Opioid mechanisms and opioid drugs

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Abstract

Opioids are effective in acute and cancer pain management and have increasingly been prescribed in chronic non-cancer pain despite concerns regarding long-term use and lack of efficacy. Opioid actions are via G protein coupled receptors, the activation of which leads to a variety of physiological consequences including analgesia. Prescribing opioids requires careful consideration of individual drug pharmacokinetics and pharmacodynamics, their actions across different physiological systems, side effect profiles and patient factors that influence the drug efficacy to ensure the best opioid is prescribed for each patient.

Keywords Analgesics; clinical polymorphism; genetic; opioid pharmacology; opioid receptors

Royal College of Anaesthetists CPD Matrix: 1A02, 1D02, 2E01, 2E02, 2E03

Learning objectives

After reading this article, you should be able to:

- describe the mechanism of action of opioids
- outline the differences between clinically available opioids
- recognize patient and drug factors that should be considered when commencing opioids

Introduction

Since early civilization the opium poppy (*Papaver somniferum*) has been used to produce opium alkaloids for the relief of pain and to produce other psychological effects. The Sumerians isolated opium from their seeds in the third millennium BC and writings by Homer allude to the use of opium in 300 BC. Clinical use commenced between 1803 and 1805 with the isolation of morphine from the opium poppy by the chemist Friedrich Sertürner.[1] However it was only from the mid 1960s an understanding of opioid mechanisms developed, alongside the discovery of specialized opioid receptors and the importance of the endogenous opioid system in pain, placebo and other physiological pathways (for example reward, the respiratory systems and gastro-intestinal function).

Opioids currently represent one of the most important classes of analgesic medications, effective in the management of acute and cancer pain. This is due to their mechanisms of action, the location of their receptors and the key role endogenous opioids play in pain sensitivity. The use of opioids in chronic pain has increased over the last 30 years and currently we face an opioid crisis in the USA[2] and other Western countries, in part a consequence of prescribing in this population. Commencing opioids in chronic non-cancer pain requires careful consideration due to risks associated with long-term use and the lack of evidence of efficacy.[3] Opioid prescribing in all circumstances relies on careful consideration of the individual drugs, their mechanisms of action within nociceptive and other physiological pathways and side-effect profiles. Appreciating circumstances that influence target site delivery is important as these influence opioid efficacy, and contribute to the highly variable inter-individual effects.

Opioids and opioid receptors

Endogenous and exogenous opioids are substances that produce morphine-type actions. Endogenous opioids are peptides found throughout the body and consist of three families (β-endorphin, enkephalins and dynorphins). This review focuses on exogenous opioids and these can be loosely classified into three groups;

1. Naturally occurring opium alkaloids. These are derived from the poppy *P. somniferum* such as morphine.
2. Semi-synthetic opioids. These are either modifications of the natural morphine structure such as diamorphine, oxycodone and hydromorphone or semi-synthetic derivatives that are structurally unrelated to morphine such as buprenorphine.
3. Synthetic derivatives. This group of drugs are structurally unrelated to morphine and include alfentanil, fentanyl, methadone, remifentanil and sufentanil.

Despite different structures, both natural and synthetic opioids exert their physiological actions via binding to opioid receptors. These G-protein-coupled receptors are found throughout the body and modulate numerous physiological functions including nociception. There are a number of opioid receptors subtypes. According to the International Union of Basic and Clinical Pharmacology (IUPHAR) these include three classical opioid receptors that demonstrate a sensitivity to naloxone, MOP (μ), KOP (κ) and DOP (δ) receptors, and a fourth 'non-opioid' receptor (nociceptin/orphanin FQ peptide receptor or NOP) that lacks sensitivity to naloxone but has significant sequence homology with opioid receptors. Opioid receptors are located in the central and peripheral nervous system including peripheral nociceptors, the dorsal horn of the spinal cord, brainstem, cerebral cortex and cerebellum. They are also found on neuroendocrine, immune and ectodermal cells. Activation of classical opioid receptors leads to analgesia through suppressing the affective and reflexive components of pain, although not all are activated by clinically available opioid medications. Furthermore activation of the three classical opioid receptors leads to differing physiological effects. MOP receptor activation can cause respiratory depression, sedation, reward and euphoria, nausea and vomiting, urinary retention, biliary spasm, constipation and placebo analgesia. DOP receptor activation is associated with reward, respiratory depression,

