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# *Control of symptoms in terminally ill patients: effectiveness of opioid treatment for breakthrough dyspnea*

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## ABSTRACT

*Introduction and objective:* Breakthrough dyspnea (BD) is frequently suffered by in terminally ill patients. The main objective of the study was to assess the degree of symptom control for patients admitted to our unit specially the effectiveness of BD therapy in terminally ill patients.

*Patients and methods:* An observational study of a registry of patients was completed and performed at a Spanish hospice care unit. Terminally ill patients presenting with BD and having undergone opioid treatment were selected. BD's intensity was measured prior to and after treatment using the Borg scale. The intensity of other symptoms was evaluated using the Edmonton Symptom Assessment System (ESAS) scale.

*Results:* One hundred patients were included in the analysis. Males comprised 65 % of the sample, being 55 % oncological patients. Sublingual fentanyl (71 %), intranasal fentanyl (18 %), oral fentanyl (1 %) and subcutaneous morphine (10 %) were administered. Treatment response was observed in 94 % of patients with improvements of two or more points on the Borg Scale for BD, with no differences between treatments. The safety profile was acceptable in all cases.

*Conclusions:* Although opioids are recommended in the first line of treatment of ID, there is not enough scientific evidence to justify its use. It was observed in the study that fentanyl may be an effective and safe therapeutic option for the control of breakthrough dyspnea in terminally ill patients.

**Key words:** Dyspnea, episodic, breakthrough, opioids, palliative, terminal

## RESUMEN

*Introducción y objetivo:* La disnea irruptiva (DI) se observa con mucha frecuencia en pacientes terminales. El objetivo principal de este estudio fue valorar el grado de control de los síntomas de los pacientes que acuden a nuestra unidad, con especial interés en la evaluación de la efectividad del tratamiento de la DI en pacientes terminales.

*Pacientes y métodos:* Se realizó un estudio observacional sobre los datos de un registro de pacientes de una unidad de hospitalización domiciliaria. Se seleccionaron pacientes con enfermedad terminal con DI que fueron tratados con un opioide. La intensidad de la DI se valoró mediante la escala de Borg antes y después del tratamiento. Se evaluó la intensidad de otros síntomas mediante la escala ESAS (Edmonton Symptom Assessment System).

*Resultados:* Se incluyeron 100 pacientes en el análisis. El 65 % de los pacientes eran hombres, siendo un 55 % pacientes oncológicos. Se administró fentanilo sublingual (71 %), fentanilo intranasal (18 %), fentanilo oral (1 %) y morfina subcutánea (10 %). El 94 % respondieron al tratamiento con mejoría de dos o más puntos en la escala de Borg. El perfil de seguridad fue aceptable en todos los casos.

*Conclusiones:* A pesar de que en la primera línea de tratamiento de la DI se recomiendan los opioides, no existe suficiente grado de evidencia científica que justifique su uso. Se observó en el estudio que el tratamiento con fentanilo puede ser una

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opción terapéutica eficaz y segura para el control de la disnea irruptiva en pacientes terminales.

**Palabras clave:** Disnea, episódica, irruptiva, opioides, paliativo, terminal

## INTRODUCTION

Patients receiving care at the Home Hospitalization Unit show a wide range of symptoms, depending on the nature and stage of their illness.

In a recent systematic review to study the prevalence of symptoms in cancer and non-cancer patients, among the eleven most common symptoms, pain, dyspnea and depression appear very frequently in all patient types (1-3).

The prevalence and intensity of dyspnea increase as the individual's hope of survival diminishes, in both cancer and non-cancer patients, and it ranges between 15% and 90%, reaching 60%-80% in patients with congestive heart failure (CHF), 70% in patients with broncho-pulmonary cancer and it may reach up to 90% in terminal patients and 90-95% in patients with chronic obstructive pulmonary disease (COPD) (4).

Studies regarding the prevalence of symptoms in terminal patients include a number of problems that obstruct their comparability, such as: the use of different definitions and measurements, different stages of the illness, presence of oncological illness or otherwise, care environment, etc. For this reason, an evaluation of symptoms should be carried out in the context where the care is given, making periodic reappraisals in order to improve general symptom control among patients attended in each service (1,2,5).

