

TITLE: Opioids for breathlessness: a narrative review of the evidence

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ABSTRACT

Chronic breathlessness is a disabling and distressing condition for which there is a growing evidence base for a range of interventions. Non-pharmacological interventions are the mainstay of management and should be optimised prior to use of opioid medication. Opioids are being implemented variably in practice for chronic breathlessness. This narrative review summarises the evidence defining current opioids for breathlessness best practice and identifies remaining research gaps.

There is level 1a evidence to support the use of opioids for breathlessness. The best evidence is for 10mg to 30mg daily *de novo* low dose oral sustained-release morphine in opioid-naïve patients. This should be considered the current standard of care following independent, regulatory scrutiny by one of the world's therapeutics regulatory bodies.

Optimal benefits are seen in steady state, however, there are few published data about longer term benefits or harms. Morphine-related adverse events are common but mostly mild and self-limiting on withdrawal of drug. Early and meticulous management of constipation, nausea and vomiting is needed particularly in the first week of administration. Serious adverse events are no more common than placebo in clinical studies. Observational studies in severe chronic lung disease do not show excess mortality or hospital admission in those taking opioids. We have no long term data on immune or endocrine function.

There are promising data regarding prophylaxis for exertion-related breathlessness, but given the risks associated with transmucosal fentanyl, caution is needed with regard to clinical use pending longer-term, robust safety data.

Key terms

Opioids; morphine; breathlessness; dyspnoea; evidence

BACKGROUND

Chronic breathlessness is a pivotal symptom in three ways. Firstly, chronic breathlessness is an important signpost to underlying pathology, although often mis-attributed as “benign” (deconditioning, ageing, obesity)^{1;2} or inevitable (“I’ve smoked for many years”) by the person with it or, if identified in a clinical consultation, by their clinician. Secondly, it is the cause of a disabling syndrome of chronic breathlessness which persists despite optimised treatment of underlying pathology³ and which affects every aspect of the person’s life and the lives of those who care for them.⁴ Thirdly, changes in chronic breathlessness are a useful way to monitor the effectiveness of treatments of underlying pathologies.⁵ Exertion-limiting breathlessness affects nearly one in ten of the general population⁶ and is associated with poorer quality of life for each successive drop in the level of exertion that can be achieved before breathlessness limits exercise,⁷ psychological morbidity (anxiety, depression and both)⁸ and increased health service utilisation.^{9;10}

The evidence base supporting interventions to modulate the generation and/or perception of breathlessness itself is growing. Recent delineation of a chronic breathlessness *syndrome*³ (disabling breathlessness which persists despite optimal treatment of the underlying patho-physiology) underlines the importance of both optimised disease-treatments and the need for breathlessness-directed interventions. The evidence emphasises the importance of a diagnostic work-up to look at disease-modifying therapies, and concomitant non-pharmacological interventions for breathlessness for managing chronic breathlessness. The evidence is also growing for additional pharmacological interventions, aiming to reduce the subjective sensation of breathlessness. In particular, the use of morphine is being implemented variably into clinical practice, and a sustained release preparation of oral morphine (Kapanol™) has had its license extended to include for the first time in the world an indication for the pharmacological treatment of chronic breathlessness.¹¹ The Therapeutics Goods Administration in Australia, as the national medication regulatory agency, independently reviewed data in order to make this decision.

This narrative review presents the current knowledge about the use of opioids in chronic breathlessness and highlights areas for further research.

