Morphine

Updated (minor change) November 2023

Class

Strong opioid analgesic.

Indications

Severe or †moderate pain, †diarrhoea, †cough, †breathlessness.

Contra-indications:

None absolute if titrated carefully against a patient's pain (also see **Strong opioids**).

Pharmacology

Morphine is the main pharmacologically active constituent of opium. Its effects are mediated by specific opioid receptors both within the CNS and peripherally. Under normal circumstances, its main peripheral action is on smooth muscle. However, in the presence of tissue injury and inflammation, the number of opioid receptors at the peripheral end of a nociceptive afferent nerve fibre increases, and exogenous and endogenous opioids (released by activated inflammatory cells in close proximity to the nerve fibre) thereby exert a peripheral analgesic action.[1] Thus, there is increasing interest in the role of topical morphine (see Dose and use). Conversely, in bone and neuropathic pain, opioid receptor expression is reduced, contributing towards a reduced response to opioids. Nonetheless, in pooled data from RCTs in pure neuropathic pain states, morphine provided a 25–33% improvement in pain in two-thirds of patients (NNT = 3.7 (95% CI 2.6–6.5)). However, this is considered very low quality evidence, mostly because of the small number of participants (≤152).[2] In practice, a multimodal approach to pain relief is followed (see **Principles of use of analgesics**).

Morphine, like all μ-opioid receptor agonists (μ agonists) increases intestinal transit time by decreasing propulsive activity and increasing non-propulsive activity via its effect on the myenteric plexus in the longitudinal muscle layer. This causes predictable opioid-induced constipation, which requires prophylactic regular laxatives when morphine is used regularly for pain (see Dose and use). Conversely, it can also be used for diarrhoea, although generally **loperamide**, a peripherally acting μ agonist, is preferred. All opioids can be used for cough and act by suppressing the cough reflex centre in the brain stem (see **Antitussives**). Morphine is also used to relieve breathlessness (see Dose and use).

The liver is the principal site of morphine metabolism.[3] Metabolism also occurs in other organs,[4] including the CNS.[5] Glucuronidation, the main metabolic pathway, is rarely impaired except in severe hepatic impairment, and morphine is well tolerated in patients with mild–moderate hepatic impairment.[6] However, with impairment severe enough to prolong the prothrombin time, the plasma halflife of morphine may be increased (see **Hepatic impairment**).[4]

The major metabolites of morphine are morphine-3-glucuronide (M3G; 55–80%) and morphine-6-glucuronide (M6G; 10–15%), which are excreted by the kidneys.[7] M6G binds to opioid receptors and contributes substantially to the effects of morphine, both desirable (e.g. analgesia) and undesirable (e.g. nausea and vomiting, sedation and respiratory depression).[8–10] In renal impairment, the plasma halflife of M6G increases from 2.5h to ≤50h, and is likely to lead to accumulation and enhanced toxicity (see **Renal impairment**). Similarly, in the last week of life, M6G accumulates as renal function deteriorates, increasing the risk of opioid toxicity and thereby delirium;[11] this may also explain why some RCTs of IV hydration at the end of life found a reduced incidence of sedation, myoclonus and delirium.[12] M3G will also accumulate, but the significance of this is unclear; it binds poorly to opioid receptors and is considered devoid of an analgesic effect. Although animal studies suggest a neuro-excitatory effect, this has not been clearly demonstrated in humans.[13]

Morphine is administered by a range of routes. Systemic absorption from topical application to ulcers or inflamed surfaces varies with the amount and concentration of the gel used; bio-availability ranges from negligible (with 0.06–0.125% gel) to almost the same as SC (0.125–0.5% gel applied to large ulcers).[14–16]

Because of the wide range in PO bio-availability, when switching from PO to SC/IM/IV morphine, the dose required is generally 1/2–1/3 of the PO dose.[17,18] In practice, for morphine, most centres use a conversion ratio of PO:SC/IM/IV of 2:1. Conversely, when switching from SC/IM/IV to PO, the PO dose should be 2–3 times greater than the SC/IM/IV dose. In an observational study, about 80% of patients achieved a satisfactory 24h PO dose at 3 times the previous 24h IV dose, rounded down to convenient-strength m/r tablets.[19]

Morphine salts include morphine sulfate, morphine hydrochloride (not UK) and morphine tartrate (not UK); for clinical purposes all three can be considered bio-equivalent.

Bio-availability 35% PO, ranging from 15–64%; 25% PR.

Peak effect ≤60min PO (immediate-release tablets); 20min IV; 30–60min IM; 50–90min SC.

Time to peak plasma concentration 15–60min PO (immediate-release tablets), 1–6h m/r (product dependent); 10–20min IM; 15min SC; 45–60min PR.

Plasma halflife 1.5–4.5h PO; 1.5h IV.

Duration of action 3–6h; 12–24h m/r (product dependent).

Cautions

Renal impairment and severe **hepatic impairment** (see also Dose and use).

Drug interactions

Concurrent treatment with ≥2 CNS depressants (e.g. benzodiazepines, gabapentinoids, opioids) increases the risk of respiratory depression, particularly in susceptible groups, e.g. the elderly and those with renal or hepatic impairment.[20]

The following have been reported with PO morphine, although their clinical relevance is unknown:

- **rifampicin** may reduce plasma levels of morphine, possibly via the induction of p-glycoprotein in the GI tract
- **quinidine** may increase plasma levels of morphine via the inhibition of p-glycoprotein in the GI tract
- morphine may increase plasma levels of **gabapentin** by slowing GI transit time

- **metoclopramide** may increase the rate of absorption of morphine via increased gastric emptying. (Conversely, morphine can also reduce the pro-kinetic effects of **metoclopramide** on gastric emptying.)

Undesirable effects

See Table 1, and **Strong opioids, Box B**.

