CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANESTHETIC and LIFE SUPPORT DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/17/97

SLIDES (ANESTA PRESENTATION)

Anesta Corp.
4745 Wiley Post Way
Salt Lake City, Utah 84116
801.595.1405

90 Minute Presentation Outline
ALSAC Meeting

September 17, 1997

Topic	Presenter
Background OTFC® and *Actiq*™ Indication (15 minutes)	**Steven A. Shoemaker, MD VP, Medical Communications Anesta Corp.**
***Actiq* Clinical Program (35 minutes)**	**Russell K. Portenoy, MD* Chairman, Dept. of Pain Medicine and Palliative Care Beth Israel Medical Center, NY (*Actiq* Consultant and Clinical Investigator)**
Safety Review (10 minutes)	**Steven A. Shoemaker, MD**
Risk Management Program (30 minutes)	**Clair Callan, MD, MBA VP, HPD, Medical, Regulatory Affairs and Advanced Research Abbott Laboratories**

* **Formerly:**
Co-Chief, Pain & Palliative Care Service
Memorial Sloan-Kettering Cancer Center

62-Year-Old White Male #32204

History:

Advanced chronic obstructive pulmonary disease

Non-small-cell lung cancer 9/95

Involving left diaphragmatic pleura

underwent left pariateral pleurectomy with decortication - closure of bronchopleural fistula

Deep venus thrombosis and pulmonary embolus 11/95

Home oxygen at 2L/min for dyspnea 2/9/96

62-Year-Old White Male #32204, cont.

Meds:

MS Contin 120 mg/d for persistent pain

Percocet 1-2 tab every 6 h prn breakthrough pain

Prednisone 30 mg/d for rheumatoid arthritis

Lanoxin 0.25 mg/d for arrhythmia

Heparin 33,000 IV anti-coagulation therapy

Lasix 20 mg/d

Shark cartilage

Zantac 300 mg haital hernia

Alkamints/Tums

62-Year-Old White Male #32204, cont.

2/29/96 Started OTFC at 200 µg

3/2/96 0600-0735 OTFC 600 µg x 3

1545 OTFC 800 x 2 with slight relief

1850 OTFC 1200 µg "lots of relief" in 15 minutes

Increasing dyspnea throughout day without temporal relationship to OTFC

3/3/96 0605 OTFC 1200 µg "lots of relief" at 30 minutes

0900 OTFC 1200 µg

Ongoing dyspnea progresses

1030 wife drives patient to emergency department

1050 patient died enroute to hospital

Investigator Assessment: Patient's death due to respiratory arrest secondary to metastatic lung cancer. It could possibly have been related to OTFC.

Questions for the Committee

Does the expected benefit to the intended clinical population outweigh the risk of accidental injury inherent in this product?

Yes.

- Large unmet clinical need
- *Actiq* has been proven effective and safe in meeting this need.
- The Risk Management program provides aggressive safeguards to reduce the risk of:
  - accidental injury to children
  - misuse in opioid non-tolerant
  - diversion and abuse

Questions for the Committee

Whether the clinical effect demonstrated in 200/013 (the controlled study in breakthrough cancer pain) represents a significant clinical effect.

- Global assessment of pain relief was significantly better with *Actiq*
- 92% of eligible patients chose to go into the long-term study
- Speed of onset demonstrated at 15 minutes is a good indicator of appropriate treatment for a rapid onset condition like breakthrough pain
- 011 study also provided well controlled efficacy data

Questions for the Committee

Whether the Sponsor has adequately identified a rational approach to finding the appropriate dose.

- The sponsor realizes that the titration scheme outlined in the PI is not as clear as it could be. The sponsor would like the committee to consider the following revised presentation of the proposed titration scheme:

Questions for the Committee

Goal: To determine the minimum dose of *Actiq* that provides safe, adequate analgesia using a single *Actiq* dosage unit per breakthrough pain episode.

Methods:

- The starting unit dose of *Actiq* must be 200 mcg
- If breakthrough pain persists after a unit is consumed, redosing with an equal strength dosage unit of *Actiq* may begin 15 minutes after previous dose is finished to a maximum of 3 units per episode of breakthrough pain.
- If adequate treatment of breakthrough pain consistently requires treatment with >1 unit per episode, an increase in dose to the next highest available strength should be considered.

Questions for the Committee

Whether the Sponsor's risk management plan is adequate.

- The Risk Management program provides aggressive safeguards to prevent inappropriate use. The risks specifically addressed include:
  - accidental access by child
  - use by opioid non-tolerant population
  - diversion or abuse
- The benefits of *Actiq* outweigh these risks. *Actiq* should be made available for in-home use, consistent with other CII products.

Actiq

(Oral Transmucosal Fentanyl Citrate)

NDA 20-747

Anesta Corp.

Steven A. Shoemaker, M.D.

Vice President Medical Communications

Anesta Corp.

Key Issues

- Breakthrough pain in cancer patients represents a large unmet medical need
- *Actiq (OTFC)* safely and effectively treats breakthrough pain in outpatients with cancer
- *Actiq* is appropriately configured and labeled to provide adequate safeguards in an outpatient environment

Actiq (*OTFC*) NDA
Presentation Outline

I. Background *OTFC* and *Actiq* Indication

Steven A. Shoemaker, M.D.
Vice President Medical Communications, Anesta Corp.

II. *Actiq* Clinical Program

Russell K. Portenoy, M.D.
Chairman, Dept. Pain Medicine and Palliative Care
Beth Israel Medical Center, NY, NY

III. Integrated Summary of Safety

Steven A. Shoemaker, M.D.

IV. Risk Management Program

Clair M. Callan, M.D.
Vice President, HPD, Medical, Regulatory Affairs and Advanced Research
Abbott Laboratories

Actiq NDA History

10/93	*Fentanyl Oralet (OTFC)* approved for marketing
4/94	Meeting with FDA, Anesta, Abbott and pain specialists
	– define clinical program
6/95	Meeting with FDA, Anesta and Abbott
	– reviewed clinical plan rationale and progress
	– proposed indication language reviewed
7/96	Controlled chronic pain trials completed
11/96	Actiq NDA submitted

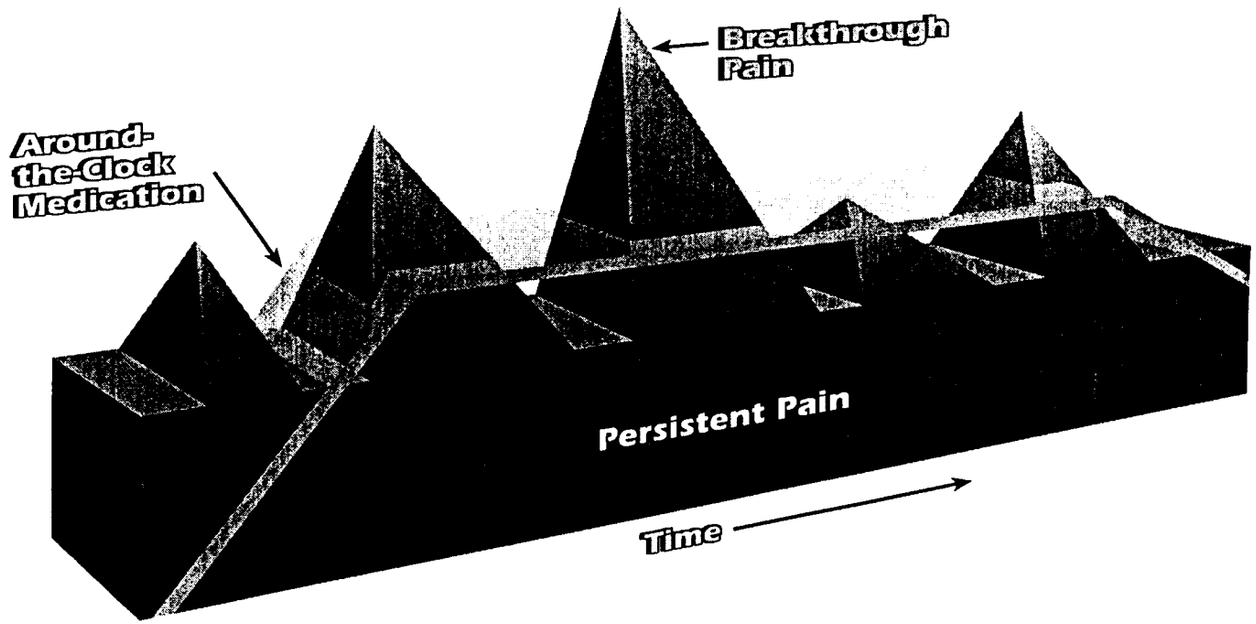
Proposed *Actiq* Indication

Actiq is indicated for the management of chronic pain, particularly breakthrough pain, in patients already receiving and who are tolerant to opioid therapy

Breakthrough Pain

Definition: Transient flare in pain, rising to moderate to severe intensity, that occurs in conjunction with otherwise controlled, persistent pain of mild or moderate intensity.

Breakthrough Pain - Definition



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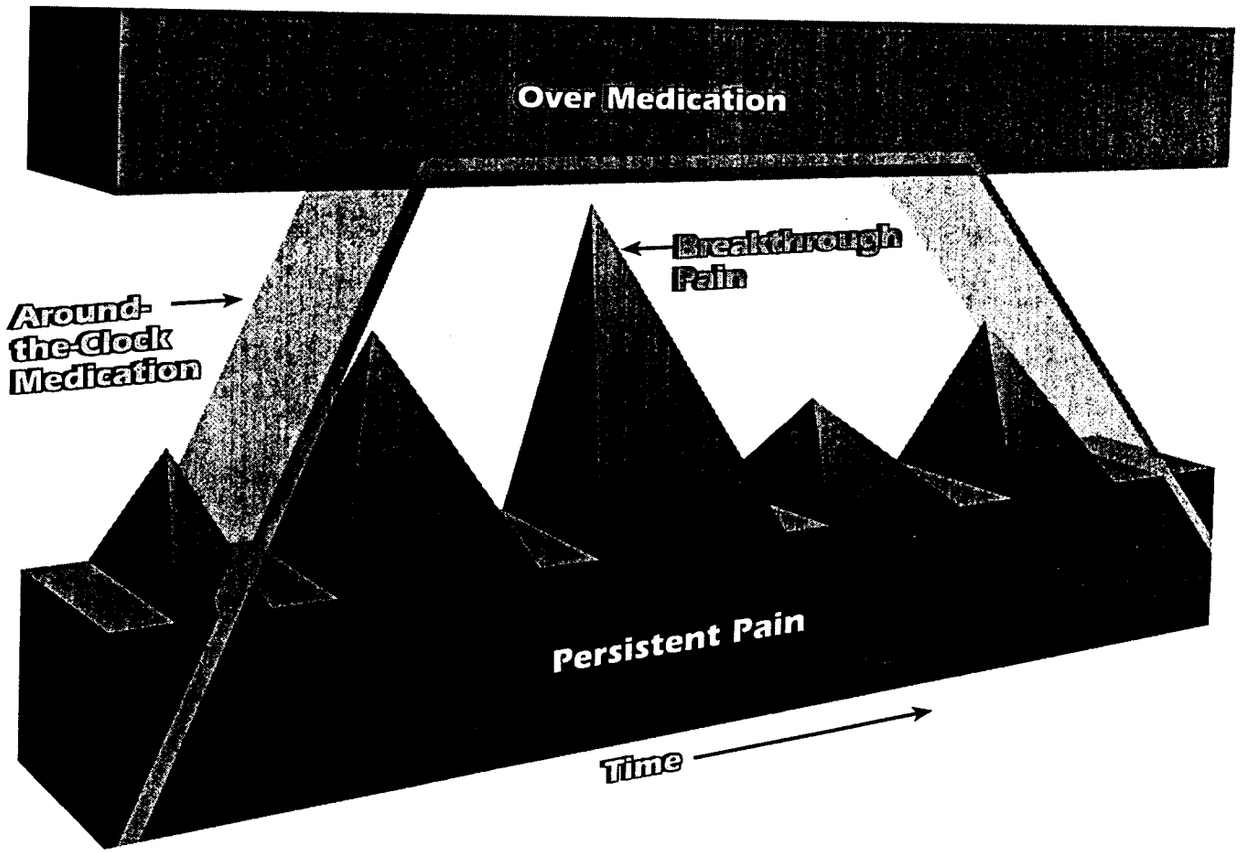
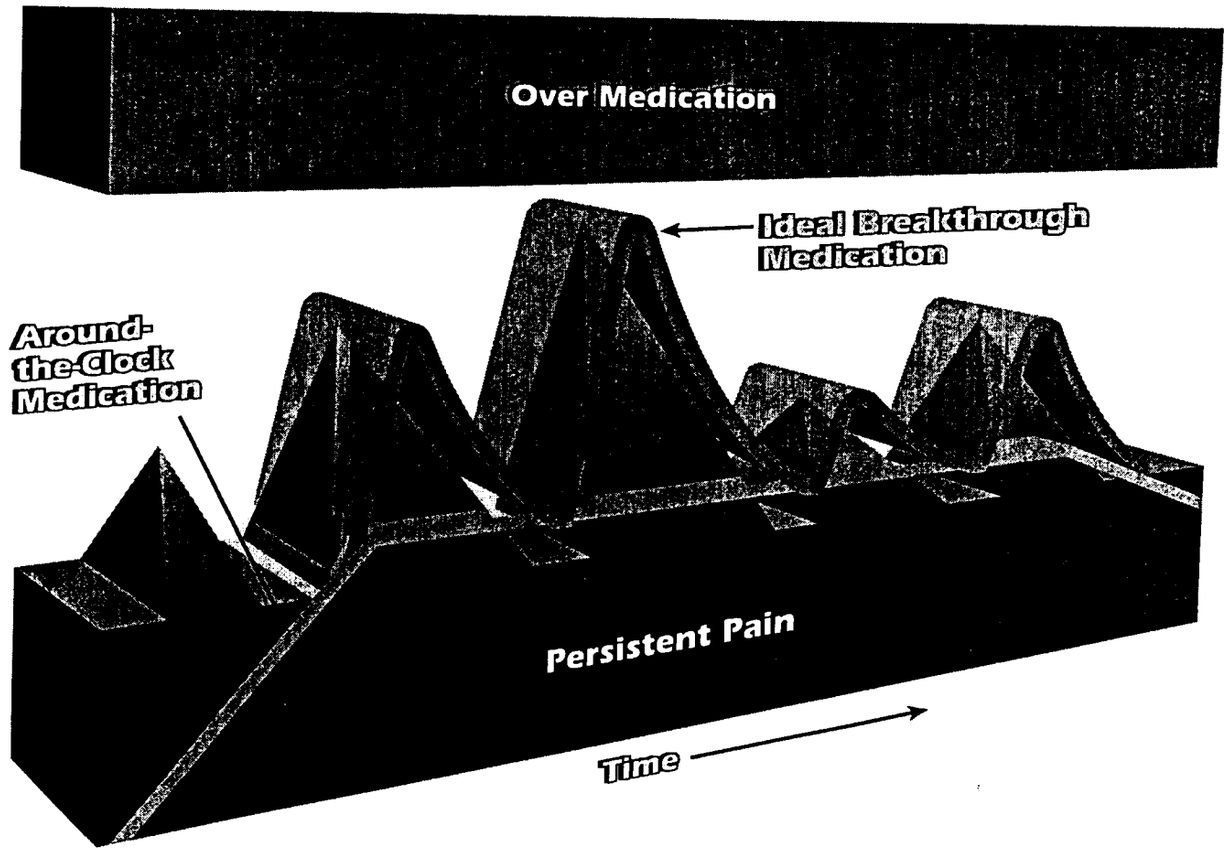
Increasing Dose of ATC Medications
Potential for More Side Effects