The use of validated scales may be a helpful strategy in standardizing the evaluation of symptoms and in being able to monitor the response objectively, although this practice is not commonly carried out in our area. The proliferation of tools in recent years, the lack of validation in many of them and, especially, the lack of studies on their real impact may explain this (6-8).

The ESAS (Edmonton Symptom Assessment System) scale is the most appropriate due to its simplicity and, accordingly, its use is recommended in clinical practice (9,10). Use of the Borg scale (8) is recommended for evaluating dyspnea.

Although there is no consensus on the definition of the term dyspnea crisis, also called breakthrough, acute, incidental, intermittent or refractory dyspnea, it is also a symptom that very often appears among patients treated in our unit, which profoundly affects their quality of life. The main objective of this study was to evaluate effectiveness in controlling dyspnea crises in terminal patients who receive care at the Home Hospitalization Unit, and as a secondary objective, to assess the control of symptoms as a measure of patient care quality, also establishing our patients' level of satisfaction after treatment.

## PATIENTS AND METHODS

### Study design and ethical standards

An observational study was carried out with data obtained from a patient registry at the home hospitalization unit of the Hospital Virgen de los Lirios in Alcoy (Alicante, Spain) whose Ethics Committee gave its approval for the study to be conducted.

### Inclusion and exclusion criteria

The selection criteria that patients had to meet were: a) men and women aged above 18 years old; b) patients with a terminal cancer or non-cancer illness; c) ECOG-PS (Eastern Cooperative Oncology Group Performance Status) with scores from 0 to 3 at the time of the visit; d) patients who suffered dyspnea crises with or without dyspnea at rest; e) patients who had signed their informed consent to take part in the study. Patients with a history of alcohol or toxic substance abuse were excluded from the study. No specific treatment was administered for the purpose of the study. All patients were managed according to standard clinical practise. Informed consent was obtained from all patients who remained alive for their inclusion in the study.

Patients were retrospectively and consecutively selected from the patient registry database. Patients included had received care at the unit between 27 March 2014 and 2 May 2016. The information analyzed in the study corresponds to data on patients at the time they were admitted to the Home Hospitalization Unit, and to evaluation of BD evolution in one of their crises.

### Evaluation variables

A dyspnea crisis was defined as an episode of acute breathlessness that appears abruptly in a patient, with or without breathing difficulty, as a baseline symptom, whether or not related with effort, self-limited in time, and lasting less than 10 minutes in most cases. Its intensity had to be greater than or equal to 6 points on a visual analogue scale of 10 points, equivalent to 6 points on the Borg scale (severe-very severe dyspnea) (11).

The score for the baseline dyspnea index was recorded by means of Mahler's multidimensional scale and the score for dyspnea intensity during the dyspnea crisis by means of the Borg scale, before and after administering treatment.

Patients were asked to record the time elapsed from administration of treatment to control the dyspnea crisis until improvement was achieved.

Information was recorded on the mean number of dyspnea crises per day that patients suffered, and on the treatment prescribed to control the crises, active agent, dose and route of administration that the physician administered following standard clinical practise. Adverse reactions relating to the treatment for dyspnea crises were recorded in the case report form, describing the event and its intensity.

Information was gathered on the age, sex, ECOG-PS functional status at the time of exploration and, upon admission to the unit, patients were evaluated for control of the symptoms associated with the illness, by means of visual analogue scales (ESAS, Edmonton Symptom Assessment System) registering pain, fatigue, depression, nausea, anxiety, drowsiness, appetite, well-being and insomnia. Symptom control was considered to be adequate when scores for symptoms were lower than or equal to 4 points on a 10-point scale, where a value of 10 represented the greatest symptom intensity, and a value of 0, absence of symptom. Patients were considered to be adequately controlled when the score was lower than or equal to 4 points in the 10 categories. Levels of patient satisfaction and physician satisfaction with dyspnea crisis treatment were assessed using a five-point Likert scale: excellent, very good, good, poor and very poor.

### Statistical analysis

The sample of 100 patients included in the analysis has a power of 87.9% to show differences of two or more points in the Borg scale, evaluated before and after treatment.

A descriptive analysis was carried out on frequencies in qualitative variables, mean, standard deviation, minimum and maximum values and confidence intervals of 95% in the quantitative variables.

