突發性癌症疼痛治療新選擇

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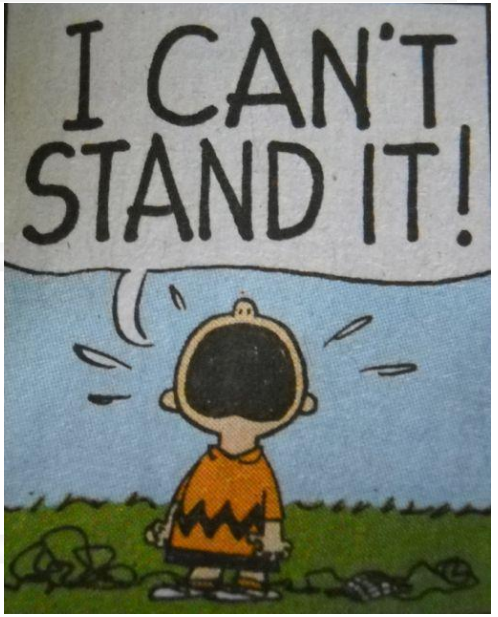
Outline

1. **cancer pain**
   癌症疼痛以及突發性癌症疼痛

2. **Breakthrough cancer pain treatment**
   突發性癌症疼痛之臨床處置

3. **New killer of breakthrough cancer pain**
   新一代癌症突發性疼痛的殺手

Current unmet needs of cancer patients



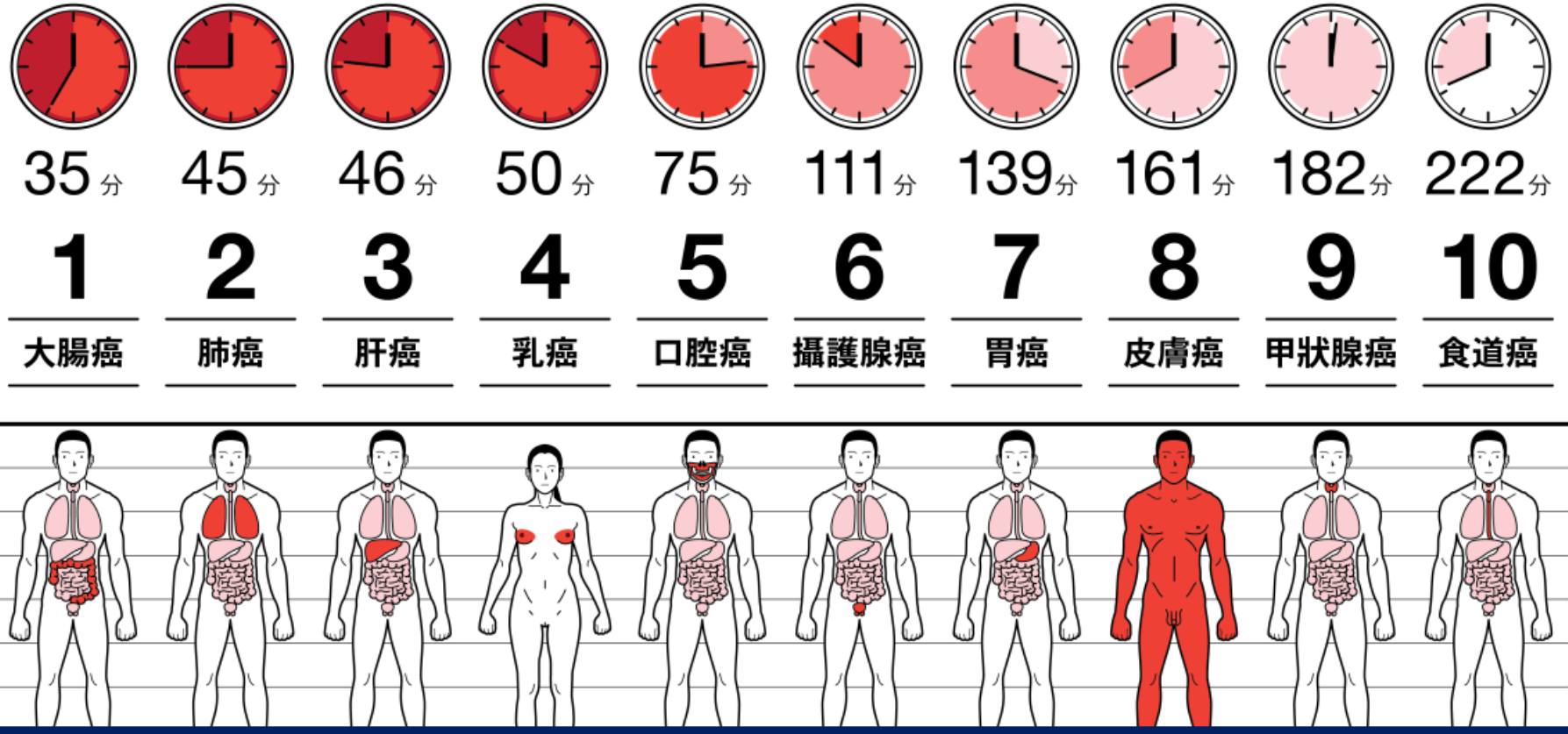
Inadequate pain assessment

is the greatest barrier to optimal pain treatment

台灣癌症人口每年新增近10萬人

-國人每5分26秒就有一人罹癌，>50%的病人曾感受疼痛

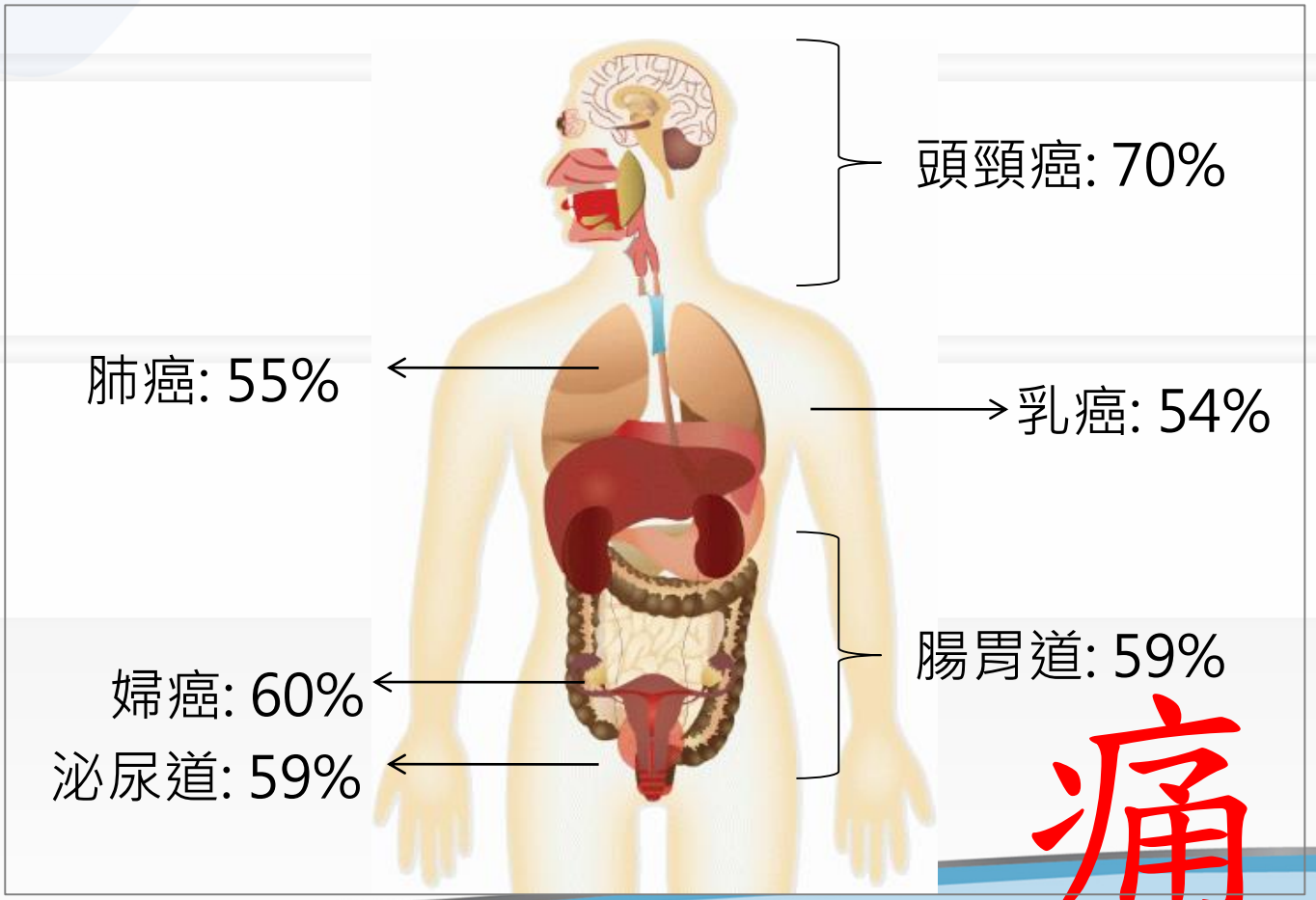
- **51~62% cancer patients experience pain**
- **60% patients in hospitals are diagnosis moderate-to-severe pain**
- **46% caner pain patients not satisfied with their pain control**