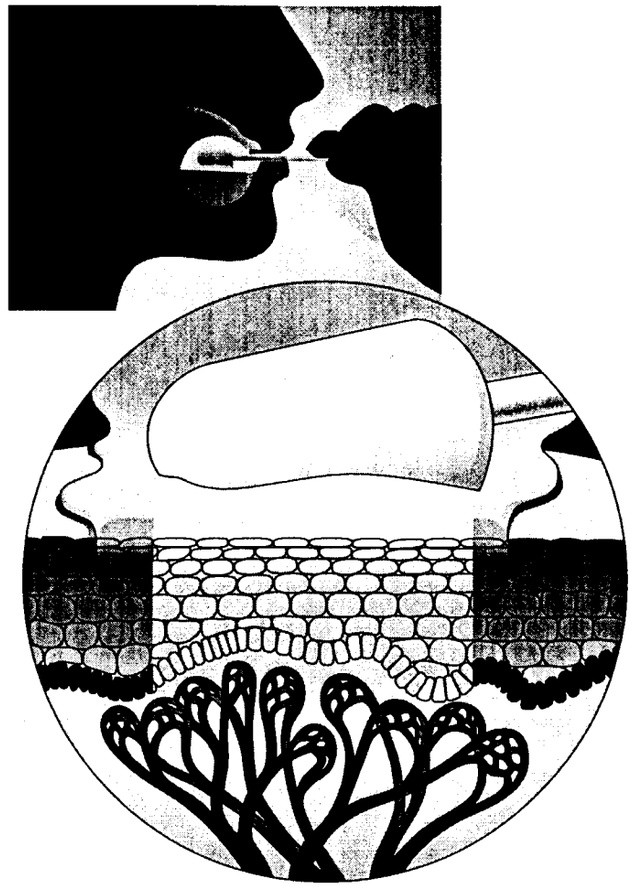
Ideal Cancer Pain Management - Hypothesis



Cancer Pain Management
Unmet Medical Need

- Undertreatment of cancer pain is well documented
- Prevalence is high
  - 30% have moderate to severe pain at diagnosis
  - 65% - 85% with advanced disease experience pain
- Barriers to effective cancer pain management
  - lack of controlled clinical trials
  - inadequate medical training
  - unreasonable fears of opioids
  - heterogeneity of cancer pain

Oral Transmucosal Fentanyl Citrate (*OTFC, Actiq*)

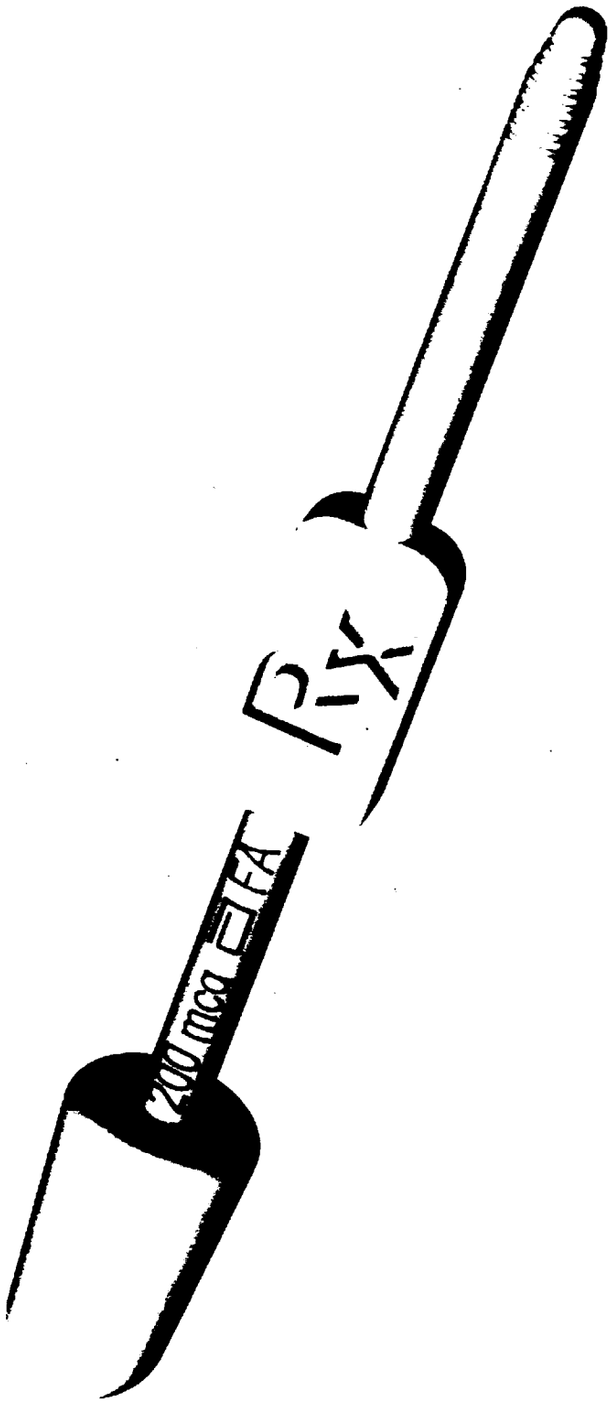


Features of oral mucosa:

- Highly permeable
- Well vascularized
- Facilitates rapid absorption

Features of OTFC delivery:

- Rapid onset of action
- Non-invasive
- Controllable delivery
- Relatively short duration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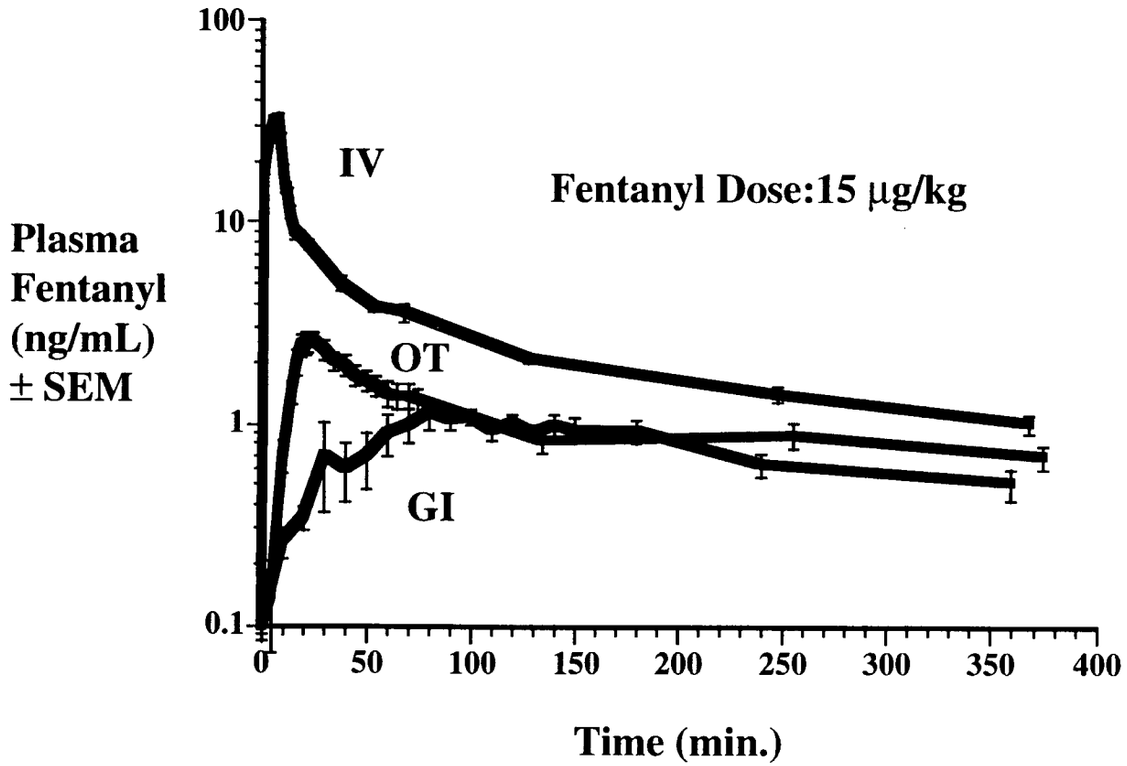
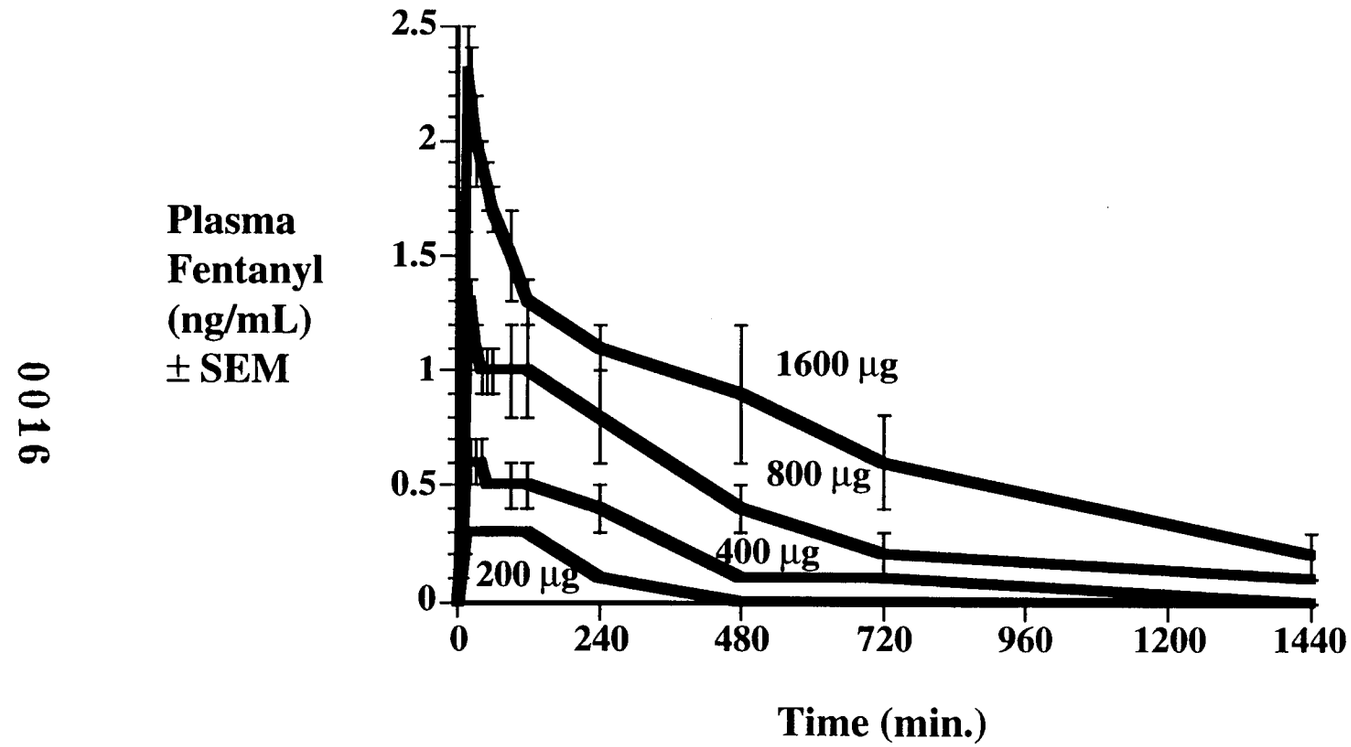
OTFC Single Dose Pharmacokinetics[1]
Rapid OT Absorption Compared to GI

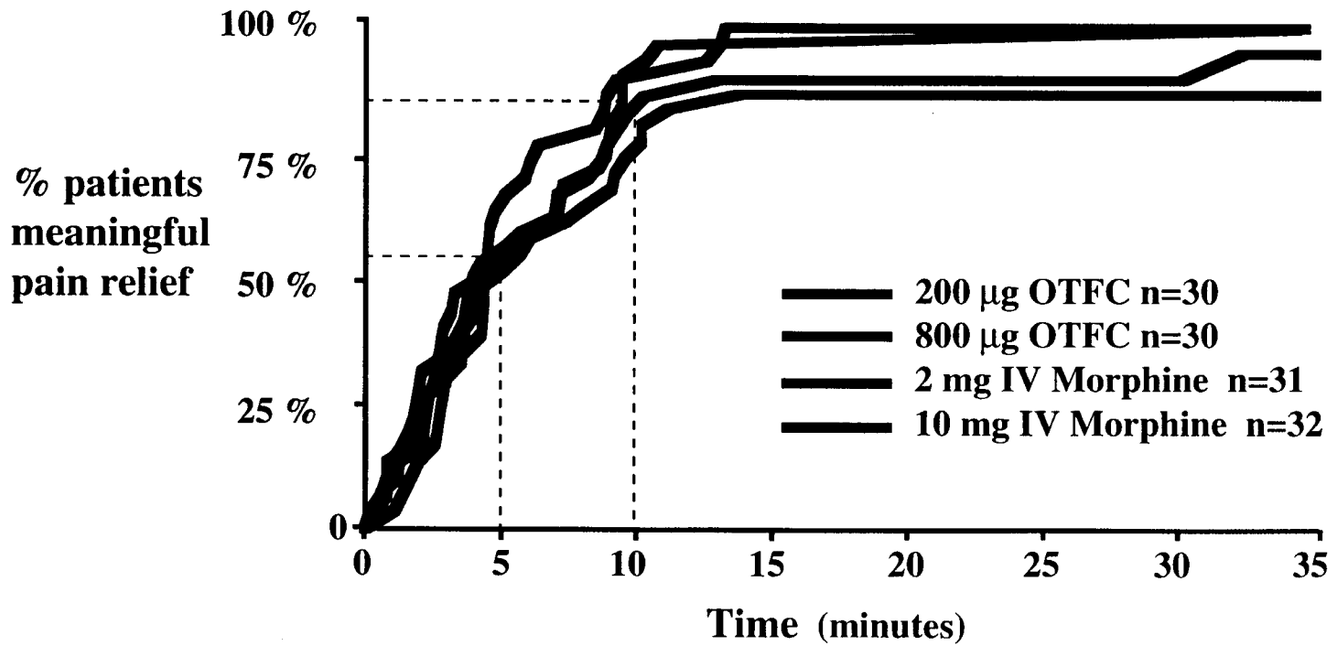


[1]Streisand JB,et al Anesthesiology, 75:223-229, 1991.