Comparisons among variables were carried out using Fisher's test or Chi-square test for qualitative variables, and the Student-t test for comparisons of independent groups in quantitative variables.

When multiple comparisons were carried out for quantitative variables, the variance analysis model was applied with Bonferroni or Games Howell corrections according to the homogeneity of variances.

Time until dyspnea relief was evaluated by Kaplan-Meier survival analysis, where the state variable was response to treatment, and the time variable was the time elapsed until dyspnea relief, comparing the survival curves according to rescue treatment by means of a log-rank (Mantel-Cox) test. Response to treatment was obtained if the score on the Borg scale improved by two or more points with regard to the score prior to treatment.

Linear regression and multivariate Cox regression analyses were carried out to evaluate the degree of dyspnea improvement and time to control the dyspnea, respectively, according to independent variables: sex, age, ECOG status upon inclusion, whether the patient had a history of COPD, pulmonary fibrosis or CHF that could influence their response to dyspnea treatment, whether or not they were a cancer patient, score on the Mahler baseline dyspnea index, Borg dyspnea score before treatment, total dose of rescue medication administered per day to treat dyspnea, and treatment administered to control the dyspnea crisis.

Scores on the visual analogue scales of the ESAS scale were analyzed in two ways: evaluating the proportion of patients with the symptom controlled, if the score on the scale was less than or equal to 4 points; evaluating the mean and confidence interval of the mean in each VAS.

The level of statistical significance was established as 0.05. Statistical analysis was carried out using the SPSS 14.0 program (SPSS Inc., Chicago, IL; U.S.A.).

## RESULTS

100 patients were included in the study; 65% men and 35% women. No data was absent in any of the study variables.

55% of patients had a history of cancer illness, and in the remaining 45% the terminal illnesses were: chronic obstructive pulmonary disease (COPD) in 18%, pulmonary fibrosis in 15% and congestive heart failure in 12%.

Patients' mean age was 74.5 years old (95% CI, 72.4-76.6), with a median of 76, minimum age of 47 and maximum of 91. No significant differences were observed in age between men and women ($p = 0.280$), but statistically significant differences were seen in the age of patients with a history of cancer ($p = 0.002$), who were 6.3 years older than non-cancer patients (95% CI, 2.3-10.2).

Table I shows the demographic and clinical characteristics of patients included in the study, according to whether they were cancer or non-cancer patients.

In cancer patients, the organ affected by the tumor was the lung in 69.1% (n = 38), breast in 10.9% (n = 6), colon and bladder in 3.6% each (n = 2), and a single case (1.8%) with cancer of the esophagus, liver, leukemia, lymphoma, rectum, kidney and thymoma. 12.7% of cancer patients(n = 7) showed metastasis at the time of their inclusion in the study.

### Symptoms present upon admission of patients in the home hospitalization unit

The patients had 3.9 dyspnea crises per day (95% CI, 3.6-4.1), with no gender differences ($p = 0.797$) nor whether or not the patient had cancer ($p = 0,973$).

Table I shows patient distribution in the categories of scores on the Mahler dyspnea index, at the time of the patient's inclusion in the study. Mean score on the Mahler dyspnea index was 1.03 (95% CI, 0.84-1.22). No differences were observed between men and women (p = 0.184) nor between cancer and non-cancer patients (p = 0.073).

The score on the Borg dyspnea scale determined at the moment when the patient suffered a crisis was 7.67 points (95% CI, 7.,4-7.9). 89% of patients had scores higher than or equal to 7 points. No significant differences between men and women were seen in scores on the Borg scale, though differences were observed between cancer and non-cancer patients (p = 0.043), standing at 0.57 points higher among cancer patients (95% CI, 0.02-1.12).

Table II shows the mean scores on the ESAS scale for cancer and non-cancer patients and the symptoms where statistically significant differences were found for: pain, fatigue, nausea, depression, anxiety, drowsiness, anorexia, well-being, dyspnea and insomnia. Statistically significant differences were found between cancer and non-cancer patients in mean scores for all the symptoms except insomnia.

