(CRITICAL APPRAISAL SKILLS PROGRAMME)
PROGRAMA DE HABILIDADES EN LECTURA CRÍTICA

Entendiendo la evidencia sobre la eficacia clínica

Taller CASPe-Ensayo Clínico. Hospital Virgen de la Salud de Elda

(Jueves, 24 de marzo de 2011)

MATERIAL DEL TALLER

Artículo de trabajo:

Coluzzi PH, Schwartzberg L, Conroy Jr JD, Charapata S, Gay M, Busch MA et al. **Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR)**. Pain 2001; 91: 123-30.

"LECTURA CRÍTICA DE LA LITERATURA"

¡Bienvenido!

Este material está diseñado para ayudarte a participar en el taller CASPe de lectura crítica de la literatura que se celebrará el jueves, 24 de marzo de 2011 en el Salón de actos del Hospital Virgen de la Salud de Elda

Contiene:

- Una introducción a la lectura crítica y los objetivos del taller
- El horario (página verde)
- El "escenario" para el taller (página amarilla)
- El artículo que se criticará en el taller: *Coluzzi PH, Schwartzberg L, Conroy Jr JD, Charapata S, Gay M, Busch MA et al.* **Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR)**. Pain 2001; 91: 123-30. (páginas blancas).
- Un pequeño glosario de términos (páginas azules)
- Algunas direcciones de interés.

Actividades esenciales antes del taller:

- Por favor, si te es posible, lee el material **antes** del taller y ponte en la situación del "escenario", sacarás más provecho del taller si lo haces.

- Si hay algo que no entiendas, búscalo en el glosario, si no aparece en él ¡no te preocupes! Probablemente no es muy importante, pero se podría discutir en el taller.

Si necesitas más información, puedes llamar a:

- **Reyes Pascual Pérez**
  e-mail : ***cperezb@coma.es***

WEB CASP España http://www.redcaspe.org

¿Qué es el CASP?

CASP (Critical Appraisal Skills Programme) (Programa de habilidades en lectura crítica) es un programa para ayudar a los "decisores" del Servicio de Salud Inglés a adquirir habilidades para hacer lectura crítica y obtener así la evidencia científica necesaria para las decisiones. Trabaja con programas locales de promoción de cuidados de salud basados en la evidencia y colabora con el Centre for Evidence-Based Medicine (Centro de la Medicina Basada en la Evidencia) de la Universidad de Oxford, que enseña a los clínicos cómo tomar decisiones, basadas en la evidencia, sobre un paciente concreto. En España existe un grupo CASP (CASP España - CASPe) radicado en Alicante, que usa la aproximación CASP a la lectura crítica y que forma parte de una organización internacional llamada CASP Internacional (CASPi).

¿Por qué la lectura crítica?

Hay un interés generalizado en hacer más eficaces a los servicios de salud para maximizar la mejoría de salud que ofrecen. Pero, ¿cómo sabemos qué servicios son verdaderamente eficaces? ¿Cómo saben los financiadores qué tratamientos y cuidados de salud deben financiar? ¿Cómo deciden los clínicos que un tratamiento concreto es útil?

Si queremos hacer lo mejor para nuestros pacientes, necesitamos basar nuestras decisiones en evidencias[1]. Pero, ¿cómo conseguirlo ante la proliferación de literatura? Una solución es seleccionar el tipo de artículos adecuado; en ese sentido el diseño de Ensayo Clínico Aleatorizado es una excelente fuente de evidencia. Sin embargo, ¿cómo saber que el ensayo clínico que nos interesa es válido y aplicable?

Aquí es donde la *lectura crítica* puede ayudar. Las habilidades en lectura crítica te permiten evaluar sistemáticamente los resultados de los trabajos publicados, su validez, su relevancia.y aplicabilidad. Durante el taller aprenderás cómo hacer lectura crítica de un Ensayo Clínico Aleatorizado.

[1] N.T Se ha preferido traducir en todo el texto *evidence* por *evidencia* debido a que es ya un término ampliamente aceptado. Queremos, sin embargo, resaltar que, el sentido en que se usa es *cosa científicamente probada*.

Objetivos del taller

Al final del taller serás capaz de:

1. Comprender la necesidad de la lectura crítica.

2. Entender los términos claves de un ***ensayo clínico.***

3. Explicar por qué estos estudios son tan importantes para fundamentar las decisiones que tomamos.

4. Aumentar la confianza acerca de la propia capacidad para hacer lectura crítica.

5. Decidir sobre la utilidad e interés de la aproximación pedagógica del "CASP".

Horario

16:00 - 16:15	Presentación del Programa: **Reyes Pascual Pérez** *Servicio de Medicina Interna.* *Hospital General Virgen de la Salud de Elda*
16:15 -17:15	Introducción a la lectura crítica: **Juan B. Cabello López** *Senior Fellow of the Centre for Evidence Based Medicine, Oxford University, UK* *Servicio de Cardiología* *Hospital U. General de Alicante* **Coordinador General CASPe**
17:15 - 17:30	Descanso
17:30 - 18:45	Lectura crítica en pequeños grupos
18:45 - 19:45	Plenario - Síntesis y Reflexión sobre la lectura crítica: **Eduardo López Briz** *Servicio de. Farmacia.* *Hospital Universitario "La Fe". Valencia* **Coordinador CASPe Comunidad Valenciana**
19:45 - 20:00	Resultado de las votaciones – Reflexión final.

Nota: La puntualidad británica es sólo comparable a la cortesía española. Se ruega un ejercicio de la segunda para que el taller se realice con la primera.