Source: 1. Pain Manag Nurs. 2011 Dec;12(4):197-205 2. Taiwan Cancer Registry 2012 the news lens 關鍵評論 3. Annals of Oncology 20: 1420-1433, 2009

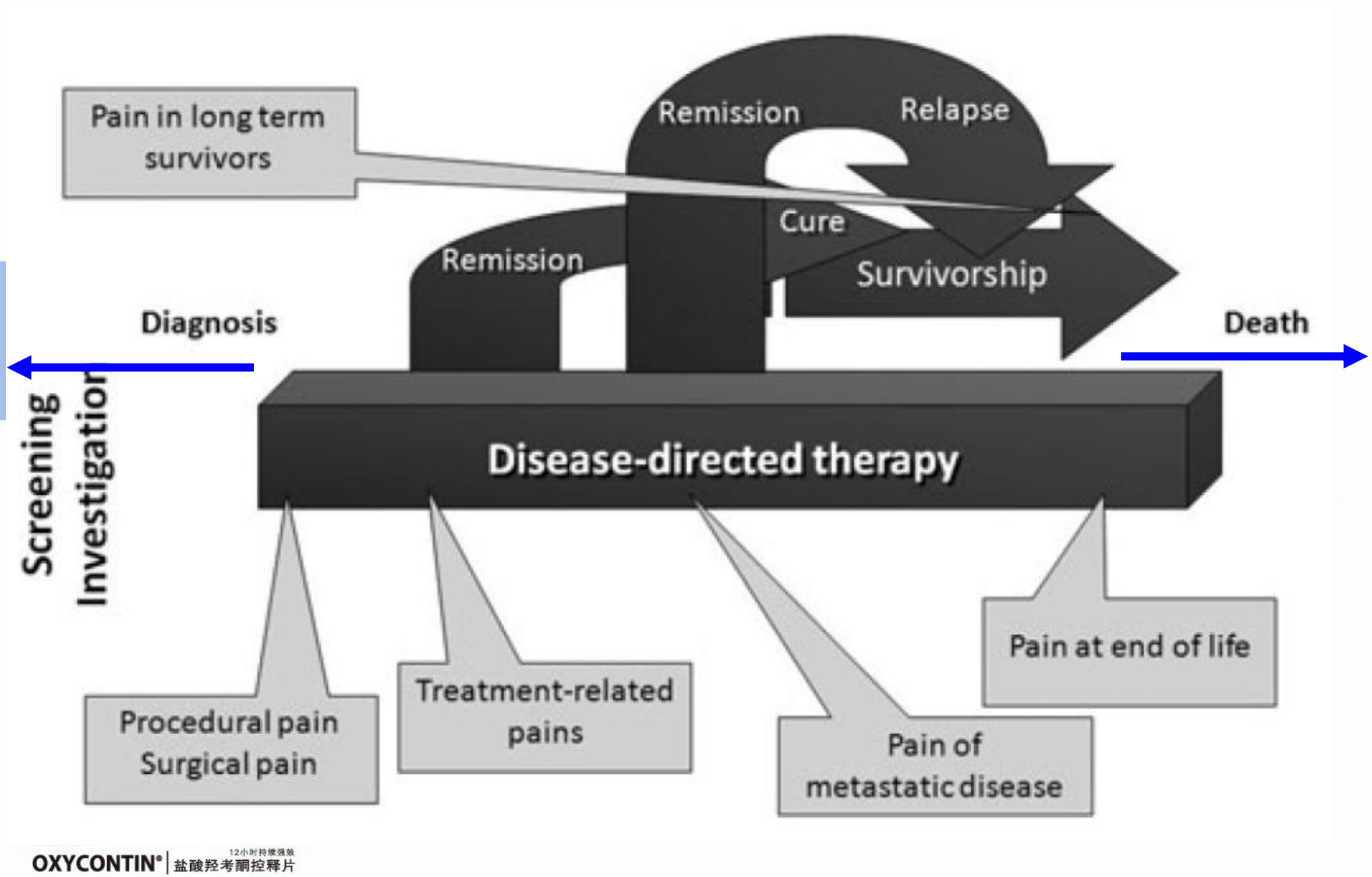
癌症疼痛是病人最困擾的問題之一

A total of 52 studies in meta-analysis pain prevalence show :
In all the cancer types, prevalence of pain >50%



van den Beuken-van Everdingen MH et al. Ann Oncol. 2007 Sep;18(9):1437-49.

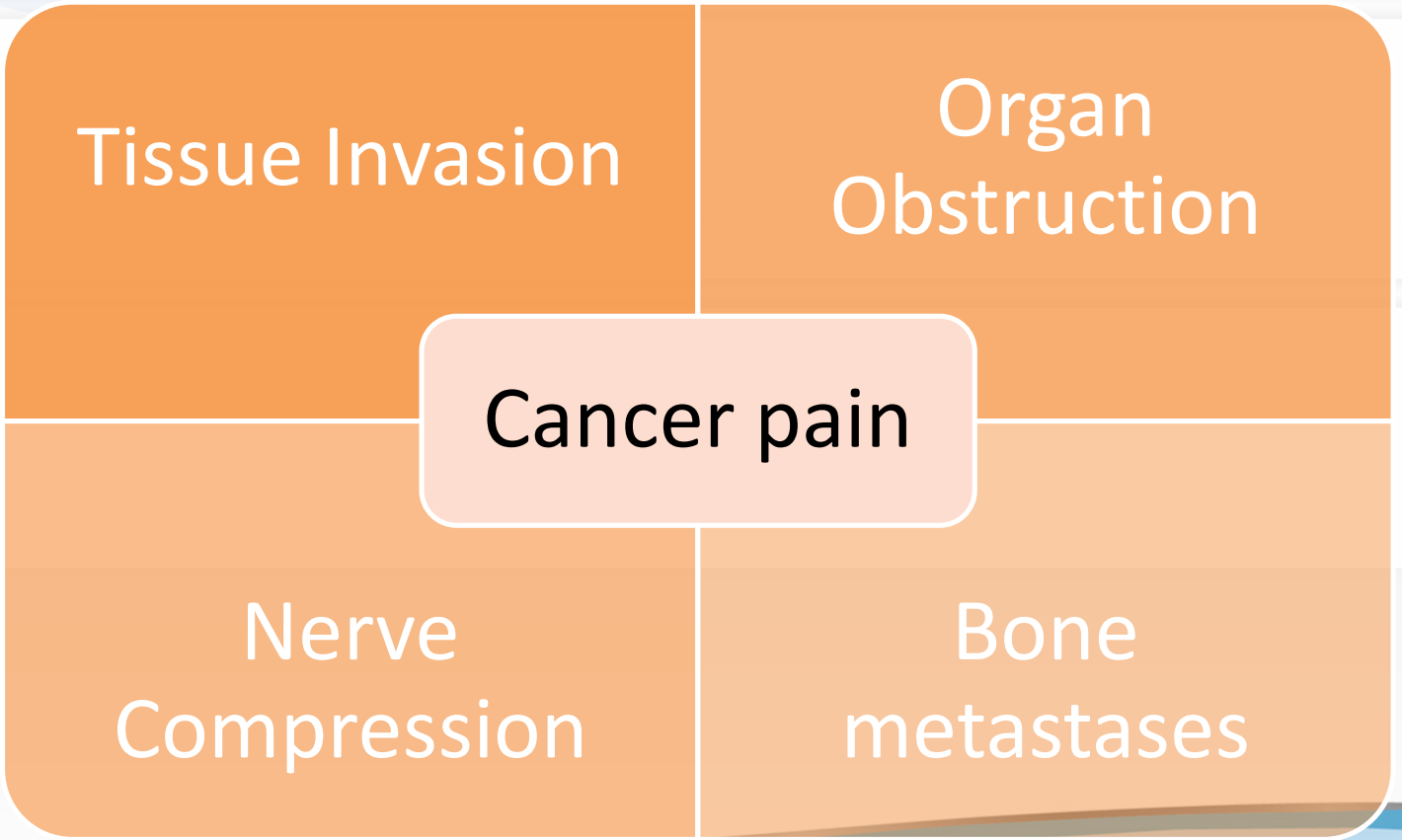
Pain is the Life-time Bothersome for Cancer Patients



Raphael J, Ahmedzai S, Hester J, et al. Pain Medicine 2010; 11: 742–764

癌痛是多重因素造成的疾病

Cancer pain may be multi-factorial, and not all types of pain experienced by cancer patients are related to the cancer itself.