Figure 1 shows the proportion of patients adequately controlled for each symptom evaluated on the ESAS scale, according to whether they are cancer or non-cancer patients, and the last column shows the proportion of patients for whom all the symptoms were found to be controlled at the time of the patient's admission to the home hospitalization unit.

No significant differences were observed between men and women in the proportion of patients with each symptom controlled. Between cancer and non-cancer patients, significant differences were seen in the proportion of controlled pain (p <0.0001), fatigue (p = 0.013), depression (p <0.001) and appetite (p = 0.001), with the largest proportion of controlled patients found among non-cancer patients.

**Treatment to manage pain and breakthrough dyspnea**

71% of patients received opioids for pain treatment. Fentanyl or subcutaneous morphine was prescribed to control breakthrough dyspnea: sublingual fentanyl to 71% of patients, intranasal fentanyl to 18% of patients, oral fentanyl to 1% of patients and subcutaneous morphine to 10%. Active agent doses were adapted to each patient.

In 34% of patients, the medication dose prescribed for breakthrough dyspnea had to be increased. No statistically significant differences were observed in the proportion of patients who required an increase in dose according to active agent or route of administration.

**Response of breakthrough dyspnea to treatment**

A statistically significant improvement (p<0.0001) was observed in the dyspnea score on the Borg scale after treatment, with a mean difference of 4.2 points (95% CI, 3.9-4.5). 94% of patients responded to dyspnea treatment, improving it by two or more points on the Borg scale. No differences were observed in response according to medication administered.

**TABLE I**
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS ACCORDING TO WHETHER OR NOT THEY HAVE A HISTORY OF CANCER

| | | *No oncológicos* | | *Cancer* | | *Total* | |
|---|---|---|---|---|---|---|---|
| | | *N* | *%* | *N* | *%* | *N* | *%* |
| Sex | Male | 30 | 66.7 | 35 | 63.6 | 65 | 65 |
| | Female | 15 | 33.3 | 20 | 36.4 | 35 | 35 |
| ECOG-PS functional status | 1 | 2 | 4.4 | 1 | 1.8 | 3 | 3 |
| | 2 | 9 | 20 | 12 | 21.8 | 21 | 21 |
| | 3 | 32 | 71.1 | 34 | 61.8 | 66 | 66 |
| | 4 | 2 | 4.4 | 8 | 14.5 | 10 | 10 |
| Mahler baseline dyspnea index | 0 | 17 | 37.8 | 13 | 23.6 | 30 | 30 |
| | 1 | 20 | 44.4 | 27 | 49.1 | 47 | 47 |
| | 2 | 6 | 13.3 | 9 | 16.4 | 15 | 15 |
| | 3 | 2 | 4.4 | 4 | 7.3 | 6 | 6 |
| | 4 | 0 | 0 | 2 | 3.6 | 2 | 2 |

**TABLE II**
ESAS SCALES SCORE FOR CANCER AND NON-CANCER PATIENTS

| | *Cancer patient* | *N* | *Mean* | *St. deviation.* | *p* |
|---|---|---|---|---|---|
| Pain | No | 45 | 2.02 | 1.6 | < 0.0001 |
| | Yes | 55 | 4.6 | 2.4 | |
| Tiredness | No | 45 | 5.33 | 2.2 | < 0.0001 |
| | Yes | 55 | 7.04 | 1.6 | |
| Nausea | No | 45 | 1.51 | .5 | 0.001 |
| | Yes | 55 | 2.16 | 1.2 | |
| Depression | No | 45 | 3.80 | 2.3 | 0.003 |
| | Yes | 55 | 5.15 | 2.1 | |
| Anxiety | No | 45 | 3.33 | 2.6 | 0.048 |
| | Yes | 55 | 4.36 | 2.6 | |
| Drowsiness | No | 45 | 2.44 | 1.7 | 0.022 |
| | Yes | 55 | 3.36 | 2.3 | |
| Anorexia | No | 45 | 5.40 | 2 | < 0.0001 |
| | Yes | 55 | 6.84 | 1.6 | |
| Well-being | No | 45 | 5.13 | 1.3 | < 0.0001 |
| | Yes | 55 | 6.29 | 1.8 | |
| Insomnia | No | 45 | 3.09 | 2.2 | 0.305 |
| | Yes | 55 | 3.56 | 2.4 | |