ESCENARIO

Tú eres un residente de tercer año de Medicina de Familia y estás rodando por la Unidad de Cuidados Paliativos de un gran hospital. Acabas de volver del Congreso de la Sociedad Española de Hospitalización a Domicilio, donde has aprendido mucho. En el Congreso, pasando por los stands de los laboratorios farmacéuticos, te detuviste en uno en el que se promocionaba un fármaco que tú no conocías. Se trataba de una forma de fentanilo en una especie de "chupa-chups" de absorción en la mucosa oral y que se usa para el llamado "dolor irruptivo", es decir, el que aparece súbitamente en pacientes con dolor maligno controlados crónicamente con opiáceos. Los delegados del laboratorio, muy amablemente, te proporcionaron la monografía del producto, que a ti te pareció de mucho nivel (¡se menciona a la MBE, una revisión de la Cochrane como referencia bibliográfica!). Además, y para reforzar, te regalaron un par de *pichigüilis* que te hicieron mucha ilusión.

Cuando vuelves al Hospital, lo comentas con los compañeros y te dicen que, en efecto, el dolor irruptivo es un problema frecuente, pero que en la Unidad se está utilizando para ese problema la morfina en solución oral.

Justamente, Francisco, el primer paciente que te toca ver ese día, te refiere que un poco antes de las dosis pautadas de morfina de liberación prolongada que está tomando por su problema oncológico tiene brotes de dolor agudo muy estresantes. Tú recuerdas lo que viste en el Congreso y te planteas usar el fentanilo "chupa-chup", pero el precio te para un poco (Francisco no parece estar en buena situación económica) y antes decides buscar el ensayo clínico que se cita en la bibliografía[1] de la monografía del producto para estudiarlo un poco.

Después de haber leído el artículo, contesta estas preguntas:

1. ¿Crees que el fentanilo transmucoso oral es más efectivo que la morfina de liberación rápida en dolor irruptivo?

2. ¿Le prescribirás fentanilo transmucoso oral a Francisco?

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[1] *Coluzzi PH, Schwartzberg L, Conroy Jr JD, Charapata S, Gay M, Busch MA et al.* **Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR)**. Pain 2001; 91: 123-30.

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Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC®) and morphine sulfate immediate release (MSIR®)

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Abstract

Oral transmucosal fentanyl citrate (OTFC®; Actiq®) is a drug delivery formulation used for management of breakthrough cancer pain. Previous studies with open-label comparisons indicated OTFC was more effective than patients' usual opioid for breakthrough pain. The objective of this study was to compare OTFC and morphine sulfate immediate release (MSIR®) for management of breakthrough pain in patients receiving a fixed scheduled opioid regimen. This double-blind, double-dummy, randomized, multiple crossover study was conducted at 19 US university- and community-based hospitals and clinics and comprised 134 adult ambulatory cancer patients. Patients were receiving a fixed scheduled opioid regimen equivalent to 60–1000 mg/day oral morphine or 50–300 μg/h transdermal fentanyl, were using a 'successful' MSIR dose (15–60 mg) as defined by entry criteria, and were experiencing 1–4 episodes of breakthrough pain per day. In open-label fashion, OTFC was titrated such that a single unit (200–1600 μg) provided adequate pain relief with acceptable side effects. Successfully titrated patients entered the double-blind phase of the study and received ten prenumbered sets of randomized capsules and oral transmucosal units. Five sets were the successful OTFC dose paired with placebo capsules, and five sets were placebo OTFC paired with capsules containing the successful MSIR dose. Patients took one set of study medication for each episode of target breakthrough pain. Pain intensity (PI), pain relief (PR) and global performance of medication (GP) scores were recorded. Pain intensity differences (PID) were calculated and 15-min PID was the primary efficacy variable. Adverse events were recorded. Sixty-nine percent of patients (93/134) found a successful dose of OTFC. OTFC yielded outcomes (PI, PID, and PR) at all time points that were significantly better than MSIR. GP also favored OTFC and more patients opted to continue with OTFC than MSIR following the study. Somnolence, nausea, constipation, and dizziness were the most common drug-associated side effects. In conclusion, OTFC was more effective than MSIR in treating breakthrough cancer pain.

Keywords: Oral transmucosal fentanyl citrate; Immediate release morphine sulfate; Pain; Cancer

1. Introduction

At least two-thirds of patients with advanced cancer report pain (WHO, 1996). Pain is typically experienced most of the time and is best managed with a fixed scheduled opioid regimen. This approach is usually effective but rarely eliminates the pain. In addition to some degree of persistent pain, one half to two thirds of patients also experience breakthrough pain, exacerbations of severe pain that occur on a background of otherwise controlled pain (Portenoy et al., 1999a; Portenoy and Hagen, 1990). Although highly variable, breakthrough pain is typically rapid in onset, moderate to severe in intensity, and relatively short in duration. The presence of breakthrough pain is associated with relatively worse psychological and functional outcomes (Portenoy et al., 1999a), and a less positive response to opioid therapy (Mercadante et al., 1992).

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Conventional treatment of cancer pain provides analgesia for both persistent and breakthrough pain (Jacox et al., 1994). Historically, controlled-release oral morphine has been the standard therapy for moderate to severe persistent pain and immediate-release oral morphine has been a commonly used analgesic for breakthrough pain. There have been no controlled trials of morphine for breakthrough pain and the time-action characteristics of this drug, which include onset in 20–30 min and peak effect at 40–60 min (Collins et al., 1998), may not be optimal for many patients with breakthrough pain.

Oral transmucosal fentanyl citrate (OTFC®; brand name Actiq®) is the first medication that has been studied specifically for breakthrough pain. The active ingredient, fentanyl, is a lipophilic opioid that passes rapidly through the oral mucosa. Absorption across the oral mucosa avoids first-pass metabolism, yielding a bioavailability substantially greater than oral administration and a peak plasma concentration about 22 min after beginning a typical 15-min administration period (Streisand et al., 1991). Once absorbed into the systemic circulation, fentanyl passes rapidly across the blood–brain barrier (Shafer and Varvel, 1991). In acute postoperative pain, OTFC had an onset of action similar to intravenous morphine; the median time to the onset of pain relief was 5 min (Lichtor et al., 1999). This rapid onset, and a relatively short duration of effect due to drug redistribution into tissues, yields a time-action relationship that more closely resembles the course of a typical breakthrough pain episode than oral morphine.