The basic science of opioids and breathlessness

1. Opioid receptors

There is good rationale to use opioids. Perceptions associated with breathlessness are processed in the insula, dorsal anterior cingulate cortex, amygdala and medial thalamus; areas shared with processing the perceptions of pain and other “threats”,¹² and richly innervated with opioid receptors.¹³

Much early laboratory work studied the effect of opioids on exercise tolerance rather than symptomatic benefits for people with chronic breathlessness.^{14;15} Most studies were single dose studies, thus limiting conclusions regarding the symptomatic benefit possible with steady state. More recent laboratory tests of the symptom impact of opioids showed that endogenous opioids reduce breathlessness; naloxone increased the perceived work of breathlessness in people with moderate to severe chronic obstructive pulmonary disease (COPD) for a given workload.^{14;15}

Endogenous opioids are thought to centrally modulate breathlessness perception to be less intense and unpleasant. A study of people with COPD given ketoconazole to cause increased beta-endorphins were randomly given placebo or naloxone.¹⁶ Those given naloxone did not gain the reduction in breathlessness seen in the placebo arm. However, Currow *et al* did not replicate these

findings in a 3-arm crossover trial of peripheral blockade (methylnaltrexone), peripheral and central blockade (naltrexone) or no blockade (placebo); there was no statistically significant difference in the primary outcome of breathlessness intensity.¹⁷ In addition, in general, nebulised opioid studies have not shown benefit¹⁸ other than one study in a specific population of people with COPD exposed to mustard gas¹⁹ and a recent crossover randomised controlled trial (RCT) of 11 people with COPD showed a statistically and clinically (reduction in breathlessness intensity of ≥ 1 point on a 0 to 10 numerical rating scale [NRS])²⁰ significant effect.²¹ However, systematic absorption of opioid was not measured in either study thus a central mechanism cannot be excluded.

The role of individual opioid receptors is not clear. The effect on mu opioid receptors appears clear from clinical and laboratory studies of morphine, fentanyl and remifentanil. What is less clear is the effect of the semi-synthetic opioid, oxycodone on symptomatic breathlessness. Its action is shared between agonist effects on mu and kappa receptors. To date, the two largest placebo controlled clinical trials of oxycodone have failed to demonstrate any signal (early evidence of benefit; the point estimate is in favour of the intervention but may not reach statistical significance) of net symptomatic benefit on chronic breathlessness.^{22;23}

2. Neuro-imaging and breathlessness perception

Much of our understanding about breathlessness perception comes from neuro-imaging studies, mainly functional magnetic resonance imaging (fMRI). Pattinson *et al* demonstrated in 2009 that remifentanil reduced the sensation, “urge to breath” and highlighted breathlessness due to disease as a potential therapeutic target for opioids.²⁴ Since then, our understanding of how the brain responds to repeated breathlessness stimuli has deepened. Based on previous experience the brain appears to create expectations and beliefs (psychological “priors”) which then influence the perception of incoming breathlessness sensations.²⁵ Thus people living with chronic breathlessness process the sensation of breathlessness involving the frontal association cortex; in the context of memory and fear associated with past experiences. Healthy volunteers do not.²⁶ Importantly, interventions such as pulmonary rehabilitation, which aim to educate and change such beliefs, also show corresponding reduction in fMRI frontal association cortex activity.²⁷ Interestingly, administration of opioid appears to reduce anticipatory breathlessness. In an fMRI study of healthy volunteers, administration of remifentanil not only depressed activity in breathlessness pathways during breathlessness, but also depressed anticipatory activity in the amygdala and the hippocampus that correlated with reductions in breathlessness unpleasantness.²⁸

In addition to the influence of prior expectations, affective states such as anxiety and depression appear to amplify perception of breathlessness. The role of any impaired affect in reducing opioid effectiveness in pain has been previously described²⁹ along with an association with escalating doses and difficulties in dose reduction, but recently has been shown to similarly reduce opioid effectiveness in breathlessness. Abdallah *et al* recently demonstrated that in both people with chronic breathlessness (using morphine) and healthy volunteers (remifentanil), even subtle reductions in measures of mood reduced breathlessness response to opioids: as depression and anxiety increased, so opioid responsiveness decreased.³⁰ This has important clinical implications. People with significant depression and/or anxiety, should therefore first be managed with non-pharm psycho-educational approaches to modify the impact of emotion on opioid

responsiveness before using opioids in order to maximise opioid-response and reduce the risk of adverse effects due to inappropriate dose escalation.