Dose Dependent Fentanyl Delivery (200-1600 µg) Single Dose Volunteer Study



Controlled Single Dose Relative Potency Study of OTFC and IV Morphine



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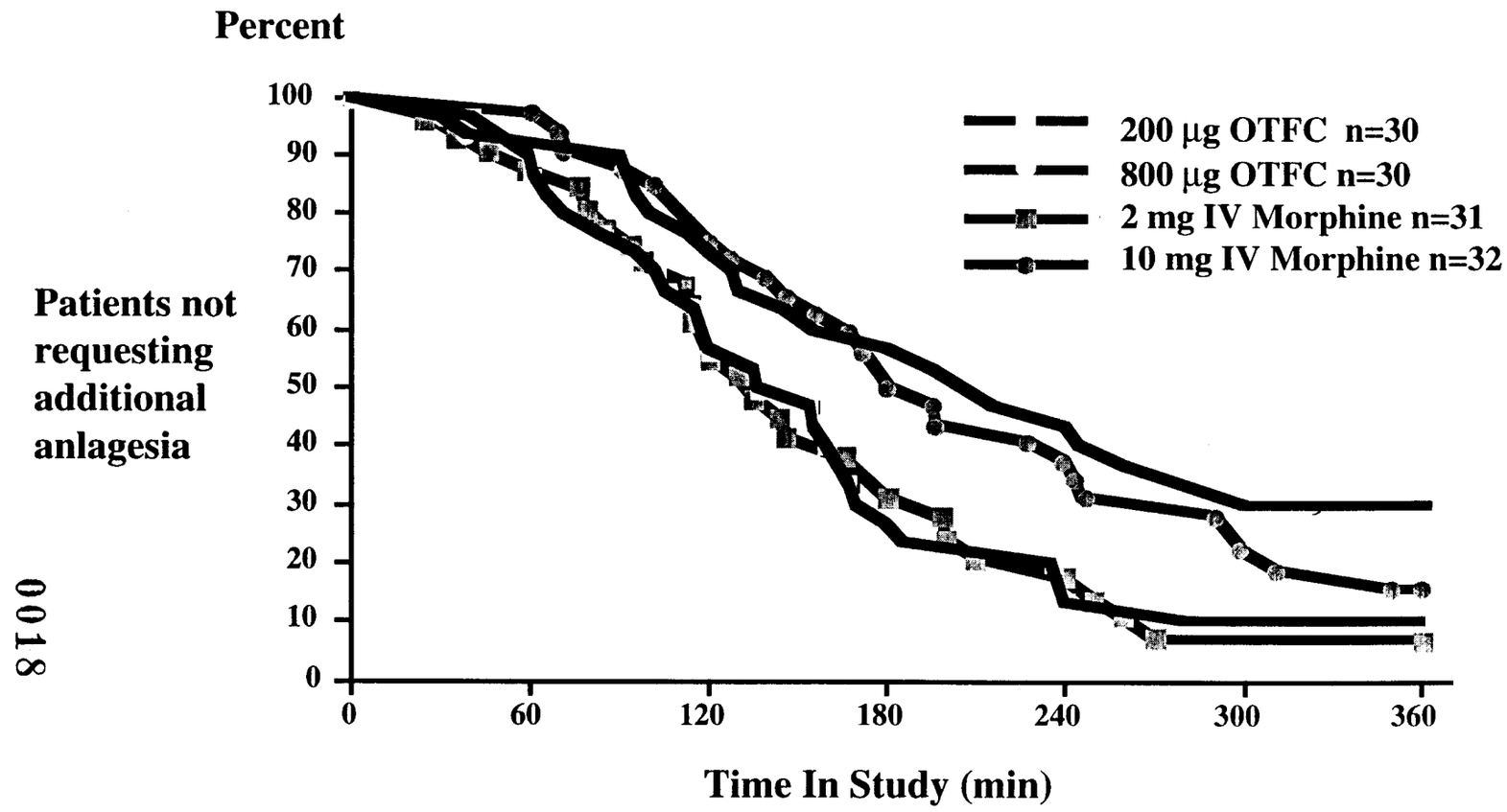
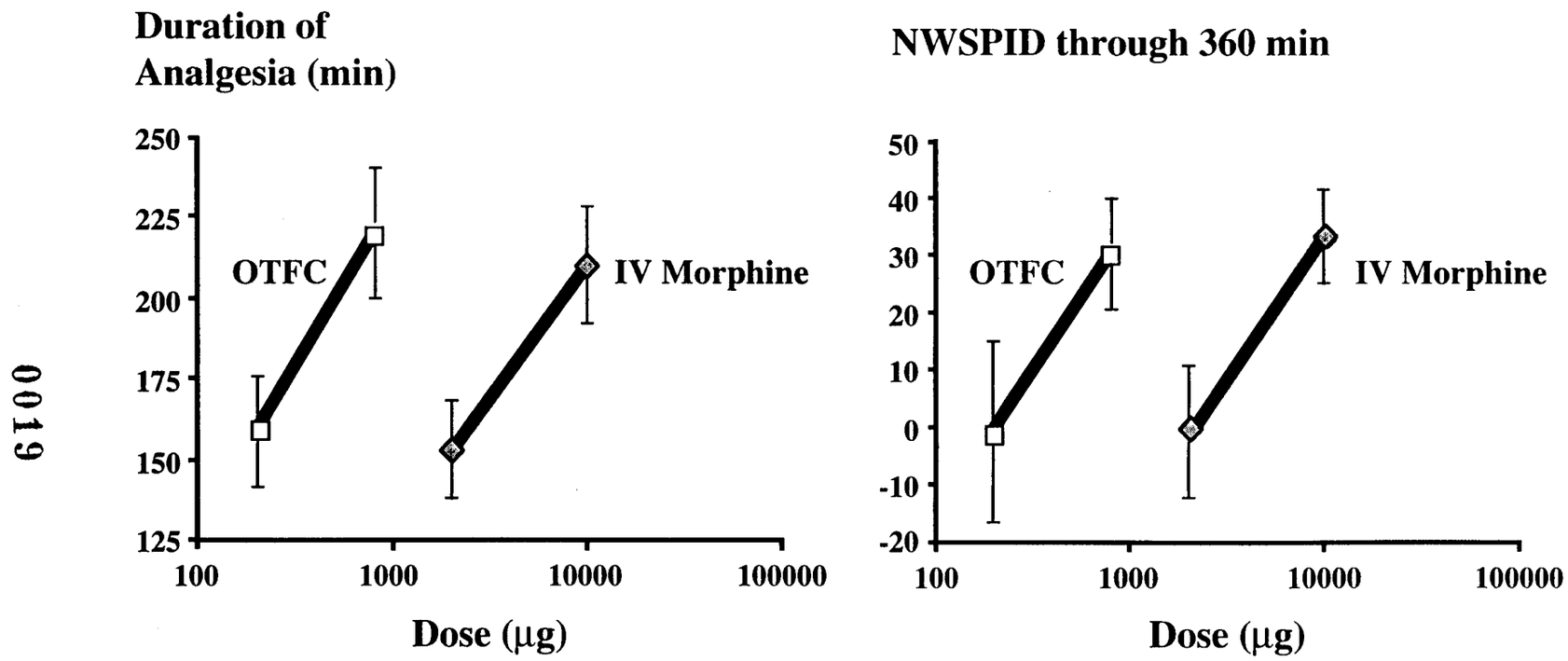
Controlled Single Dose Relative Potency Study of OTFC and IV Morphine



Controlled Single Dose Relative Potency Study of OTFC and IV Morphine



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Relative potency for pain intensity difference and duration approximately 10:1 (range 8-14:1)

Oral Transmucosal Fentanyl Citrate

- Non-invasive route of administration
- Controllable delivery
- Rapid onset of pain relief (similar to IV MS, 5-10 min)
- Relatively short duration (2.5 - 3.5 hrs, 200-800 µg)
- Relative potency with IV morphine 10:1 (range 8-14:1)
  - 8 mg IV morphine: 800 µg OTFC

Actiq NDA history

10/93	*Fentanyl Oralet (OTFC)* approved for marketing
4/94	Meeting with FDA, Anesta, Abbott and pain specialists – define clinical program
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Summary

- Breakthrough pain represents an unmet medical need
- Important clinical features of *OTFC*
  - rapid onset of pain relief
  - non-invasive, controllable delivery system
  - relatively short duration
- *OTFC* applicable for management of breakthrough pain

Breakthrough Pain Background

- Cancer pain is highly prevalent and represents a major public health problem
- Conventional practice involves the long-term, in-home use of opioids, including both long-acting and short-acting formulations
- Opioid doses must be individualized according to patient need; the goal is always satisfactory pain control with a favorable balance between analgesia and side effects
- Breakthrough pain is highly prevalent and undermines the outcome of opioid therapy
- Current breakthrough pain management uses supplemental opioid doses empirically selected and titrated to effect

Challenges in Studying Breakthrough Pain

- Breakthrough pain is a heterogeneous transient and often unpredictable phenomenon
- Clinically relevant studies must be done in outpatients
- Patients often have severe underlying illness
- No previous controlled trials to model

OTFC for Breakthrough Pain
Clinical Program Objectives

To Demonstrate:

- Predictable single dose and multidose pharmacokinetics
- Dose proportionality
- Efficacy of OTFC compared with placebo for treating breakthrough pain in outpatients with cancer
- Relative analgesic potency of OTFC and IV morphine
- Titratability of OTFC therapy in outpatients such that an OTFC dose provides adequate analgesia with acceptable adverse events
- Safety of chronic OTFC use in outpatients with cancer

Placebo-Controlled OTFC Trial

Aim

To demonstrate that OTFC is more effective than placebo for treating breakthrough pain in cancer patients taking stable doses of around-the-clock opioids

Placebo-Controlled OTFC Trial

Design

Multicenter, randomized, double-blind, placebo-controlled crossover trial

Patients

Cancer patients (n=130) using oral opioid equivalent to 60 - 100 mg/day morphine or 50 - 300 µg/hr transdermal fentanyl to treat stable persistent pain and experiencing 1 - 4 breakthrough pain episodes per day

Placebo-Controlled OTFC Trial

Phase 1		**Phase 2**
Open titration of OTFC Define Successful Dose (200 µg - 1600 µg)[a]	→	10 episodes treated, 7 with OTFC and 3 with placebo

After Tx rate:

- Pain Intensity
- Pain Relief
- Medication Performance
- Adverse Events

0028

[a]Dose at which 1 OTFC unit provides adequate analgesia with acceptable side effects

Placebo-Controlled OTFC Trial

Patient Completion Status	No.	
Received drug and entered titration phase	130	100%
Withdrew due to AE in titration phase	22	17%
Withdrew due to other reason in titration phase	15	12%
Completed titration phase	93	72%
Completed titration phase and entered double-blind phase	92	100%
Withdrew due to AE in double-blind phase	7	8%
Withdrew due to other reason in double-blind phase	13	14%
Completed 10 episodes in double-blind phase	72	78%

Placebo-Controlled OTFC Trial

Patient Characteristics (n = 92)

Age (yr)		Gender	
Mean ±SD	54±12	Female	51 (55%)
Range	27-84	Male	41 (45%)
Weight (kg)		Race	
Mean ±SD	70±20	Black	5 (5%)
Range	40-129	Asian	1 (1%)
		Other	86 (93%)

Placebo-Controlled OTFC Trial

Patient Characteristics (n = 92)		
Breast	21	(23%)
Lung	17	(18%)
Colon/Rectal	12	(13%)
Uterine	7	(8%)
Multiple Myeloma	5	(5%)
Non-Hodgkin's Lymphoma	5	(5%)
Ovarian	4	(4%)
Kidney	3	(3%)
Pancreatic	3	(3%)
Leukemia	2	(2%)
Unknown Primary	2	(2%)
Miscellaneous[a]	14	(22%)

[a] Miscellaneous diagnoses (1 occurrence each) included: bladder, Ewing's sarcoma, gastroesophageal, head and neck, leiomyosarcoma, liver, melanoma, mesothelioma, prostate, sarcoma, and squamous cell cancer.

Placebo-Controlled OTFC Trial

Around-the-clock		
• Morphine	63	(68%)
• Fentanyl transdermal	21	(23%)
• Methadone	5	(5%)
• Oxycodone	3	(3%)

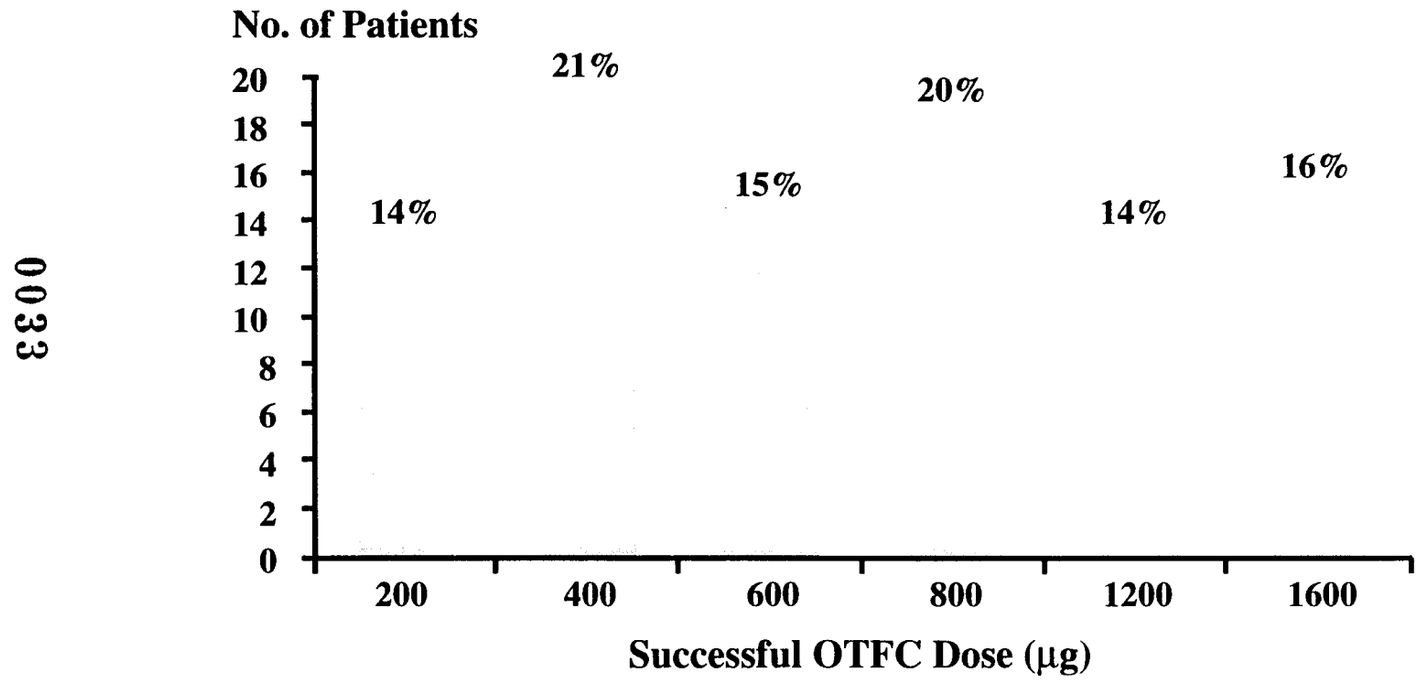
Supplemental Medications		
• Morphine (short acting)	24	(34%)
• Oxycodone	26	(37%)
• Hydrocodone	9	(13%)
• Hydromorphone	8	(11%)
• Codeine	1	(1%)
• Morphine (long acting)	1	(1%)
• Propoxyphene	1	(1%)
• Unknown	1	(1%)

Around-the-clock Dose	
• mean mg/d	166 ± 137
• range (mg)	

Short-Acting Opioid Dose	
• mean mg/episode	18 ±18
• range (mg)	

Placebo-Controlled OTFC Trial

Distribution of Successful Doses
Patients Entering Double-Blind Phase (n=92)



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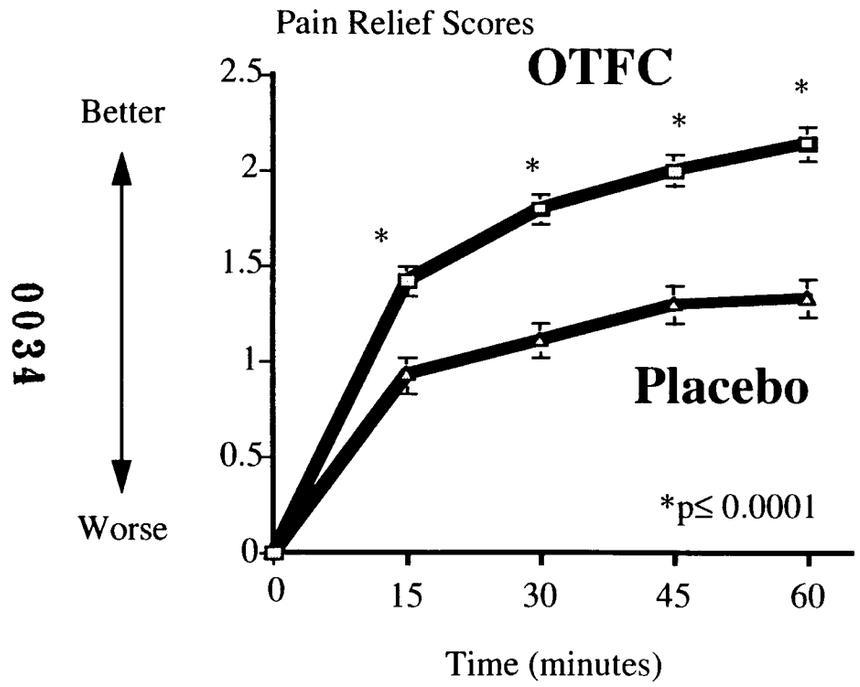
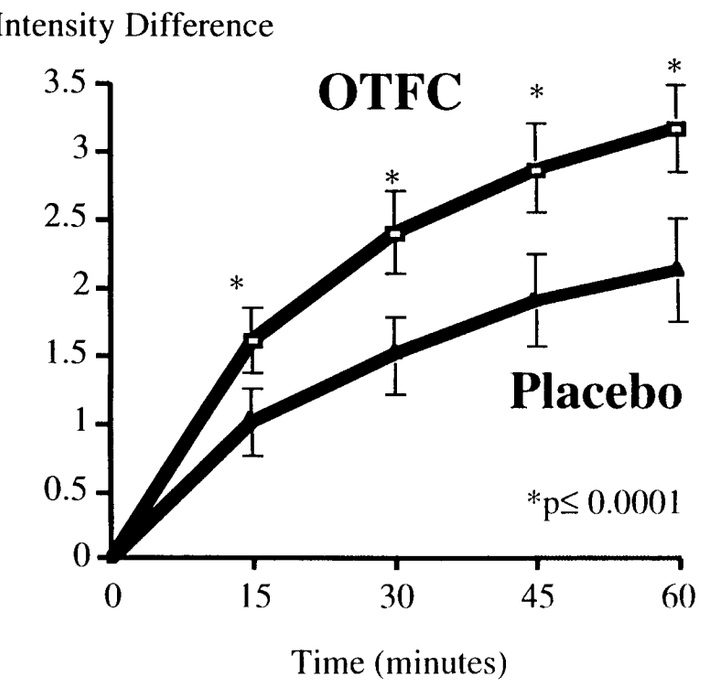
Placebo-Controlled OTFC Trial