The dosing guidelines for OTFC were derived from the findings of three controlled studies in populations with cancer-related breakthrough pain (Portenoy et al., 1999b; Christie et al., 1998; Farrar et al., 1998). Two randomized, blinded dose titration studies demonstrated that the optimal dose of OTFC requires titration and is not predicted by the total daily dose of the fixed scheduled regimen pain (Portenoy et al., 1999b; Christie et al., 1998). This finding contrasts with published guidelines for the use of other short-acting supplemental opioids for breakthrough pain (Derby et al., 1998). These guidelines have been derived from clinical experience and have never been formally studied.

The OTFC titration studies also included open-label comparisons of OTFC and the usual oral opioids used for breakthrough pain (i.e. immediate-release morphine, immediate-release oxycodone, hydromorphone, and hydrocodone) (Portenoy et al., 1999b; Christie et al., 1998). Although both studies reported superior efficacy for OTFC, neither was designed to validly assess this comparison. The present study is a randomized controlled comparison of morphine and OTFC at doses judged by the patients to be satisfactory for the management of breakthrough pain.

2. Methods and materials

This double-blind, double-dummy, multiple cross-over study compared OTFC (developed by Anesta Corp., Salt Lake City, UT, and manufactured and distributed by Abbott Laboratories, Abbott Park, IL) with morphine sulfate immediate release (MSIR®) capsules for the treatment of breakthrough pain in cancer patients receiving a stable opioid regimen for persistent pain. The study was conducted at 19 sites geographically dispersed throughout the United States. Each site obtained Institutional Review Board approval for the study and all patients gave written informed consent prior to participation.

2.1. Study population

Adult patients with cancer-related pain were eligible for participation in the study if they were regularly having at least one, but no more than four, episodes of breakthrough pain per day while using a stable fixed schedule oral opioid regimen equivalent to 60–1000 mg of oral morphine per day, or transdermal fentanyl therapy equal to 50–300 μg/h. Breakthrough pain was defined as a transitory flare of moderate to severe pain that occurred on a background of persistent pain controlled to moderate intensity or less by the opioid regimen. If patients had more than one type of breakthrough pain, or had breakthrough pain in more than one location, they identified only one of the pains as a 'target' breakthrough pain. Study medication was used to treat the patient's target breakthrough pain exclusively.

Patients entering the study had to be using a 'successful' dose of 15-, 30-, 45-, or 60-mg MSIR to treat their target breakthrough pain. Patients who were being considered for this trial often underwent changes in their breakthrough pain regimen as the clinicians involved pursued conventional practice in an effort to optimize this therapy. Patients who reported that the MSIR dose was successful in controlling breakthrough pain for at least three days could be recruited into the study. The criteria for a successful MSIR dose were: (1) the dose used to treat at least three of four target breakthrough pains during the 3 days prior to enrolling in the study was effective without the need for additional medication; and (2) the patient rated the efficacy of the dose as 'good' or better using a categorical 5-point scale (0 = poor through 4 = excellent).

Patients were excluded from the study if they had uncontrolled or rapidly escalating pain; hypersensitivities, allergies or contraindications to any compound present in study medications; recent history of substance abuse; cardiopulmonary disease that would increase the risk of potent opioids; neurologic or psychiatric disease that would compromise data collection; strontium 89 therapy within 60 days prior to entering the study; any therapy prior to the study that could alter pain or response to pain medication; or moderate or severe mucositis.

2.2. Procedures

Throughout the study, patients continued their fixed scheduled opioid regimens. For any non-target break-

through pain episodes, patients used their usual supply of MSIR.

The first phase of the study was an open-label, OTFC dose-titration phase. The objective was to titrate each patient to a successful dose, which was defined as that unit size (200, 400, 600, 800, 1200, or 1600 μg fentanyl) that optimally treated the target breakthrough pain with acceptable side effects. A titration protocol was used to identify this unit dose. Specifically, for each episode of breakthrough pain treated with OTFC, patients self-administered an entire OTFC unit in as close to 15 min as possible, without biting or chewing the unit. Following a 15-min waiting period (30 min following the start of the previous unit), patients could consume a second OTFC unit if needed. Up to two additional units could be consumed after this, again with 15-min waiting periods between the completion of one unit and the start of the next. Thus, during titration patients could take up to four OTFC units for each episode of breakthrough pain. Patients' MSIR was available as well.

Patients were started at the 200 μg OTFC. If more than one unit was required to treat the breakthrough pain, a larger size unit could be used for the subsequent pains. Patients maintained close contact with the study staff to ensure safe and rapid titration. Once a unit dose size was found that consistently achieved relief using a single unit, the patients could enter the double-blind, crossover phase of the study. If a patient was unable to achieve effective relief of the target breakthrough pain from the highest tolerated dose, or if dose titration continued for more than 2 weeks, the patient was discontinued from the study.

For the double-blind phase, patients were given ten prenumbered sets of oral transmucosal units and capsules. Every set had one unit and a number of capsules. Five of the sets contained the successful OTFC dose paired with placebo capsules, and five of the sets were placebo OTFC paired with enough capsules to provide the patient's successful dose of MSIR. The placebo doses for OTFC and MSIR were formulated and packaged identically to the respective active medication.

The order in which the patient received treatments (active capsules or active OT units) was determined by a computer generated randomization code. The randomization code was maintained in a secure location by both the study pharmacist and sponsor such that, in the event of an emergency, the study blind could be broken to reveal the sequence of active treatments.

At home, if a patient opted to target a breakthrough pain episode, he or she consumed one full set of study medication, taking the capsule(s) first and then the corresponding oral transmucosal unit. Patients were not allowed to use additional medication(s) for 1 h following administration of study medication. New episodes of breakthrough pain could be treated with study medication after 2 h had elapsed. Patients remained in the double-blind phase of the study until all ten sets of study medication had been taken or until 14 days had passed.

