

An die Krankenkasse

Absender / Arztstempel

Datum

Anfrage zur Kostenübernahme des Opioid-haltigen Präparates

Handelspräparat

Sehr geehrte Damen und Herren,

Patienten der GKV haben nach § 2 SGB V einen Anspruch auf Leistungen, die in ihrer Qualität und Wirksamkeit dem allgemein anerkannten Stand der medizinischen Erkenntnisse entsprechen und den medizinischen Fortschritt berücksichtigen. Dieser Standard kann durchaus außerhalb der zugelassenen Indikation eines Arzneimittels liegen. Das oben genannte Präparat soll bei

der/dem Versicherten _____

geboren am _____

Versicherungsnummer _____

zur Linderung von Atemnot, als Symptom der Erkrankung COPD, verordnet werden. Die Anwendung von Opioiden zur Linderung von Atemnot aufgrund einer chronisch obstruktiven Lungenerkrankung (COPD) ist durch zahlreiche Studien wissenschaftlich belegt. Entsprechend erfolgt die Verordnung nach dem anerkannten und aktuellen Stand der medizinischen Erkenntnisse. Die entsprechende wissenschaftliche Literatur ist ab Seite 2 dieses Dokuments aufgeführt.

Da es sich beim Einsatz des oben genannten Präparates um einen Off-Label Use handelt, bitte ich Sie um kurzfristige schriftliche Bestätigung, dass die Verordnung des oben genannten Arzneimittels für die angegebene Indikation aus Ihrer Sicht nicht beanstandet und in Kenntnis der aktuellen BSG-Rechtsprechung nicht zu einem Antrag auf Regress bzw. Erstattung eines sonstigen Schadens durch Sie führen wird.

Mit freundlichen Grüßen,

Unterschrift

Literatur

Abernethy, P. A, Currow, C. D, Frith, P., Fazekas, S. B, McHugh, A. et al: Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003, 327(7414):523-528.

Abstract: OBJECTIVE: To determine the efficacy of oral morphine in relieving the sensation of breathlessness in patients in whom the underlying aetiology is maximally treated. DESIGN: Randomised, double blind, placebo controlled crossover study. SETTING: Four outpatient clinics at a hospital in South Australia. PARTICIPANTS: 48 participants who had not previously been treated with opioids (mean age 76, SD 5) with predominantly chronic obstructive pulmonary disease (42, 88%) were randomised to four days of 20 mg oral morphine with sustained release followed by four days of identically formulated placebo, or vice versa. Laxatives were provided as needed. MAIN OUTCOME MEASURES: Dyspnoea in the morning and evening as shown on a 100 mm visual analogue scale, quality of sleep, wellbeing, performance on physical exertion, and side effects as measured at the end of the four day treatment period. RESULTS: 38 participants completed the study; three withdrew because of definite and two because of possible side effects of morphine (nausea, vomiting, and sedation). Participants reported significantly different dyspnoea scores when treated with morphine: an improvement of 6.6 mm (95% confidence interval 1.6 mm to 11.6 mm) in the morning and of 9.5 mm (3.0 mm to 16.1 mm) in the evening ($P = 0.011$ and $P = 0.006$, respectively). During the period in which they were taking morphine participants also reported better sleep ($P = 0.039$). More participants reported distressing constipation while taking morphine (9 v 1, $P = 0.021$) in spite of using laxatives. All other side effects were not significantly worse with morphine, although the study was not powered to address side effects. CONCLUSIONS: Sustained release, oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnoea in the community setting.

Clemens, E. K, Klaschik, E.: Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. J Pain Symptom Manage 2007, 33(4):473-481.

Abstract: This study assessed the effect of opioid treatment on ventilation in dyspneic palliative care patients who received symptomatic treatment with strong opioids. The assessments measured changes in peripheral arterial oxygen saturation (SaO_2), transcutaneous arterial pressure of carbon dioxide (tcPCO_2), respiratory rate (f), and pulse rate (PF) during the titration phase with morphine or hydromorphone. The aims of the study were to verify the efficacy of opioids for the management of dyspnea, assess the effect on ventilation, and show whether nasal O_2 insufflation before opioid application leads to a decrease in the intensity of dyspnea. Eleven patients admitted to our palliative care unit were included in this prospective, nonrandomized trial. At admission, all patients suffered from dyspnea. tcPCO_2 , SaO_2 , and PF were measured transcutaneously by means of a SenTec

Digital Monitor (SenTec AG, Switzerland). During O₂ insufflation, the intensity of dyspnea did not change. In contrast, the opioid produced a significant improvement in the intensity of dyspnea ($P=0.003$). Mean f decreased as early as 30 minutes after the first opioid administration, declining from 41.8 ± 4.7 (35.0-50.0) to 35.5 ± 4.2 (30.0-40.0), and after 90 minutes, to 25.7 ± 4.5 (20.0-32.0) breaths/min. Other monitored respiratory parameters, however, showed no significant changes. There was no opioid-induced respiratory depression.

Currow, C. D, McDonald, C., Oaten, S., Kenny, B., Allcroft, P. et al: Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage 2011, 42(3):388-399.