Inter-individual variation in response to exogenous opioid

It is apparent that not everyone's breathlessness responds to opioid.^{31;32} A large cross-sectional pharmacogenetics study³³ of people taking morphine were three times more likely to have more intense breathlessness if they had a single nucleotide polymorphism on the HTR3B gene. No relationship with candidate single nucleotide polymorphisms tested was identified for people taking oxycodone or fentanyl. This biologically plausible SNP (associated with opioid receptors) warrants further investigation and is awaiting confirmation in other prospective studies.

Table 1 summarises the key messages.

Table 1. Summary Basic Science: opioids and breathlessness

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| <ul style="list-style-type: none">● Endogenous opioids modify perception of breathlessness● Evidence for a central modulation is the dominant evidence in the literature● Opioids reduce the sensation "urge to breathe" through cortical mechanisms● The response to opioids is reduced by impaired affect (anxiety, depression)● Opioids appear to be able to modulate anticipatory breathlessness as well as the sensation of breathlessness itself |
|--|
- There is inter-individual breathlessness response to opioids due to varying affective state and pharmacogenetics

Clinical studies: effectiveness, dosing and safety

1. Effectiveness

Most participants in clinical trials to date have been in people with COPD and the majority of people randomised in placebo controlled, double blind studies have been treated with once daily, sustained release morphine in the active arm. A sizable number of people with cancer and heart failure have been included, but few with interstitial lung disease or other conditions that also cause chronic breathlessness.

Meta-analyses of randomised placebo-controlled trials have studied the evidence base for the use of opioids for breathlessness. The first (2002) found moderate evidence to support a symptomatic benefit in reducing breathlessness for systemic opioids but not for nebulised opioids.³⁴ A subsequent second systematic review (2014) of only people with COPD, demonstrated moderate level evidence that morphine in this setting is effective and safe.³⁵ The benefit was most marked in people in steady state with a standardised mean difference (SMD) of -0.44 (95% CI, -0.68 to -0.19) compared with -0.30 (95% CI, -0.59 to -0.02) for all studies. Such a difference translates into a difference in breathlessness score beyond the minimum clinically important difference for reduction in breathlessness.²⁰ These data challenge the widespread practice using small doses of immediate

release morphine at widely spaced dosing intervals for up to several weeks before considering a change to sustained release preparations. This delays achievement of steady state and fits with neither the pharmacokinetic nor pharmacodynamics effects of morphine for the symptomatic reduction of chronic breathlessness. It is also consistent with the potential reduction in anticipatory breathlessness afforded by opioid discussed earlier (neuro-imaging and breathlessness perception); having persistent levels of opioid around the clock may modulate the central response with regard to expectation .²⁸

In general, nebulised opioid studies have not shown benefit¹⁸ other than one study in a specific population of people with COPD exposed to mustard gas¹⁹ and a recent crossover RCT of 11 people with COPD showed a clinically and statistically significant effect.²¹ However, systematic absorption of opioid was not measured in either study thus a central mechanism cannot be excluded.

A third systematic review and meta-analysis in 2016³⁶ found a smaller effect with lower precision. However, they did not account for the cross-over design of all except one of the studies, used a fixed rather than random-effect model despite study heterogeneity and used a sample size of < 50 (irrespective of statistical power or cross-over design) as a marker of low quality evidence. A subsequent meta-analysis of the same papers which addressed these methodological concerns¹⁸ found an increased effect size and improved precision - a moderate level evidence of benefit of a magnitude consistent with the known clinical important difference (distribution and patient anchor) of 1 point on a 0-10 NRS scale.²⁰

Since this review, the largest to date phase III clinical trial of 7 days oral low dose sustained release morphine and placebo for chronic breathlessness due to various conditions has reported.³⁷ This study was larger than the population even in the most recent review.¹⁸ There was no benefit for the primary outcome of *breathlessness now* over placebo but methodological issues³⁸ make interpretation difficult:

- i) due to slow recruitment, eligibility criteria were expanded to include people with less severe breathlessness. As people with more severe breathlessness are more likely to respond to morphine,³² and are those in whom morphine is clinically indicated^{32;39} this may have reduced the power of the trial to detect benefit in those in whom it would be used clinically.
- i) there was no measure of physical activity and so morphine-related improvement of exercise tolerance would have been undetected in those who continued exercising until stopped by the same worst intensity of breathlessness,
- ii) and immediate release morphine was available in both arms with greater use in the placebo arm.