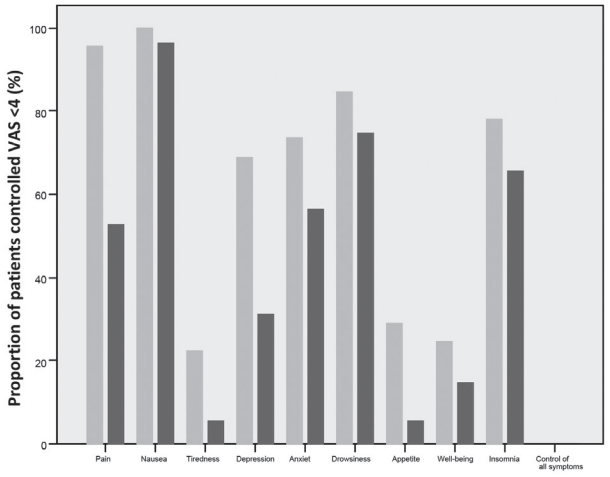


**Fig. 1.** Proportion of patients with symptoms controlled at the first consultation in the home hospitalization unit, in cancer and non-cancer patients.

Statistically significant differences were observed in the time elapsed until dyspsnea control. Table III shows mean and median time in minutes until dyspnea crisis relief, which was significantly less in patients treated with intranasal fentanyl, followed by sublingual fentanyl and subcutaneous morphine: intranasal versus sublingual fentanyl, p = 0.01; intranasal fentanyl versus subcutaneous morphine, p = 0.005; sublingual fentanyl versus subcutaneous morphine, p = 0.056. Figure 2 shows the survival curve according to treatment, adjusted by covariables.

No significant differences were observed among the different dyspnea treatments, nor in the degree of dyspnea relief nor in the time until its control in the multivariate analysis (p = 0.066).

### Adverse effects of breakthrough dyspnea treatment

42% of the patients included in the study had at least one adverse event after treatment for breakthrough dyspnea. Seven patients had two adverse events. The total sum of adverse events observed was 49. 71.4% of the adverse events (n = 35) were slight, and 28.6% (n = 14) moderate or intense. No serious adverse events were observed.

The proportion of patients who experienced adverse events following dyspnea crisis treatment was significantly larger if the patient was being treated with opioids for the baseline illness, 54.9% (n = 39) in comparison with 10.3% (n = 3) if they were not being treated with opioids (p <0,0001). Drowsiness was the most commonly observed adverse effect (39 events), 23 events with sublingual fen-

**TABLE III**
TIME UNTIL DYSPNEA RELIEF DURING A CRISIS

| *Medication for breakthrough dyspnea* | *Mean* | | | | *Median* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Minutes* | *Standard error* | *95% confidence intervalo* | | *Minutes* | *Standard error* | *95% confidence interval* | |
| | | | *Lower limit* | *Upper limit* | | | *Lower limit* | *Upper limit* |
| Sublingual fentanyl | 10.063 | 0.615 | 8.858 | 11.267 | 10.000 | 0.654 | 8.718 | 11.282 |
| Intranasal fentanyl | 6.875 | 0.774 | 5.358 | 8.392 | 5.000 | . | . | . |
| Subcutaneous morphine | 14.500 | 2.930 | 8.758 | 20.242 | 10.000 | 1.936 | 6.204 | 13.796 |
| Oral fentanyl | 20.000 | 0.000 | 20.000 | 20.000 | 20.000 | . | . | . |
| Overall | 10.099 | 0.595 | 8.933 | 11.265 | 10.000 | 0.592 | 8.839 | 11.161 |

tanyl, 8 with intranasal fentanyl and 8 with subcutaneous morphine, followed by disorientation (3 events), constipation (2), dizziness (2) and sweating (1), only observed after the administration of sublingual fentanyl, and xerostomia (1) after the administration of subcutaneous morphine.

### Patient and physician satisfaction with the treatment for breakthrough dyspnea

87% of physicians and 87% of patients rated their satisfaction with the treatment as good, and 13% as poor, without no differences according to the type of medication administered.

## DISCUSSION

The study's main objective was to analyze the effectiveness of treatment for breakthrough dyspnea in terminal patients who received care at our home hospitalization unit, and to evaluate these patients' level of satisfaction after the treatment administered.