疼痛降低生活品質，也影響存活期

- 良好的疼痛控制可以幫助病人活得更久又更好

Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials

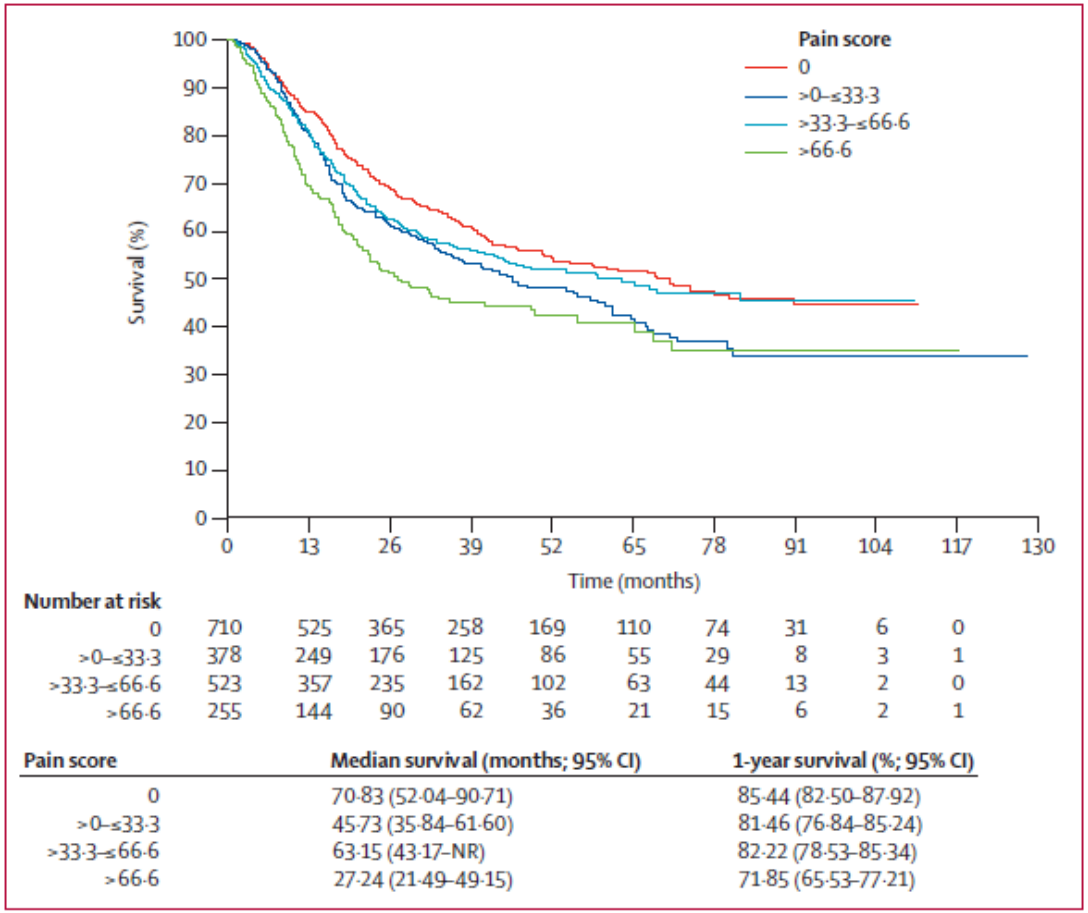
Chantal Quinten, Corneel Coens, Murielle Mauer, Sylvie Comte, Mirjam A G Sprangers, Charles Cleeland, David Osoba, Kristin Bjordal, Andrew Bottomley, on behalf of the EORTC Clinical Groups

	Median Survival (Month)
No Pain (Score: 0 分)	70.83
Severe Pain (Score: > 66.6 分)	27.24

當病人不再苦於疼痛，

中位存活期可以多3.6年

30 randomised Controlled Trials,
10,108 cancer p’ts



Number at risk										
0	710	525	365	258	169	110	74	31	6	0
>0–≤33·3	378	249	176	125	86	55	29	8	3	1
>33·3–≤66·6	523	357	235	162	102	63	44	13	2	0
>66·6	255	144	90	62	36	21	15	6	2	1

Pain score	Median survival (months; 95% CI)	1-year survival (%; 95% CI)
0	70·83 (52·04–90·71)	85·44 (82·50–87·92)
>0–≤33·3	45·73 (35·84–61·60)	81·46 (76·84–85·24)
>33·3–≤66·6	63·15 (43·17–NR)	82·22 (78·53–85·34)
>66·6	27·24 (21·49–49·15)	71·85 (65·53–77·21)

Lancet Oncol 2009; 10: 865–71

主動定時疼痛評估為良好疼痛治療基礎

以病患主觀感受為評估標準

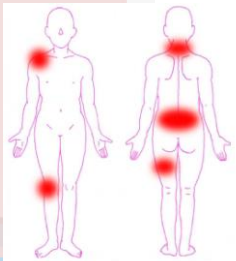
- 疼痛是主觀感受
- 相信病人所說的，以病人主訴為標準

主動定時評估疼痛嚴重度

- 疼痛0-10分法 (NRS Score: 0-10)
  (1-3: 輕度; 4-6: 中度; 7-10: 重度)
- 吃不吃得下? 睡不睡得著?

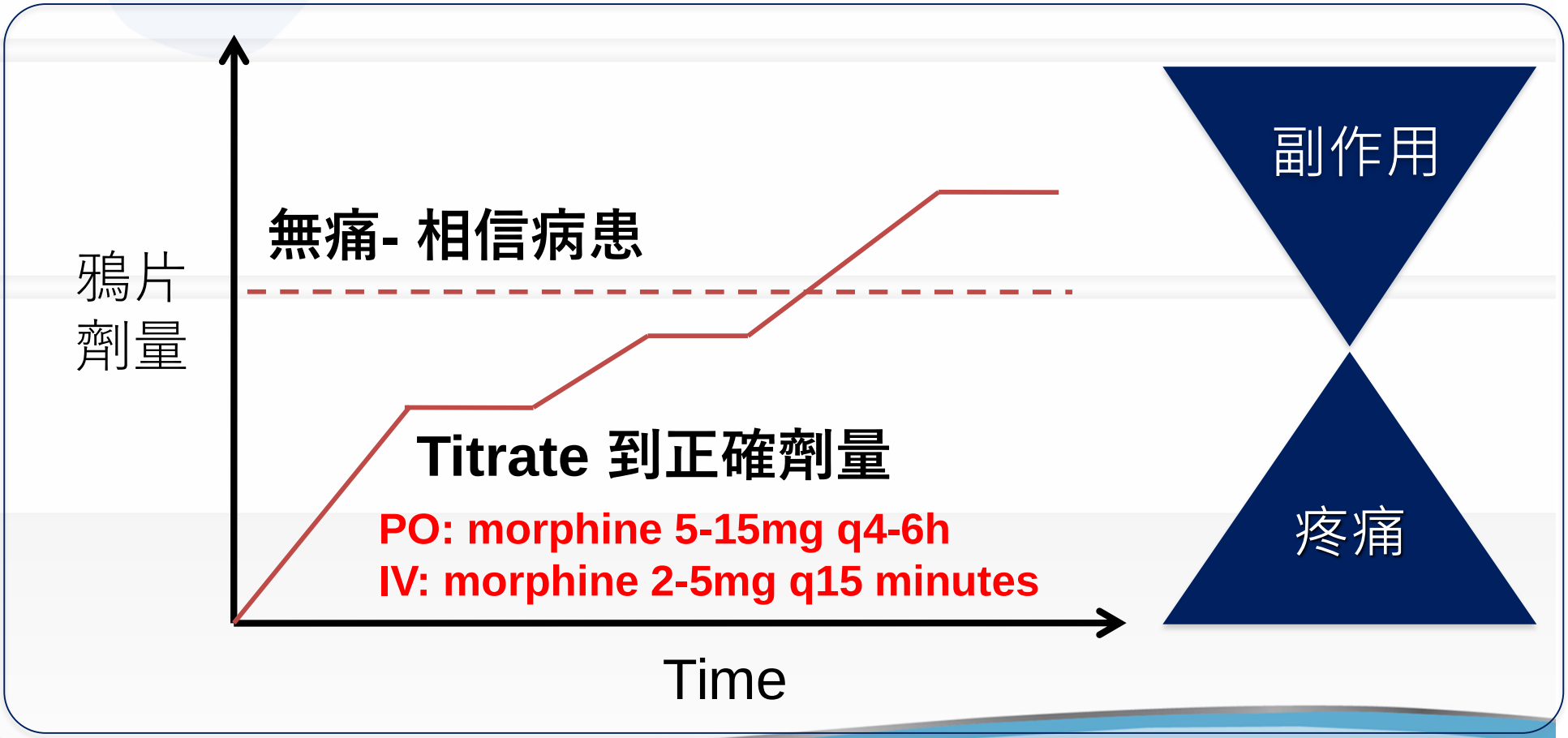
評估疼痛類型

- 哪裡痛: 內臟痛 ? 軀體痛 ? 神經痛 ?
- 怎麼痛:內臟悶痛? 神經麻刺痛?
- 痛多久: 三個月?