Therefore, previous level 1a (meta-analysis) evidence, and basic science data should not be discarded in the light of this trial and we await results from soon to report subsequent studies which restrict eligibility to more severe breathlessness, do not allow “as needed” immediate release morphine and include measures of physical activity to help interpret changes in breathlessness severity (see section below: Ongoing, or still-to-be-reported clinical trials).

A further trial of regular, low dose, oral sustained-release morphine for heart failure related breathlessness, has also reported.⁴⁰ The trial was closed early due to difficulties in recruitment, but showed greater within arm improvements in the morphine arm than placebo for all breathlessness

measures except *average breathlessness*. This trial provides the first reported longer-term placebo-controlled data.

Breathlessness due to all diseases may not respond to morphine. A phase II trial recently reported worse outcome in the morphine arm compared to placebo in every symptom measure in people with primary pulmonary hypertension.⁴¹ Due to the signals of harms, a further phase III trial could not be justified.

As discussed in the first section, placebo-controlled trials so far have failed to show benefit for oxycodone.^{22;23}

2. Trials of opioids and exertional breathlessness

As physical exertion generates breathlessness, central "blunting" of breathlessness perception may allow more physical exertion. If so, this could have clinical implications for both daily activity in people with severe chronic breathlessness and for use with interventions such as pulmonary rehabilitation where breathlessness is a reason for low rates of referral, poor attendance if referred and increased drop-out.⁴² Unfortunately, a phase II trial of opioids during pulmonary rehabilitation did not demonstrate feasibility due to poor recruitment because people with the most severe breathlessness were not referred to pulmonary rehabilitation services.⁴³

The Ekström review³⁵ failed to demonstrate benefit for exercise capacity. However, although there are no phase III trials of prophylactic opioid administration, there are a number of small pilot/feasibility phase II trials indicating before-after within arm benefit in terms of exercise-induced breathlessness intensity and greater exercise endurance with subcutaneous,⁴⁴ transnasal,⁴⁵ buccal,⁴⁶ or nebulised fentanyl⁴⁷ although none was powered for between-arm comparison. More recently, in a dose-finding pilot study, Hui *et al* randomised 50 opioid-tolerant people with cancer to receive one of two doses of fentanyl sublingual spray or placebo prior to a shuttle walk test.⁴⁸ The higher dose group reported significantly improved breathlessness and walk distance (pre-post analysis) compared with placebo. The lower dose group had significantly improved walk distances and a non-significant improvement in breathlessness. In addition, Abdallah *et al* randomised 20 adults with advanced COPD and chronic breathlessness syndrome to receive oral immediate release morphine or placebo prior to constant-load cardiopulmonary cycle exercise testing⁴². Those receiving morphine had better exercise endurance (increased exercise endurance time by 2.5 ± 0.9 min; $p \leq 0.014$) and reduced exertional breathlessness at isotime (1.2 ± 0.4 Borg units; $p \leq 0.014$).

However, despite the promise of these early trials, it must be emphasised that there are very few long-term data on use of transmucosal fentanyl for breathlessness. The only published data relate to a case report of abuse of transmucosal fentanyl for breathlessness (a patient with COPD who had been prescribed up to 4 doses of 50 micrograms daily for the past 3 years, who presented using 40 doses each day) with withdrawal during rationalisation of regimen.⁴⁹ The misuse potential of transmucosal fentanyl should be systematically investigated prospectively before this approach is used routine in clinical practice.