2.3. Outcome measures

Before the study, patients completed a questionnaire that elicited information about their cancer, medical co-morbidities and treatments, and both persistent and breakthrough pains. Throughout the study a daily diary was used to record information about persistent and breakthrough pains, treatment for target breakthrough pain episodes, and changes in medical condition.

Immediately before a set of study medications was consumed, and at 15-, 30-, 45-, and 60-min following the start of administration, pain intensity (PI) was noted using a numeric scale that ranged from 0 (no pain) through 10 (pain as bad as you can imagine). At the 15-, 30-, 45- and 60-min assessments, patients also recorded their pain relief (PR) using a 5-point categorical scale (0 = none, 1 = slight, 2 = moderate, 3 = lots, 4 = complete). Patients completed a global evaluation of medication performance at the 60-min time point using a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent). They also recorded any additional medication used to treat an episode of breakthrough pain. Patients who treated at least one episode of breakthrough pain with study medication during the double-blind phase were considered the intent-to-treat (ITT) population.

2.4. Data analysis

Based on pain intensity data acquired during previous OTFC studies, the sample size needed to show group differences was estimated to be approximately 80 patients. With this sample size, the power to detect a true difference in pain intensity of 0.30 was 0.67 and the power to detect a true difference of 0.42 was 0.92.

Pain intensity difference (PID) was calculated for the 15-, 30-, 45-, and 60-min time points. The primary efficacy measure in this study was the 15-min PID score. For PID and the other outcome variables, the means (across episodes) for each of the two treatments was calculated for each patient at each time point. These means from each time point were analyzed separately using a three-way analysis of variance model, with terms for treatment, center, patient within center, and treatment by center. For the 15-min PID score, the proportion of treated episodes that had a change in pain intensity ≥33% was calculated for each study medication. For the intent to treat analyses, there was no imputing of data and no data were deleted. For other analyses, missing primary outcome data (PI, PID, and PR) were accounted for using imputed scores with the last observation carried forward. If all time points of the episode were entirely unevaluable, the primary outcome data, global performance evaluation, and measurement of additional breakthrough pain medication were deleted.

All statistical calculations were done using SAS (version 6.12; SAS Institute, Cary, NC). For all analyses, a (two-

sided) P-value <0.05 was considered statistically significant.

3. Results

Of the 134 patients enrolled in the study, 93 (69%) patients could be titrated to a unit OTFC dose that successfully treated the target breakthrough pain. The most common reason for withdrawal from the open-label titration phase was inability or unwillingness to comply with study requirements (Fig. 1). Approximately 10% of the patients withdrew during titration due to an adverse event. However, only five patients withdrew due to an adverse event associated with study drug; the other nine patients withdrew for adverse events unrelated to study drug. Five patients (4%) did not achieve adequate pain relief with OTFC at the highest dose available.

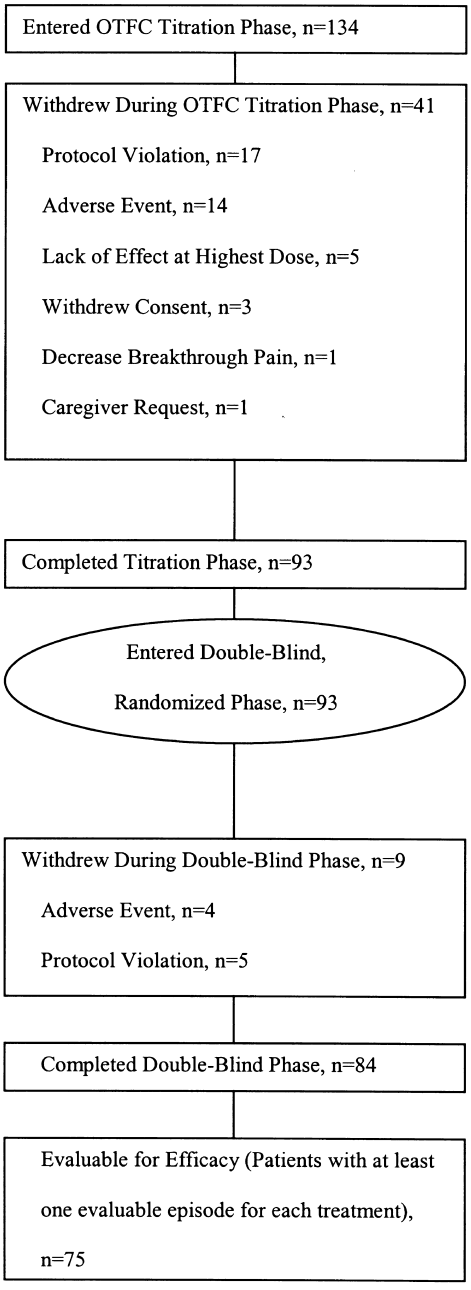

Fig. 1. Patient disposition.

Eighty-nine of the 93 patients used at least one set of study medication. This sample was included in the ITT analyses (Table 1). Seventy-five patients treated at least one episode of breakthrough pain with each study drug (OTFC and MSIR). This sample was included in efficacy analyses.

Approximately half of the patients were female (47%) and the mean (±SD) age was 55 ± 11 years. The most common tumor types were lung, breast, and colorectal. Sixty-one patients were receiving an oral opioid regimen, with long-acting morphine most common, and 28 patients used transdermal fentanyl. Morphine alone was used by 66 of the 89 patients (74%) to treat breakthrough pain episodes prior to enrollment in the study. The 23 patients who were also receiving other opioids had been provided oxycodone/acetaminophen ($n = 11$), hydrocodone/acetaminophen ($n = 4$), hydromorphone ($n = 3$), oxycodone ($n = 1$), propoxyphene/acetaminophen ($n = 1$), ibuprofen ($n = 1$), naproxen ($n = 1$), and unknown ($n = 1$). At screening, the mean intensity of the persistent pain (pain on average during the day) was 4.8 (SD 1.8, range 1–9) on a numeric scale of 0–10.