給藥足量為良好疼痛治療的關鍵

有效且可耐受劑量就是正確止痛劑量 (WHO)



Modified from www.medicine.ox.ac.uk/bandolier;
World Health Organization: Cancer Pain Relief With a Guide to Opioid Availability. Geneva, Switzerland 1996

確保良好疼痛治療:

定時評估療效與安全性

疼痛評估

↓

藥物治療

↓

再評估

↓

疼痛持續

↓

診斷是否正確?
修正治療

↓

再評估

副作用
可耐受/ 可預防

突發疼痛發作
<3次/ 天

疼痛嚴重程度
<3分

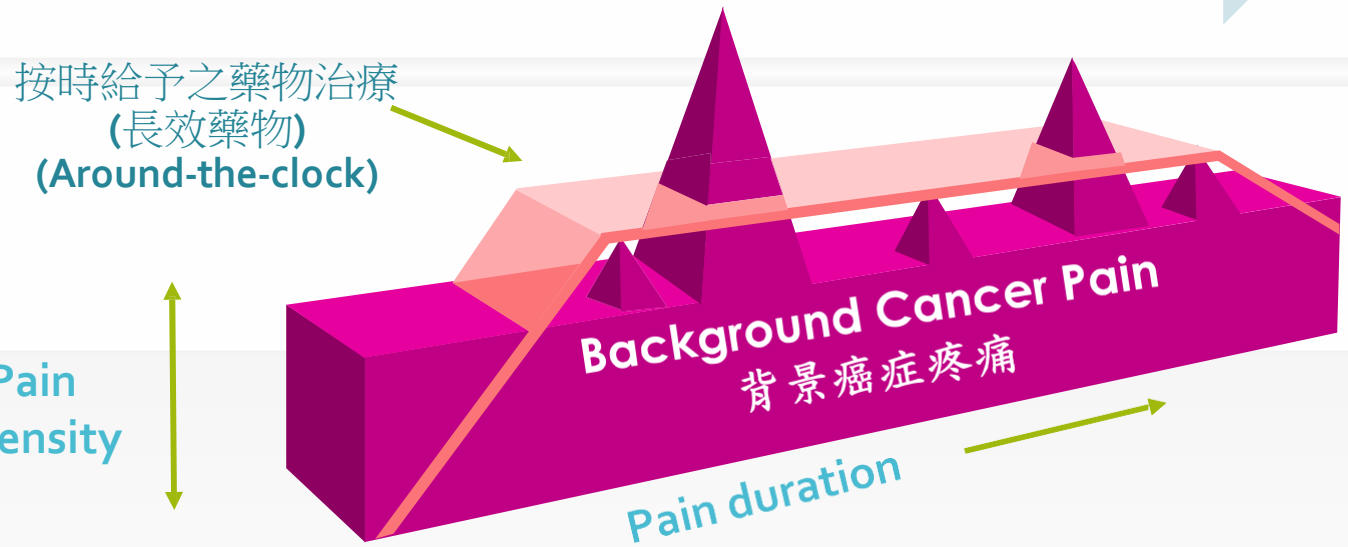
Optimal treatment of Cancer Pain:

Good Pain Control with No (or Low) Toxicity

Short acting
Oral morphine 15mg
IV morphine

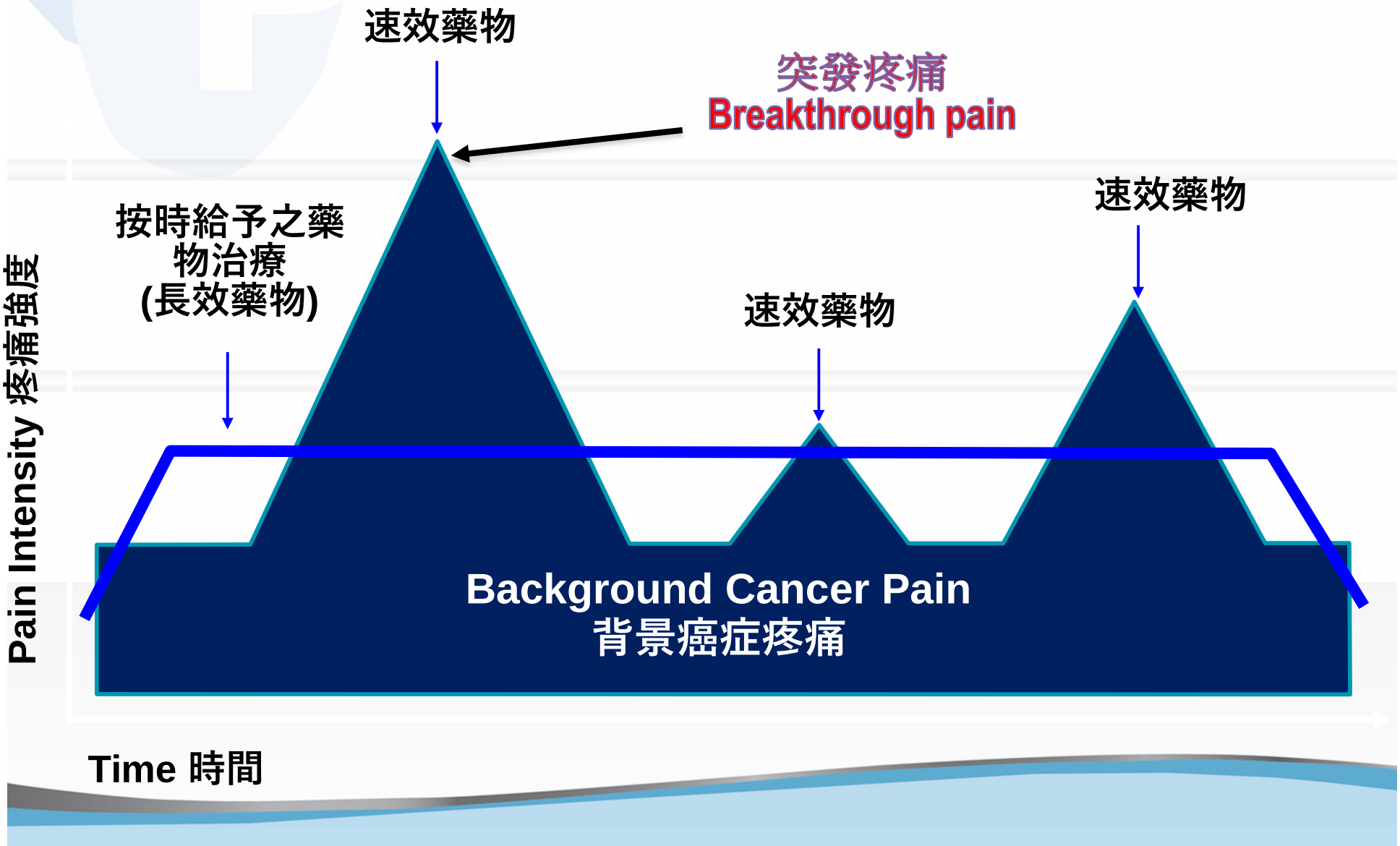
Long Acting
MST 30~60mg
MXL 60mg
Junista 8mg

Super long Acting
Fentanyl transdermal patch
12~25,50,75 mcg/h



長效與速效藥物搭配使用有效治療癌痛

- 突發性疼痛速效藥物劑量為日劑量的1/6



The Diagnosis and Treatment of Breakthrough Pain. 2008

Breakthrough Pain (BTP)
A Component of Chronic Cancer Pain

患有”慢性癌症疼痛”的病患，已規則服用鴉片類止痛藥物治療下，所發生的突發性疼痛

Definition:
Breakthrough cancer pain (BTcP)突發性疼痛定義

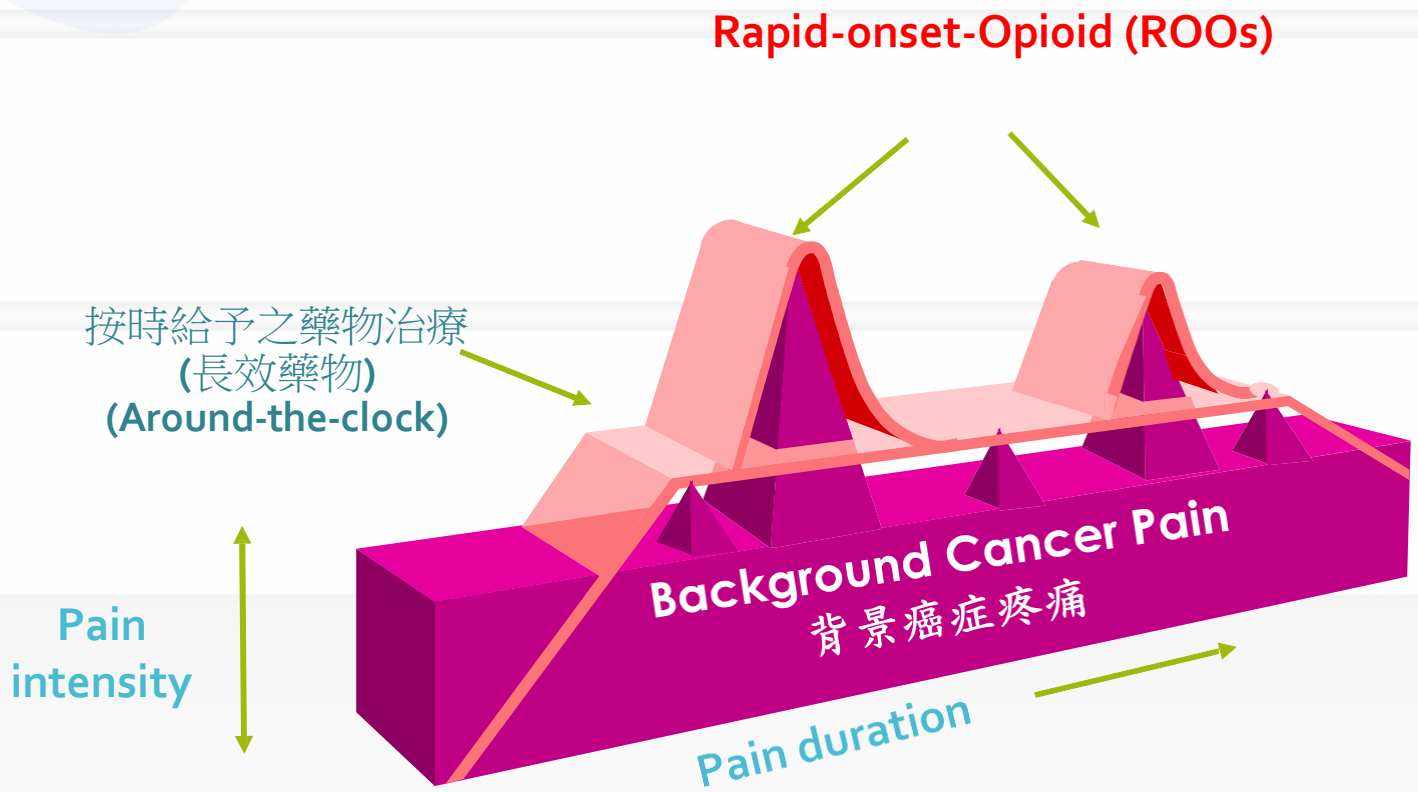
- **Moderate-to-severe pain** 中度至重度疼痛
- **Occurred at a specific site** 發生於特定部位
- **Background of persistent pain controlled**背景疼痛已控制
- **The frequency averages 1-4 episodes per day**