3. Ongoing, or still-to-be-reported clinical trials

All but one reported randomised study to date has a short follow up (4 to 7 days at most). There are currently 3 ongoing or imminently reporting phase III trials in people with chronic breathlessness, all of which have longer follow up. The MORDYC trial has completed recruitment and used 20mg daily modified release morphine in a 3 month, parallel group, placebo-controlled trial in people with

COPD with health-related quality of life as the primary outcome.⁵⁰ [NCT02429050] The BEAMs trial (Breathlessness, Exertion And Morphine Sulphate) has also completed recruitment and is a placebo-controlled dose titration, three arm trial of regular, low dose, sustained release oral morphine (0mg, 8mg 16mg) in people with COPD.⁵¹ This study includes a blinded extension from the primary end point for up to six months for each participant. A third phase III placebo-controlled RCT using a dose increase step from 10mg – 20mg oral modified release morphine daily depending on breathlessness response is in start-up. [ISRCTN87329095] These studies will also help address the current unknowns regarding longer-term use.

Two placebo controlled, randomised studies: 5mg of immediate release morphine four times daily [NCT02622022] or once daily sustained release morphine 20mg [ACTRN12611000711910] in people with interstitial lung disease are soon due to report or complete, respectively. It will be interesting to see whether there is a symptomatic response achieved or whether the outcomes are more akin to the pulmonary artery hypertension study.

Table 2 summarises the key messages.

Table 2. Summary Effectiveness

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| <ul style="list-style-type: none"> ● Opioids have moderate level 1a evidence (systematic review and meta-analysis) for effectiveness for breathlessness ● Most evidence is in people with COPD ● The largest randomised clinical trials use regular, low dose, sustained release morphine <i>de novo</i> in opioid-naïve participants ● Opioids are most effective in steady state rather than single dose studies ● There is preliminary evidence to support prophylaxis for exertion-induced breathlessness for both morphine and fentanyl but the risk-benefit balance is not known, especially with longer term use ● Not all disease states may have breathlessness which respond to morphine |
|--|
- Not all opioids show reduction in breathlessness
 - There are very few placebo-controlled data to date regarding medium or long term use. Recent trials are due to report soon.

4. Dosing and dose titration

A phase II dose ranging study was conducted with a lower dose daily capsule of extended release morphine.³¹ People were commenced on 10mg daily for a week and if they had a response (pre-defined as >10% reduction over baseline breathlessness), they went to the pharmacovigilance extension phase at that dose. If they received no benefit, the dose was increased to 20mg for a week and that algorithm was repeated up to 30mg as necessary. In all, 83 people were enrolled of whom two out of three derived symptomatic benefit. Seventy percent of those deriving benefit did so at 10mg/24 hours, 20% at 20mg/24 hours and 8% at 30mg/24 hours. There were nine people who had no toxicity but had still not experienced a symptomatic benefit at 30mg. Patients were followed for up to 22 months after commencing extended release morphine. Once again, most participants had

COPD. Importantly, no tachyphylaxis (benefit was maintained without dose increase) was observed over follow up.

A secondary analysis of this dose ranging study looked at people who had a successful titration from either 10mg-20mg or 20mg-30mg.⁵² Those improving on titration experienced a marked improvement in the first 24 hours but that initial benefit continued to increase over the ensuing six days without further changes in dose. As such, in people taking extended release morphine, when a symptomatic benefit is achieved, the maximal benefit is several days later; hence upward titration should not occur within one week of upward dose titration.

One study addresses the issue of how opioids for breathlessness should be titrated for people who are already taking opioids for pain.⁵³ The randomised, double blind study showed that people who had a 25% increase in the opioid dose taken for breakthrough pain derived benefit for breathlessness, but a dose increment of 50% delivered no more symptomatic benefit than one of 25%. There was no placebo comparator and thus we do not know if the benefit seen was greater than no treatment.

5. Safety

Opioids have been used for centuries to relieve pain and other symptoms, and the safety profile is well studied and understood. The risk of respiratory compromise in people with conditions causing breathlessness has led to opioids being (almost absolutely) contra-indicated in these patients, but in the clinical studies described above there were no reported cases of respiratory depression or obtundation, despite these problems being actively sought.