During the open-label OTFC titration phase, patients required a median of two dose titrations (range 0–9) before

Table 1
Patient characteristics ($n = 89$)

Variable	
Sex	
No. Females (%)	42 (47)
No. Males (%)	47 (53)
Age (years)	
Mean ± SD	55 ± 11
Range	21–87
Height (cm)	
Mean ± SD	170 ± 9
Range	155–193
Weight (kg)	
Mean ± SD	71 ± 20
Range	40–140
Race	
No. Black (%)	6 (7)
No. Hispanic (%)	1 (1)
No. White (%)	82 (92)
Cancer type	
No. Lung & bronchus	15 (17)
No. Breast (%)	14 (16)
No. Colon/rectal	13 (15)
No. Prostate	7 (8)
Other	40 (45)
Predominant pain type	
No. Nociceptive	71 (80)
No. Neuropathic	17 (19)
Other	1 (1)

finding their successful doses. Titration to a successful dose required a median of 5 days (range 1–22, mode 3); 73 of 89 patients (82%) were able to find an optimal dose within 9 days.

The distributions of successful OTFC doses and MSIR doses used during the double-blind phase are shown in Fig. 2. The mean (±SD) MSIR dose in the double-blind phase was 31.0 ± 13.5 mg and the mean (±SD) OTFC dose was 811 ± 452 mcg. There was no relationship between the OTFC and MSIR doses ($R^2 = 0.065$, $n = 93$). There were also no relationships between breakthrough pain medication dose (OTFC or MSIR) and the fixed schedule dose (oral opioid or transdermal fentanyl). Fig. 3 shows scatterplots of each of the relationships.

For the efficacy sample ($n = 75$), no significant differences were observed in mean baseline pain prior to consumption of study medication (OTFC vs. MSIR; $P = 0.244$). During the treatment phase, mean PI scores at each time point were lower (indicating less pain) for OTFC than MSIR (P-values at each time point ≤0.033). Mean PID across all time points also significantly favored OTFC (P-values at each time point <0.008, Fig. 4). Similarly, pain relief (PR) scores were significantly higher for OTFC than MSIR at each time point (P-values at each time point ≤0.009, Fig. 5).

PI and PR scores for the ITT population were consistent with scores from the efficacy population, OTFC produced significantly lower PI scores than MSIR at all time points after baseline (P-values at each time point ≤0.019). Similarly, OTFC yielded significantly higher PR scores at each time point than MSIR (P-values at each time point ≤0.011).

OTFC produced a >33% change in 15-min PID score for 42.3% of the episodes treated. In comparison, MSIR produced a ≥33% change in PID score for 31.8% of the episodes treated ($P < 0.001$).

Mean global medication performance rating for OTFC was significantly higher than for MSIR in the efficacy population (2.5 vs. 2.1, $P < 0.001$) and in the ITT population (2.3 vs. 2.0, $P < 0.001$). The percentage of breakthrough pain episodes for which patients required additional medication were similar for OTFC and MSIR (2% vs. 1% episodes; $P = 0.5385$, efficacy population). Of 68 patients who chose to enroll in an open-label, follow-on study during which they could continue to receive free study medication of their choice, 64 patients (94%) chose to continue receiv-

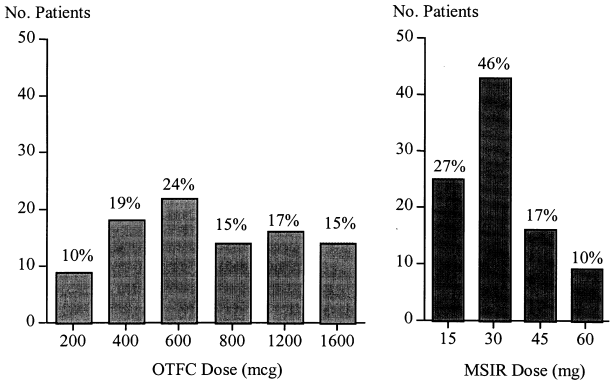

Fig. 2. Distribution of OTFC and MSIR doses used by patients ($n = 93$).

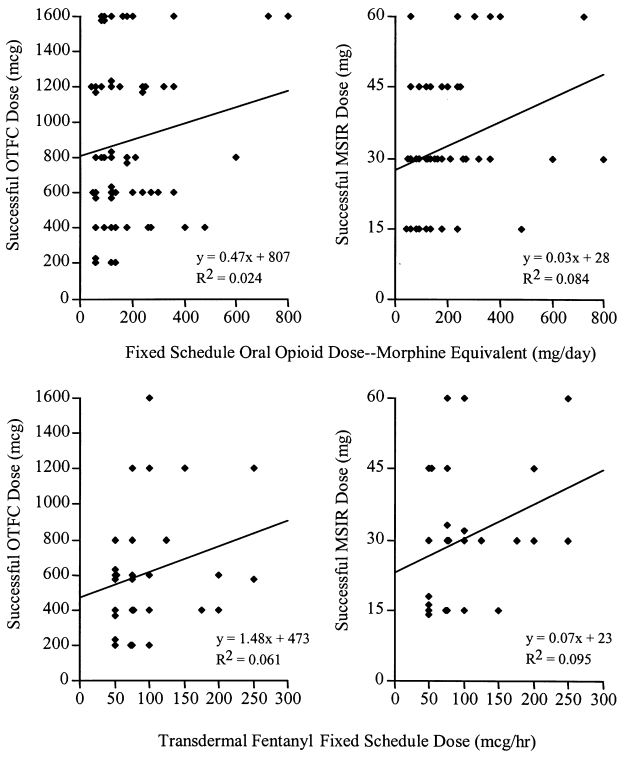

Fig. 3. Successful doses of OTFC and MSIR in relation to fixed schedule opioid dose for patients using oral opioids ($n = 64$) and patients using transdermal fentanyl ($n = 29$).