Table 1 Potential intolerable effects of morphine

Type	*Effects*	*Initial action*	*Comment*
For general undesirable effects of opioid analgesics, see **Strong opioids, Box B**.			
Gastric stasis	Epigastric fullness, flatulence, anorexia, hiccup, persistent nausea	Prescribe a prokinetic, e.g. **metoclopramide** 10mg PO/SC t.d.s.	If the problem persists, change to an alternative opioid with less impact on the GI tract
Sedation	Intolerable persistent sedation	Reduce dose of morphine; consider a **psychostimulant**, e.g. methylphenidate 5mg PO b.d.	Sedation may be caused by other factors; stimulant rarely appropriate
Cognitive failure	Hyperactive delirium with hallucinations	Prescribe an antipsychotic, e.g. **haloperidol** 500microgram PO/SC stat & q2h p.r.n.; reduce dose of morphine and, if no improvement, switch to an alternative opioid	Some patients develop intractable delirium with one opioid but not with an alternative opioid
Myoclonus	Multifocal twitching ± jerking of limbs	Prescribe a **benzodiazepine**, e.g. diazepam 5mg PO or midazolam 2.5mg SC stat & q1h p.r.n.; reduce dose of morphine but increase again if pain recurs	Uncommon with typical oral doses; more common with high dose IV and spinal morphine
Neurotoxicity	Abdominal muscle spasms, symmetrical jerking of legs; whole-body allodynia, hyperalgesia (manifests as excruciating pain)	Prescribe a **benzodiazepine**, e.g. diazepam 5mg PO or midazolam 2.5mg SC stat & q1h p.r.n. Reduce dose of morphine; consider changing to an alternative opioid	A rare syndrome in patients receiving intrathecal or high dose IV morphine; occasionally seen with typical oral and SC doses
Vestibular stimulation	Movement-induced nausea and vomiting	Prescribe an antihistaminic antimuscarinic anti-emetic, e.g. **cyclizine** 50mg PO or 25mg SC b.d.–t.d.s.	If intractable, try **levomepromazine** or switch to an alternative opioid

Pruritus	Whole-body itch with systemic morphine; localized to upper body or face/nose with spinal morphine	With systemic opioids, prescribe PO H_1-antihistamine (e.g. chlorphenamine 4mg PO stat; if beneficial continue with 4mg t.d.s. or q4h p.r.n. for 2–3 days). Possibly switch opioids, e.g. morphine → oxycodone. For spinal opioids, see **Spinal analgesia**	Pruritus after systemic opioids is uncommon. It can sometimes be caused by cutaneous histamine release and be self-limiting, but the most distressing cases are chronic and antihistamine-resistant. Centrally acting opioid antagonists also relieve the pruritus but will also antagonize analgesia [21]
Histamine release	Life-threatening compromise in airway/breathing and/or circulation	Treat as for **anaphylaxis**. Change to a chemically distinct opioid immediately, e.g. methadone	Very rare

Dose and use

Patients using opioids must be monitored for undesirable effects, particularly nausea and vomiting, and constipation. Depending on individual circumstances, an anti-emetic should be prescribed for regular or p.r.n. use (see **QCG: Nausea and vomiting**) and, routinely, a laxative prescribed (see **QCG: Opioid-induced constipation**).

Opioids can impair driving ability, and patients should be counselled accordingly. Morphine is included in a law in England, Wales and Scotland relating to driving with certain drugs above specified plasma concentrations (see **Drugs and fitness to drive**).

Based on familiarity, availability and cost, morphine is the strong opioid of choice for moderate–severe cancer pain. [22,23] However, in terms of efficacy and undesirable effects, morphine, **hydromorphone** and **oxycodone** are essentially similar. [24–26] Morphine is generally prescribed with a non-opioid when the non-opioid + a weak opioid does not provide adequate relief (see **Principles of use of analgesics**).

There is no pharmacological need for weak opioids in cancer pain (see **Principles of use of analgesics**). Low doses of morphine (or an alternative strong opioid) generally provide quicker and better relief from cancer pain than a weak opioid. [22,27] Moving directly from a non-opioid to a strong opioid is increasingly preferred in adults, and is the norm in children, in whom weak opioids are generally contra-indicated (see **Prescribing for children**).

Oral

Morphine is available as:

- immediate-release products: tablets, orodispersible tablets, solutions

- modified-release (m/r) products: tablets, capsules, suspensions (not UK).

Most m/r products are administered b.d., some once daily. Because the pharmacokinetic profiles of m/r products differ,[28-30] it is best to keep individual patients on the same brand. M/r tablets should be swallowed whole; crushing or chewing them will lead to a rapid release of an overdose of morphine. For administration of immediate-release and m/r morphine to patients with swallowing difficulties or enteral feeding tubes see Supply and **Swallowing difficulties and EFT, Table 2**.

Patients can be started on either an ordinary (immediate-release) or an m/r formulation (Box A).[31,32] An observational study supports a starting dose of 5mg q4h as generally safe for opioid-naïve patients, and 10mg q4h for those being switched from a regular weak opioid.[33] However, slight variation exists between guidelines, e.g. in the recommended starting dose.[34] It is important to recognize that guidelines are just guidelines; for each patient, when deciding the starting dose, it is necessary to consider the individual circumstances, e.g. severity of the pain, current analgesia, presence of renal impairment, increasing age or frailty. In every case, the patient must be monitored closely and the dose titrated as necessary.

Box A Starting a patient on PO morphine

The starting dose of morphine is calculated to give a greater analgesic effect than the medication already in use:

- if the patient was previously receiving a weak opioid regularly (e.g. codeine 240mg/24h or equivalent), give morphine 10mg q4h or m/r 20–30mg q12h, but less if suspected to be a poor codeine metabolizer (see **codeine phosphate**)
- if changing from an alternative strong opioid (e.g. fentanyl, methadone), a much higher dose of morphine may be needed
- if the patient is frail, elderly, or opioid-naïve, a lower dose helps to reduce initial drowsiness, confusion and unsteadiness, e.g. morphine 5mg q4h or m/r 10–15mg q12h
- because of accumulation of an active metabolite, a lower and/or less frequent regular dose may suffice in mild–moderate renal impairment, e.g. morphine 5–10mg q6–8h (but the use of a renally safer opioid is generally advisable with moderate–severe renal impairment (see **below**, and **Renal impairment**).

When adjusting the dose of morphine, p.r.n. use should be taken into account; increments should not exceed 33–50% every 24h. As a general rule, the p.r.n. dose must be increased when the regular dose is increased.

Patients using opioids must be monitored for undesirable effects, particularly nausea and vomiting, and constipation (see **Strong opioids, Box B**). Depending on individual circumstances, an anti-emetic should be prescribed for regular or p.r.n. use (see **QCG: Nausea and vomiting**) and, routinely, a laxative prescribed (see **QCG: Opioid-induced constipation**).

Opioids can impair driving ability, and patients should be counselled accordingly. Morphine is included in a law in England, Wales and Scotland relating to driving with certain drugs above specified plasma concentrations (see **Drugs and fitness to drive**).

Upward titration of the dose of morphine should stop when either the pain is relieved or unacceptable undesirable effects occur. In the latter case, it is generally necessary to consider alternative measures. The aim is to have the patient free of pain and mentally alert after the initial drowsiness has cleared.

Because of poor absorption, m/r morphine may not be satisfactory in patients troubled by frequent vomiting or those with diarrhoea or an ileostomy.