Placebo-Controlled OTFC Trial

Adverse Events

The most common AEs in all 130 patients at least possibly related:

Dizziness	22	(17%)
Nausea	17	(13%)
Somnolence	11	(8%)
Vomiting	4	(3%)

Three patients withdrew with AE's at least possibly related: shortness of breath, chest pains, disorientation, unsteady gait, weakness, dizziness, blurred vision, flushing, nausea

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Aim

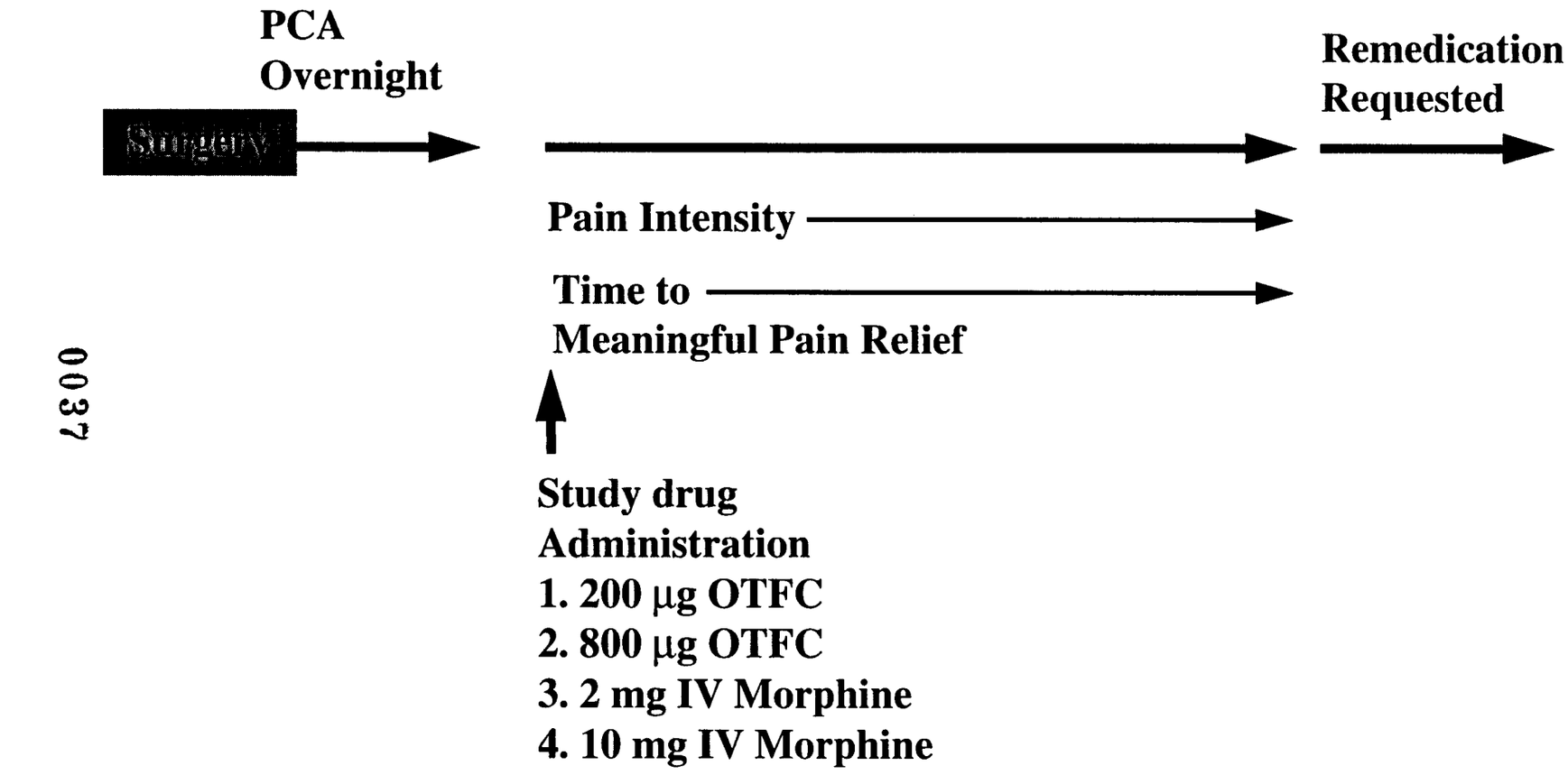
To determine the relative potency of OTFC and IV MS

Design

Multicenter, randomized, double-blind, graded single dose trial

- OTFC: 200 µg and 800 µg
- MS: 2 mg and 10 mg

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine



Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Patient Characteristics (n = 133)[a]

Type of Surgical Procedure

Hysterectomy (non cancer)	55	(41%)
Hysterectomy (cancer)	25	(19%)
Other Gynecological	29	(22%)
Colorectal	5	(4%)
Other	6	(5%)

[a] Some patients had more than one surgical procedure

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Patient Characteristics (n = 133)

	OTFC		IV Morphine	
	200 µg	400 µg	2 mg	10 mg
Age (yrs)				
Mean	42	41	43	47
Range	21-60	28-61	21-65	26-63
Weight (kg)				
Mean	71	71	71	73
Range	45-100	51-96	51-120	51-92

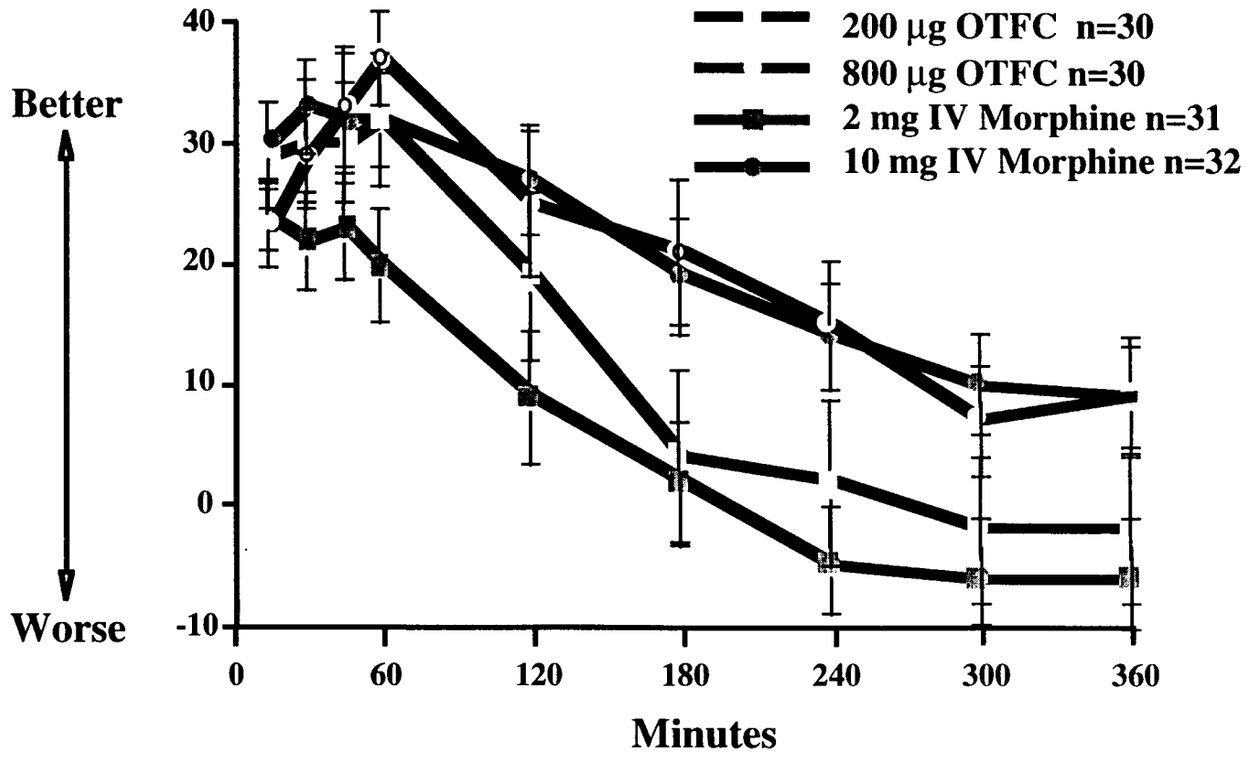
Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Patient Characteristics (n = 133)

	OTFC		IV Morphine	
	200 µg	400 µg	2 mg	10 mg
Gender				
Female	30	31	33	33
Male	3	1	1	1
Race				
Black	15	17	14	13
White	14	11	20	20
Other	4	4	0	1

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Pain Intensity Differences



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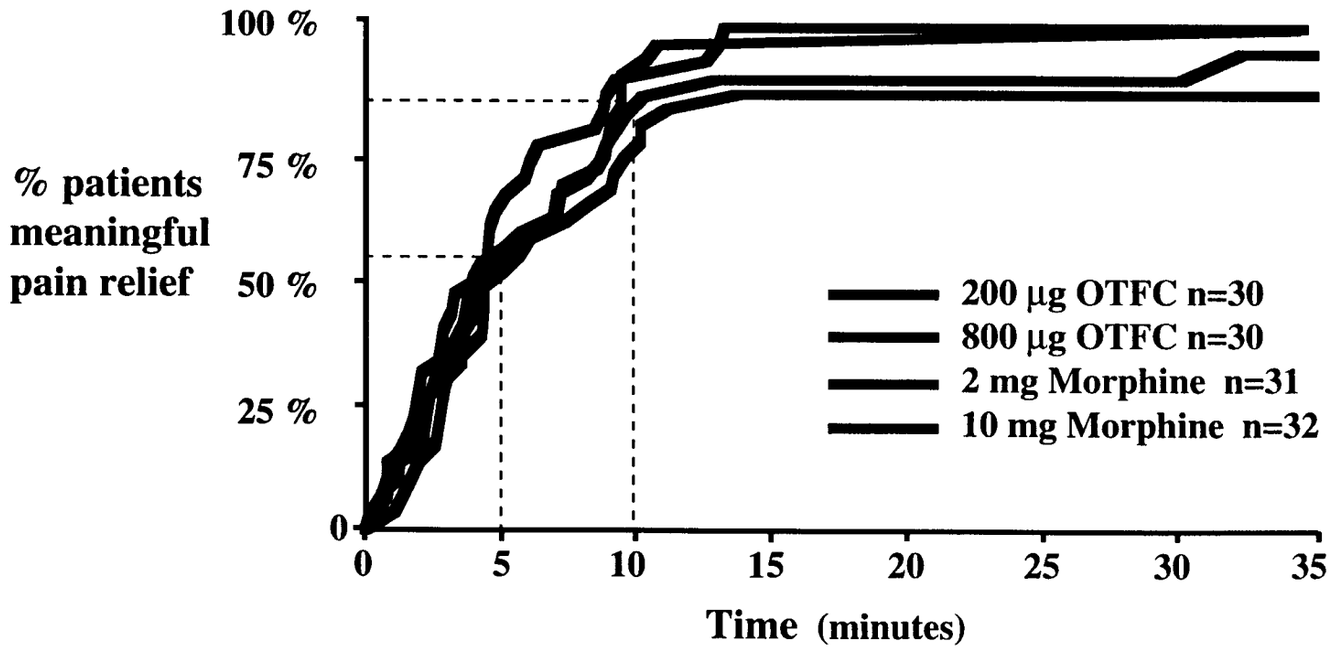
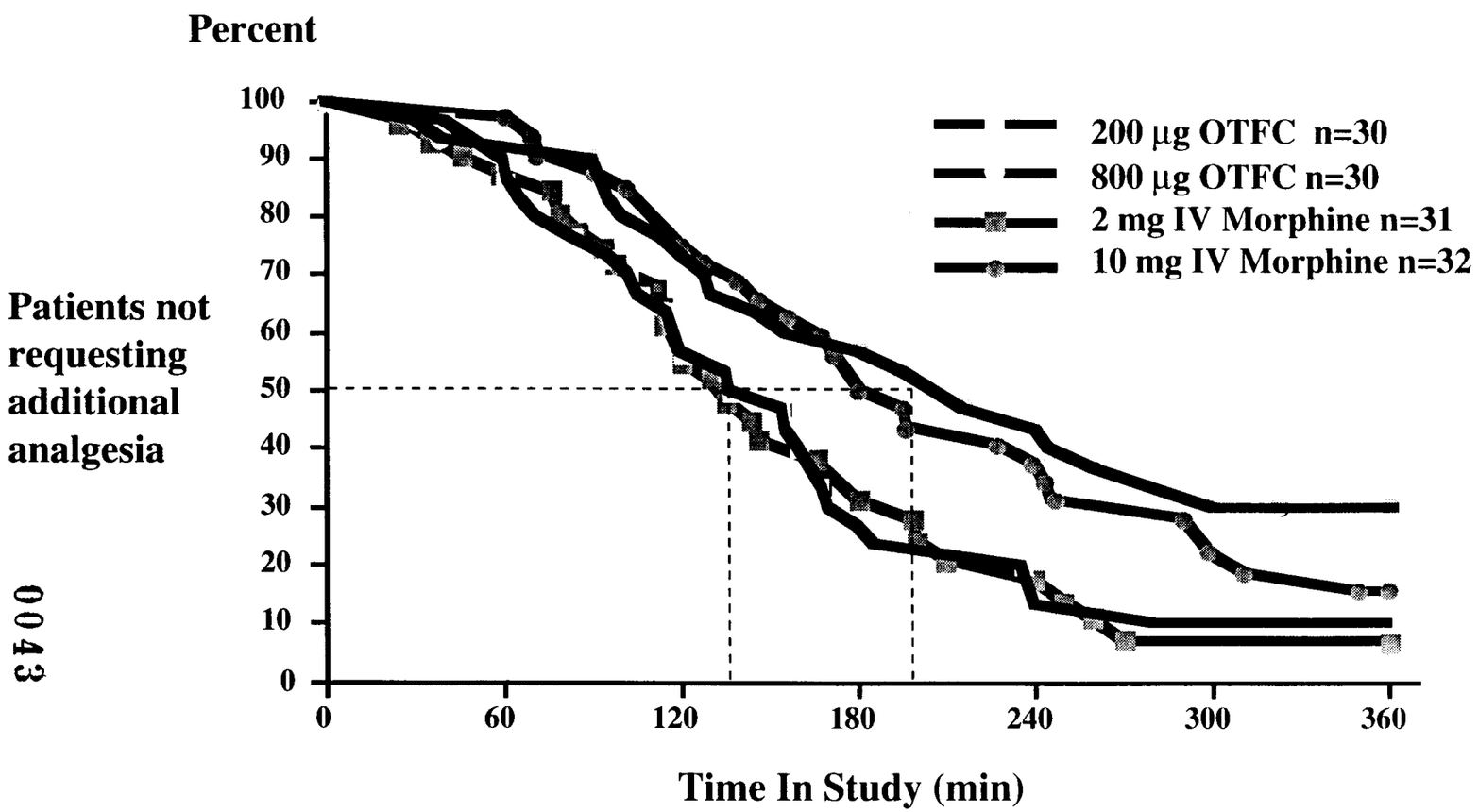
Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