We observed that the daily frequency of dyspnea crisis occurring, 3.9 crises per day, and the mean intensity of 7.67 points, was comparable to the findings of other studies carried out to evaluate breakthrough dyspnea (13-15).

After the administration of treatment for breakthrough dyspnea in one of the crises, we observed a difference of 4.2 points on a 10-point scale among patients, a similar variation to the observations of other studies (16-18). 94% of patients responded to treatment, improving the dyspnea by two or more points on the Borg scale, with no differences found according to active agent or route of administration. We consider this proportion a highly satisfactory response, but because breakthrough dyspnea appears abruptly and

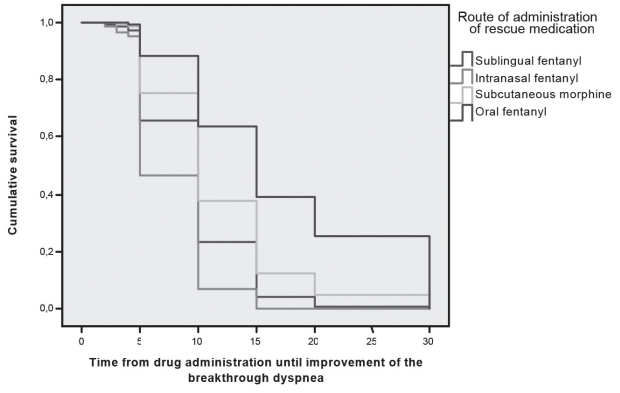


**Fig. 2.** Survival curves of time until dyspnea crisis relief according to medication administered.

has a limited duration - in general less than 30 minutes-, it was also important to evaluate the time until the symptom's relief. The study found that the time was significantly less in patients treated with intranasal fentanyl, followed by sublingual fentanyl and subcutaneous morphine (Table III and Figure 2). Although no significant differences among treatments ($p = 0.066$) were observed in the multivariate analysis, a trend was seen in favor of the results observed in the univariate analysis.

The treatment's safety profile was wholly acceptable, with a greater incidence of adverse effects found among patients who were already receiving opioids to manage pain for the baseline illness, but it was well-tolerated by all patients. 87% of patients, and also the same percentage of physicians, rated their satisfaction with the treatment for dyspnea crises as good; in this response patients integrated their opinion on the treatment's effectiveness and safety; in our opinion, we consider this was a very high level of satisfaction.

At the time of admitting the patient to the unit, it was seen that terminal cancer patients had less control of the main symptoms in comparison to non-cancer patients using the ESAS scale (Figure 1), with fatigue, appetite and well-being as the worst-controlled symptoms in the two patient types. No patient showed adequate control of all the symptoms, at the time they entered the home hospitalization unit. Subsequent to the time when the study was carried out, most of the symptoms improved significantly.

As it was an observational, non randomized study, the results observed could be affected by unknown factors that should not be distributed homogeneously among the treatment groups compared. Although the evaluation of dyspnea relief was subjective (Borg scale), it is currently the valid, recommended method for measuring it in clinical trials (5).

In a recent systematic review of episodic or breakthrough dyspnea, which included 27 studies, just eight included the investigation of breakthrough dyspnea as their main objective. In general, it was found that breakthrough dyspnea is barely defined, although its prevalence is very widespread (81-85%), its frequency of daily appearance is very high, and its intensity is severe (20).

Although breakthrough dyspnea is a very common symptom among patients with advanced or terminal illnesses, information on its characteristics and management is very limited (5,20). Furthermore, as there exists no consensus on a definition, identifying it and comparing the results of its treatment are difficult.

With this study, we may conclude that, according to our experience, we consider immediate-release fentanyls to be a good therapeutic option to control breakthrough dyspnea in terminal patients. As the effect of morphine is much slower, we find it more appropriate to treat BD with opioids that exert their action more rapidly, adapting to dyspnea crises' characteristics. In conclusion, after analyzing the study data, we insist on the need to carry out randomized clinical trials that compare different options of treatment with opioids, including immediate-release opioids, which would in principle adapt better to the characteristics of breakthrough dyspnea, and which are options used in clinical practise.

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