  平均每日發生1-4次

- In 1990, Russell K. Portenoy and Neil A. Hagen published a paper on a specific pain syndrome named breakthrough pain (BTP).

Optimal treatment of Cancer Pain:

Good Pain Control with No (or Low) Toxicity



Diagnosis of Breakthrough cancer Pain

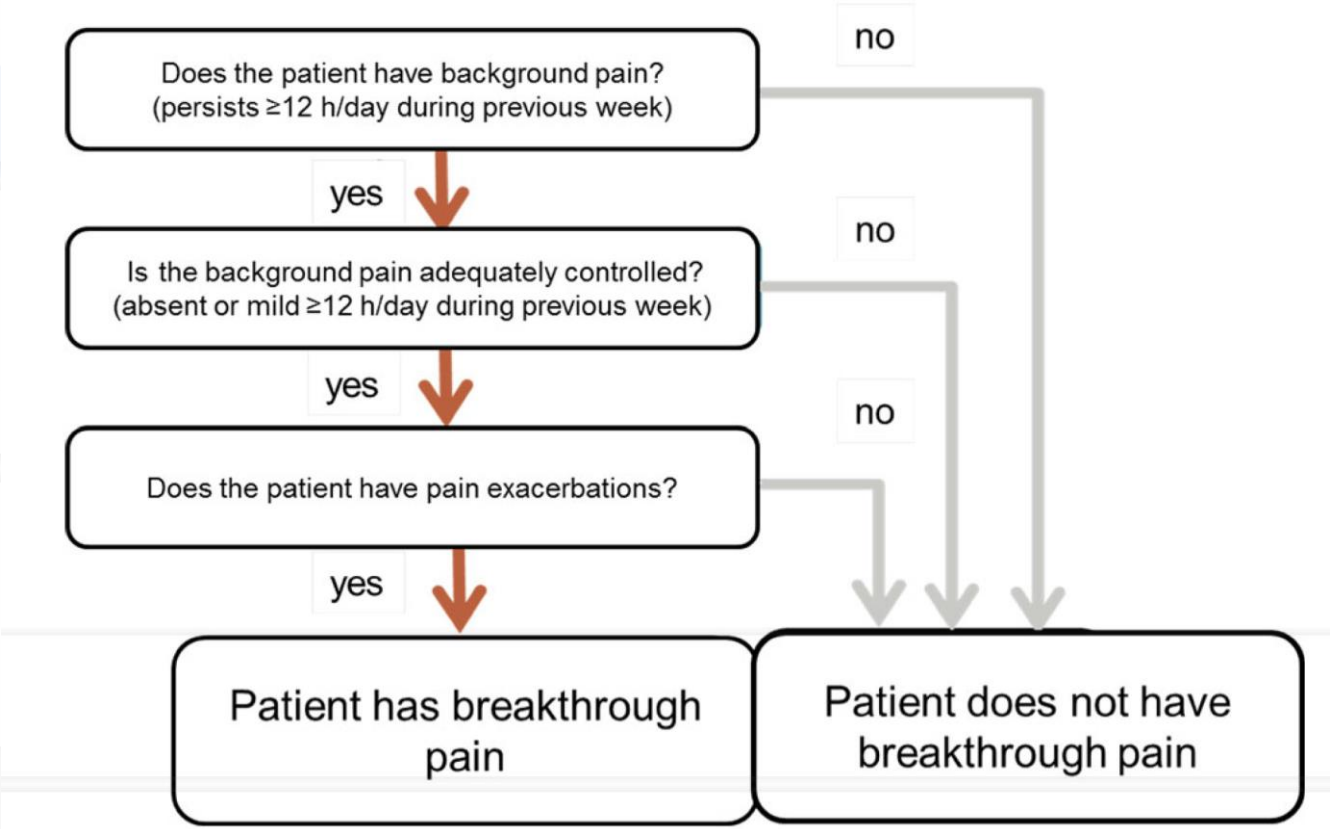
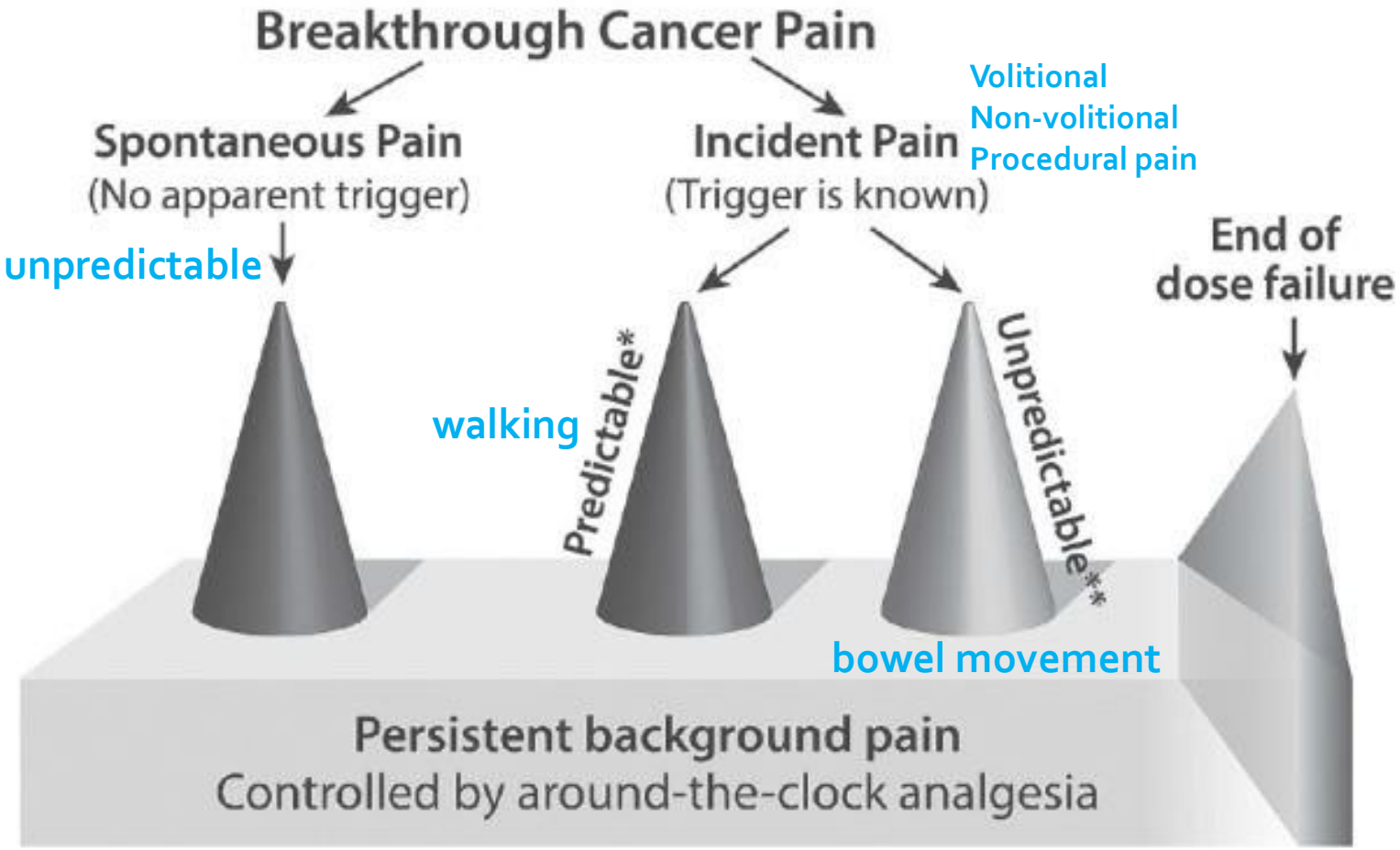


Fig. 2 Davies diagnostic algorithm

Clin Transl Oncol. 2016 Nov;18(11):1088-1097.