Scheme 1: immediate-release morphine

- give morphine q4h 'by the clock' with p.r.n. doses 1/10–1/6 of the 24h dose
- after 1–2 days, recalculate q4h dose by dividing the total used in previous 24h (regular + p.r.n. use) by 6
- continue q4h and p.r.n. doses
- increase the regular dose until there is adequate relief throughout each 4h period, taking p.r.n. use into account
- a double dose at bedtime obviates the need to wake the patient for a dose during the night
- >90% of patients achieve satisfactory pain relief within 5 days.

Scheme 2: immediate-release morphine and modified-release (m/r) morphine

- begin as for Scheme 1
- when the q4h dose is stable, replace with m/r morphine q12h, or once daily if a 24h product is prescribed
- the q12h dose will be three times the previous q4h dose; a q24h dose will be six times the previous q4h dose, rounded to a convenient number of tablets or capsules
- continue to provide immediate-release morphine for p.r.n. use; give 1/10–1/6 of the 24h dose q2–4h.

Scheme 3: m/r morphine and immediate-release morphine

- generally start with m/r morphine 20–30mg q12h, or 10–15mg q12h in frail or elderly patients
- use immediate-release morphine for p.r.n. medication; give 1/10–1/6 of the 24h dose q2–4h
- if necessary, increase the dose of m/r morphine every 2–3 days until there is adequate relief throughout each 12h period, guided by p.r.n. use.

Traditionally, to make things easier for patients, morphine q4h has been given on waking, 1000h, 1400h, 1800h with a double dose at bedtime. Despite contrary results in a non-blinded study, [35] RCT evidence has shown that this approach results in less pain through the night, better sleep, and no increase in early morning pain. [36]

When adjusting the dose of morphine, p.r.n. use should be taken into account; increments should not exceed 33–50% every 24h. [37] Instructions must be clear: extra p.r.n. morphine does not mean that the next regular dose is omitted.

P.r.n. doses of morphine for break-through cancer pain are typically 1/10-1/6 of the regular 24h dose but, as with the regular dose, individual titration is required to find the optimal dose. In practice, satisfactory p.r.n. doses vary from 1/20 (5%) to 1/5 (20%) of the 24h dose (see **Break-through pain**).

As a general rule, the p.r.n. dose should be increased when the regular dose is increased. A p.r.n. dose is generally permitted every q2-4h as required (up to q1h when pain severe, or in the last days of life). However, frequent use of p.r.n. doses, i.e. ≥2 a day, should prompt a review of pain management. The mean time to onset of effect is 15min with a PO solution of morphine compared with 30min after an immediate-release tablet, suggesting that morphine solution is the better option for p.r.n. use (see also **Fentanyl (transmucosal)**).

There are no clinical comparisons of morphine PO solution with the orodispersible morphine tablet. However, pharmacokinetic characteristics of the latter are similar to the standard immediate-release PO morphine tablet with both producing a lower C_{max} than an equivalent dose of morphine solution. [38]

An anti-emetic, e.g. **haloperidol** 500microgram PO, should be supplied for p.r.n. use during the first week or prescribed regularly if the patient has had nausea with a weak opioid (see **QCG: Nausea and vomiting**). Warn patients about the possibility of initial drowsiness. A laxative should be prescribed routinely unless there is a definite reason for not doing so, e.g. the patient has an ileostomy (see **QCG: Opioid-induced constipation**). *Constipation may be more difficult to manage than the pain.* Laxative suppositories and enemas continue to be necessary in about one third of patients. [39]

Subcutaneous administration

In the UK, if the PO route becomes an unreliable means of administering regular morphine, e.g. because of vomiting or difficulty swallowing, generally the **CSCI** route is used.

In strong opioid-naïve patients:

- start with 20mg/24h CSCI and 5mg SC p.r.n. (halve both doses in the frail, elderly or mild–moderate renal impairment)
- if necessary, titrate the dose upwards, guided by p.r.n. use.

For general considerations when switching routes, see **Opioid dose conversion ratios**. When switching morphine PO to CSCI, most centres divide the total daily PO dose by 2 and re-titrate as necessary, e.g.:

- patient taking m/r morphine 30mg PO b.d. = 60mg/24h PO
- divide 60mg/24h by 2 = 30mg/24h CSCI
- the p.r.n. dose is 1/10–1/6 of the 24h dose, i.e. 3–5mg SC p.r.n.

For CSCI dilute with WFI, sodium chloride 0.9% or glucose 5%.

CSCI compatibility with other drugs: there are 2-drug compatibility data for morphine sulfate in WFI with **clonazepam**, **cyclizine**, **glycopyrronium**, **hyoscine *butylbromide***, **hyoscine *hydrobromide***, **ketamine**, **levomepromazine**, **metoclopramide** and **octreotide**.

Morphine sulfate is *incompatible* with **ketorolac** and may be *incompatible* with higher concentrations of **haloperidol** or **midazolam**.

For more details and 3-drug compatibility data, see Compatibility **Chart 1** and **Chart 5**.

Information on compatibility in sodium chloride 0.9% is also available, see Compatibility **Chart 8** and **Chart 12**.

Renal or hepatic impairment

Because of the risk of impaired metabolism or elimination:

- lower than usual starting doses are advised in mild–moderate renal impairment, e.g. 5–10mg PO q6–8h, and severe **hepatic impairment**
- the use of a renally safer opioid is generally advisable with severe **renal impairment** or ESRF. If the use of morphine is unavoidable, start with 1.25-2.5mg PO/SC p.r.n., and once the pain is controlled consider switching to an equivalent dose of **buprenorphine** or **fentanyl** TD.

For a general approach when renal or hepatic function deteriorates rapidly, see **Strong opioids**.

Intravenous administration

IV morphine is widely used for the rapid relief of severe pain caused by acute trauma or medical emergencies.

In opioid-naïve patients:

- give a prophylactic anti-emetic IV, e.g. **metoclopramide** 10mg
- over 5–10min, give a total of morphine 5–10mg (2.5–5mg in the elderly) IV
- when insufficient, give additional morphine at a rate not exceeding 1–2mg/min until satisfactory relief obtained; monitor for undesirable effects, e.g. excessive sedation, respiratory depression
- the dose can be repeated q2–4h as required.

Although uncommon in UK, CIVI morphine and/or p.r.n. IV morphine are used in palliative care units in Europe and North America. [40,41] Generally, this is in the context of the first few days of an inpatient admission for pain control. Subsequently, patients can be switched from IV to PO (see Pharmacology).

