Table 62: Navigante 2006[345]

Study	Navigante 2006[345]
Study type	RCT (Patient randomised; Parallel.)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Argentina; Setting: Cancer Institute.
Line of therapy	Unclear.
Duration of study	Intervention time: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Life expectancy <1 week.
Stratum	Breathlessness management: Severe dyspnoea at rest.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People who could provide informed consent and who were 18 years of age or older, with a documented diagnosis of terminal advanced cancer, life expectancy less than a week, Mini-Mental Status Exam (MMSE) > 23/30, severe dyspnoea at rest, and a performance status of 4 (Eastern Cooperative Oncology Group categorical scale, where 0 is “fully active” and 4 is “completely disabled”).
Exclusion criteria	Chronic obstructive pulmonary disease with hypercapnia, non-compensated congestive heart failure, severe renal or hepatic failure (clinically and/or biochemically detected), and other uncontrolled (numerical rating scale > 3/10) symptoms (excepting anxiety associated with dyspnoea) that could require the use of opioids, benzodiazepines, glucocorticosteroids, phenothiazines, bronchodilators, or methylxanthines.
Recruitment/selection of patients	Not stated.

Age, gender and ethnicity	Age - Mean (SD): 57.3. Gender (M:F): 47/53%. Ethnicity: Not stated.
Further population details	
Extra comments	11% were opioid naive. Modified Borg scale may not be appropriate in this population.
Indirectness of population	No indirectness.
Interventions	(n=35) Intervention 1: Opioids - Morphine. Around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the daily subcutaneous equivalent dose of morphine (DsEDM)for those receiving baseline opioids) with midazolam rescues (5 mg) in case of breakthrough dyspnoea. Total daily opioid dose was calculated and converted to oral morphine equivalents. A 3:1 ratio was used to convert oral dose to subcutaneous dose of morphine. If the DsEDM was lower than 15 mg, then people were considered opioid naïve. If the DsEDM was equal to or higher than 15 mg, people received an increase in dose equal to 25% of their respective DsEDM. All drugs were given subcutaneously through a butterfly needle located in the infraclavicular space. . Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion but people who received morphine were systematically premedicated with laxatives. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Opioid 3. Route of administration: Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication. (n=33) Intervention 2: Benzodiazepines - Midazolam. Around-the-clock midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of breakthrough dyspnoea. All drugs were given subcutaneously through a butterfly needle located in the infraclavicular space.. Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Benzodiazepine 3. Route of administration : Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication. (n=33) Intervention 3: Opioid + benzodiazepine - Morphine + midazolam. Around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the DsEDM) plus midazolam (5 mg every 4 hours) with

	morphine rescue doses (2.5 mg) in case of breakthrough dyspnoea. Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion, but people who received morphine were systematically premedicated with laxatives. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Not applicable / Not stated / Unclear (Combination). 3. Route of administration: Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication.
Funding	Funding not stated.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus MORPHINE Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 2/33, Group 2: 6/35; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 1/33, Group 2: 4/35; Risk of bias: High; Indirectness of outcome: No indirectness. Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 17/23, Group 2: 21/24; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 12/26, Group 2: 20/29; Risk of bias: High; Indirectness of outcome: No indirectness. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE + MIDAZOLAM versus MORPHINE Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 3/33, Group 2: 6/35; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 0/33, Group 2: 4/35; Risk of bias: High; Indirectness of outcome: No indirectness.	

Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 22/23, Group 2: 21/24; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 23/25, Group 2: 20/29; Risk of bias: High; Indirectness of outcome: No indirectness. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE + MIDAZOLAM versus MIDAZOLAM Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 3/33, Group 2: 2/33; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 0/33, Group 2: 1/33; Risk of bias: High; Indirectness of outcome: No indirectness. Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 22/23, Group 2: 17/23; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 23/25, Group 2: 12/26; Risk of bias: High; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at Any; Sedation (GCS/AVPU) at Any; Control of anxiety at Any; Control of agitation at Any; Control of delirium at Any; Duration of symptom control at Any; Time to symptom control at Any; Duration of institutional care at Any; Carer satisfaction at Any; Time to death at Any; Pain control at Any.