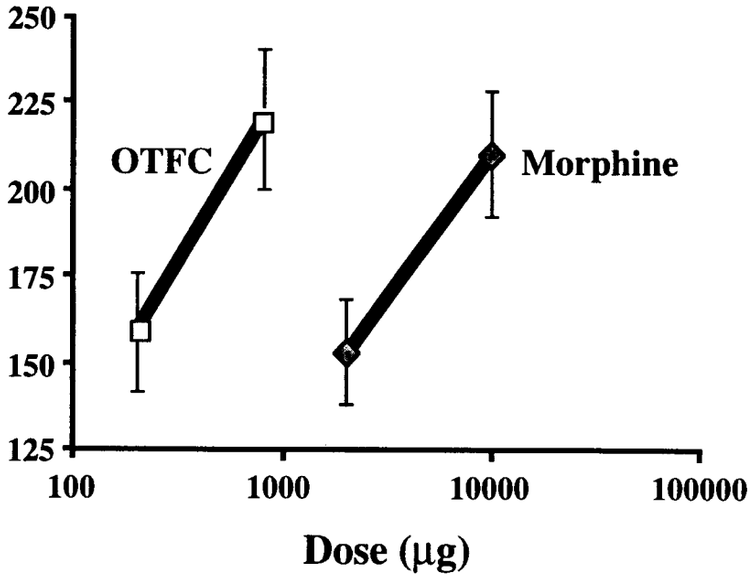


Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

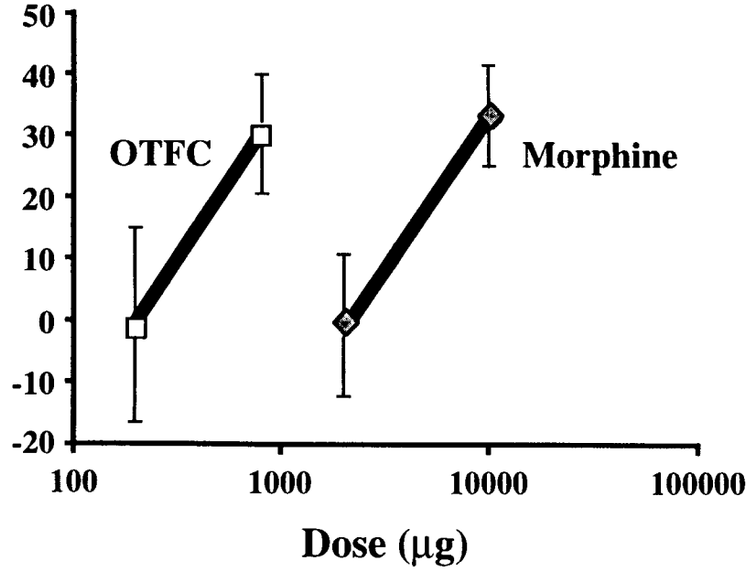


Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Duration of Analgesia



NWSPID through 360 min



Relative potency for pain intensity difference and duration approximately 10:1 (range 8-14:1)

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Adverse Events

	200 µg OTFC n=33	800 µg OTFC n=32	2 mg IV MS n=34	10 mg IV MS n=34
Fever	12 (36%)	3 (9%)	9 (26%)	11 (32%)
Nausea	5 (15%)	5 (16%)	6 (18%)	10 (29%)
Pruritus	5 (15%)	1 (3%)	6 (18%)	8 (24%)
Supplemental O_2	1 (3%)	0	0	1 (3%)

No serious AE's related to either study drug

Controlled Single Dose Relative Potency Study of OTFC and IV Morphine

Conclusions:

- OTFC: IV Morphine relative potency is approximately 10:1
  - 800 μg OTFC is equivalent to 8 mg IV MS
- Onset of pain relief and duration with OTFC was similar to IV morphine
- OTFC was well tolerated

OTFC Titration Study in Patients Receiving Oral Opioids

Aim

To demonstrate that a titration process can be used to identify a dose of OTFC that safely and effectively treats breakthrough pain in cancer patients receiving around-the-clock (ATC) oral opioids for chronic pain

Secondary Aims

- Compare OTFC with usual breakthrough pain meds
- Assess dose response
- Establish OTFC dosing guidelines
- Define safety profile

OTFC Titration Study in Patients Receiving Oral Opioids

Design

Multicenter, randomized, double-blind, dose titration

Patients

Cancer patients (n=65) using oral opioid equivalent to 60-1000 mg/d morphine for persistent pain and experiencing 1-4 breakthrough episodes/d

OTFC Titration Study in Patients Receiving Oral Opioids

Phase 1

Assess Baseline Performance Usual Short-Acting Opioid for Breakthrough Pain

- **2 day observation**
- **2 episodes / day**
- **After Tx rate:**
  - **Pain intensity**
  - **Pain relief**
  - **Medication performance**
  - **Adverse events**

Phase 2

OTFC Titration

Define Successful Dose: (200 μg-1600 μg)[a]

Phase 3

Assess Performance of OTFC at Successful Dose for Breakthrough Pain

- **2 day observation**
- **2 episodes / day**
- **After Tx rate:**
  - **Pain intensity**
  - **Pain relief**
  - **Medication performance**
  - **Adverse Events**

[a] **Dose at which 1 OTFC unit provides adequate analgesia with acceptable side effects**

0049

OTFC Titration Study in Patients Receiving Oral Opioids

Procedure

- Start at 200 μg or 400 μg OTFC
- Use up to 4 units/episode; treat up to 2 episodes/d
- Increase dosage unit size if > 1 unit needed per episode
- One-third of the orders to increase dose ignored
- Investigator and patient blind to starting and titrated doses
- Titrate until one unit OTFC effective on two occasions
- Outcome data at baseline and after successful titration

OTFC Titration Study in Patients Receiving Oral Opioids

Patient Characteristics (n = 65)

Age (yr)		Gender	
Mean	53	Females	37 (57%)
Range	26-74	Males	28 (43%)
Weight (kg)		Race	
Mean	70	Black	5 (8%)
Range	27-137	Hispanic	7 (11%)
		White	53 (82%)

OTFC Titration Study in Patients Receiving Oral Opioids

Patient Characteristics (n = 65)

Breast	17	(26%)
Lung	7	(11%)
Colon/Rectal	6	(9%)
Head and Neck	6	(9%)
Renal	3	(5%)
Non-Hodgkin's Lymphoma	3	(5%)
Sarcoma	3	(5%)
Uterine	3	(5%)
Unknown Primary	3	(5%)
Miscellaneous[a]	14	(22%)

[a] gastroesophageal, melanoma, pancreatic, Bartholin's gland carcinoma, Hodgkin's lymphoma, plasma cell dyscrasia, neuroepithelioma, liver, ovarian, prostate, testicular

OTFC Titration Study in Patients Receiving Oral Opioids

Around-the-clock			**Short-Acting**		
• Morphine	60	(92%)	• Morphine	34	(53%)
• Hydromorphone	2	(3%)	• Oxycodone	14	(22%)
• Oxycodone	2	(3%)	• Hydromorphone	8	(12%)
• Methadone	1	(2%)	• Hydrocodone	6	(9%)
			• Codeine	3	(5%)
Around-the-clock Dose			**Short-Acting Opioid Dose**		
• mean mg/d	208 ± 177		• mean mg/episode	26 ± 22	
• range (mg)	60 - 800		• range (mg)	5 - 100	

OTFC Titration Study in Patients Receiving Oral Opioids

Titration Results

Found a successful dose of OTFC	48	(74%)
Withdrew due to an adverse event[a]	8	(12%)
Not successful at 1600 µg	5	(8%)
Other withdrawal[b]	4	(6%)

[a] 4 related to OTFC

[b] breakthrough pain ceased, scheduled for chemo, incomplete pain relief, change in ATC dose

OTFC Titration Study in Patients Receiving Oral Opioids

Blinded Dose Response: Group Comparison

	Started at 200 µg (n = 32)	Started at 400 µg (n = 33)	P-value	90% CI
Successful dose (mean µg)	640	548	0.13	89%, 133%
Mean number of titrations	1.56	.70	.051	

OTFC Titration Study
in Patients Receiving Oral Opioids

Blinded dose response: ignored titration increases

(11/48 successful patients had titration increases ignored)

	no. of times
Dose titration increase ignored	15
Subsequent increase to successful dose	12
Successful found dose immediately after ignore	3

OTFC Titration Study in Patients Receiving Oral Opioids

Blinded Dose Response: Within Patient Comparison

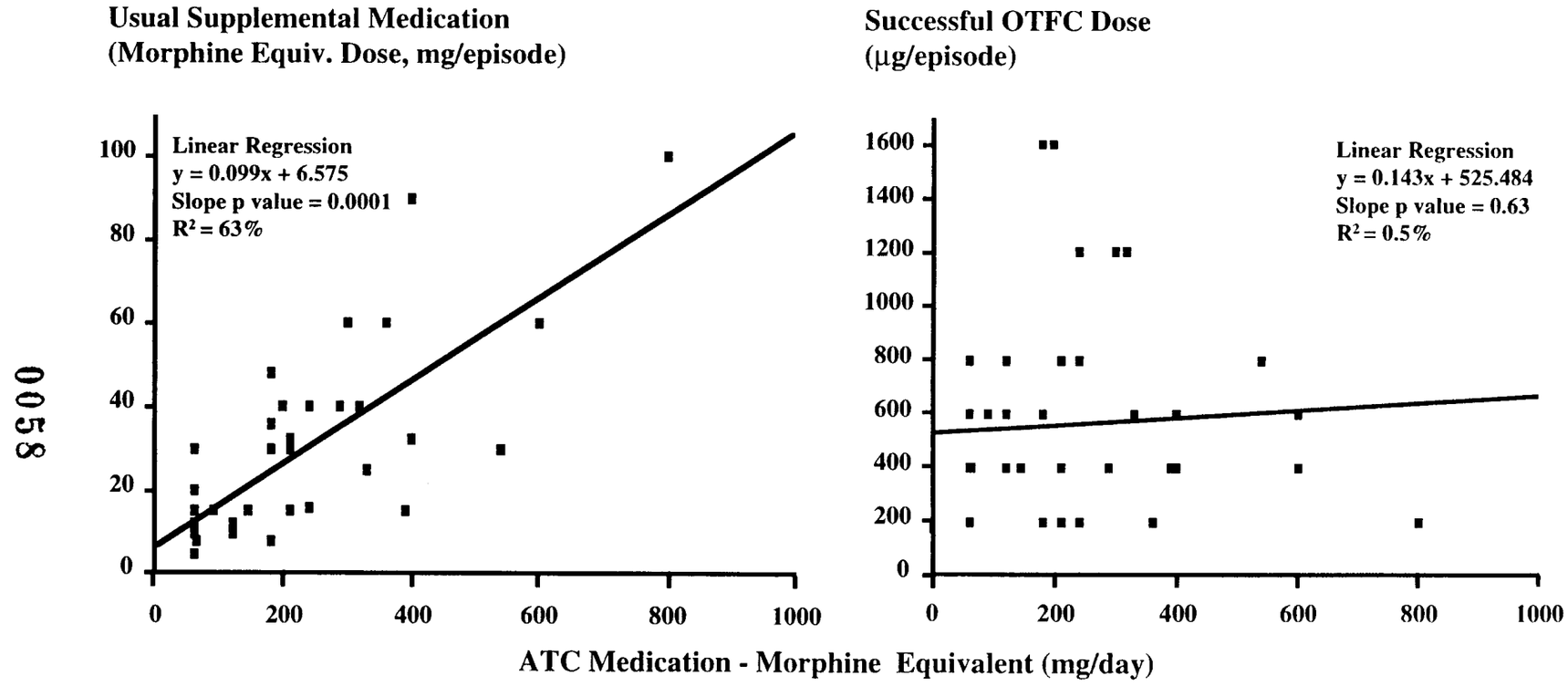
	n	First Dose (low)	Last Dose (high)	P-value[b]
PI @ 0 min	24	6.94	6.89	0.82
PID @ 15 min	24	1.32	2.24	0.002
PR @ 15 min	24	0.84	1.65	0.0001
Medication Performance[a]	33	1.21	2.39	0.0001

[a] Includes only patients whose last dose was higher than their first dose

[b] Paired t-test (first and last dose)

OTFC Titration Study
in Patients Receiving Oral Opioids

Breakthrough Pain Medication Dose Versus ATC Dose



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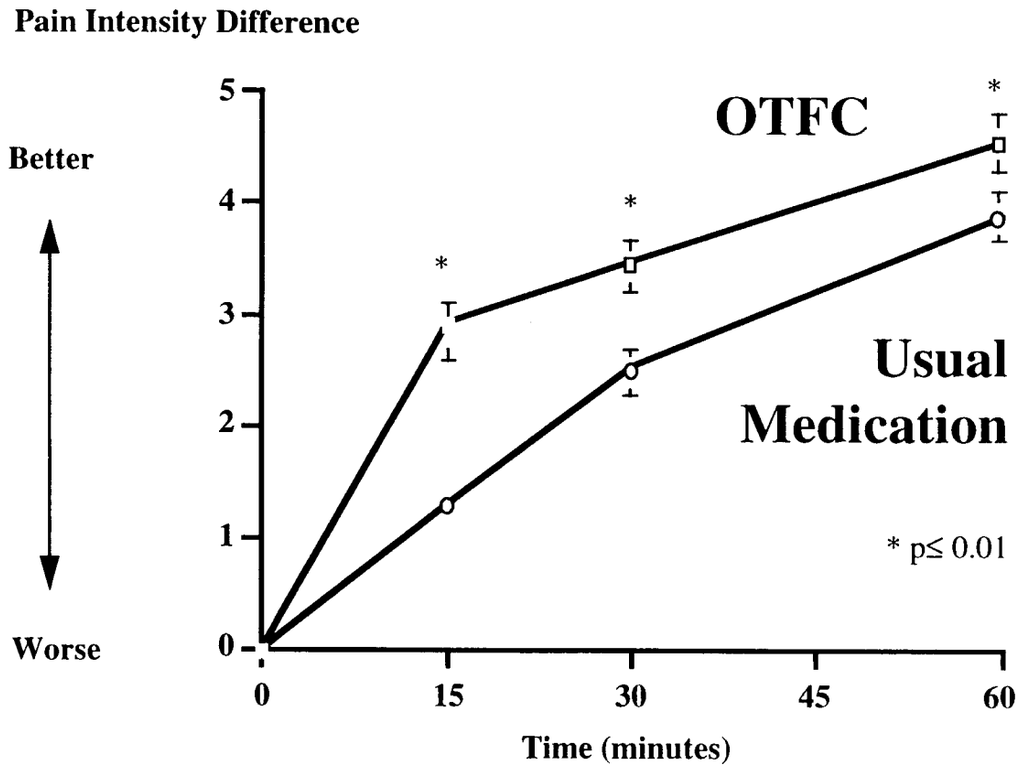
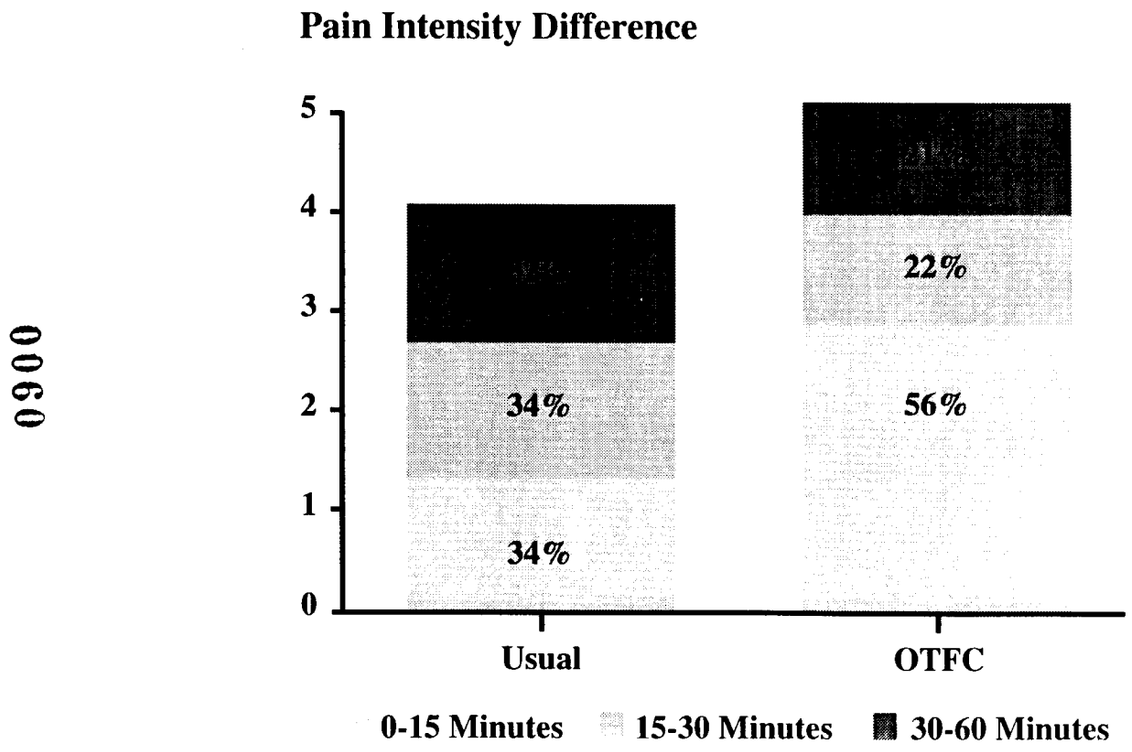
OTFC Titration Study in Patients Receiving Oral Opioids