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convulsions and mood changes including anxiety and depression. It has a more restricted central nervous system distribution compared with other opioid receptors and its respiratory and analgesic effects are likely co-dependent on the presence of MOP receptors. KOP receptors play a role in dysphoria, sedation and diuresis. In contrast, NOP receptors are found in the spinal cord and supraspinally. They have conflicting actions in pain pathways including analgesia and pronociceptive/anti-opioid effects (such as inhibiting both endogenous and exogenous opioid analgesia).[4] A comprehensive review of these receptors and their function can be found by McDonald and Lambert.[4] All opioid receptors are structurally similar, with seven transmembrane domains and all have well-defined signalling pathways. Within nociceptive pathways once a ligand binds, there is intracellular coupling to inhibitory G proteins, which dissociate into the Gα and Gβγ subunits. The Gα subunit inhibits adenylate cyclases and reduces cAMP levels whereas the Gβγ subunit decreases voltage gated Ca^{2+} channel conduction or opens rectifying K^{+} channels. Through modulating pre- and post-synaptic calcium channels all three classical opioid receptors suppress the influx of calcium into neurons and reduce their excitability, as well as reducing pronociceptive neurotransmitter release.[5] In the dorsal root ganglia actions are more complex. Here activation of opioid receptors not only opens potassium channels via inhibitory G proteins, it also leads to inhibition of sodium, transient receptor potential vallanoid 1 (TRPV1) and acid sensitizing channels (ASICs) to reduce neuronal excitation and action potential propagation. Furthermore in the spinal cord, activated opioid receptors reduce excitatory glutamate driven postsynaptic currents leading to overall reduction in excitability and transmission of nociceptive and pain pathways.

Opioid pharmacology

Although the common feature of exogenous opioids is their interaction with the MOP receptor, they exhibit distinct physicochemical and pharmacokinetic characteristics. This is in part a consequence of differing chemical structures between drug subclasses. General aspects regarding opioid pharmacology are listed below with individual characteristics of drugs shown in Table 1.

Receptor binding

Receptor binding and transmembrane flux (such as across the blood–brain barrier, BBB) of opioid medications are influenced by both relative lipophilicity of the drug and its degree of ionization at physiological pH. For example, fentanyl is more lipophilic than morphine, hence it passes through lipid-rich membranes more easily. This accounts for the ease of absorption of fentanyl through mucous membranes and the skin. In comparison, morphine being more hydrophilic, will remain in the compartment where it is administered for longer. Subarachnoid morphine will escape into the blood circulation less rapidly than fentanyl due to these properties.

Absorption

Opioids in general are readily absorbed within the gastrointestinal tract following oral administration; however, their bioavailability and ability to reach effector sites in adequate concentrations can be considerably influenced by first-pass metabolism (e.g. for fentanyl, sufentanil and buprenorphine). Additionally, there is some evidence that low bioavailability following oral administration may also be related to opioid membrane transporters such as efflux p-glycoproteins. These are found in the BBB but also in the gastrointestinal tract epithelium and they transport absorbed opioids back from enterocytes into the gut lumen. These may influence fentanyl oral absorption. Additionally, other drug transporters such as the solute carrier (SLC) influx transporters can facilitate passage into hepatocytes and have been linked to tramadol metabolite pharmacokinetics.