Rapid IV/SC titration of morphine dose for severe cancer pain

Although rapid IV/SC titration of morphine is generally *not* necessary, it can be useful in patients with severe acute pain, whether already taking opioids ('opioid-tolerant') or opioid-naïve. [42,43] Further, because of difficulties in relation to follow-up, rapid IV titration is the norm at some centres in India for new patients presenting with pain of ≥5 out of 10.

Two IV methods are included here: the first with 10min and the second with 1min intervals between each IV bolus (Box B and Box C). [43-47] In India, a single cumulative IV dose is given, followed immediately by PO medication (Box B). About 80% of patients obtain relief with 10mg or less. [44,45] At the Cleveland Clinic (USA), patients are maintained on CIVI for several days before conversion to PO medication (Box C). Although these methods have been used safely in many patients, **naloxone** should be readily available (see **QCG: Reversal of opioid-induced respiratory depression**).

Box B Rapid titration of morphine dose in opioid-naïve patients (Institute of Palliative Medicine, India) [44,45]

Prerequisites

Pain ≥5/10 on a numerical scale.

Probability of a partial or complete response to morphine. [a]

Method

Obtain venous access with a butterfly cannula.

Give metoclopramide 10mg IV routinely, if no contra-indications.

Dilute the contents of 15mg morphine ampoule in a 10mL syringe. [b]

Inject 1.5mg (1mL) every 10min until the patient is pain-free or complains of undue sedation. [c]

If patients experience nausea, give additional metoclopramide 5mg IV.

Results

Dose required (with approximate percentages):

- 1.5–4.5mg (40%)
- 6–9mg (40%)
- 10.5–15mg (15%)
- >15mg (5%).

Complete relief in 80%; none in 1%.

Drop-outs 2%.

Undesirable effects: sedation 32%; other 3%.

Ongoing treatment

Prescribe a dose of oral morphine q4h similar to the IV dose, rounded to nearest 5mg, e.g. needed morphine 3–6mg IV → 5mg PO; the minimum dose is 5mg.

Advise about p.r.n. doses and, if >2/24h needed, to increase the dose the next day.

In practice, 20% of patients need a dose increase within 3 days.

---

a. most patients will already be taking an NSAID

b. ampoule strengths varies from country to country; use local standard

c. if ampoule = 10mg/mL (diluted to 10mg in 10mL), a bolus dose of 2mg would be reasonable.

Box C Rapid titration of morphine dose in both opioid-tolerant and opioid-naïve patients (based on practice at Cleveland Clinic, Ohio, USA) [42, 46, 47]

Sequence	***IV***	***SC***
Dose	1mg/min up to 10mg	2mg q5min up to 10mg
Pause	5min	10min
Dose	1mg/min up to 10mg	2mg q5min up to 10mg
Pause	5min	10min

Sequence	*IV*	*SC*
Dose	1mg/min up to 10mg	2mg q5min up to 10mg

Review cause if relief inadequate after a total of 30mg.

Maintenance IV/SC dose

Regard cumulative effective dose as the equivalent of a q4h dose, and prescribe accordingly.

Example
Cumulative effective IV dose = 9mg.
If giving intermittent injections, dose = 9mg q4h, rounded to 10mg.
If CIVI, total daily IV dose = 9mg x 6 = 54mg/24h.
Round this up or down to convenient number of ampoules, i.e. 50mg or 60mg.
P.r.n. dose = 5–10mg q1h.

IV patient-controlled analgesia (PCA) can also be used but is more costly, requires inpatient admission and may take >10h to achieve relief.[48,49] Some centres use a more rapidly acting strong opioid, e.g. IV **fentanyl**, with subsequent doses given after pauses of only 5–10min.[50]

Note. Patients who have required a rapid escalation in opioid requirements must be monitored closely. The underlying cause may be transient, e.g. haemorrhage into a liver metastasis, and a subsequent reduction in dose will be necessary.

Buccal morphine

Morphine is only slowly absorbed through the buccal mucosa.[51,52] Thus, most of a morphine solution given sublingually or into the gingival gutter will be swallowed and absorbed from the GI tract. Nonetheless, in the past, this route was successfully used in moribund patients.

Rectal morphine

Morphine is absorbed from suppositories.[53] From the lower and middle rectum, it will enter the systemic circulation bypassing the liver. From the upper rectum, it will undergo hepatic first-pass metabolism after it enters the portal circulation. However, there are extensive anastomoses between the rectal veins which make it impossible to predict how much will enter the portal circulation.[54,55] Despite the uncertainty, in practice the same dose is given PR as PO and titrated as necessary.

Morphine suppositories are no longer commercially available in the UK. Although not authorized for this route and not generally recommended, m/r morphine oral tablets have been used PR to provide analgesia in moribund patients, generally while organizing a more reliable delivery method.[56]

Spinal morphine

In the UK, <5% of cancer patients needing morphine receive it spinally, i.e. ED or IT. This route of administration (see **Spinal analgesia**) is normally undertaken by an anaesthetist. Particularly with neuropathic pain, morphine is generally combined with a local anaesthetic (e.g. **bupivacaine**), and sometimes with **clonidine**.

Topical morphine

The number of peripheral opioid receptors increases in nociceptive afferent nerve fibres in the presence of local inflammation.[1,15,57] This property is exploited in joint surgery, where morphine is given intra-articularly at the end of the operation.[58] Topical morphine has also been used successfully to relieve otherwise intractable pain associated with cutaneous ulceration, often decubitus ulcers.[59–62] It is often given as a 0.1% (1mg/mL) gel, using IntraSite®. If prepared under sterile conditions, morphine sulfate is stable for at least 28 days when mixed with IntraSite® gel at a concentration of 0.125% (1.25mg/mL). This preparation can be made by thoroughly mixing 1mL of morphine sulfate 10mg/mL injection with 8g of IntraSite® gel.[63] Morphine 0.1% and 0.2% in Intrasite® gel is also available as a special order product.

Higher concentrations, namely 0.3–0.5%, have been used when managing pain associated with:

- vaginal inflammation associated with a fistula
- rectal ulceration.[60]

The amount of gel applied varies according to the size and the site of the ulcer, but is typically 5–10mL applied b.d.–t.d.s. The topical morphine is kept in place with either a non-absorbable pad or dressing, e.g. Opsite® or Tegaderm®, or gauze coated with petroleum jelly. Other morphine 0.2% ointments and gels have been locally prepared.[64] Other opioids, e.g. **diamorphine** or **methadone**, and other carriers, e.g. Stomahesive® paste or **metronidazole** gel, have also been used.[62,65]

For cancer-treatment-related oral mucositis, an oral morphine solution *without alcohol* of 2mg/mL can be used (special order, see Supply). Use 15mL to rinse the mouth for 2min q2–3h (see **Drugs for oral inflammation**). It provides better pain relief than a placebo mouthwash or one containing **co-magaldrox** + **lidocaine** + **diphenhydramine**.[66,67] Significant relief occurs after about 30min, and lasts about 3.5h.[68]

In vitro and animal studies suggest that topical morphine may also aid wound healing by stimulating angiogenesis.[69] However, no such benefit was seen in an RCT of patients with ulcerative oral lichen planus.[70]

†Morphine for breathlessness

Opioids are used for breathlessness which persists despite optimal treatment of the underlying cause, along with non-drug approaches relevant to the performance status and prognosis of the patient.[71] Most experience is with morphine.