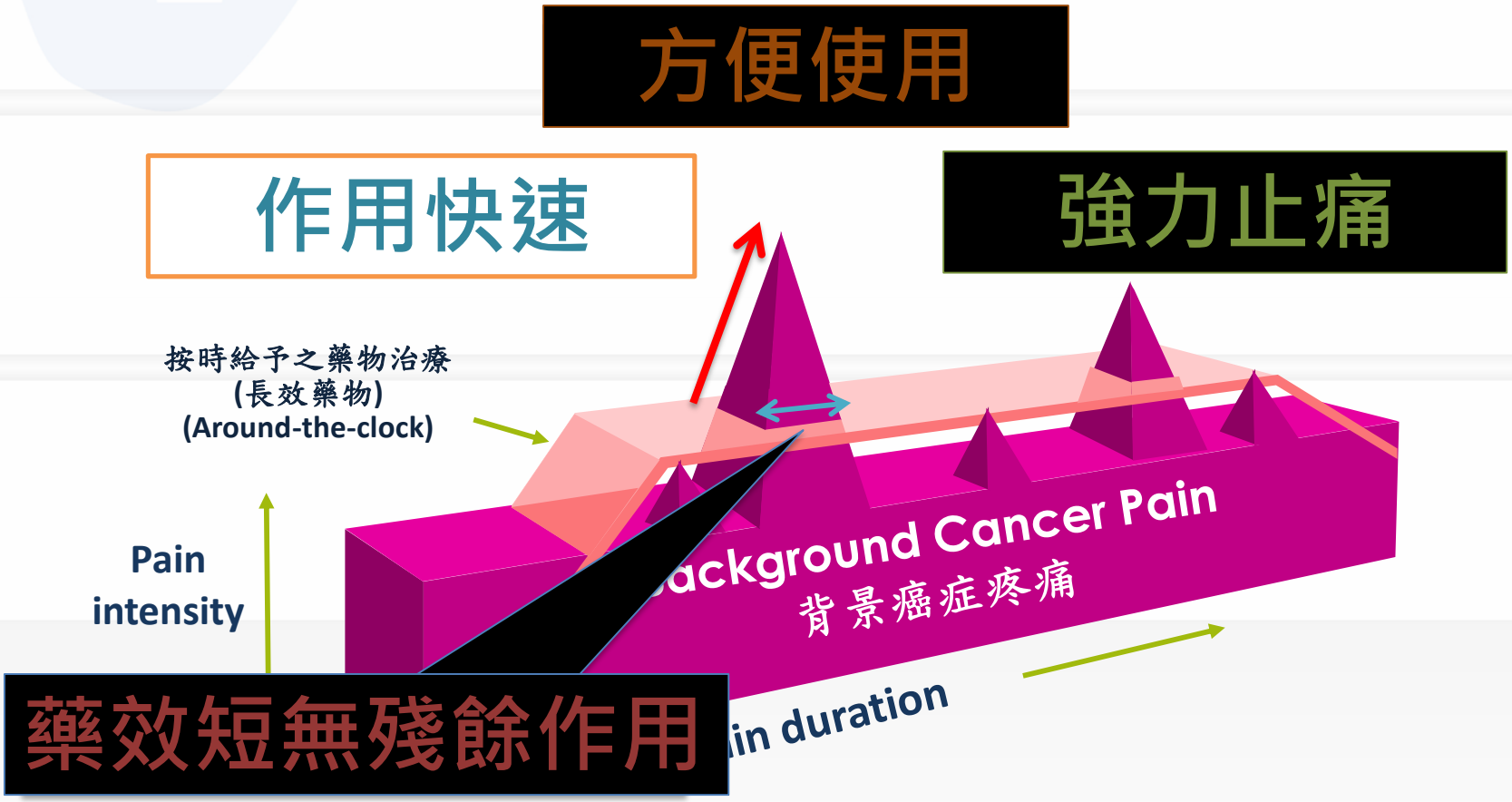
Types of Breakthrough Cancer Pain



Daeninck P, et al. *Curr Oncol.* 2016

Optimal treatment of Cancer Pain:

Good Pain Control with No (or Low) Toxicity



Outline

1. **Characteristics of breakthrough cancer pain**
   何謂突發性癌症疼痛
2. **Breakthrough cancer pain treatment**
   突發性癌症疼痛之臨床處置
3. **New killer of breakthrough cancer pain**
   新一代癌症突發性疼痛的殺手

MANAGEMENT OF BREAKTHROUGH PAIN

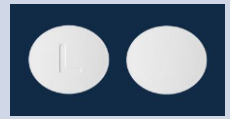
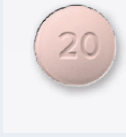
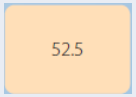
- Traditional backbone: oral morphine
- However, the pharmacokinetic profile of these agents
  - Slow onset of analgesia

  (time to achieve maximal plasma concentration [t max] for normal-release morphine is 1.1 hours and onset of analgesia ~ 30 minutes),
  - Long half-life

    (t ½ ; 2 hours for oral morphine)
  - Extensive first – pass
  - Poor bioavailability

    (20– 40 %)
- Does not manage BTP well.

台灣現有五大長短效類鴉片 藥物

	Morphine	Oxycodone	Fentanyl	Hydromorphone	Buprenorphine
速效藥物 Breakthrough Pain	 Morphine IR 10mg  Morphine Injection	 OxyNorm® 5mg	 Fentanyl Buccal Films		 Temgesic SL 0.2mg
長效藥物 Background Pain	 Morphine SR 30 mg  MST® 60 mg  MXL® 60 mg	 OxyContin® 10mg  OxyContin® 20mg	 12.5 µg/h  25 µg/h  50 µg/h	 Hydromorphone OROS 8 mg	 Transtec 35µg/h  Transtec 52.5µg/h

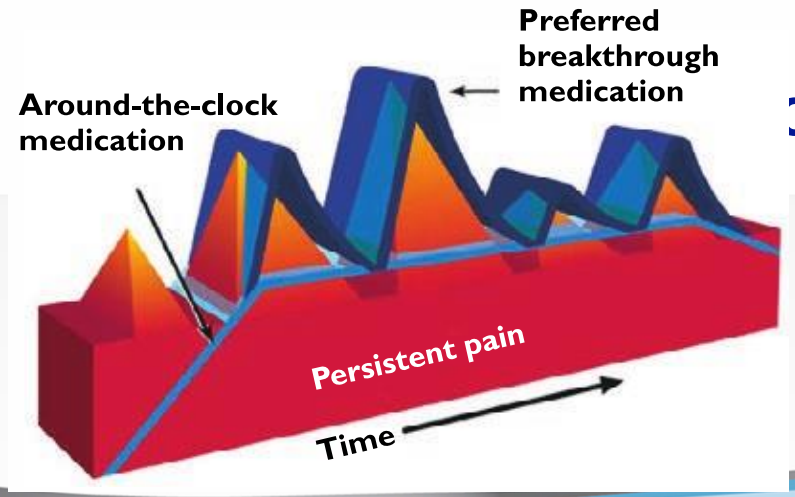
BTP MEDICATION IN TAIWAN

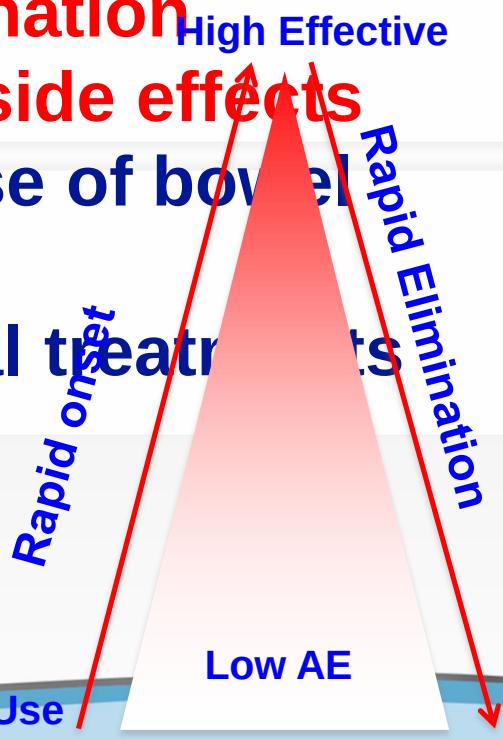
Opioid analgesics	Strong	Strong	Strong	Strong	Weak	Weak
Receptor	μ、κ-receptor			μ- receptor partial agonist & κ- antagonist /Ceiling effect	selective for the mu receptor	weak mμ-opioid agonists
學名	Morphine			Buprenorphine Temgesic	Codeine phosphate	Pethidine Hydrochloride
成分含量	10mg	15mg	2 mg/ml	0.2mg	15mg/30mg	50mg
劑型	Tablet	Tablet	solution	Sublingual	Tablet	Tablets
Onset	30~40 mins		30 min	30-60 mins	30-45 mins	15 mins
Duration	2-7 hours		2-7 hours	8-12 hours	4-6 hours	2.4~4 hours
Peak	50~90 mins		50~90mins	1.5 hours	1-2 hours	60-90 mins

The gold standard treatment for BTcP

1. **Rapidly** effective
2. To avoid accumulation and long-lasting side effects: **rapid elimination**
3. Well tolerated with **few side effects**
4. **Easy to use**, even in case of bow[illegible]

[illegible]onventional treatm[illegible]ts





Current Opinion in Oncology 2010, 22:302–306

Bennett, D., et al, P&T 2005; 30:354-8

FENTANYL FOR BTP （脂溶性）

- A μ -opioid receptor agonist with anaesthetic and analgesic properties
- highly lipophilic, so it diffuses quickly across the blood-brain barrier
- equilibration t ½ of 6 mins compared with 2–3 hours for morphine (match BTP!)