Distribution

Once absorbed, drugs need to reach their effector site or target. The most important target for opioids is the central nervous system (spinal cord, brainstem and brain). Therefore sufficient transfer needs to occur across the BBB. This occurs through limited passive diffusion, some active uptake and active efflux by opioid transporter proteins.[6] Morphine is a substrate of the efflux p-glycoprotein, MDR1a, which is found in the BBB and acts to remove morphine from the central nervous system. It can be inhibited by a number of clinically relevant drugs including quinidine, cyclosporin and verapamil, and while co-administration could theoretically affect opioid concentrations in the brain, whether this leads to clinically relevant changes in morphine efficacy remains unclear. Other opioids such as fentanyl, sufentanil and alfentanil are not substrates of p-glycoproteins and are unaffected by this process. In addition there is some evidence that other opioid transporters exist and enabling inward transfer of opioids such as oxycodone, potentially influence effector site concentrations. Additionally distribution of opioids is affected by protein binding, which varies significantly between opioids. For example, oxycodone and morphine are approximately 40% protein bound whereas for fentanyl protein binding is approximately 90%.

Metabolism and excretion

Most opioids are metabolized via phase II metabolism employing glucuronidation or methylation (dealkylation) in the liver. For morphine, hydromorphone and buprenorphine, glucuronidation is the major metabolic pathway. However, for other opioids, such as fentanyl, oxycodone, tramadol and codeine, the main metabolic pathways are phase I metabolism via cytochrome p450 (CYP) isoenzymes, mainly CYP2D6 and CYP3A4/5. CYP3A4/5 is inducible (becomes more effective and increases drug metabolism) by drugs such as carbamazepine or rifampicin and inhibited (metabolism is less effective) by other substances such as ciprofloxacin. Additionally, genetic variability in cytochrome p450 isoenzymes exists. CYP2D6 genetic variation can significantly influence metabolism. Around 5–10% of Caucasians have reduced activity therefore are less effective at metabolizing prodrugs such as codeine into their active components. Conversely, gene duplication, in around 3% of Caucasians, is associated with ultrarapid metabolism of codeine to morphine. Individuals achieve high levels of morphine quickly following codeine administration. This can be dangerous in children under 12 years old who receive higher morphine doses than expected from a standard codeine dose, and in lactating mothers who will have higher concentrations of morphine in their breast milk, both of which risks opioid overdose and side effects such as respiratory depression.[7] Other metabolic pathways such as human uridine 5

Opioid medication pharmacokinetics and pharmacodynamics

	Terminal half life hours	Clearance ml/kg/min [L/min]	Oral bioavail. (%)	Protein binding (%)	Main Metabolic Pathways	Active Metabolite	Partition coefficient as log P values at pH 7.4	Accumulation in liver/kidney failure
Morphine	2.5 (2–2.9)	21 (20–23)	[19–47]	36	UGT1A1, 2B7	Morphine-6-glucuronide	-0.21	++/+++
Fentanyl	8.3 (6.9–9.6)	[0.7–1.5]	<2	84	CYP3A4/5	none	4.12	+/+
Alfentanil	1.9 (1.5–2.3)	3.9 (3.4–4.4)		92		none		+++/+
Sufentanil	3.8 (3.4–4.1)	12.6	13 (11–15)	93		none		+/+
Remifentanil	0.3 (0.28–0.33)	44 (40–47)		70	Hydrolysis by plasma and tissue esterases	GI-90291		N/A
Oxycodone	3.5 (2.7–4.3)	[0.4–1.1]	[40–130]	45	CYP3A4/5, 2D6	Oxymorphone	1.26	+++/+++
Hydromorphone	2.9 (2.5–3.3)	[0.4]	24 (21–28)	71	UGT1A1, 2B7	None		++/++
Methadone	29 (25–33)	2.4 (1.9–2.9)	[60–90]	89	CYP3A4/5, 2D6, 1A2, 2B6, 2C19	None	1.82	+++/+
Codeine	[3–4]	[0.6–0.9]	[60–90]	N/A	CYP3A4/5, 2D6	Morphine	1.19	
Tramadol	[5–6]	5.9	75	20	CYP3A4/5, 2D6	O-Desmethyltramadol	1.35	
Tapentadol	4.3 (4.5–5.1)	[1.5]	32	56	UGT1A6, UGT1A9, UGT2B7	None	2.87	+/+
Buprenorphine	[20–25]	[1.2]		96	CYP3A4/5, UGT1A1, 2B7	Norbuprenorphine-3-glucuronide		

Unless stated values are mean (95% CI) [range]. For partition coefficients, a small coefficient represents hydrophilicity and a large coefficient represents lipophilicity.[14–16]

Table 1

diphosphoglucuronsyltransferases (e.g. UGT2B7) show genetic polymorphisms; however, the clinical impact of these is not clear, and these enzymes can also be both inhibited or induced by other medications.