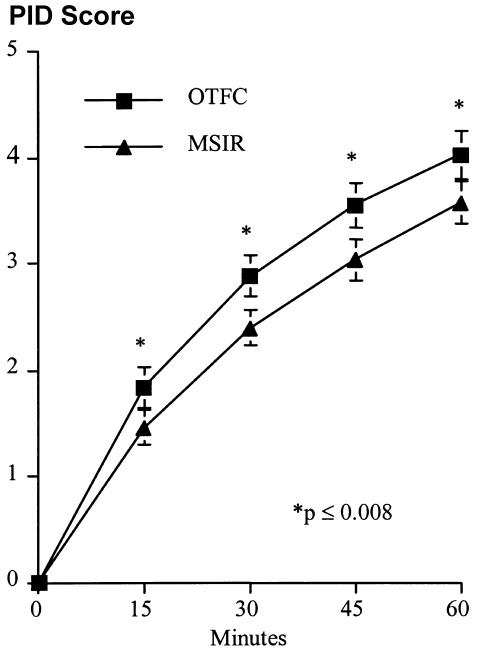

Fig. 4. Mean ± SEM pain intensity differences (PID) following OTFC and MSIR ($n = 75$).

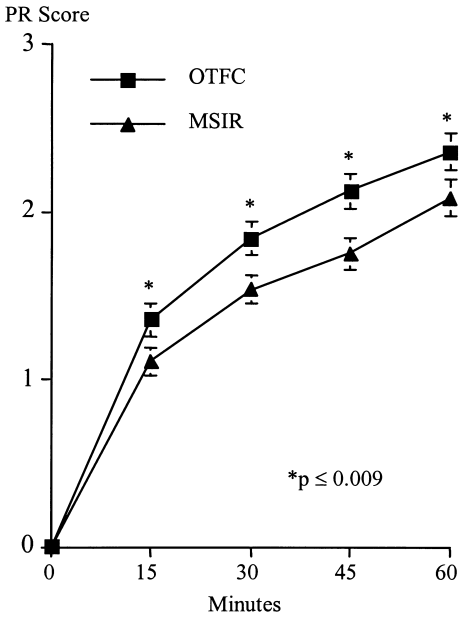

Fig. 5. Mean ± SEM pain relief (PR) scores following OTFC and MSIR ($n = 75$).

ing OTFC and four patients chose to continue receiving MSIR.

Most adverse events reported during the study were considered unrelated or unlikely to be related to study medication. The more frequent drug-related adverse events included somnolence (reported by 20 of 134 patients, 15%), nausea (18/134, 13%), constipation (14/134, 10%), and dizziness (10/134, 7%). These events were generally mild to moderate in intensity. The design of this study was such that patients' MSIR doses were adjusted before their entry into the study. Therefore, all adverse events and withdrawals occurred during either the OTFC titration phase or double-blind phase, at which time patients were receiving concomitant around-the-clock opioids as well as OTFC and MSIR. As a result, it was difficult to attribute an adverse event to OTFC or MSIR. Eighteen patients (13%) were withdrawn from the study due to an adverse event, six of which were considered at least possibly related to study medication. Of these six patients, five withdrew due to opioid-related adverse events such as nausea, vomiting, sedation, and dizziness. One patient was withdrawn due to a hospitalization for intractable pain, hallucinations, and confusion during the OTFC titration phase of the study. The investigator considered the hallucinations and confusion to be probably related to study drug. This patient was known to have had a previous intolerance to transdermal fentanyl. Of the nine deaths during or following the study, none were attributable to study medication.

4. Discussion

Breakthrough pain is a transitory flare of pain that occurs on top of an otherwise stable pattern of controlled baseline pain. More than half of cancer patients with pain experience these transitory pains (Portenoy et al., 1999a; Portenoy and Hagen, 1990). Despite the availability of supplemental, short-acting opioid drugs ('rescue' doses), the occurrence of breakthrough pain is associated with greater psychological distress and pain-related disability (Portenoy et al., 1999a).

Both the prevalence and impact of breakthrough pain suggest the need for improved treatment guidelines and new therapeutic approaches. Although the mainstay approach-the oral 'rescue dose'-may be adequate for many patients, oral administration yields a time-action profile that may not be optimal. MSIR, for example, may take more than 30 min to take effect and peak pharmacological effect may occur only after 40–60 min (Collins et al., 1998). This onset of action may not be fast enough to relieve breakthrough cancer pain adequately. Moreover, the duration of effect may be too long for breakthrough pain episodes.

OTFC is a fentanyl-containing matrix that dissolves in the mouth. Because fentanyl is potent and highly lipophilic, it is readily absorbed from the oral mucosa and rapidly crosses the blood–brain barrier. There is evidence that OTFC has a more rapid onset than oral opioids (Lichtor et al., 1999; Portenoy et al., 1999b; Christie et al., 1998) and this characteristic was primary in its development as a specific therapy for cancer-related breakthrough pain. Fentanyl's rapid distribution into tissues also allows a relatively short duration of effect.

Previous controlled trials of OTFC established safety and efficacy but allowed only tentative conclusions about the relative efficacy of this formulation and typical oral breakthrough pain medication. The present study directly compared these treatments in a randomized, double-blind, crossover design, in which both drugs were tested at doses deemed to be successful by the patient. The results of our study demonstrated that 69% of patients were able to identify a safe and effective dose of OTFC that could adequately treat a target breakthrough pain episode with a single unit. It would be anticipated that the success rate of titration would be better in actual clinical practice where there are no study requirements for patients and physicians. Seventeen patients (13%) did not complete the titration phase of the study because of their inability or unwillingness to comply with study requirements. Examples of these violations included patient inability or unwillingness to complete study diaries correctly, too few episodes of breakthrough pain, and noncompliance. Moreover, it is expected that withdrawals will occur more often in a cancer pain study than in an acute pain study because these patients frequently have concurrent pathologic conditions and are receiving medications in addition to study medication. Nine patients (7%) withdrew due to adverse events that were unrelated to study medication, but were related to their underlying disease.