OTFC Titration Study in Patients Receiving Oral Opioids



OTFC Titration Study in Patients Receiving Oral Opioids

Adverse Events

The most common AEs at least possibly related:

Somnolence	18	(28%)
Dizziness	9	(14%)
Nausea	5	(8%)

Four patients withdrew with AE's at least possibly related: somnolence, dizziness, hallucination, body numbness, dry mouth, headache, nausea, vomiting.

OTFC Titration Study in Patients Receiving Oral Opioids

Conclusions

- Dose titration can identify an OTFC dosage unit that safely and effectively treats breakthrough pain in patients receiving around-the clock oral opioids.
- The optimal dose of OTFC is determined by titration and is not predicted by the ATC dose.
- The onset of pain relief appears to be faster with OTFC compared with typical oral supplemental opioids.
- The most common side effects, somnolence, nausea and dizziness, are typical of opioids and did not limit OTFC use.

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Aim

To demonstrate that a titration process can be used to identify a dose of OTFC that safely and effectively treats breakthrough pain in cancer patients receiving around-the-clock (ATC) transdermal fentanyl for chronic pain

Secondary Aims

- Compare OTFC with usual breakthrough pain meds
- Assess dose response
- Establish OTFC dosing guidelines
- Define safety profile

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Design

Multicenter, randomized, double-blind, dose titration

Patients

Cancer patients (n=62) using transdermal fentanyl
50 - 300 µg/hr for persistent pain and experiencing
1-4 breakthrough episodes/d

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Phase 1	Phase 2	Phase 3
Assess Baseline Performance Usual Short-Acting Opioid for Breakthrough Pain →	**OTFC Titration Define Successful Dose: (200 µg-1600 µg)[a]** →	**Assess Performance of OTFC at Successful Dose for Breakthrough Pain**
• 2 day observation • 2 episodes / day • After Tx rate: - Pain intensity - Pain relief - Medication performance - Adverse events		• 2 day observation • 2 episodes / day • After Tx rate: - Pain intensity - Pain relief - Medication performance - Adverse Events

0065

[a] Dose at which 1 OTFC unit provides adequate analgesia with acceptable side effects

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Patient Characteristics (n = 62)

Age (yr)			Gender		
Mean	59		Females	33	(53%)
Range	25-91		Males	29	(47%)
Weight (kg)			Race		
Mean	67		White	57	(92%)
Range	39-101		Hispanic	3	(5%)
			Asian	2	(3%)

9906

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Patient Characteristics (n = 62)

Lung	16	(26%)
Breast	7	(11%)
Prostate	6	(10%)
Pancreatic	5	(8%)
Ovarian	5	(8%)
Head/neck	3	(5%)
Colon/rectal	3	(5%)
Gastroesophageal	2	(3%)
Leukemia	2	(3%)
Unknown primary	2	(3%)
Miscellaneous[a]	11	(18%)

[a] appendix, basal cell carcinoma, brain, carcinoid tumor, giant cell tumor of sacrum, kidney, non-Hodgkin's lymphoma, melanoma, myelofibrosis, schwannoma, uterine

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Short-Acting Supplemental Opioid

• Oxycodone	16	(26%)
• Morphine	15	(24%)
• Hydromorphone	11	(18%)
• Hydrocodone	10	(16%)
• Propoxyphene	6	(10%)
• Codeine	2	(3%)
• Tramadol	1	(2%)

Around-the-clock Dose

• mean µg/d	103 ± 63
• range (µg)	50 - 300

Short-Acting Opioid Dose

• mean mg/episode	21 ± 20
• range (mg)	5 - 100

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Titration Results (n = 62)

Found a successful dose of OTFC	47	(76%)
Withdrew due to an adverse event[a]	6	(10%)
Not successful at 1600 µg	4	(6%)
Other withdrawal[b]	5	(8%)

6900

[a] 3 related to OTFC

[b] desire not to comply with study procedures (n=2), left on vacation, unable to consume first unit, inadequate pain relief

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Blinded Dose Response: Group Comparison

	Starting Dose				
	Assigned to 200 µg (n = 33)	Randomized to 200 µg (n = 18)	Randomized to 400 µg (n = 11)	P-value	90% CI
Successful dose (mean µg)	469	677	825	0.58	50%, 109%
Mean number of titrations	0.81	1.54	1.88	0.67	

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Blinded dose response: ignored titration increases

(14/47 successful patients had titration increases ignored)

	no. of times
Dose titration increase ignored	18
Subsequent increase to successful dose	9
Successful found dose immediately after ignore	9

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Blinded Dose Response: Within Patient Comparison

	n	First Dose (low)	Last Dose (high)	P-value[b]
PI @ 0 min	26	6.00	6.33	0.21
PID @ 15 min	26	0.84	1.99	0.002
PR @ 15 min	26	0.78	1.46	0.002
Medication Performance[a]	32	0.78	2.11	0.0001

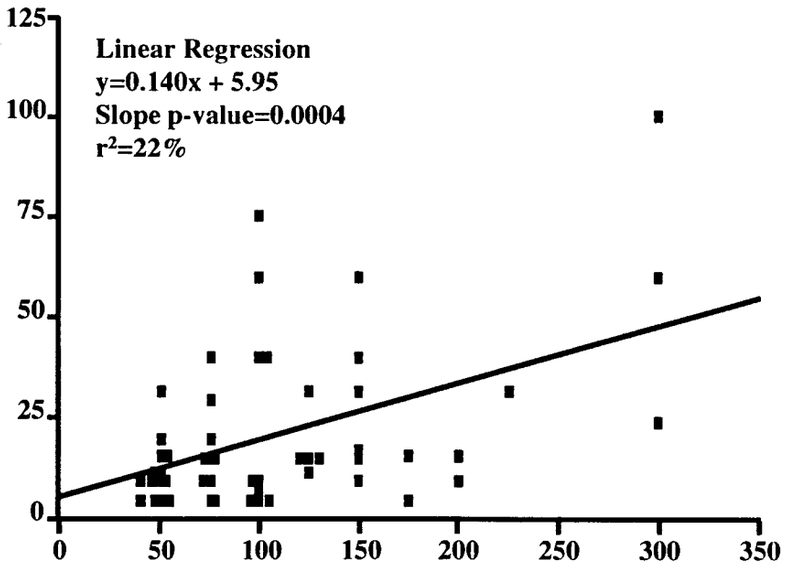
[a] Includes only patients whose last dose was higher than their first dose

[b] Paired t-test (first and last dose)

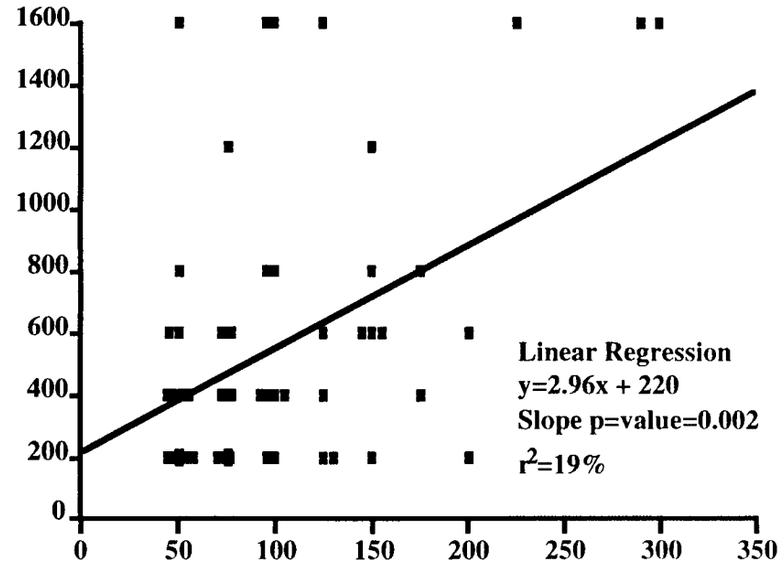
OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Breakthrough Pain Medication Dose Versus ATC Dose

Usual Supplemental Medication
(Morphine Equiv. Dose, mg/episode)



Successful OTFC Dose
(μg/episode)



ATC Medication - Transdermal Fentanyl (μg/hr)

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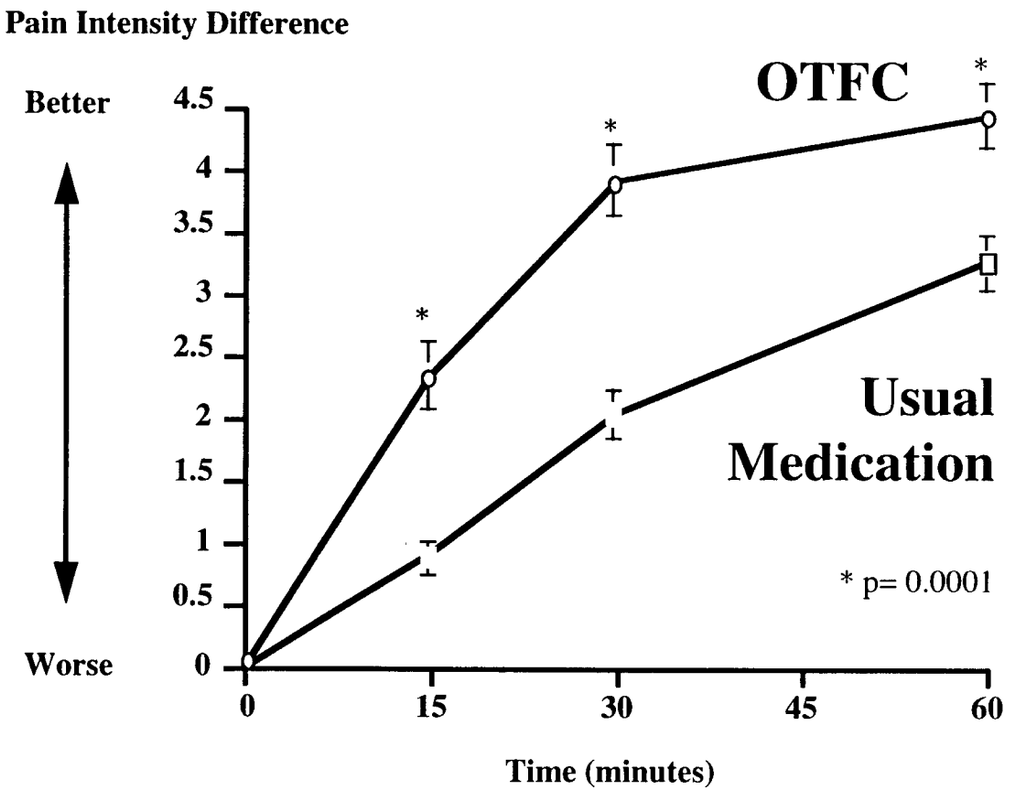
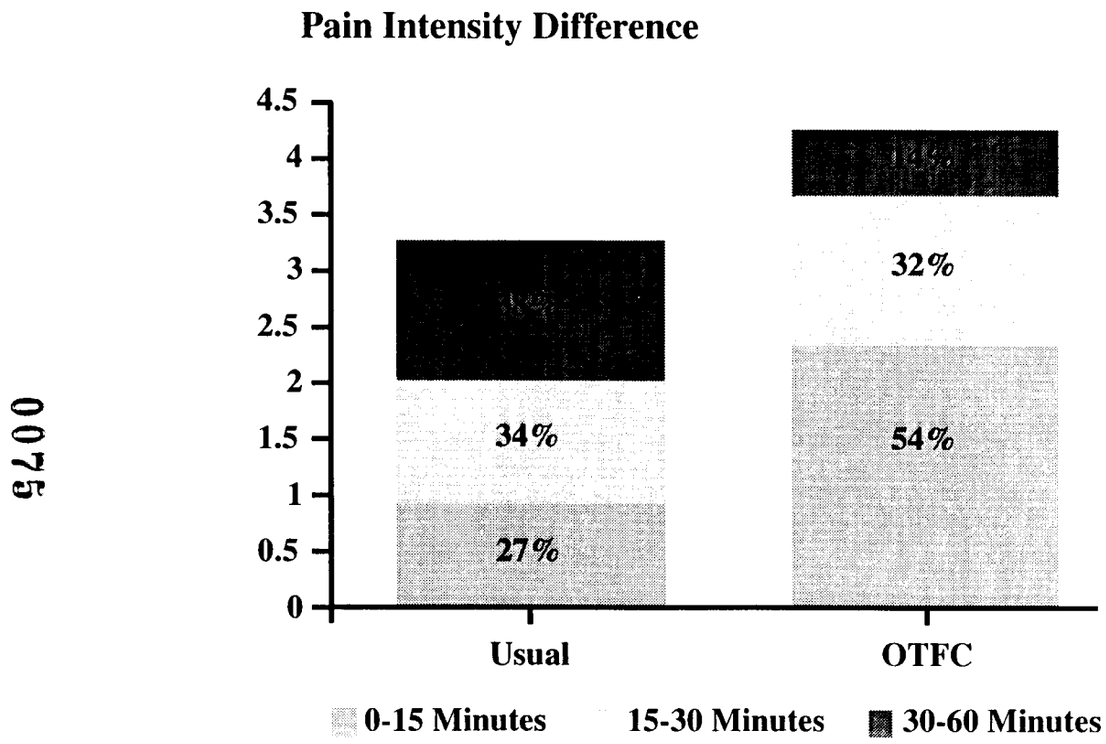
OTFC Titration Study in Patients Receiving Transdermal Fentanyl



OTFC Titration Study in Patients Receiving Transdermal Fentanyl



OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Adverse Events

The most common AEs at least possibly related:

Somnolence	11	(18%)
Nausea	7	(11%)
Dizziness	6	(10%)
Vomiting	3	(5%)

Three patients withdrew with AE's at least possibly related: shortness of breath, chest pains, disorientation, unsteady gait, weakness, dizziness, blurred vision, flushing, nausea

OTFC Titration Study in Patients Receiving Transdermal Fentanyl

Conclusions

- Dose titration can identify an OTFC dosage unit that safely and effectively treats breakthrough pain in cancer patients receiving transdermal fentanyl.
- The optimal dose of OTFC is determined by titration and is not predicted by the ATC dose
- The onset of pain relief appears to be faster with OTFC compared with currently available supplemental opioids.
- The most common side effects, somnolence, nausea, dizziness, and vomiting, are typical of opioids and did not limit OTFC use.