Most opioid metabolites are renally excreted. Therefore should renal function be impaired, those drugs with active metabolites can have continued opioid effects due to metabolite accumulation and can potentially develop opioid toxicity.

Individual characteristics of opioid drugs

Each opioid has unique characteristics that should be considered when choosing the most appropriate drug for the patient. These are outlined below and can be seen in Table 1.

Morphine

This is the prototypical MOP receptor agonist against which all opioids are compared. It is therefore assigned a clinical potency of 1. Morphine can be applied orally, intrathecally, epidurally, subcutaneously and intravenously. It might however be associated with increased histamine release compared to other opioids.

Fentanyl

This synthetic opioid is short acting, and due to its lipid solubility can be given intravenously, intrathecally or transdermally. It has over a thirty times higher MOP receptor binding affinity than morphine and around 100 times higher clinical potency. It can be associated with chest wall rigidity.

Sufentanil

Sufentanil is a highly potent synthetic opioid that is about 500–1000 times more potent than morphine. It is most often given intravenously and epidurally but can also be administered sublingually. It has a shorter context-sensitive half-life and has more sedative effects compared to fentanyl. Both sufentanil and fentanyl exert only minor effects on the cardiovascular system and hence help to achieve stable haemodynamics.

Alfentanil

This is a short-acting synthetic opioid. It has large inter-individual variability in its clinical effects and duration of action, influenced by CYP3A4. It is mainly used as opioid for short operative and clinical procedures.

Remifentanil

Remifentanil is an extremely short-acting synthetic opioid, metabolized by non-specific blood and tissue esterases. It has a terminal half-life of around 20 minutes. It has a primary and active metabolite GI-90291 that is excreted unchanged in the urine but is less potent that remifentanil and has negligible clinical effects.

Oxycodone

This semi-synthetic opioid has a lower MOP receptor affinity than morphine or methadone. Around 10% is metabolized to its active metabolite oxymorphone, which has a higher binding affinity than the parent drug. Due to higher bioavailability oxycodone is two to three times as potent than morphine when given orally. It has significantly lower efficacy than morphine when given intrathecally in animal models. This is similar to findings from clinical studies, as when given epidurally after surgery it requires a dose ratio of around 1:9 (morphine:oxycodone) to achieve equivalent analgesia.

Hydromorphone

Hydromorphone is a semi-synthetic opioid analgesic that can be given orally, rectally or parenterally. It has a similar onset of action and duration as morphine, however, it is a more potent respiratory depressant. Orally it is about 7–8 times more potent than morphine while it is five times more potent than morphine when given intravenously. It is metabolized mainly to hydromorphone-3-glucuroide. This has no analgesic activity but can accumulate in renal failure causing neuroexcitation and cognitive impairment.

Methadone

This is a long-acting synthetic opioid. It has an altered duration of action dependent on the length of its administration. Racemic methadone consists of two enantiomers. L-Methadone is responsible for MOR effects and non-competative antagonism of nicotinic acetyl choline receptors; however, both enantiomers are non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists. As metabolism rates vary greatly between individuals, patients who take the drug for the first time should be closely followed for adverse events.

Codeine

Is a prodrug of morphine. It lacks potency as it requires metabolism for effect. There is wide inter-individual variability in its effect, influenced by genetic polymorphisms of its metabolizing enzymes (see above). As morphine is its active metabolite it is associated with histamine release.

Tramadol

Tramadol has only weak affinity to MOP receptors. Its opioid effects are mediated by its metabolite (o-desmethyltramadol), which has 200 times greater affinity. Clinically it exerts about a fifth to a tenth of the potency of morphine. Its analgesic actions are mainly related to inhibition of noradrenaline and serotonin reuptake. Care needs to be taken when it is prescribed with selective serotonin reuptake inhibitors such as fluoxetine and paroxetine. These are inhibitors of CYP2D6 thus decreasing its metabolism and also increase serotonergic activity potentially leading to serotonergic syndrome.