Current evidence and clinical experience supports the use of regular opioids for patients who are breathless at rest, but not for those breathless only on exertion.[72] For the latter group, a p.r.n. dose of an opioid also has limited utility because exertional breathlessness generally recovers within 5–20min, much quicker than the time it takes to locate, administer and obtain benefit from an opioid.[73] Thus, non-drug measures are of primary importance in this circumstance.[71]

Systematic reviews ± meta-analyses of RCTs mostly in COPD, CHF and cancer support the use of opioids by the oral and parenteral but *not* the nebulized route.[74–76] A specific review of nebulized (and nasal) opioids concluded the same, and these should not be used outside of a clinical trial.[71,77]

Data from larger RCTs of oral opioids are emerging, mostly in COPD, cancer and CHF.[78–80] **Oxycodone** was ineffective,[78] and benefit from morphine limited to those with more severe functional limitation (i.e. modified MRC breathlessness grade ≥3).[79,81] However, because of slow recruitment, some trials were stopped early (and are consequently underpowered)[78,80,82] or abandoned completely.[83] Most authors concluded that further trials are required.

Morphine and other opioids reduce the ventilatory response to hypercapnia, hypoxia and exercise, decreasing respiratory effort and breathlessness.[71] Improvements are seen at doses that do *not* cause respiratory depression.[81,84,85]

Generally, small doses are sufficient, typically PO morphine 10–30mg/24h, but sometimes less, and only rarely more.[81,86-91] For opioid-naïve patients, some advocate starting with an m/r product, others an immediate-release one (Box D). Both approaches have specific advantages, e.g. the m/r approach is simpler, provides relief more quickly for some patients, and opioid plasma concentrations fluctuate less over a 24h period; the immediate-release approach identifies those patients who benefit from doses <10mg/24h and appears to be associated with fewer withdrawals because of undesirable effects.[90,91] RCT supporting evidence is greater for the m/r approach. Only Australia has a morphine product authorized for chronic breathlessness, a once daily m/r product (Kapanol®).

Box D Starting PO morphine for breathlessness in opioid-naïve patients[90,91]

Approaches using either m/r or immediate-release morphine products have been described for patients with moderate–severe breathlessness, mostly with COPD or lung cancer. Whichever is used, because of the risk of undesirable effects, it is important to provide appropriate explanation, laxatives, anti-emetics and monitoring. In studies of 3–6 months' duration, benefit is generally maintained at the same dose after the initial titration.

M/r approach

- start with MST Continus® 5mg PO b.d. for 1 week
- if baseline VAS/NRS breathlessness is not reduced ≥10%, increase by 10mg/24h weekly
- usual maximum 30mg/24h.

In one study using this approach,[91] about 60% of patients benefited from morphine, most at 10mg/24h. However, undesirable effects, e.g. drowsiness, confusion, nausea and vomiting, and constipation, were a common cause of discontinuation during initial titration (20%).

Immediate-release approach

Mostly in an attempt to minimize the risk of undesirable effects and maintain the confidence of patients who may be wary of taking an opioid, others advocate slower initial titration, with immediate-release morphine solution increased until breathlessness is tolerable, e.g.:

- in the first week, start with 500microgram PO b.d. and increase at 48h intervals → 500microgram q.d.s. → 1mg q4h
- then, at weekly intervals, increase the q4h dose to 2mg → 3mg → 5mg
- if necessary, continue to adjust each week using 30–50% dose increments
- reduce dose if undesirable effects occur; if persistent, consider a switch to an alternative opioid
- when the dose is unchanged for 2 weeks, consider switching to an m/r formulation.

In one study using this approach, [90] a similar overall response rate of 60% was obtained, with most of those switched to a m/r formulation requiring 10–15mg/24h (only one required 20mg/24h). However, 40% remained on an immediate-release formulation requiring doses ≤10mg/24h.

Undesirable effects were a less frequent cause of discontinuation during initial titration (7%). However, unlike in the m/r study, a switch to an alternative opioid was permitted in cases of intolerance, and was necessary in about 10%.

In patients already taking morphine for pain, there are limited data to guide practice. One study suggests a reasonable starting point to be: [92]

- divide the 24h dose by 6 (e.g. morphine 60mg/24h ÷ 6 = 10mg q4h)
- start with p.r.n. doses equivalent to 25% of what would be the q4h analgesic dose (e.g. 10mg ÷ 4 = 2.5mg); this may suffice in those with mild–moderate breathlessness at rest
- if necessary, increase to 50% of the q4h analgesic dose (e.g. 10mg ÷ 2 = 5mg)
- if frequent p.r.n. doses are needed, the regular background opioid dose should be increased accordingly.

As with pain, individual titration is required for optimal benefit, and p.r.n. doses equal to or higher than the q4h analgesic dose may be required. In some patients, morphine by CSCI is better tolerated and provides greater relief, possibly by avoiding the peaks (with undesirable effects) and troughs (with loss of effect) of oral medication. If using an alternative opioid to morphine, adopt the same approach.

Generally, the average reduction in breathlessness as assessed by NRS (0–10) or VAS (0–100mm) is relatively small, e.g. about 1 point/10mm respectively. Nonetheless, this represents a change that is clinically important. [93]

Several adverse effects (e.g. excess exacerbations, emergency department visits, hospitalizations, deaths) have been associated with the use of opioids and/or benzodiazepines in patients with COPD. [75, 94] Although some found a relationship with any opioid dose, others reported no excess deaths or hospitalizations with lower opioid doses (± benzodiazepines) equivalent to morphine ≤30mg/24h PO. [75] This supports limiting the dose of morphine to within this dose range in this group of patients.

Breathlessness in the last days of life

The incidence of breathlessness increases as death approaches. For severe breathlessness in the last days of life:

- patients often fear suffocating to death, and a positive approach to the patients, their family and colleagues about the relief of terminal breathlessness is important
- no patient should die with distressing breathlessness
- failure to relieve terminal breathlessness is a failure to utilize drug treatment correctly.