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Aim

To evaluate the long-term safety and efficacy of OTFC in cancer patients with breakthrough pain

Design

Multicenter, open-label survey

Patients

Adult outpatients (n=155) with cancer who successfully completed a short-term, titration trial of OTFC and continue to experience 1-4 episodes of breakthrough pain per day

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Dosing

- Continue ATC medications and start OTFC at successful dose from their previous study
- Treat up to 4 episodes per day
- OTFC dose titrations made as clinically indicated

Study Outcomes

- Number of breakthrough pain episodes per day
- Medications used to treat breakthrough pain episodes
- Global satisfaction with OTFC
- Side Effects

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Patient Characteristics

Gender			**Weight**		
Females	87	(56%)	Mean	69± 20 kg	
Males	68	(44%)	Range	26-139 kg	
Age (yrs)			**Race**		
<35	10	(7%)	White	144	(93%)
36-65	112	(72%)	Black	5	(3%)
>65	21	(22%)	Hispanic	3	(2%)
Mean (SD)	54	(12) yrs	Asian	3	(2%)
Range	26 - 91 yrs				

0080

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Patient Exposure

- 92% of eligible patients chose to participate in the study (n=155)
- Number of treatment days
  - range: 1 to 423
  - mean: 92
- Average of 2.5 episodes per day were treated with OTFC
- 41,766 OTFC units used
- 38,595 episodes treated

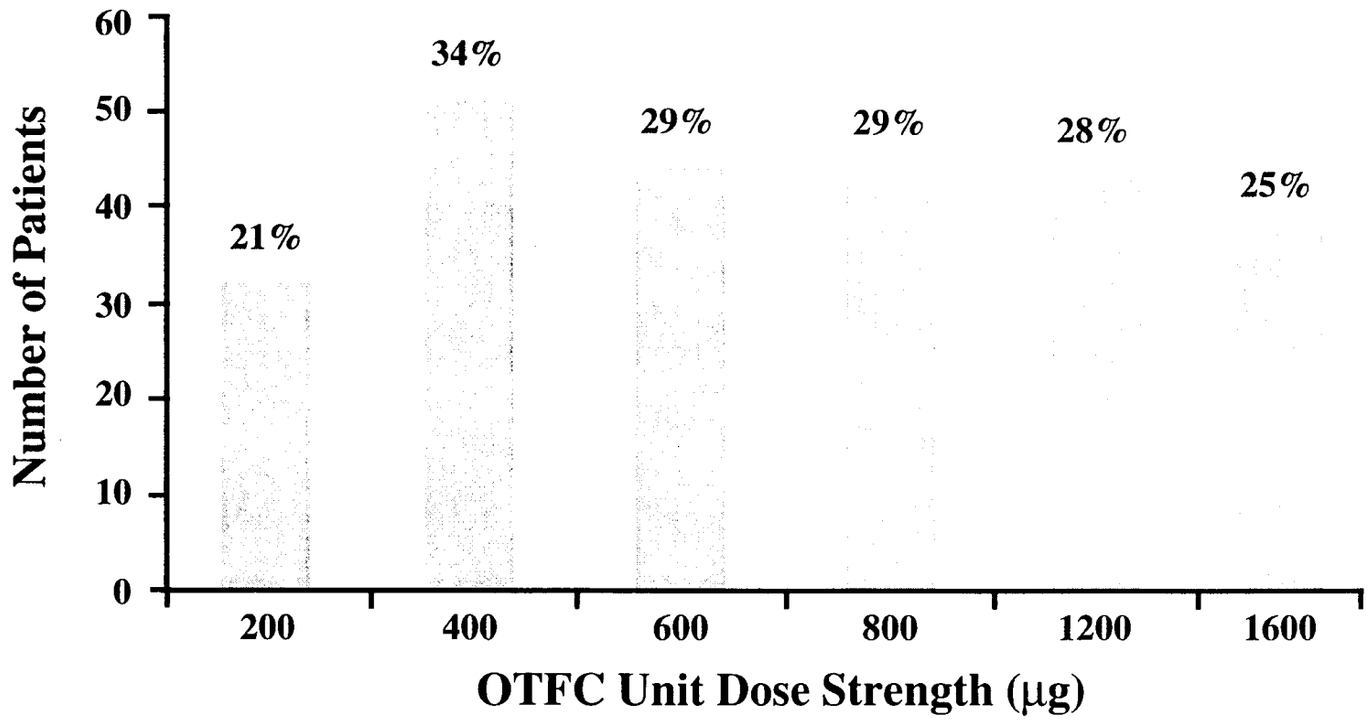
Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Results

- Patients experienced mean 2.9 episodes per day
- Patients treated mean 2.5 episodes per day with OTFC
- 92% of episodes successfully treated with OTFC
- Mean medication performance 3.1 (very good to excellent)
- 66% remained on same or lower dose during study

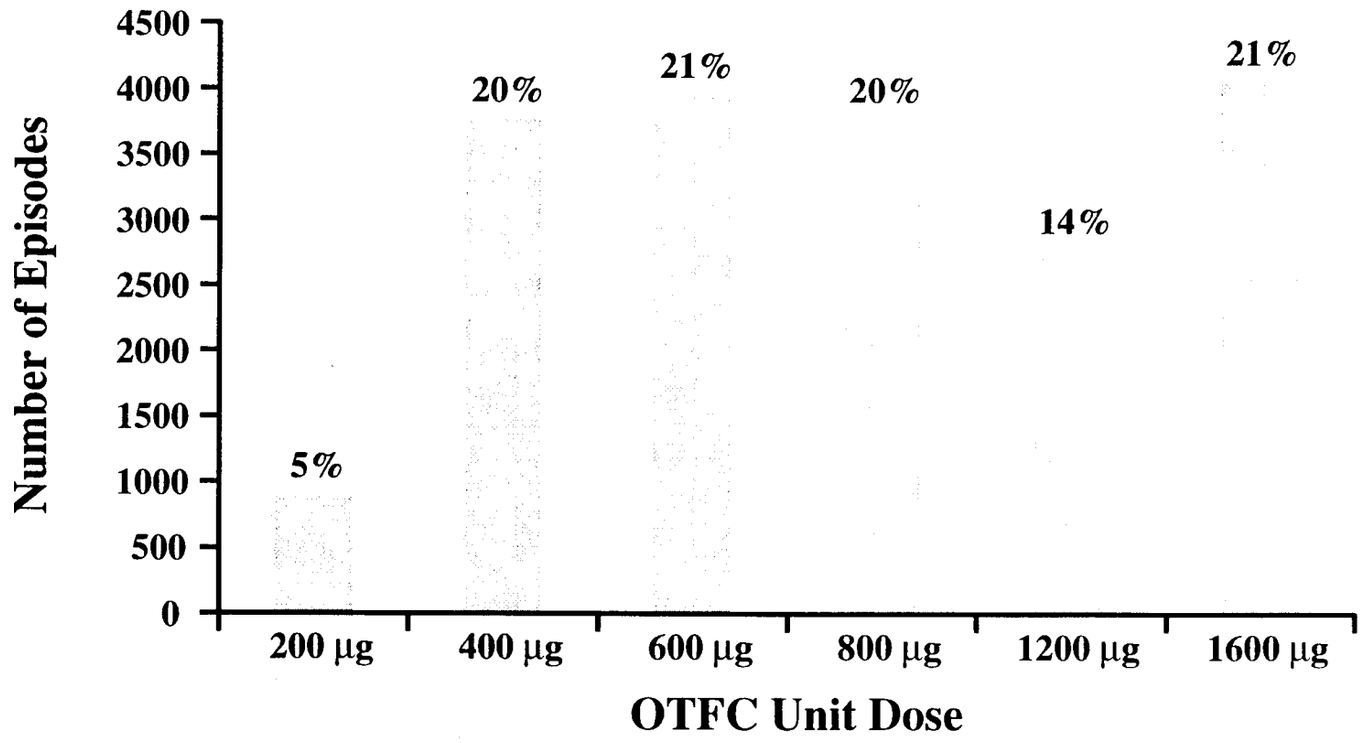
Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Patient Doses



Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Episodes Treated by Unit Dose



Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Withdrawals due to AEs

	Withdrawals due to Adverse Events	Patients with SAEs	With SAEs Not Death	Deaths
Unrelated	**37**	**61**	**48**	**29**
Unlikely to be Related	**11**	**18**	**16**	**2**
Possibly Related	**5**	**0**	**0**	**0**
Probably Related	**0**	**0**	**0**	**0**
Almost Certainly Related	**1**	**0**	**0**	**0**
Total	**54**	**79**	**64**	**31**

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Adverse Events

The most common AEs at least possibly related:

Somnolence	14	(9%)
Constipation	13	(8%)
Nausea	12	(8%)
Dizziness	12	(8%)
Vomiting	8	(5%)

Six patients withdrew with AE's at least possibly related: itching, rash, nausea, vomiting, dizziness and mouth sores

Long-term, Open-label Use of OTFC in Cancer Patients with Breakthrough Pain

Conclusions

- OTFC was used safely and effectively to treat breakthrough cancer pain
  - over 41,500 units
  - over 38,500 breakthrough pain episodes
  - up to 423 days of therapy
- Satisfaction ratings very good to excellent pain relief
- No trend toward decreased effectiveness over time
- Toxicity profile was favorable with very few withdrawals due to adverse events

Extent of Exposure

	Number of Patients
Chronic Pain Patients	257
Postoperative Pain Patients	212
Normal Volunteers	48
Total	517

Demographics
Chronic Pain Patients from Controlled Clinical Trials[a]

A total of 257 patients enrolled

		OTFC Any Dose
Age	≤ 35	16 (6%)
	36-65	185 (72%)
	> 65	56 (22%)
Gender	Female	145 (56%)
	Male	112 (44%)
Race	Black	15 (6%)
	Hispanic	10 (4%)
	White	229 (89%)
	Other	3 (1%)

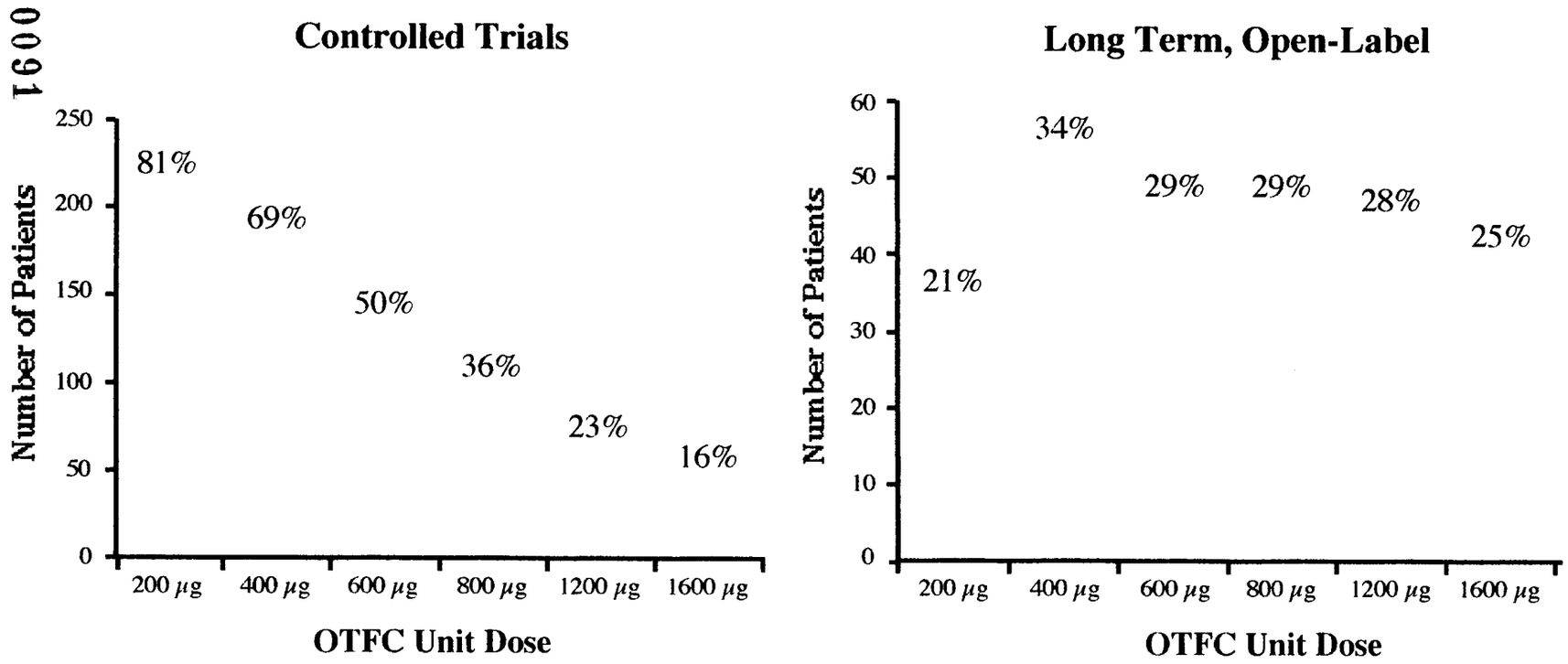
[a]Trials: AC 200/011, 200/012, 200/013

Primary Cancer Diagnoses

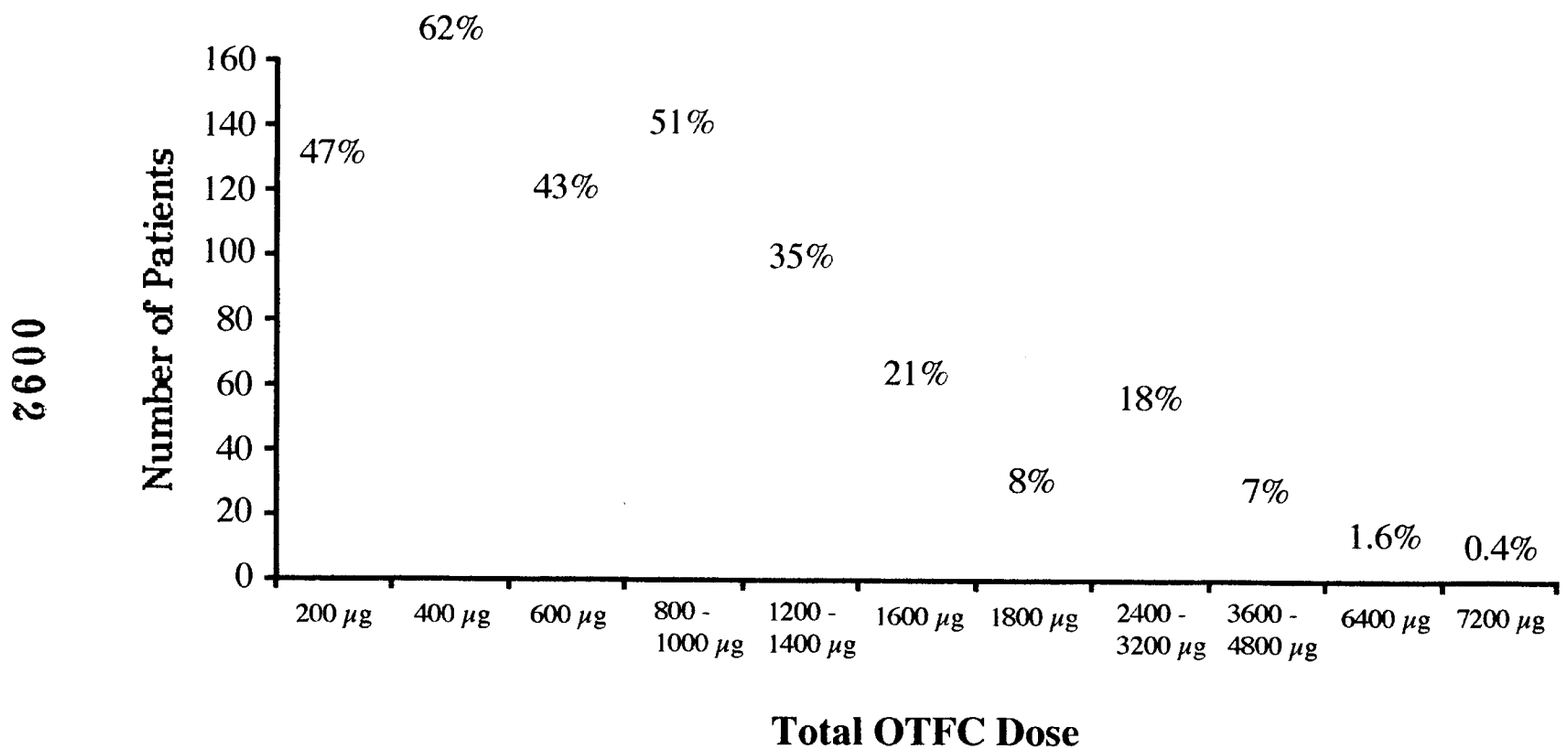
		Number of Patients	(%)
1	Breast	51	(20%)
2	Lung	50	(20%)
3	Colon/Rectum	26	(10%)
4	Ovary	14	(5%)
5	Head/Neck	11	(4%)
6	Uterine	11	(4%)
7	Non-Hodgkins Lymphoma	10	(4%)
8	Pancreatic	10	(4%)
9	Sarcomas	10	(4%)
10	Unknown Primary	9	(4%)
11	Kidney	8	(3%)
12	Prostate	8	(3%)
13	Other[a]	39	(15%)
Total		257	