Scott J et al. Anesthesiology 1985; 62 (3):234-41
Browne B, Linter S. Br J Psychiatry 1987; 151: 210-2
Insler SR et al. Anesth Analg 1994; 78 (3): 593-7

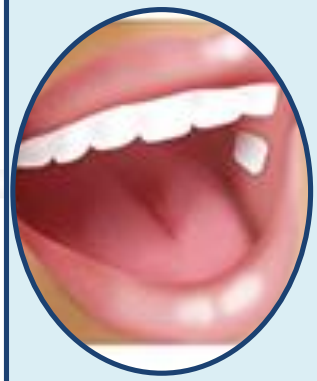
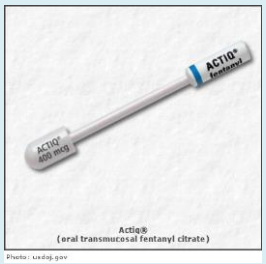
EAPC GUIDELINES

了解病因 快反應
口服或鼻吸

- Breakthrough pain should be specifically evaluated to try to establish its etiology, physiopathology, and any factor indicating or contraindicating specific interventions and should be effectively treated with immediate-release oral opioids or with oral or intranasal fentanyl formulations

1: Association for Palliative Medicine of Great Britain and Ireland; 2009. http://www.breakthroughcancerpain.org/pain-management/apm-recommendations.
2:*Lancet Oncol*. 2012; 13(2):e58–e68.

BTcP therapies: delivery systems

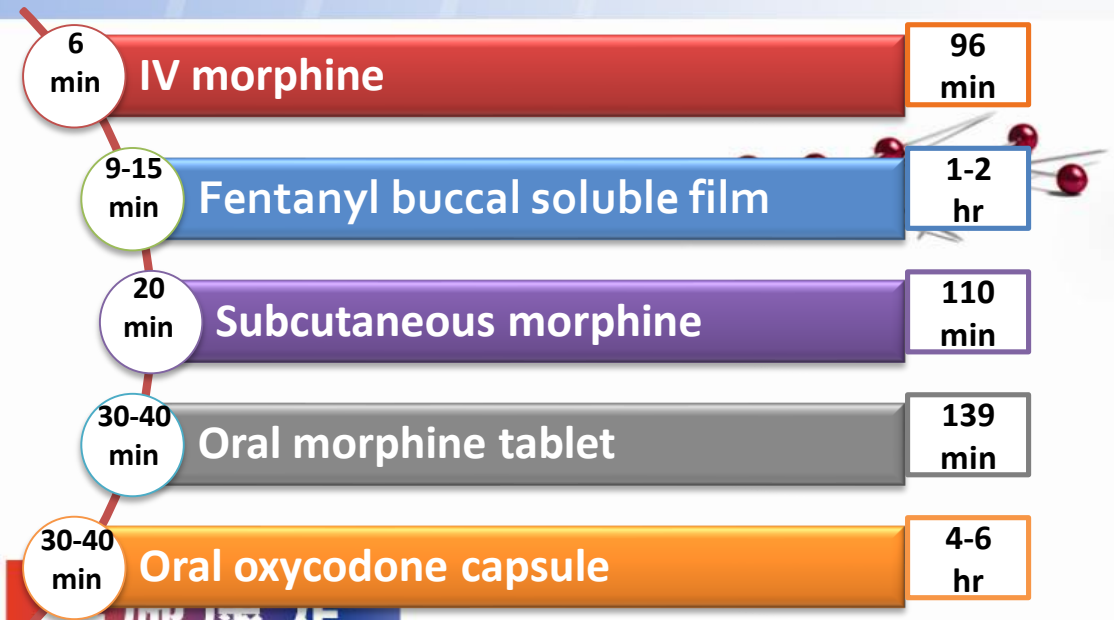
1st generation in buccal	2st generation	3rd generation	Sublingual	Intra nassal	Intra nassal
					
1998 Oral trans-mucosal fentanyl citrate OTFC/Actiq®	2006/2008 Fentora®(US)/Effentora®(EU)	2009 Onsolis®(US) FBSF	2008 Rapinyl®/Abstral®(EU) SLF	2009 Instanyl® (EU) INFS	2009 NasalFen(EU)FPNS
					
Oral transmucosal lozenge	Fentanyl buccal tablet	Fentanyl buccal soluble film	Sublingual Fentanyl	Intranasal Fentanyl spray	Fentanyl Pectin nasal spray

Fentora® Painkyl®

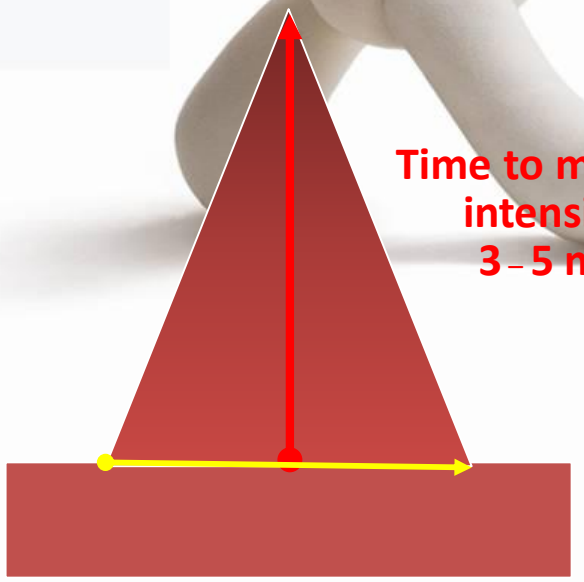
Onset of different opioid formulations

- The slow onset of oral morphine does not correlate with the sudden onset and short time to maximum severity of BTcP[1].
- ROOs with fast onset and short duration are needed to avoid cumulated toxicity.

Onset of different opioid formulations[2-4]



BTcP



BTcP=breakthrough cancer pain; IV=intravenous; ROO=rapid-onset opioid.

1. Smith H. CNS Drugs. 2012;26(6):509-35. 2. Upton RN, et al. Clin Pharmacokinet. 1997;33(3):225-44.
3. Vasisht N, et al. Clin Drug Investig. 2009;29(10):647-54. 4. Mercadante S. Drugs. 2012;72(2):181-90.

WHY BUCCAL DRUG DELIVERY?

- Rapid drug delivery to systemic circulation
- No GI degradation
- No GI motility effects (nausea) on absorption
- No hepatic first-pass metabolism
- Ease of administration and good patient compliance

快 方便

不經腸 肝

RAPID-ONSET OPIOIDS (ROO)

經鼻經口黏膜

- The first ROO indicated for BTP in opioid-tolerant patients with cancer was oral transmucosal fentanyl citrate (OTFC),
  - a lozenge containing fentanyl citrate
  - incorporated into a dissolvable sugar-based matrix
- Since the approval of OTFC, several other formulations and delivery routes have been developed for this indication.