Safety has been further measured in a number of ways. An updated systematic review, including a subgroup meta-analysis of studies measuring changes in oxygenation and carbon dioxide retention, concluded that the doses of systemic opioid used did not affect oxygenation nor worsen carbon dioxide retention in a clinically meaningful way (mean partial pressure of carbon dioxide was 0.27 kiloPascals (kPa) higher [0.08 to 0.45 kPa higher] in the opioid group; mean partial pressure of oxygen and mean oxygen saturation was 0.26 kPa lower [0.68 to 0.15 kPa higher] and 0.47 % lower [0.87% to 0.07% lower] respectively in the opioid group).⁵⁴ This review included all study designs, including case reports. There was only one report of clinically meaningful respiratory depression described in a single case report of a patient taking regular sustained release morphine for cancer pain who required short-term respiratory assistance following a nebulised dose of morphine for breathlessness.⁵⁵ Since this review there have been two further case reports: one in a patient with COPD taking background sustained release morphine and concomitant immediate release morphine presenting with respiratory depression following a large immediate release dose,⁵⁶ the other was of the COPD patient with transmucosal fentanyl discussed above.⁴⁹

The largest longer term studies have been conducted as observational consecutive cohort studies looking at outcomes after opioids are started. At doses of 30mg of morphine equivalent per 24 hours or less, Ekström's large consecutive COPD and long term oxygen cohort with 4 years' follow up showed no increase in hospital admissions nor in mortality when opioids were commenced at a morphine equivalent daily dose of ≤ 30 mg.⁵⁷ A subsequent study in people with interstitial lung disease again showed no excess mortality or hospital admissions in people taking opioids.⁵⁸ Recent publication from a large Canadian population of people with COPD has shown a very small absolute excess respiratory adverse effects over the first 30 days of prescription in those using opioids,⁵⁹ but the data carry the usual challenges of interpretation with regard to defining an association, given

unmeasured confounders. In such a study, cause and effect cannot be attributed, and there is no information regarding the clinical circumstances regarding initiation or monitoring of drug. Further, most appear to be given for musculo-skeletal pain rather than breathlessness. The authors aimed to reduce confounding due to patients with advanced disease by excluding patients who had a coded palliative care consult. Given the well-recognised very poor referral rates for people with COPD to palliative care, this is unlikely to have been effective.⁶⁰

Morphine-related harms are well understood. In the morphine/placebo clinical studies where these have been systematically sought and reported, treatment-emergent adverse events (those which appear or worsen compared with baseline [TEAEs]) are mainly mild and are self-limiting on withdrawal of morphine, with no excess serious adverse events in the morphine arm.⁶¹⁻⁶³ The exception was the heart failure trial, where TEAEs were more common in the morphine group although all except one were mild and were more likely in participants with worse renal function (estimated glomerular filtration [eGFR] <54 mls/min, the group's mean value).⁴⁰ Of note, most events occurred in the first week of administration suggesting dosing is otherwise well tolerated up to three months. A recent analysis⁶⁴ of treatment-emergent adverse events in the largest morphine/placebo trial showed only 4% of potentially morphine-related adverse events in the dataset as a whole were classified as serious. Importantly, there was no statistically significant difference in either non-serious or serious TEAEs between the two groups. However, in a number of the clinical studies more participants withdrew from study drug in the morphine arm indicating a qualitative difference in experience even if this was not captured quantitatively.^{40;64} We do not have safety data beyond three months, or data on immune or endocrine function in the longer term. As people with chronic lung and heart conditions may live with chronic breathlessness for some years, we should not initiate morphine for breathlessness in those with only mild or moderate symptom, and in those who have not been optimised with non-pharmacological treatment.

Table 3 summarises the key messages.

Table 3. Summary Clinical Studies: dose and safety

- Most of those with morphine-responsive breathlessness respond to doses of ≤30mg/24 hours orally
- 70% of responders do so by 10mg/24 hours orally
- Respiratory adverse effects appear to be minimal especially when using regular, sustained release morphine, and clinically relevant respiratory depression limited to single case reports from sub-optimally monitored clinical practice
- Placebo-controlled trials report no excess serious treatment-emergent adverse events in the morphine arm
- Morphine-related adverse events are generally mild and include constipation, nausea and vomiting, the latter two of which are mostly self-limiting
- Morphine-related adverse events in steady state are more likely in people with fluctuating renal function, especially if renal function was reduced in the first place

What studies are likely to report in the near future?