[a] Gastroesophageal, Multiple Myeloma, Leukemia, Melanoma, Liver, Mesothelioma, Other Gynecologic, Bartholin's Gland Carcinoma, Bladder, Hodgkin's Lymphoma, Squamous Cell Carcinoma, Appendix, Basal Cell Carcinoma, Brain, Carcinoid Tumor, Giant Cell Tumor Of Sacrum, Myelofibrosis, Neuroepithelioma, Plasma Cell Dyscrasia, Schwannoma, Testicular

Patient Exposure by Unit Dose
Chronic Pain



Patients Treated by Total Dose/Episode
Chronic Pain - Controlled Trials



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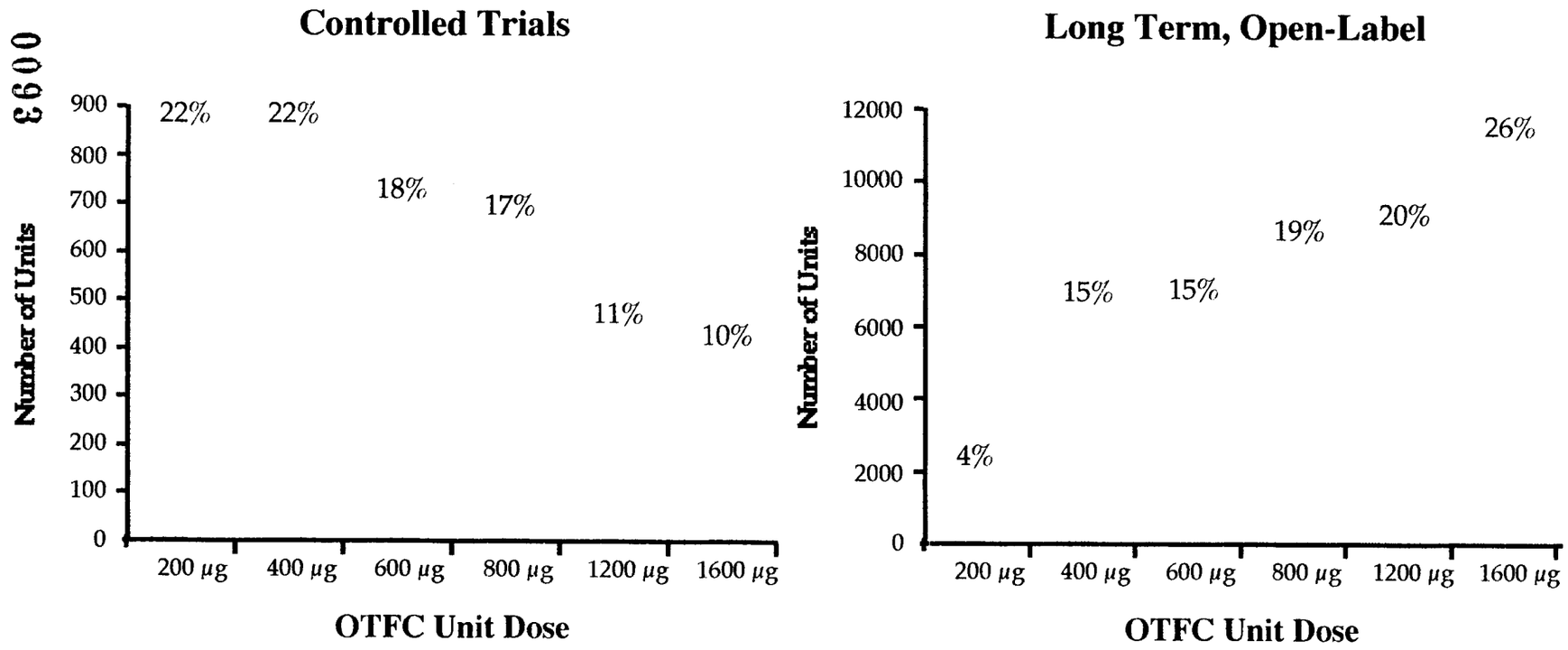
Units Administered by Dose
Chronic Pain



Treatment Related Adverse Events
Combined Clinical Trials

≥ 10% Patients		3 - 10% Patients		1 - 2% Patients	
Somnolence	(18%)	Constipation	(6%)	Headache	(2%)
Dizziness	(16%)	Vomiting	(6%)	Pain	(2%)
Nausea	(15%)	Asthenia	(4%)	Abdominal Pain	(2%)
		Confusion	(3%)	Dyspepsia	(2%)
				Dry Mouth	(2%)
				Vasodilatation	(2%)
				Dyspnea	(2%)
				Pruritus	(2%)
				Diarrhea	(1%)
				Hallucinations	(1%)
				Thinking Abnormal	(1%)
				Vertigo	(1%)
				Sweating	(1%)

Serious Adverse Events and Withdrawals due to Adverse Events by Treatment Relationships

Long Term, Open-Label Trial

	Withdrawals due to Adverse Events	Patients with SAEs	With SAEs not Death	Deaths
Unrelated	37	61	48	29
Unlikely to be Related	11	18	16	2
Possibly Related	5	0	0	0
Probably Related	0	0	0	0
Almost Certainly Related	1	0	0	0
Total	54	79	64	31

Serious Adverse Events and Withdrawals due to Adverse Events by Treatment Relationships

Controlled Trials

	Withdrawals due to Adverse Events	Patients with SAEs	With SAEs not Death	Deaths
Unrelated	23	23	21	7
Unlikely to be Related	4	4	3	1
Possibly Related	13	4	3	1
Probably Related	3	0	0	0
Almost Certainly Related	2	0	0	0
Total	45	31	27	9

Adverse Events in Opioid Naive Subjects
Background

- Different AE risk in postoperative pain patients and volunteers
  - usually not opioid tolerant
  - most clinically significant AE is respiratory depression
- Complicating issues
  - postoperative patients: 96/212 (45%) on concurrent IV morphine
  - volunteers: no concurrent medications, also no pain

Specific Adverse Events in Postoperative Patients
Incidence ≥ 10%

OTFC (n = 212)		Placebo (n = 56)		IV Morphine (n = 68)	
Nausea	(32%)	Nausea	(57%)	Fever	(29%)
Vomiting	(16%)	Vomiting	(27%)	Nausea	(24%)
Urinary Retention	(16%)	Urinary Retention	(23%)	Pruritus	(21%)
Fever	(16%)	Hypoventilation	(18%)	Abdominal Pain	(13%)
Pruritus	(14%)	Tachycardia	(11%)	Vomiting	(10%)
Hypoventilation	(12%)			Taste Perversion	(10%)

Respiratory Adverse Events
Postoperative Pain Patients (N=336)

Number of patients with hypoventilation, oxygen administered for desaturation, and naloxone administration by unit dose strength

	OTFC Any Dose n = 212	**OTFC 200 µg n = 43**	**OTFC 400 µg n = 69**	**OTFC 600 µg n = 6**	**OTFC 800 µg n = 94**	**Placebo n = 56**	**IV Morphine n = 68**
Number Experiencing Hypoventilation	25 (12%)	1 (2%)	8 (12%)	0 (0%)	16 (17%)	10 (18%)	1(2%)
Oxygen Received for Desaturation	7 (3%)	1 (2%)	2 (3%)	0 (0%)	4 (4%)	3 (5%)	1(2%)
Naloxone Administered	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0(0%)

Respiratory Adverse Events
Normal Volunteers (N=48)

None of the volunteers withdrew due to adverse events or experienced and SAE

	OTFC Any Dose n = 48	**OTFC 200 μg n = 12**	**OTFC 400 μg n = 11**	**OTFC 800 μg n = 47**	**OTFC 1600 μg n = 12**	**IV Fentanyl n = 12**
Number Experiencing Hypoventilation	19 (40%)	2 (17%)	5 (46%)	17 (36%)	12 (100%)	8 (67%)
Oxygen Received for Desaturation	16 (33%)	1 (8%)	3 (27%)	11 (23%)	10 (83%)	N/A[a]
Naloxone Administered	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[a] All subjects received supplemental oxygen at time of IV infusion

Actiq (OTFC) NDA
Safety Summary

Chronic Pain Patients (n=257)

- 45,521 units, up to 423 days
- 22% over age 65
- All stages of disease progression
- Most common treatment related AEs
  - nausea (15%)
  - somnolence (18%)
  - dizziness (16%)

Opioid Non-tolerant

- Expected dose-dependent respiratory depression

Actiq Risk Management Program

Clair M. Callan, M.D., M.B.A.

Vice President, HPD,

Medical, Regulatory Affairs and Advanced Research

Abbott Laboratories

All Opioid Therapy Benefits Come With Potential Risks

- Child safety
- Opioid non-tolerant
- Diversion and abuse potential

Program Objectives

- Protect availability of *Actiq* for cancer patients who need it
- Minimize potential for product misuse
- Innovative risk management program will
  - provide appropriate child safety protections
  - emphasize approved indication
  - minimize diversion and abuse

Preventing Child Access Risk
Actiq Product Presentation

- Individually sealed, child resistant pouches
  - allows for more child safety features and better communication of warnings

- Multiple dosage strengths provided for total unit consumption

- Clear and repetitive disposal instructions provided

Child Safe Warning Labels

Keep this and all medications out of the reach of children

Be sure to keep *Actiq* away from children. *Actiq* contains a strong medicine in an amount that could be life-threatening to a child.

0106

DO NOT leave unused or partially used *Actiq* in places where children can get to it.

Disposal Information

After you finish *Actiq*, dispose of the handle right away. If any of the medicine is left, place the handle under warm running tap water until the remaining portion of the medicine is dissolved. Throw away the handle.

Dispose of any *Actiq* as soon as you no longer need them.

DO NOT leave unused or partially used *Actiq* in places where children or pets could get it.

Preventing Child Access Risk
Patient and Caregiver Education

- Physician office counseling
- In patient education materials
- Pharmacy counseling
- On the dispensed pharmacy package
- In the patient instructions
- On the pouch at the point of use

CII Packaging Comparison

	CII Oral Products	***Actiq***
Always Dispensed in CR packages	Optional	Yes
Units individually CR?	No	Yes
Detectable if child consumes?	No	Yes
Detailed Patient Instructions?	No	Yes
Child safe warnings on each unit?	No	Yes
Black Box Warnings?	No	Yes
"Musts" vs. "Shoulds" in PI?	No	Yes
Increased toxicity if chewed?	Yes for sustained release orals	No

Preventing Misuse in Opioid Non-Tolerant Patients Product Labeling

- Clearly indicated for use in opioid tolerant patients
- Specifically contraindicated for acute pain
- "Musts" in lieu of "shoulds"
- Black Box warning

Preventing Misuse
PI: Black Box Warning

Actiq is indicated for the management of chronic pain, particularly breakthrough pain, in patients **already receiving and who are tolerant to opioid therapy.**

Because serious or life-threatening hypoventilation could occur, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Preventing Misuse
Promotional Program Focus

- Appropriate patient selection and access is our key objective
- Promotional efforts will be focused on physicians who treat cancer pain
- Educational efforts to the general physician population to discourage inappropriate use

Preventing Misuse--Target Clinicians

- Promotional focus
  - Hem/Oncs and cancer pain specialists
  - nursing support staff
- Launch educational programs
  - direct mail
  - electronic instructional program (CD ROM, website)
  - professional journal supplements
  - symposia (local, state, regional, national)
- Complementary programs for RPhs, RNs and patients

Preventing Misuse-- Other Identified Opioid Prescribers

- Educational letters on appropriate use
- Clearly defined warning information
- Access to electronic instructional programs

Preventing Misuse
"Pharmacist as Gatekeeper"

- Educational programs
  - journals, website, symposia
  - retail chains
- CII's receive special attention
- Computer system reminders and controls
- Warnings on shelf carton
- Patient counseling

Preventing Misuse
Point of Use Warnings

- Patient educational materials
- Patient Package Insert
- Warnings on pouch and shelf carton
- In-office and pharmacist counseling

Preventing Diversion or Abuse

- All opioids have abuse potential
- CII provides highest level of accountability and control
- Abuse liability assessment involves both pharmacology and availability

Schedule II Status

- Most restrictive schedule
- No refills. Requires triplicate Rx in some states
- Limited (if any) telephone or fax options
- RPh required to ensure "legitimate medical purpose"
- A step above other schedules in requirements
  - separate records
  - more stringent order tracking
  - bi-annual inventory exact count

Abuse Potential
Pharmacology

- Speed of onset and duration of action affect abuse liability
  - speed of onset favors abuse potential compared to orals
  - short duration mitigates use to maintain addiction

- *Actiq* profile vs. other CII drugs
  - Speed of Onset: IV >> *Actiq* > Orals
  - Duration of Action: IV << *Actiq* < Orals

Abuse Potential
Availability / Other

- *Actiq* accessibility
  - CII restrictions
  - *Actiq* patients parallel current CII distribution
- *Actiq* cost: Most costly per morphine equivalent
- *Actiq* packaging
  - Relatively bulky and obvious
  - Individually audited / counted
- *Actiq* detectability
  - *Actiq* requires 15 min consumption to max effect
  - Obvious handle

	Possible Risk Events		
Plan Elements	Child Access	Opioid Naive Patients	Diversion & Abuse
PI / Black Box	√	√	√
Patient PI	√	√	√
Shelf Carton Warnings	√	√	√
Pouch Warning	√	√	√
Child Resistant Pouch	√		
Handle Design	√		
Schedule II	√	√	√
Patient Ed/Aid Materials	√	√	√
MD/Nurse CE	√	√	√
Pharmacy CE	√	√	√
Computer System Reminders	√	√	√
RPh - Patient Counseling	√	√	√

Quality Assurance Program

- Surveillance programs
  - adverse event reports
  - off-label use
  - accidental exposures
  - diversion and abuse
- Continuous audits and response
  - labeling and/or packaging
  - educational programs
  - promotional activity

Example

Situation: It is determined that *Actiq* has been used for post-op pain.

Interventions:

- Identify sites of possible misuse
- Contact responsible parties
- Reinforce indications and contraindications
- Additional follow-up as needed

Summary

Abbott and Anesta are committed to executing an innovative risk management program that

- Protects availability of *Actiq* for cancer patients who need it, and
- Strongly deters product misuse