics, and hormone concentrations (estrogens and testosterone) have all been implicated as potential basis for these differences. In a randomized, double-blind, comparison of the MOR receptor agonist morphine sulfate and the KOR (OP_2, κ) receptor agonist butorphanol in 94 patients with acute moderate to severe pain following injury showed that women preferred butorphanol (130). Even though the degree of analgesia experienced indicated a sex difference, the adverse effects reported were similar in the two groups. In another study of sex differences in analgesic responses to the KOR receptor partial agonist pentazocine, using an experimentally induced pain model in 41 healthy women and 38 healthy men, there were significant analgesic responses in both sexes, with no sex difference (131). The most likely explanation is that an apparent different occurs when the pain assays used are not objective and standardized.

Renal disease

Renal insufficiency can result in clinically significant accumulation of pharmacologically active opioid metabolites and prolonged narcosis; such patients must be monitored for signs of toxicity (SEDA-17, 79) (SEDA-21, 85)

(132,133). To date, this effect has only been reported with codeine, morphine, and pethidine. Dextropropoxyphene is not recommended in renal insufficiency, as its metabolite norpropoxyphene, which is eliminated by the kidneys, accumulates, causing cardiac depression (SEDA-17, 79) (SEDA-21, 85).

Other features of the patient

In patients with reduced respiratory reserve, such as those with emphysema, severe obesity, cor pulmonale, and kyphoscoliosis, opioids must be used with caution. The relative benefits and harms of using opioids in patients taking monoamine oxidase inhibitors, those with a history of drug abuse, asthma, hepatic impairment, hypotension, raised intracranial pressure, or head injury, and during pregnancy or breast feeding, should be carefully considered. Dextropropoxyphene, pethidine, and methadone should be used with caution (SEDA-21, 85).

Drug Administration

Drug administration route

The usefulness and adverse effects of different administration routes of opioids have been discussed in several articles.

Oral

Oral administration is the method most often used because it is non-invasive, convenient, and easy to titrate. In chronic pain oral opioid formulations that provide longer duration of effect are preferred, because they provide more stable pain control, better tolerability, and increased convenience, patient options, and flexibility.

Modified-release oxymorphone is a new oral tablet formulation aimed to provide a 12-hour dosing interval. In a prospective, open, sequential crossover pilot study patients with cancer with moderate or severe pain, using either modified -release morphine or oxycodone, were safely switched to modified-release oxymorphone at a lower equivalent dosage, with no reduction in pain relief or increase in adverse effects (134). This study was a pilot study with a small sample size. Further studies are required for more robust findings.

In another study oral and rectal tramadol were compared (135). The two routes were equally effective in pain relief and were associated with similar adverse events. However, both patients and physicians preferred the oral route. Nevertheless, rectal administration of tramadol can be safe, reliable, and non-invasive for patients who cannot take oral tramadol.

Sublingual

The combination of naloxone and buprenorphine has been used sublingually, with the aim of reducing the abuse potential of buprenorphine. When crushed and injected, naloxone will exert its opioid receptor antagonist properties. This review reported that the combination drug, when administered parenterally to non-physically dependent individuals, attenuated (but did not block) the effects of buprenorphine (136).

Rectal

Transdermal fentanyl patches typically contain large amounts of fentanyl, thus giving the potential for abuse and toxicity. Fentanyl toxicity has been reported after rectal insertion of fentanyl patches (137).

- A 41 year old man became comatose after inserting three fentanyl patches (100 micrograms/hour) into his rectum. He was given naloxone 6 mg without a response. The patches were removed digitally and he recovered 1 hour later.

This report shows the importance of being aware of the toxic potential of patches. Increased absorption by the rectal mucosa and the relatively high rectal temperature facilitate rapid release and high fentanyl concentrations. The authors pointed out that the low price of the patches could result in more cases of accidental, abusive, or intentional fentanyl toxicity.

Intramuscular and subcutaneous

The intramuscular and subcutaneous routes are most often used in postoperative analgesia (138). The limitations are: discomfort due to repeated injections; large interpersonal variation in dosage requirements; peaks and troughs in blood concentrations, with inconsistent pain relief and incidence of adverse effects; and delayed response times from staff in delivering the analgesic (138).

In patients undergoing posterior lumbar interbody fusion, continuous epidural morphine was compared with continuous subcutaneous morphine as pre-emptive analgesia (139). There were no differences in analgesic effects. However, there more adverse effects were with epidural morphine, despite the fact that subcutaneous doses of morphine were about three times higher. In addition, preoperative epidural catheterization was difficult without seeing the dura mater. Thus, continuous epidural morphine was not suitable for pre-emptive analgesia; continuous subcutaneous morphine was the preferred option because of technical ease and fewer complications.

Inhalation

The pharmacokinetics, pharmacodynamics, safety, and efficacy of therapeutic inhalational opioids have been reviewed (140). Pulmonary delivery of opioids facilitates rapid and increased absorption, making this route suitable for management of acute pain. However, there are very few published data on their safety and efficacy. The literature suggests that this technique is well tolerated and is associated with adverse effects similar to those associated with other routes. The authors highlighted the importance of increased regulatory control of the technique, because of the associated potential for abuse.