Tapentadol

Tapentadol has a dual mechanism of action. First via MOP receptors, where it has fifty times less binding affinity than morphine yet nearly 90% of its binding efficacy. Second, it is selective for the noradrenaline transporter protein resulting mainly in the inhibition of the reuptake of noradrenaline. Its analgesic actions are independent of its metabolism, as it has no active metabolites. It has less gastrointestinal adverse effects and pruritis than pure MOP receptor agonists.

Buprenorphine

This is a mixed agonists-antagonists that may act as an agonist at low doses and as an antagonist (at the same or a different receptor type) at higher doses. It demonstrates less gastric hypomotility and biliary spasm than morphine, as well as a ceiling effect on respiratory depression. It can, however, exhibit ceiling effects for analgesia, and may elicit an acute withdrawal syndrome when administered together with a pure agonist.

Non-nociceptive effects of opioids

Opioids have numerous physiological functions in addition to anti-nociception. They impact on systems involved in the stress response, hormonal functions, digestion and respiration. They influence mood, reward, learning, appetite, sleep, social separation and affiliative processes. MOP receptors are found in the brain stem and impact on arousal, respiration and nausea and vomiting. Respiratory depression occurs due to activation of receptors in the respiratory centres in the medulla that decrease the sensitivity of chemoreceptors to carbon dioxide.[8] Opioid-induced respiratory depression is increased in those with central sleep apnoea and there is increasing concern regarding its development in those co-administered sedatives. Opioid receptors in the chemoreceptor trigger zone in the medulla are important in signalling to the vomiting centre via dopaminergic D2 receptors, and opioid receptors in the vestibular apparatus signal to the vomiting centre via histamine H1 and cholinergic pathways. In addition, nausea and vomiting also occur with opioids through inhibition of gut motility.[8] Opioid receptors found peripherally in the gut lead to increased absorption of water and gut spasticity (reduced motility) as a consequence of inhibition of myenteric neurons (nerves in the mesenteric plexus). This leads to visceral smooth muscle constriction and can cause constipation.[8]

Chronic opioid use is associated with effects on the endocrine system, primarily hypogonadism or opioid-induced androgen deficiency. This occurs through central suppression of gonadotropin-releasing hormone, and decreased levels of pituitary luteinizing hormone, adrenal dehydroepiandrosterone and testosterone, estradiol and progesterone in women and decreased testicular testosterone in men. It is characterized clinically by loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and mass, osteoporosis, impotence and menstrual irregularities. It occurs particularly in males with most studies reporting the incidence of testosterone deficiency in males on chronic opioids for non cancer pain at over 50%.

Opioid receptors may be involved in angiogenesis and tumor growth, alongside influencing inflammation and causing immune modulation. The influence of opioids on the immune system is complex, with a close connection existing between the immune and neuroendocrine systems. Many immune cells have opioid receptors, and the traditional view was that opioids suppress the immune system. Preclinical research highlights that certain opioids such as morphine inhibit cellular components of innate immunity such as macrophages, natural killer (NK) cells, mast cells, neutrophils and dendritic cells. Additionally with respect to

the adaptive immunity response, prolonged morphine treatment can alter cytokine production and impair T and B cell activity. However, clinical literature supporting this is less conclusive. Here researchers consider the effect of opioids in two main circumstances. Firstly, whether the immune response to infections is influenced by opioid use. Recent studies suggest there is an increased risk of developing serious infections with long-term opioid; however, this may be associated with only certain and not all opioids.[9] Secondly, investigators have considered whether opioids affect the growth and spread of tumours, as such the tumour-specific immune response. A recent large prospective cohort study from Denmark showed no clinically relevant association between breast cancer recurrence and opioid prescriptions[10] and the last consensus statement from the British Journal of Anaesthesia Workshop on Cancer and Anaesthesia stated it was unclear whether opioid administration augments the risk of recurrence or metastasis after cancer surgery.[11]

Additional consequences that should be considered in all patients on long-term opioids include tolerance (increasing doses required to maintain analgesia), dependence (physical and psychological), hyperalgesia (paradoxical increase in pain sensitivity) and addiction (inability to control continued use despite harm and negative consequences).