Two large studies will report in 2020: one from The Netherlands⁵⁰ and the other from Australia / New Zealand.⁵¹ Both have been designed explicitly to extend the understanding of the role of

controlled/extended release morphine in the symptomatic reduction of chronic breathlessness. These studies have been conceived given current understanding of the measurement and impact of chronic breathlessness on patients and their caregivers. The studies have complementary outcome measures and, importantly, blinded longer term data to define the net effects for up to six months. Measures on quality of life will allow better estimates of health economic impacts. Seeking baseline clinical demographic predictors of response and a pharmacogenetics sub-study (the Australasian study) will further our understanding of people most likely to benefit.

Other potential studies

Cancer-related pain control can be achieved more rapidly and with fewer side-effects in opioid-naïve patients when titrated *de novo* with controlled release opioids than with immediate release opioid solutions.⁶⁵ This raises the question of whether a head-to-head study using the same design in chronic breathlessness can be justified, although it may be argued that the two paradigms are not necessarily the same. The pharmacokinetics and existing evidence support the use of sustained release morphine where it is available, and where it is not available or affordable, the use of immediate release solution administered regularly to achieve steady state creates a viable alternative.

The symptomatic management of acute-on-chronic breathlessness is a challenge.

Non-pharmacological measures such as a hand-held electric fan and psycho-educational interventions are of benefit. Evidence to date suggests that the duration of such episodes, especially if occurring with an obvious precipitant, are brief and no pharmacological agent to date has the combined pharmacokinetic / pharmacodynamic characteristics to provide predictable reduction of acute-on-chronic breathlessness in a timely way and the risk of abuse or harm is considerable.

Preliminary studies of prophylactic transmucosal fentanyl for exertion-induced breathlessness in opioid-tolerant people suggest that a phase III placebo-controlled RCT is warranted. However, because of the risk of escalating use for any exertion where other management approaches are safer and as, if not more, effective, the patient population should be carefully defined. This approach should be limited to people with severe functional impairment due to acute-on-chronic breathlessness related to specified activities and when the benefits likely outweigh potential risks. In addition, careful choice of fentanyl preparation is important as they carry different pharmacokinetic profiles,⁶⁶ e.g. intranasal sprays have a rapid rise and fall profile (time to maximal level [TMax] up to 15 minutes), buccal tablets have a rapid increase with sustained intensity (TMax up to 90 minutes), and oral transmucosal fentanyl citrate has a slow onset and longer duration (TMax up to 120 minutes).

Of note, as most episodes of acute-on-chronic breathlessness take less than half an hour to recover these pharmacokinetic profiles suggest that transmucosal fentanyl has a limited, if any, role in the acute management of acute-on-chronic breathlessness episodes. Given these timeframes, any immediate benefit is likely to be due to psychological mechanisms such as “doing something” or even cold stimulation of the nasal mucosae.

CONCLUSIONS

There is level 1a evidence to support the use of opioids for breathlessness. The best evidence is for low dose oral sustained release morphine at doses of between 10mg to 30mg daily *de novo* in

opioid-naïve patients, which should be considered the current standard of care following independent, regulatory scrutiny by one of the world's therapeutics regulatory bodies.

Optimal benefits are seen in steady state from regular dosing, however, there are few published data about longer term benefits or harms. However, morphine related adverse events are common mostly mild and self-limiting on withdrawal of drug. Serious adverse events are no more common than placebo in clinical studies. Observational studies in severe COPD and ILD do not show excess mortality or hospital admission in those taking opioids. We do not have long term data on immune or endocrine function.

There are promising data regarding prophylaxis for exertion-related breathlessness, but given the risks associated with transmucosal fentanyl, caution is needed with regard to clinical use pending longer-term, robust safety data.

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