Intranasal

Intranasal diamorphine spray has been compared it with injectable diamorphine for maintenance treatment (141).

Intranasal diamorphine was easier of use associated with reduced stigma and a reduced risk of adverse effects due to injection.

Spinal

Compared with conventional routes, spinal opioid administration carries potentially greater morbidity and can only be justified if it produces equal or superior pain relief compared with conventional methods, with fewer unwanted effects (SED-11, 139).

Although the analgesic effect of spinal opioids is largely due to a spinal effect, the opioid can spread rostrally to the brainstem and higher centers, and can cause delayed adverse effects. Lipid solubility affects the rate at which an opioid is absorbed into the spinal cord from the cerebrospinal fluid (CSF), and therefore predicts the likelihood of rostral spread. Hydrophilic drugs, such as morphine, will linger in the CSF and produce prolonged analgesia that may last 12 hours or more. Such drugs can float rostrally, producing more widespread but less intense analgesia. However, if the drug reaches opioid receptors in the respiratory center in the fourth ventricle, delayed respiratory depression can occur. In contrast to morphine, fentanyl is very lipid-soluble but short-acting; a single dose will produce intense highly segmental analgesia lasting 2–3 hours. These properties make it suitable for continuous epidural infusion.

When an opioid is used as the sole agent by the epidural or intrathecal route, the results are disappointing, because of unwanted adverse effects, such as pruritus, nausea, vomiting, respiratory depression, and effects on the neonate, caused by significant systemic absorption (SEDA-17, 85). Hypotension and changes in fetal heart rate are not uncommon (SEDA-21, 91). Combinations of opioids (alfentanil, fentanyl, morphine, sufentanil) with local anesthetics (for example bupivacaine) have therefore been suggested to yield better results (SEDA-18, 83).

The use of alfentanil with bupivacaine via continuous epidural infusion during labor resulted in a significant reduction in motor blockade compared with bupivacaine alone. There was no respiratory depression in the mothers, although shivering and pruritus were more frequent with alfentanil. There were no differences in the neonatal Apgar scores between the groups (SEDA-18, 83).

There has been a comparison of the effects of fentanyl and sufentanil, combined with bupivacaine and adrenaline, given by PCA after cesarean section (SEDA-18, 83). The numbers of requests were greater in the fentanyl group, but there was no difference between the groups with regard to sedation, pruritus, or nausea. However, those who received sufentanil had a significantly higher incidence of vomiting, light-headedness, and dizziness.

It is uncertain whether the addition of adrenaline to intrathecal sufentanil increases the duration of analgesia during labor. In one study, the addition of adrenaline to intrathecal sufentanil did not prolong the duration of analgesia, but reduced the incidence and severity of pruritus (SEDA-18, 83), whereas in another the addition of adrenaline or morphine to intrathecal sufentanil prolonged the duration of analgesia (SEDA-18, 83). However, those given morphine had significantly more nausea and pruritus.

In another comparison of a single dose of epidural morphine with PCA epidural fentanyl after cesarean section, pain relief and the incidence of nausea were similar, but pruritus was significantly less with fentanyl (SEDA-18, 83).

Epidural methadone and diamorphine are useful analgesics during cesarean section, but oxygen desaturation and nausea are more frequent with diamorphine (SEDA-18, 83).

Combined spinal-epidural administration achieves almost instantaneous analgesia with longer pain relief (142). This method gives a faster onset of analgesia and less motor blockade than standard epidural analgesia (143).

Several studies have highlighted the benefits of giving adequate postoperative analgesia in cardiac patients, and the use of intrathecal and epidural anesthesia and analgesia for cardiac surgery has been reviewed (144). Effective postoperative analgesia reduces the risk of postoperative stress and morbidity, hospital stay, and cost, and increases patient satisfaction. There is a role for intravenous opioids in such patients, but those are associated with significant adverse effects. On the other hand, several studies of intrathecal techniques have shown that these provide adequate analgesia although they do not significantly attenuate the stress response associated with cardiac surgery. Despite potentially inducing cardiac sympathectomy, total spinal anesthesia remains unacceptable. Epidural techniques provide adequate analgesia and can attenuate the stress response associated with cardiac surgery, as well as induce thoracic cardiac sympathectomy. There are significant adverse effects associated with the administration of opioids by intrathecal or epidural techniques. The most common is pruritus; nausea and vomiting occur in about 30% of cases and urinary retention occurs mostly in young men. Respiratory depression requiring intervention occurs in about 1% of cases, similar to the incidence after intramuscular or intravenous use. Intrathecal or epidural fentanyl or sufentanil is associated with early respiratory depression (within minutes), whereas morphine is associated with delayed depression (hours). Intrathecal use increases the risk of respiratory depression. Hematoma formation is another complication associated with both intrathecal and epidural techniques. These techniques are therefore associated with significant risks, which make their clinical implementation controversial.

Intrathecal route

Technical problems after intrathecal opioids are rare, although catheter occlusion and leakage of CSF have been reported (SEDA-17, 85) (145–147). In 121 patients with mean follow-up of 68 days (maximum 13 months) there was an incidence of less than 10% (148).