Because of the distress, inability to sleep and exhaustion, patients and their carers generally accept that drug-related drowsiness may need to be the price paid for greater comfort. However, unless there is overwhelming distress, sedation is not the primary aim of treatment, and some patients become mentally brighter when their breathlessness is reduced.

Even so, because increasing drowsiness also generally reflects the deteriorating clinical condition, it is important to stress the gravity of the situation and the aim of treatment to the relatives. Drug treatment typically comprises:

- parenteral administration of an opioid and a sedative-anxiolytic; e.g. for opioid-naïve patients, start with:
  - morphine 5–10mg/24h + **midazolam** 10mg/24h by CSCI *and*
  - morphine 2.5mg + **midazolam** 2.5mg SC p.r.n. q1h
  - for those already receiving PO morphine or another opioid, convert to the equivalent parenteral 24h and p.r.n. doses
  - titrate both p.r.n. and regular doses to obtain satisfactory relief

- **haloperidol** or **levomepromazine** if the patient develops a hyperactive delirium; see **Benzodiazepines, Box B** (may be aggravated by a benzodiazepine). [95–97]

Supply

Unless indicated otherwise, all products are Schedule 2 **CD**.

All products listed below are morphine sulfate.

Immediate-release oral products

> Morphine oral solution is available in two strengths, 2mg/mL and a high potency concentrate of 20mg/mL supplied with a calibrated syringe. *Deaths have occurred from accidental overdose with the concentrated solution*, mostly when doses prescribed in *mg* were administered as *mL*. Prescribing should be in *mg* not mL to minimize the risk of *20 times* the prescribed dose being given. [98]

Sevredol ® (Napp)
Tablets 10mg, 20mg, 50mg; 10mg and 100mg dose = £0.09 and £1 respectively.

Actimorph ® (Ethypharm)
Orodispersible tablets 1mg, 2.5mg, 5mg, 10mg, 20mg and 30mg; 10mg dose = £0.08; *contains benzyl alcohol. Tablets disperse in the mouth before swallowing. For patients with swallowing difficulties, the tablet may be dispersed in water on a spoon.*

Morphine sulfate (generic)
Oral solution 2mg/mL (**PoM**); 10mg dose = £0.10; *may contain alcohol.*
Oral solution (alcohol-free) 2mg/mL (**PoM**), 10mg dose = Price unavailable, (unauthorized product, available as a **special order**).

Oramorph ® (Glenwood GmbH)
Oral solution 2mg/mL (**PoM**); 10mg dose = £0.10; *contains alcohol.*
Concentrated oral solution 20mg/mL, 100mg dose = £0.75.

Modified-release products

> As for all m/r opioids, **brand prescribing** is recommended to reduce the risk of confusion and error in dispensing and administration.

Modified-release 12-hourly oral products

Morphgesic ® SR (Advanz Pharma)

Tablets m/r 10mg, 30mg, 60mg, 100mg, 28 days @ 30mg q12h = £8.50.

MST Continus ® (Napp)

Tablets m/r 5mg, 10mg, 15mg, 30mg, 60mg, 100mg, 200mg, 28 days @ 30mg q12h = £12.

Zomorph ® (Ethypharm)

Capsules containing m/r granules 10mg, 30mg, 60mg, 100mg, 200mg, 28 days @ 30mg q12h = £8. *May be swallowed whole or opened and the granules sprinkled on cold soft food and swallowed whole. Can also be given via gastric or gastrostomy tubes >16Fr with an open distal end or lateral pores (see SPC and* ***Swallowing difficulties and EFT, Table 2****).*

Modified-release 24-hourly oral products

MXL ® (Napp)

Capsules containing m/r granules 30mg, 60mg, 90mg, 120mg, 150mg, 200mg, 28 days @ 60mg *once daily* = £15. *May be swallowed whole or opened and the granules sprinkled on cold soft food and swallowed whole.*

Parenteral products

Morphine *sulfate* (generic)

Injection 1mg/mL (1mL, 5mL and 10mL amp = £3.75, £4.75 and £1.50); 10mg/mL (1mL amp = £1.75); 15mg/mL (1mL amp = £1); 20mg/mL (1mL amp = £13); 30mg/mL (1mL and 2mL amps = £1.50 and £2).

Infusion 1mg/mL 50mL vial = £4.50, 2mg/mL 50mL vial = £6.50.

References

1. Smith HS (2008) Peripherally-acting opioids. *Pain Physician*. **11**: S121–S132.
2. Cooper TE *et al.* (2017) Morphine for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews*. **5**: CD011669. **www.cochranelibrary.com**.
3. Hasselstrom J *et al.* (1986) The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *British Journal of Clinical Pharmacology*. **29**: 289–297.
4. Mazoit J-X *et al.* (1987) Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. *Anesthesia and Analgesia*. **66**: 293–298.
5. Sandouk P *et al.* (1991) Presence of morphine metabolites in human cerebrospinal fluid after intracerebroventricular administration of morphine. *European Journal of Drug Metabolism and Pharmacology*. **16**: 166–171.
6. Regnard CFB and Twycross RG (1984) Metabolism of narcotics (letter). *British Medical Journal*. **288**: 860.
7. McQuay HJ *et al.* (1990) Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clinical Pharmacology and Therapeutics*. **48**: 236–244.
8. Osborne RJ *et al.* (1986) Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *British Medical Journal*. **292**: 1548–1549.
9. Thompson P *et al.* (1992) Mophine-6-glucuronide: a metabolite of morphine with greater emetic potency than morphine in the ferret. *British Journal of Pharmacology*. **106**: 3–8.

10. Klimas R and Mikus G (2014) Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *British Journal of Anaesthesia*. **113**: 935–944.

11. Franken LG *et al.* (2016) Pharmacokinetics of morphine,morphine-3-glucuronide and morphine-6-glucuronide in terminally ill adult patients. *Clinical Pharmacokinetics*. **55**: 697–709.

12. Good P *et al.* (2014) Medically assisted hydration for adult palliative care patients. *Cochrane Database of Systematic Reviews*. **4**: CD006273. **www.cochranelibrary.com**.

13. Gretton S and Riley J (2008) Morphine metabolites: a review of their clinical effects. *European Journal of Palliative Care*. **15**: 110–114.

14. Westerling D *et al.* (1994) Transdermal administration of morphine to healthy subjects. *British Journal of Clinical Pharmacology*. **37**: 571–576.

15. Ribeiro MD *et al.* (2004) The bioavailability of morphine applied topically to cutaneous ulcers. *Journal of Pain and Symptom Management*. **27**: 434–439.