In the double-blind phase of the study, OTFC produced a statistically significant increase in pain relief relative to

MSIR. In order to evaluate the clinical significance of this difference, the proportion of treated episodes that resulted in a ≥33% change in the 15-min PID score was calculated. The 33% cut-off point was based on a recent analysis that was undertaken to define clinically important measurements in pain outcome measures (Farrar et al., 2000). In their analysis, Farrar et al. (2000) determined the level of change in pain intensity that was best associated with a patient's own evaluation of a clinically important difference. The reference standard used for a clinically important difference in the Farrar et al. (2000) study was whether a patient received enough relief in a given time period to forego additional analgesic therapy (i.e. rescue medication for an episode). For PID scores, the 33% cut-off point was determined to be the best cut-off point for predicting adequate relief. In the present study, a greater proportion of episodes treated with OTFC had a ≥33% change in 15-min PID than MSIR (OTFC 42.3% vs. MSIR 31.8%, $P < 0.001$). The fact that global medication performance scores were significantly better with OTFC than with MSIR was also supportive of a clinically meaningful difference between treatments. In addition, 94% of patients chose to continue using OTFC ($n = 64$) rather than MSIR ($n = 4$) during an extension trial.

The most common side effects that occurred in this study were opioid-related and included sedation, nausea, constipation, and dizziness. Because all patients in the study were receiving a concomitant fixed scheduled opioid regimen, MSIR, OTFC, and possibly other opioids to treat non-target breakthrough pain episodes, it was difficult to associate specific adverse events with OTFC or MSIR. No opioid is universally accepted as being better or worse than another with respect to side effects and individual variation is very substantial.

There were several limitations in the design of the present study. MSIR doses were always identified before the OTFC dose and the identification of a successful MSIR dose was not accomplished in the same protocol-driven manner as the identification of the successful OTFC dose. Additionally, in many cases a number of days had passed between the time that the MSIR dose was set and the time OTFC was titrated. If these procedures led to the use of MSIR and OTFC doses that varied systematically in potential efficacy, then the comparison during the controlled phase of the study would not be valid. There are several factors, however, that argued that the patients were probably not underdosed with MSIR. First, the design attempted to minimize this possibility by applying similar criteria for the designation of a successful dose, specifically, three of four monitored episodes had to be treated successfully (i.e. episodes could not require additional medication) and patients had to rate the efficacy of the dose as 'good' or better using a categorical 5-point scale (0 = poor through 4 = excellent). Second, the mean doses used in the double-blind phase of the study were 31 mg MSIR and 811 μg OTFC. In an earlier standard four-point relative potency study in postoperative patients, the OTFC:IV morphine equivalence was determined to be approximately 1:10 (Lichtor et al., 1999). Based on this estimate, 800-μg OTFC would be equivalent to 8-mg intravenous morphine, which is equivalent to 24-mg oral morphine, suggesting that the patients were not underdosed with MSIR. Third, as shown in Fig. 2 the proportion of patients on doses above the mean dose of each study medication (i.e. >800 μg OTFC or >30 mg MSIR), was similar between the groups with 32% of patients using an OTFC dose greater than 800 μg and 27% of patients using an MSIR dose greater than 30 mg.

Selection bias also could be a limitation of this design. Most patients entered the trial already using oral morphine as their breakthrough pain medication. If the desire to participate was determined in part by lack of satisfaction with the current therapy, the sample could be biased against MSIR. This potential for selection bias was presumably reduced by enrolling only those patients who had found a successful MSIR dose and maintaining a strict double-blind throughout the study.

OTFC has a high degree of safety in this opioid-exposed population. Because of the risk of respiratory depression in opioid-naïve patients, prescribing directions for this product emphasize that OTFC is indicated only for patients who are taking at least 60 mg/day oral morphine or an equianalgesic dose of another oral opioid, or 50 μg/h transdermal fentanyl, for a week or longer. In the United States, OTFC is specifically contraindicated for the management of acute pain, including postoperative pain. Because OTFC contains an amount of fentanyl that could be fatal to a child if accidentally ingested, patients and their caregivers must be instructed to properly store, handle and dispose of OTFC properly.

OTFC represents the first opioid analgesic delivery system specifically investigated for control of breakthrough pain. This study and the previous controlled studies of OTFC represent an important step in applying analgesic trial methodology to the study of breakthrough pain in cancer patients. In this study, OTFC provided superior efficacy to MSIR in managing breakthrough cancer pain. This new delivery system offers a highly effective alternative to commonly used oral morphine.

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GLOSARIO

La Colaboración Cochrane (The Cochrane Collaboration) es un empeño internacional en el que gente de muy distintos países busca sistemáticamente, critica y revisa la evidencia disponible a partir de los ECC's. Los objetivos de la Cochrane son el desarrollo y mantenimiento de revisiones sistemáticas, la puesta al día de los ECC's en todas las formas de cuidados de salud y hacer que esta información esté realmente accesible para los clínicos y otros "decisores" en todos los niveles de los sistemas de salud. El Centro Coordinador de la Colaboración Cochrane Latinoamericana está en el Hospital de la Santa Cruz y San Pablo de Barcelona.

Controles (Controls) en un ECC son los individuos que forman el grupo de comparación. Reciben el tratamiento convencional (o placebo) mientras que el grupo experimental recibe el tratamiento que se está probando.

Ensayo clínico controlado (ECC) (Randomised controlled trial (RCT)) es un diseño de estudio en el que los sujetos son aleatoriamente asignados a dos grupos: uno (grupo experimental) recibe el tratamiento que se está probando y el otro (grupo de comparación o control) recibe un tratamiento alternativo. Los dos grupos son seguidos para observar cualquier diferencia en los resultados. Así se evalúa la *eficacia* del tratamiento.