Intrathecal opioids used in obstetrics are well tolerated by mother and child (SED-11, 139, 140) (149–151).

Morphine is the opioid most often chosen for intrathecal administration.

In a comparison of intrathecal morphine and remifentanil in patients undergoing off-pump coronary surgery, opioid related cardiac effects were similar; intrathecal morphine did not produce central neuroaxial hematoma or post-spinal tap headache (152).

The preoperative use of intrathecal morphine 0.5 mg and fentanyl 15 micrograms has been evaluated in 40 patients undergoing major liver resection in a randomized, double-blind, placebo-controlled study (153). Preoperative intrathecal analgesia significantly reduced the need for postoperative morphine for pain management three-fold and was not associated with a significant difference in adverse effects.

Respiratory

Respiratory depression occurs more often after intrathecal than after epidural opioid administration and can be more of a problem in old age or when there is pre-existing respiratory disease (SED-11, 139) (154,155). The time of onset is variable but usually occurs within 6–10 hours of the opioid injection, although delays of up to 11 hours have been reported (156). There have been two cases of prolonged respiratory depression lasting 18 hours after single doses of 3 and 5 mg (156). Repeated doses of naloxone were required, but each incremental dose did not alter the level of analgesia.

It has been suggested that opioid-naive patients may be more susceptible to respiratory depression and that posture may also be important (SED-11, 139) (157).

Return of normal respiration can take up to 23 hours. Peak expiratory flow rate (PEFR) was significantly better in patients who had received intrathecal rather than intravenous morphine after cardiac surgery, but mean $PaCO_2$ was significantly higher in patients given intrathecal morphine 2 mg, rather than intrathecal or intravenous morphine 1 mg (158). The effect was dose-dependent (159).

Nervous system

Central adverse effects are as expected; with the exception of constipation, urinary retention, and respiratory depression, these effects tend to be transient and disappear within a few days of starting therapy.

Drowsiness, miosis, and respiratory depression have been reported after intracerebroventricular administration of morphine in two of 55 patients who received morphine 1–1.5 mg (160). A third patient developed visual hallucinations and behavioral disorders after 1 mg. All effects were rapidly reversed by naloxone.

Myoclonic spasms of the legs have been described after intrathecal morphine, and were abolished by intrathecal bupivacaine (161).

Hyperalgesia and myoclonus were reported after high-dose intrathecal morphine (SEDA-17, 87).

Temporary, totally reversible motor and sensory paralysis has been reported after intrathecal morphine 1.6 mg and was attributed not to a direct spinal action of morphine but to cardiovascular changes occurring as a result of pain relief (162).

Long-term intrathecal administration of pethidine may be associated with toxicity, owing to accumulation of its metabolite norpethidine. This was explored in a study in 10 patients with neuropathic cancer pain, who had not responded sufficiently to recommended regimens (163). There were high plasma concentrations of pethidine and norpethidine in three subjects; however, norpethidine concentrations were still below the concentration reported to induce nervous system toxicity, i.e. under 500 ng/ml, and no patient had evidence of nervous system toxicity. One patient developed a tremor and twitches on day 7; however, these were unlikely to have been due to nervous system excitability, because they resolved spontaneously in 3 hours and further administration of pethidine was not accompanied by further excitation.

Gastrointestinal

There is a high incidence of nausea and vomiting with intrathecal diamorphine, which may not be dose-related (164). Two studies have suggested that the incidence of nausea and vomiting in labor is higher with intrathecal than with epidural opioids (165,166).

Urinary tract

Urinary retention has been described in one of a series of patients who had been given pentazocine 5 mg intrathecally (167); others have since reported similar findings.

Skin

Pruritus is a frequent adverse effect after intrathecal administration, with an incidence of one-third with buprenorphine (168) and diamorphine (169) and over 70% for both diamorphine and morphine (170,171). In one study the incidence of pruritus was higher with morphine than with methadone; analgesia was also superior (170). Pruritus has also been reported with intrathecal pethidine (meperidine). Treatment was not reported to be necessary. This effect is not reported to occur after intrathecal beta-endorphin (172,173). The mechanism of pruritus is not well understood and has been attributed to a disturbance of thiamine metabolism (174) and to a disturbance of afferent input at supraspinal as well as at spinal receptor sites (175).

In a comparison of sufentanil 7.5 micrograms intrathecally and 7.5 micrograms intravenously, intrathecal sufentanil had superior analgesic efficacy (176). There was pruritus in significantly more patients with intrathecal sufentanil (5 versus 0). Peripheral oxygen desaturation was only observed with intravenous sufentanil (n = 6).

Infection risk

Reactivation of *Herpes simplex* infection after epidural administration of opioids is well known. However, there have been reports of reactivation of *Herpes simplex* after intrathecal morphine for cesarean section (SEDA-17, 87) (SEDA-18, 84).

Concern has also been raised about the possible association of pruritus with re-activation of herpes labialis virus type II. Reactivation of oral *Herpes simplex* infection has been explored in patients receiving intrathecal