Considerations when commencing opioids

As healthcare evolves, there is a constant push towards personalized medicine with specific treatment tailored to individual patients. At a simplistic level this involves carefully considering patient factors that could influence drug effects and individual pharmacological factors regarding each specific drug and preparation.

Opioid use with liver and renal dysfunction

The metabolism of most opioids are highly dependent on the liver. As highlighted above, some opioids are prodrugs requiring this metabolism for action, and others have active metabolities. In most cases this leads to accumulation of the parent drug within the body and the need for lower doses, with extended dosing intervals. In patients with severe liver disease, however, there is an increased sensitivity to opioids due to an altered BBB and an upregulation of MOP receptors in the brain, and opioids may precipitate encephalopathy.

Clinical observational studies highlight that a significant proportion of patients with renal dysfunction (defined as a creatinine clearance of <50 mL/min), receive opioids for pain. For example, in one American cohort of patients on maintenance dialysis over 60% had one opioid prescription each year, with nearly a fifth receiving chronic opioid prescriptions.[12] Here a balance needs to be struck between ensuring adequate pain control and minimizing the risk of toxicity and overdose due to accumulation of the parent drug or its metabolites through reduced drug clearance secondary to renal dysfunction. Prescribing of opioids requires consideration of the pharmacodynamics and pharmacokinetic properties of each individual opioid drug, the degree of renal failure of the patient and whether they undergo dialysis. In general, lipophilic opioids without active metabolites, such as fentanyl and methadone, are more useful. Hydrophilic opioids (e.g. morphine and codeine) that have active metabolites should be avoided. Tramadol and oxycodone should be used with caution due to the risk of accumulation of both metabolites and the parent drug.

Routes of opioid administration

Routes of administration depend on physicochemical and other properties of individual opioids. Alongside oral, intrathecal and intravenous administration, certain opioids can be delivered via alternative routes for which there are certain considerations. Lipophilic drugs such as fentanyl can be given via membranes that is, skin and mucous. Transdermal, transmucosal and intravenous routes are also useful for opioids, such as fentanyl, that undergo high first-pass metabolism. Transdermal fentanyl causes a depot of the drug to be formed in the upper layers of the skin (stratum corneum) from which the drug then passively diffuses into the dermis and is taken up initially into microcirculation and then systemic circulation. Changes in skin perfusion alter the available drug in circulation. For example, fever, saunas or hot baths will all increase absorption, whereas a reduction in perfusion associated with hypoperfusion or vasoconstriction will decrease available doses. These factors as well as body mass index account for wide variability in absorption and drug availability. Additionally, transdermal routes can take hours to reach steady-state plasma concentrations when first initiated and therefore need to be commenced in patients whose opioid requirements are stable. Transmucosal preparation include buccal tablets, oral lozenges and intranasal sprays. These were developed for rapid relief of breakthrough cancer pain and are available for drugs including sufentanil, fentanyl and diamorphine. However, due to their rapid onset of action they might predispose vulnerable patients to addiction.

Pharmacogenetics and opioids

It is widely appreciated that inter-individual responses to opioids exist, and that these in part relate to genetic polymorphisms of enzymes involved in opioid metabolism. These genetic differences can influence both pharmacokinetics and pharmacodynamics of the drugs. Described above are the genetic polymorphisms that influence the pharmacokinetics of opioids such as the CYP enzymes involved in phase I metabolism and UGT enzymes involved in phase II metabolism. Additional polymorphisms that may be important include those associated with the catechol-O-methyltransferase (COMT) enzyme, which is involved in the metabolism of catecholamine neurotransmitters, and is thought to play a role in both analgesic response to morphine and variation in side effect profiles. The effect of polymorphisms associated with the p-glycoproteins ABCB1 transporter is unclear as altered responses to methadone have been seen, but not to oxycodone and morphine.[13] As far as opioid pharmacodynamics is concerned much effort has focused on opioid receptor polymorphisms. The MOP receptor gene OPRM1 was among the first genes screened for functional relevance with regard to analgesia. Human SNP OPRM1 118 A $>$ G is the most investigated candidate to date. Altered binding affinity, signal transduction and expression is seen in vitro; however, meta-analysis demonstrated these findings only translate to small clinical effects without major relevance. While our comprehensive knowledge of