Efectividad clínica (Clinical effectiveness) es la magnitud en la que una intervención (tratamiento, procedimiento o servicio) mejora los resultados para los pacientes en la práctica. También se le denomina simplemente **'efectividad'**.

Eficacia (Efficacy) es la magnitud en la que una intervención (tratamiento, procedimiento o servicio) mejora los resultados para los pacientes en condiciones ideales (típicamente un ECC).

Homogeneidad (Homogeneity) significa "similaridad". Se dice que unos estudios son homogéneos si sus resultados no varían entre sí más de lo que puede esperarse por azar. Lo opuesto a homogeneidad es **heterogeneidad**.

Intervalo de confianza (IC) (Confidence interval (CI)) es el intervalo dentro del que se encuentra la verdadera magnitud del efecto (nunca conocida exactamente) con un grado prefijado de seguridad. A menudo se habla de “intervalo de confianza al 95%" (o "límites de confianza al 95%”). Quiere decir que dentro de ese intervalo se encontraría el verdadero valor en el 95% los casos.

Lectura crítica (Critical Appraisal) es el proceso de evaluar e interpretar la evidencia aportada por la literatura científica, considerando sistemáticamente los resultados que se presentan, su validez y su relevancia para el trabajo propio.

MEDLINE es una base de datos informatizada que resume miles de artículos de investigación biomédica publicados en revistas seleccionadas. Está disponible en la mayoría de las bibliotecas sanitarias y es accesible mediante CD-ROM y por otros medios.

Meta-análisis (Meta-analysis) es una técnica estadística que permite integrar los resultados de distintos estudios en un único estimador, dando más peso a los resultados de los estudios más grandes.

Número necesario a tratar (Number needed to treat) (NNT) es una medida de la eficacia de un tratamiento. Es el número de personas que se necesitaría tratar con un tratamiento específico (vgr. aspirina a quienes han sufrido un ataque cardíaco) para producir, o evitar, una ocurrencia adicional de un evento determinado (vgr. prevención de muerte). Del mismo modo se define **número necesario para perjudicar (NNP) (number needed to harm (NNH))** para evaluar efectos indeseables.

Odds es un término poco usado fuera del juego (en Inglaterra) y la estadística. Se define como el cociente entre la probabilidad de que un evento ocurra y la de que no ocurra. Piensa en él como una medida del "riesgo".

Odds ratio (OR) es una medida de la eficacia de un tratamiento. Si es igual a 1, el efecto del tratamiento no es distinto del efecto del control. Si el OR es mayor (o menor) que 1, el efecto del tratamiento es mayor (o menor) que el del control. Nótese que el efecto que se está midiendo puede ser adverso (vgr. muerte, discapacidad) o deseable (vgr. dejar de fumar).

Placebo es un tratamiento inactivo dado a menudo como control en los ECC. El ***placebo*** se suministra en una forma que es aparentemente idéntica a la del tratamiento activo que se está probando, para eliminar los efectos psicológicos.

Revisión (Review) es cualquier resumen de la literatura.

Revisión sistemática (Systematic review) es una ***revisión*** en la que la evidencia sobre un tema ha sido sistemáticamente identificada, criticada y resumida de acuerdo a unos criterios predeterminados.

Sesgo (Bias) es la desviación sistemática entre el resultado obtenido y el verdadero valor, debido a la forma en que se hizo el estudio.

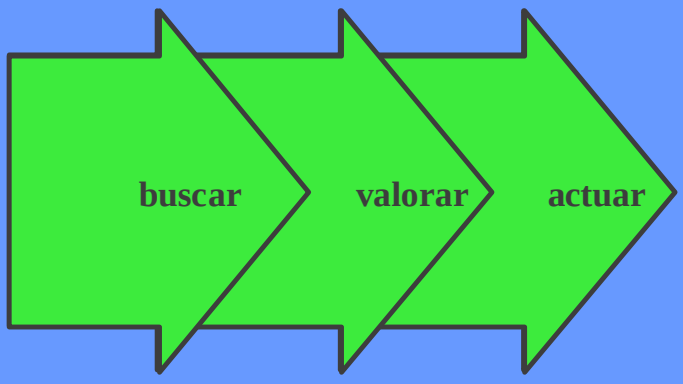
Sesgo de publicación (Publication bias) refleja la tendencia reconocida a publicar sólo estudios con resultados "positivos".

Validez (Validity) se refiere a la solidez o rigor de un estudio en relación con el grado de aproximación a la 'verdad' de sus resultados. Un estudio es válido si el modo en que ha sido diseñado y realizado hace que los resultados **no** estén sesgados, es decir, nos da una 'verdadera' estimación de la efectividad clínica.

EL LOGOTIPO DEL CASP

¿Qué significa?

El logotipo del CASP son tres flechas que se solapan. Éstas representan los tres pasos necesarios a seguir para usar la evidencia en tu trabajo.



EQUATOR NETWORK

Con frecuencia una buena evidencia de la investigación se ve socavada por la presentación de informes de mala calidad.

La Red Equator es una iniciativa internacional que busca mejorar la fiabilidad y el valor de la literatura de investigación médica mediante la promoción de una información transparente y precisa de los estudios de investigación **(http://www.equator-network.org)**

Este objetivo se logrará a través de:

1. La sensibilización de la importancia de una información de calidad de la investigación.
2. Convertirse en un centro global y reconocido para la provisión de recursos, educación y formación en la presentación de informes de la investigación en salud y para el uso de las directrices de presentación de informes.
3. Ayudar en el desarrollo, difusión y aplicación de las recomendaciónes sobre presentación de informes.
4. Seguimiento de la situación de la calidad de la información a través de la literatura de investigación en salud.
5. La investigación sobre la calidad de la información.