Abstract: CONTEXT: Randomized controlled trials can answer questions of efficacy, but long-term pharmacovigilance studies generate complementary safety data. OBJECTIVES: Level I evidence supports short-term efficacy of opioids in reducing chronic refractory dyspnea. This study aimed to determine the minimum effective once-daily dose of sustained-release morphine, and whether net clinical benefits are sustained safely. METHODS: In a Phase II dose increment study, 10mg daily of sustained-release morphine was administered, and increased in nonresponders by 10mg daily each week to a maximum of 30 mg daily. The participant was withdrawn if there were unacceptable side effects or no response to maximum dose. If participants had a 10% improvement in dyspnea over their own baseline, they joined a long-term Phase IV effectiveness/safety study at that dose. Complying with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, response and side effects are described, with demographic and clinical characteristics of responders. RESULTS: Eighty-three participants (53 males, mean age 75 years, 54% with chronic obstructive pulmonary disease) provided more than 30 patient-years of data. Fifty-two participants derived $\geq 10\%$ benefit (on average 35% improvement over baseline), giving a response rate of 62% (number needed to treat of 1.6: number needed to harm 4.6); for 70%, this dose was 10mg/24h. Benefit was maintained at three months for 28 (33%) people. Ranking of breathlessness was reduced significantly ($P<0.001$), but constipation increased ($P<0.001$) despite laxatives. There were no episodes of respiratory depression or hospitalizations as a result of the sustained-release morphine. Overall, one in three people continued to derive benefit at three months. CONCLUSION: Ten milligrams of sustained-release oral morphine once daily is safe and effective for most people who respond.

Jennings, L. A, Davies, N. A, Higgins, P. J, Broadley, K.: Opioids for the palliation of breathlessness in terminal illness. Cochrane Database Syst Rev 2001(4):CD002066.

Abstract: BACKGROUND: Breathlessness is a common symptom in people with advanced disease. The most effective treatments are aimed at treating the underlying cause of the breathlessness but this may not be possible and symptomatic treatment is often necessary. Strategies for the symptomatic

treatment of breathlessness have never been systematically evaluated. Opioids are commonly used to treat breathlessness: the mechanisms underlying their effectiveness are not completely clear and there have been few good-sized trials in this area. OBJECTIVES: To determine the effectiveness of opioid drugs given by any route in relieving the symptom of breathlessness in patients who are being treated palliatively. SEARCH STRATEGY: An electronic search was carried out of Medline, Embase, Cinahl, the Cochrane library, Dissertation Abstracts, Cancercd and SIGLE. Review articles and reference lists of retrieved articles were hand searched. Date of most recent search: May 1999 SELECTION CRITERIA: Randomised double-blind, controlled trials comparing the use of any opioid drug against placebo for the relief of breathlessness were included. Patients with any illness suffering from breathlessness were included and the intervention was any opioid, given by any route, in any dose. DATA COLLECTION AND ANALYSIS: Studies identified by the search were imported into a reference manager database. The full texts of the relevant studies were retrieved and data were independently extracted by two reviewers. Studies were quality scored according to the Jadad scale. The primary outcome measure used was breathlessness and the secondary outcome measure was exercise tolerance. Studies were divided into non-nebulised and nebulised and were analysed both separately and together. A qualitative analysis was carried out of adverse effects of opioids. Where appropriate, meta-analysis was carried out. MAIN RESULTS: Eighteen studies were identified of which nine involved the non-nebulised route of administration and nine the nebulised route. A small but statistically significant positive effect of opioids was seen on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids. REVIEWER'S CONCLUSIONS: There is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. No evidence was found to support the use of nebulised opioids. Further research with larger numbers of patients, using standardised protocols and with quality of life measures is needed.

Jennings, L. A, Davies, N. A, Higgins, P. J, Gibbs, S. J, Broadley, E. K: A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002, 57(11):939-944.

Abstract: BACKGROUND: Opioids are commonly used to treat dyspnoea in palliative medicine but there has been no formal evaluation of the evidence for their effectiveness in the treatment of dyspnoea. A systematic review was therefore carried out to examine this. METHODS: The criteria for inclusion required that studies were double blind, randomised, placebo controlled trials of opioids for the treatment of dyspnoea secondary to any cause. The methods used to identify suitable studies included electronic searching of the literature, hand searching of the literature, and personal contact with relevant individuals and organisations. Random effects meta-analyses were performed on all included studies and on various subgroups (studies involving nebulised opioids or patients with

chronic obstructive pulmonary disease (COPD)). Subgroups were compared using meta-regression. Some studies included in the systematic review could not be included in the meta-analysis because insufficient data were presented. RESULTS: Eighteen studies fulfilled the criteria for the review. The meta-analysis showed a statistically significant positive effect of opioids on the sensation of breathlessness ($p=0.0008$). Meta-regression indicated a greater effect for studies using oral or parenteral opioids than for studies using nebulised opioids ($p=0.02$). The subgroup analysis failed to show a positive effect of nebulised opioids on the sensation of breathlessness. The results of the subgroup analysis of the COPD studies were essentially similar to the results of the main analysis. CONCLUSION: This review supports the continued use of oral and parenteral opioids to treat dyspnoea in patients with advanced disease. There are insufficient data from the meta-analysis to conclude whether nebulised opioids are effective, but the results from included studies that did not contribute to the meta-analysis suggest that they are no better than nebulised normal saline.

Rocker, G., Horton, R., Currow, D., Goodridge, D., Young, J. et al: Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. Thorax 2009, 64(10):910-915.

Abstract: Chronic obstructive pulmonary disease (COPD) will be the third leading cause of death worldwide by 2020. The burdens of this increasingly prevalent illness borne by patients, their family caregivers and the healthcare system are substantial. Dyspnoea as the predominant symptom becomes increasingly difficult to palliate as COPD progresses through advanced stages and, for 50% of patients, can become refractory to conventional treatment. This narrative review focuses on the potential role for carefully initiated and titrated opioids in the management of dyspnoea for patients with advanced COPD who are not yet in a terminal stage, yet struggle with symptoms that reflect underlying mechanisms of dyspnoea that lend themselves to this approach. The many barriers that currently exist to the provision of opioids in this setting are addressed, and recommendations are provided for an approach that should engender confidence among patients, their caregivers and the physicians who treat them.