16. Watterson G *et al.* (2004) Peripheral opioids in inflammatory pain. *Archives of Disease in Childhood*. **89**: 679–681.

17. Hanks G *et al.* (2001) Morphine and alternative opioids in cancer pain: the EAPC recommendations. *British Journal of Cancer*. **84**: 587–593.

18. Takahashi M *et al.* (2003) The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. *Palliative Medicine*. **17**: 673–678.

19. Lasheen W *et al.* (2010) The intravenous to oral relative milligram potency ratio of morphine during chronic dosing in cancer pain. *Palliative Medicine*. **24**: 9–16.

20. MHRA (2020) Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression. *Drug Safety Update*. **www.gov.uk/drug-safety-update**.

21. Twycross RG *et al.* (2003) Itch: scratching more than the surface. *Quarterly Journal of Medicine*. **96**: 7–26.

22. Caraceni A *et al.* (2012) Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncology*. **13**: e58–e68.

23. Fallon M *et al.* (2018) Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*. **29 (Suppl 4)**: iv166–iv191.

24. Caraceni A *et al.* (2011) Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliative Medicine*. **25**: 402–409.

25. Schmidt-Hansen M *et al.* (2022) Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews*. **6**: CD003870. **www.cochranelibrary.com**.

26. Li Y *et al.* (2021) Hydromorphone for cancer pain. *Cochrane Database of Systematic Reviews*. **8**: CD011108. **www.cochranelibrary.com**.

27. Bandieri E *et al.* (2016) Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain. *Journal of Clinical Oncology*. **34**: 436–442.

28. Bloomfield S *et al.* (1993) Analgesic efficacy and potency of two oral controlled-release morphine preparations. *Clinical Pharmacology and Therapeutics*. **53**: 469–478.

29. Gourlay G *et al.*, editors. A comparison of Kapanol (a new sustained-release morphine formulation), MST Continus and morphine solution in cancer patients: pharmacokinetic aspects. The Seventh World Congress on Pain; 1993; Seattle: IASP Press.

30. West R and Maccarrone C, editors. Single dose pharmacokinetics of a new oral sustained-release morphine formulation, Kapanol capsules. The Seventh World Congress on Pain; 1993; Seattle: IASP Press.

31. Mercadante S (2007) Opioid titration in cancer pain: a critical review. *European Journal of Pain*. **11**: 823–830.

32. De Conno F *et al.* (2008) The MERITO Study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain. *Palliative Medicine*. **22**: 214–221.

33. Ripamonti CI *et al.* (2009) Normal-release oral morphine starting dose in cancer patients with pain. *Clinical Journal of Pain*. **25**: 386–390.

34. Taubert M *et al.* (2010) Re: Update on cancer pain guidelines. *Journal of Pain and Symptom Management*. **24**: 1–5.

35. Todd J *et al.* (2002) An assessment of the efficacy and tolerability of a 'double dose' of normal-release morphine sulphate at bedtime. *Palliative Medicine*. **16**: 507–512.

36. Dale O *et al.* (2009) A double-blind, randomized, crossover comparison between single-dose and double-dose immediate-release oral morphine at bedtime in cancer patients. *Journal of Pain and Symptom Management*. **37**: 68–76.

37. Carver AC and Foley KM (2001) Symptom assessment and management. *Neurologic Clinics*. **19**: 921–947.

38. Atrux-Tallau N *et al.* (2022) Pharmacokinetics of morphine sulfate orodispersible tablets and bioequivalence with immediate-release oral morphine sulfate formulations in healthy adult subjects under fasting conditions: single-dose comparative bioavailability studies. *Clinical Drug Investigation*. **42**: 1101–1112.

39. Twycross RG and Harcourt JMV (1991) The use of laxatives at a palliative care centre. *Palliative Medicine*. **5**: 27–33.

40. Mercadante S *et al.* (2008) Intravenous morphine for breakthrough (episodic-) pain in an acute palliative care unit: a confirmatory study. *Journal of Pain and Symptom Management*. **35**: 307–313.

41. Mercadante S (2010) Intravenous morphine for management of cancer pain. *Lancet Oncology*. **11**: 484–489.

42. Hagen N *et al.* (1997) Cancer pain emergencies: a protocol for management. *Journal of Pain and Symptom Management*. **14**: 45–50.

43. Davis MP *et al.* (2004) Opioid dose titration for severe cancer pain: a systematic evidence-based review. *Journal of Palliative Medicine*. **7**: 462–468.

44. Kumar K *et al.* (2000) Intravenous morphine for emergency treatment of cancer pain. *Palliative Medicine*. **14**: 183–188.

45. Harris JT *et al.* (2003) Intravenous morphine for rapid control of severe cancer pain. *Palliative Medicine*. **17**: 248–256.

46. Davis MP (2004) Acute pain in advanced cancer: an opioid dosing strategy and illustration. *American Journal of Hospice and Palliative Care*. **21**: 47–50.

47. Davis MP (2005) Rapid opioid titration in severe cancer pain. *European Journal of Palliative Care*. **12**: 11–14.

48. Radbruch L *et al.* (1999) Intravenous titration with morphine for severe cancer pain: report of 28 cases. *Clinical Journal of Pain*. **15**: 173–178.

49. Schiessl C *et al.* (2010) Rhythmic pattern of PCA opioid demand in adults with cancer pain. *European Journal of Pain*. **14**: 372–379.

50. Soares LG *et al.* (2003) Intravenous fentanyl for cancer pain: a "fast titration" protocol for the emergency room. *Journal of Pain and Symptom Management*. **26**: 876–881.

51. Coluzzi P (1998) Sublingual morphine: efficacy reviewed. *Journal of Pain and Symptom Management*. **16**: 184–192.

52. Dyal BW *et al.* (2019) Sublingual versus swallowed morphine: a comparison. *Cancer Nursing*. **44**: e13–e22.

53. deBoer AG *et al.* (1982) Rectal drug administration: clinical pharmacokinetic considerations. *Clinical Pharmacokinetics*. **7**: 285–311.

54. Johnson AG and Lux G (1988) Progress in the Treatment of Gastrointestinal Motility Disorder. The role of cisapride. Excerpta Medica, Amsterdam.

55. Ripamonti C and Bruera E (1991) Rectal, buccal and sublingual narcotics for the management of cancer pain. *Journal of Palliative Care*. **7**: 30–35.

56. Wilkinson T *et al.* (1992) Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients. *Cancer Chemotherapy and Pharmacology*. **31**: 251–254.