pharmacogenetics is limited, appreciating an individual's genetic predisposition to opioid efficacy and toxicity could lead to the ability in the future to tailor a patients opioid to their genetic background. ◆

REFERENCES

1 Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci USA* 1993; **90:** 5391–3.

2 Gostin LO, Hodge JG, Noe SA. Reframing the opioid epidemic as a national emergency. *JAMA, J Am Med Assoc* 2017; **318:** 1539–40. https://doi.org/10.1001/jama.2017.13358.

3 Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a national institutes of health pathways to prevention Workshop. *Ann Intern Med* 2015; **162:** 276. https://doi.org/10.7326/M14-2559.

4 McDonald J, Lambert DG. Opioid mechanisms and opioid drugs. *Anaesth Intensive Care Med* 2016; **17:** 464–8. https://doi.org/10.1016/j.mpaic.2016.06.012.

5 Stein C. Opioid receptors. *Annu Rev Med* 2016; **67:** 433–51. https://doi.org/10.1146/annurev-med-062613-093100.

6 Chaves C, Remiao F, Cisternino S, Decleves X. Opioids and the blood-brain barrier: a dynamic interaction with consequences on drug disposition in brain. *Curr Neuropharmacol* 2017; **15:** 1156–73. https://doi.org/10.2174/1570159X15666170504095823.

7 Niesters M, Overdyk F, Smith T, Aarts L, Dahan A. Opioid-induced respiratory depression in paediatrics: a review of case reports. *Br J Anaesth* 2013; **110:** 175–82. https://doi.org/10.1093/bja/aes447.

8 Imam MZ, Kuo A, Ghassabian S, Smith MT. Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. *Neuropharmacology* 2018; **131:** 238–55. https://doi.org/10.1016/j.neuropharm.2017.12.032.

9 Wiese AD, Griffin MR, Schaffner W, et al. Long-acting opioid use and the risk of serious infections: a retrospective cohort study. *Clin Infect Dis*, September 2018; https://doi.org/10.1093/cid/ciy809.

10 Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, et al. Opioids and breast cancer recurrence: a Danish population-based cohort study. *Cancer* 2015; **121:** 3507–14. https://doi.org/10.1002/cncr.29532.

11 Buggy DJ, Borgeat A, Cata J, et al. Consensus statement from the BJA Workshop on cancer and Anaesthesia. *Br J Anaesth* 2015; **114:** 2–3. https://doi.org/10.1093/bja/aeu262.

12 Kimmel PL, Fwu C-W, Abbott KC, Eggers AW, Kline PP, Eggers PW. Opioid prescription, morbidity, and mortality in United States dialysis patients. *J Am Soc Nephrol* 2017; **28:** 3658–70. https://doi.org/10.1681/ASN.2017010098.

13 Nerenz RD, Tsongalis GJ. Pharmacogenetics of opioid use and implications for pain management. *J Appl Lab Med An AACC Publ* 2018; **2:** 622–32. https://doi.org/10.1373/jalm.2017.023150.

14 Kalso E. Clinical pharmacology of opioids in the treatment of pain. In: Sommer C, Wallace MS, Cohen SP, Kress M, eds. Pain 2016: refresher courses. Washington D.C.: IASP Press, 2016; 449–60.

15 Wagner BKJ, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet* 1997; **33:** 426–53. https://doi.org/10.2165/00003088-199733060-00003.

16 Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol* 2013; **75:** 60–78. https://doi.org/10.1111/j.1365-2125.2012.04317.x.