57. Krajnik M and Zylicz Z (1997) Topical opioids – fact or fiction? *Progress in Palliative Care*. **5**: 101–106.

58. Likar R *et al.* (1999) Dose-dependency of intra-articular morphine analgesia. *British Journal of Anaesthesia*. **83**: 241–244.

59. Back NI and Finlay I (1995) Analgesic effect of topical opioids on painful skin ulcers. *Journal of Pain and Symptom Management*. **10**: 493.

60. Krajnik M *et al.* (1999) Potential uses of topical opioids in palliative care - report of 6 cases. *Pain*. **80**: 121–125.

61. Twillman R *et al.* (1999) Treatment of painful skin ulcers with topical opioids. *Journal of Pain and Symptom Management*. **17**: 288–292.

62. Gutierrez Y *et al.* (2021) Topical opioid use in dermatologic disease: a systematic review. *Dermatologic Therapy*. **34**: e15150.

63. Zeppetella G and Ribeiro MD (2005) Morphine in intrasite gel applied topically to painful ulcers. *Journal of Pain and Symptom Management*. **29**: 118–119.

64. Cialkowska-Rysz A and Dzierzanowski T (2019) Topical morphine for treatment of cancer-related painful mucosal and cutaneous lesions: a double-blind, placebo-controlled cross-over clinical trial. *Archives of medical science: AMS*. **15**: 146–151.

65. Le Bon B *et al.* (2009) Effectiveness of topical administration of opiods inpalliative care a systematic review. *Journal of Pain and Symptom Management*. **37**: 913–917.

66. Cerchietti LC *et al.* (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer*. **95**: 2230–2236.

67. Vayne-Bossert P *et al.* (2010) Effect of topical morphine (mouthwash) on oral pain due to chemotherapy- and/or radiotherapy-induced mucositis: a randomized double-blinded study. *Journal of Palliative Medicine*. **13**: 125–128.

68. Cerchietti LC *et al.* (2003) Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain*. **105**: 265–273.

69. Ondrovics M *et al.* (2017) Opioids: Modulators of angiogenesis in wound healing and cancer. *Oncotarget*. **8**: 25783–25796.

70. Zaslansky R *et al.* (2018) Topical application of morphine for wound healing and analgesia in patients with oral lichen planus: a randomized, double-blind, placebo-controlled study. *Clinical Oral Investigations*. **22**: 305–311.

71. Twycross *et al.* (2016) *Introducing Palliative Care*. (6e). Pharmaceutical Press, London. pp. 149–159.

72. Johnson MJ *et al.* (2016) Opioids, exertion, and dyspnea: a review of the evidence. *American Journal of Hospital Palliative Care*. **33**: 194–200.

73. Mercadante S *et al.* (2016) Epidemiology and characteristics of episodic breathlessness in advanced cancer patients: an observational study. *Journal of Pain and Symptom Management*. **51**: 17–24.

74. Barnes H *et al.* (2019) Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database of Systematic Reviews*. **3**: CD011008. **www.cochranelibrary.com**.

75. Ekstrom M *et al.* (2018) One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax*. **73**: 88–90.

76. Kohberg C *et al.* (2016) Opioids: an unexplored option for treatment of dyspnea in IPF. *European Clinical Respiratory Journal*. **3**: 30629.

77. Bausewein C and Simon ST (2014) Inhaled nebulized and intranasal opioids for the relief of breathlessness. *Current Opinion in Supportive and Palliative Care*. **8**: 208–212.

78. Ferreira DH *et al.* (2020) Controlled-release oxycodone versus placebo in the treatment of chronic breathlessness - a multi-site randomised placebo controlled trial. *Journal of Pain and Symptom Management*. **59**: 581–589.

79. Currow D *et al.* (2020) Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. *Thorax*. **75**: 50–56.

80. Johnson MJ *et al.* (2019) Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial. *ESC Heart Failure*. **6**: 1149–1160.

81. Verberkt CA *et al.* (2020) Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Internal Medicine*. **180**: 1306–1314.

82. Ferreira DH *et al.* (2018) Extended-release morphine for chronic breathlessness in pulmonary arterial hypertension-a randomized, double-blind, placebo-controlled, crossover study. *Journal of Pain and Symptom Management*. **56**: 483–492.

83. Kochovska S *et al.* (2019) A randomized, double-blind, multisite, pilot, placebo-controlled trial of regular, low-dose morphine on outcomes of pulmonary rehabilitation in COPD. *Journal of Pain and Symptom Management*. **58**: e7–e9.

84. Lopez-Saca JM and Centeno C (2014) Opioids prescription for symptoms relief and the impact on respiratory function: updated evidence. *Current Opinion in Supportive and Palliative Care*. **8**: 383–390.

85. Verberkt CA *et al.* (2017) Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *European Respiratory Journal*. **50**: 1701153.

86. Cohen M *et al.* (1991) Continuous intravenous infusion of morphine for severe dyspnoea. *Southern Medical Journal*. **84**: 229–234.

87. Boyd K and Kelly M (1997) Oral morphine as symptomatic treatment of dyspnoea in patients with advanced cancer. *Palliative Medicine*. **11**: 277–281.

88. Abernethy AP *et al.* (2003) Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *British Medical Journal*. **327**: 523–528.

89. Allen S *et al.* (2005) Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliative Medicine*. **19**: 128–130.

90. Rocker GM *et al.* (2013) Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *Canadian Medical Association Journal Open*. **1**: e27–e36.

91. Currow DC *et al.* (2011) Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *Journal of Pain and Symptom Management*. **42**: 388–399.

92. Allard P *et al.* (1999) How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *Journal of Pain and Symptom Management*. **17**: 256–265.

93. Johnson MJ *et al.* (2013) Clinically important differences in the intensity of chronic refractory breathlessness. *Journal of Pain and Symptom Management*. **46**: 957–963.

94. Vozoris NT *et al.* (2016) Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *European Respiratory Journal*. **48**: 683–693.

95. Navigante AH *et al.* (2006) Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. *Journal of Pain and Symptom Management*. **31**: 38–47.

96. Matsuda Y *et al.* (2017) Low-dose morphine for dyspnea in terminally ill patients with idiopathic interstitial pneumonias. *Journal of Palliative Medicine*. **20**: 879–883.

97. Mori M *et al.* (2021) How successful is parenteral oxycodone for relieving terminal cancer dyspnea compared with morphine? A multicenter prospective observational study. *Journal of Pain and Symptom Management*. **62**: 336–345.

98. FDA (2011) Medwatch safety alert. Morphine sulfate oral solution 100mg per 5mL (20mg/mL): medication use error - reports of accidental overdose. Available from: **www.fda.gov/Safety/MedWatch/SafetyInformation** (archived).