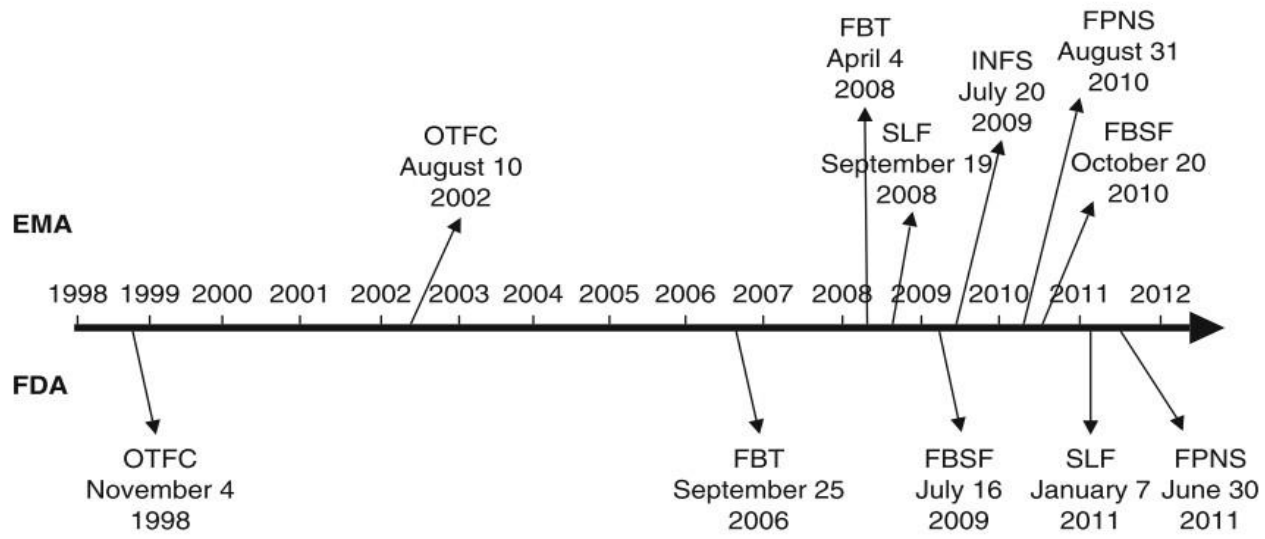


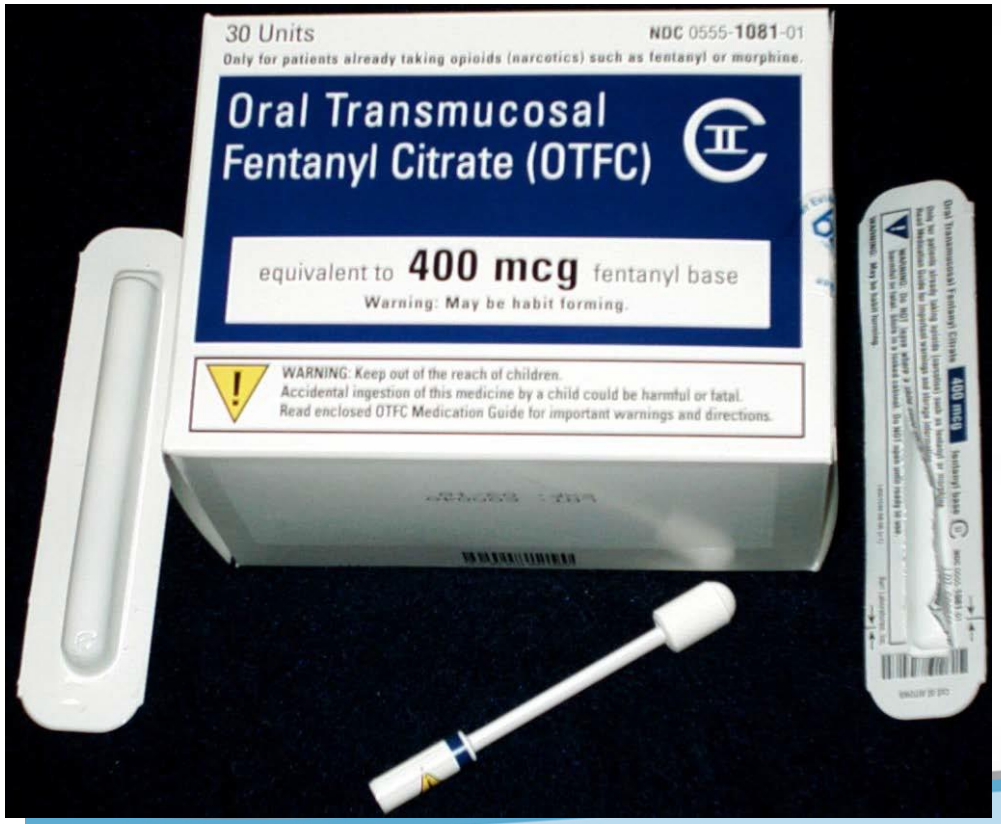
Fig. 2. Timeline of rapid-onset opioid approval in the US and EU. **EMA** = European Medicines Agency; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl.

Smith, H. (2012). "A comprehensive review of rapid-onset opioids for breakthrough pain."CNS Drugs 26(6): 509-535.

ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC)

塗的棒棒糖

A sweetened lozenge; need 15 mins



Anesta Corp. Cephalon Inc, USA(1998); EUR(2003)

http://drugline.org/drug/medicament/430/

http://www.troikaa.com/oraltransmucosalfentanylcitrate200mcg.html

INTRANASAL FENTANYL SPRAY (INFS)

鼻腔內噴劑

Developed by Nycomed, approved in EU (2009); not in US
50, 100 and 200 µg / spray
Tmax : 12-15 minutes
Bioavailability: 89%, t ½ = 6.5 mins

http://www.mims.co.uk/news/946947

FENTANYL PECTIN NASAL SPRAY (FPNS)

Figure A

Figure B

特殊轉開裝置

Figure C

Figure D

Figure E

[PecFent (EU trade name), Lazanda (US trade name)]
Archimedes Pharma; approved in EU(2010); US(2011)

http://www.drugs.com/pro/lazanda-nasal-spray.html

FENTANYL BUCCAL TABLET (FBT)

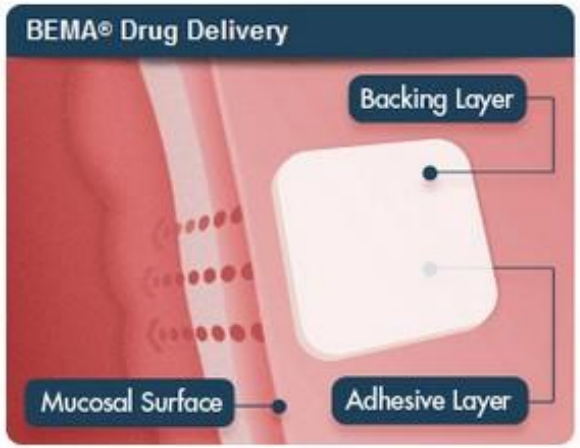
口腔黏膜壓溶

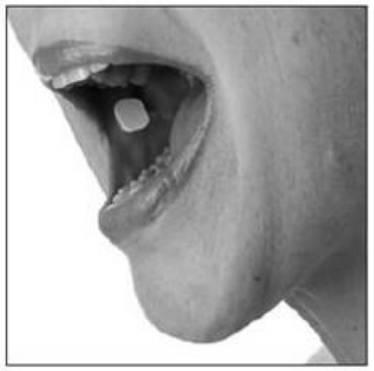
- OraVescent delivery technology
- alter the pH of the oral environment
- assist with dissolution and maximize absorption
- 溶解14-25mins; 50%可由黏膜吸收; 比OTFC口服利用利用率高，first-pass effects減少

Cephalon Inc, US(2006); EU(2008)

FENTANYL BUCCAL SOLUBLE FILM (FBSF)

口腔黏膜貼片





BEMA® Technology; Onsolis ™

- Adhere to oral mucosa in less than 5 seconds
- Optimize delivery across the oral mucosa
- Completely dissolve within 15 to 30 minutes

Approved in US (2009); EU (2010)

Oral Morphine & Oxycodone

The pharmacokinetic profile of oral morphine

Slow onset of analgesia: **30-45 minutes**

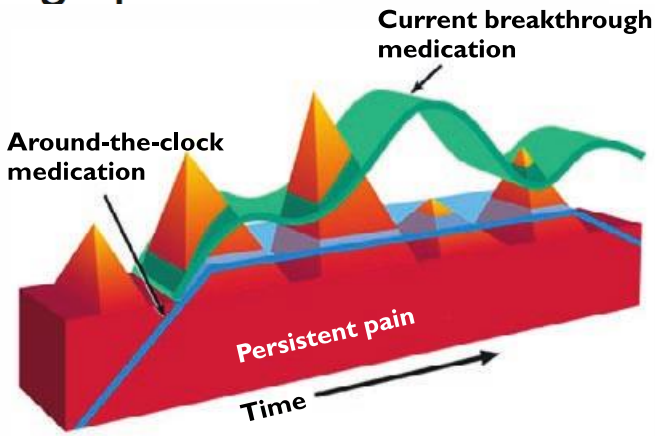
Extensive first – pass

Poor bioavailability: 20~40%

Does not manage BTcP well

Table I. Characteristics of opioids used for breakthrough pain

Opioid	Analgesic onset (min)	Availability (%)
Oral morphine	30–45	30
Oral oxycodone	30–45	40–50

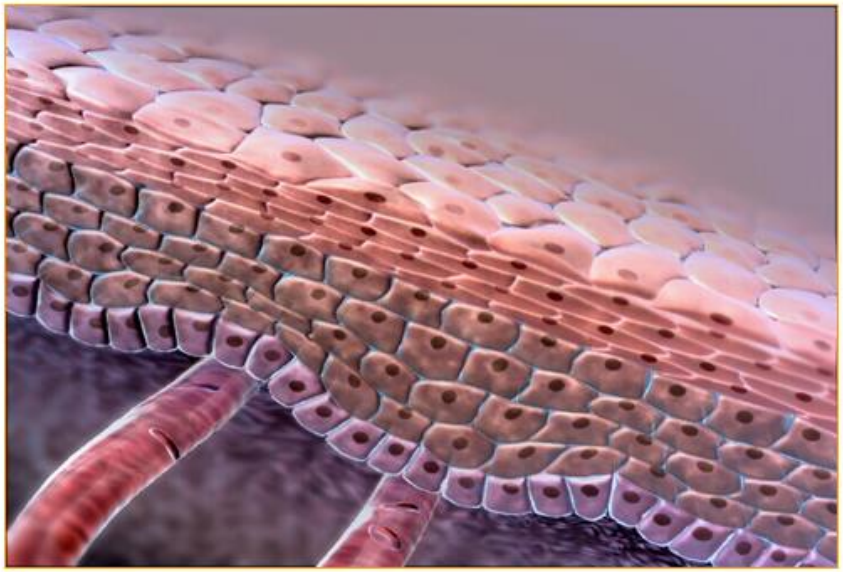


Drugs 2012; 72 (2): 181-190
Smith, H. (2012). "A comprehensive review of rapid-onset opioids for breakthrough pain."CNS Drugs **26**(6): 509-535.
Bennett, D., et al, P&T 2005; 30:354-8

Most ROOs are buccal delivery Transmucosal absorption rate and potency

Characteristics of Buccal Mucosa

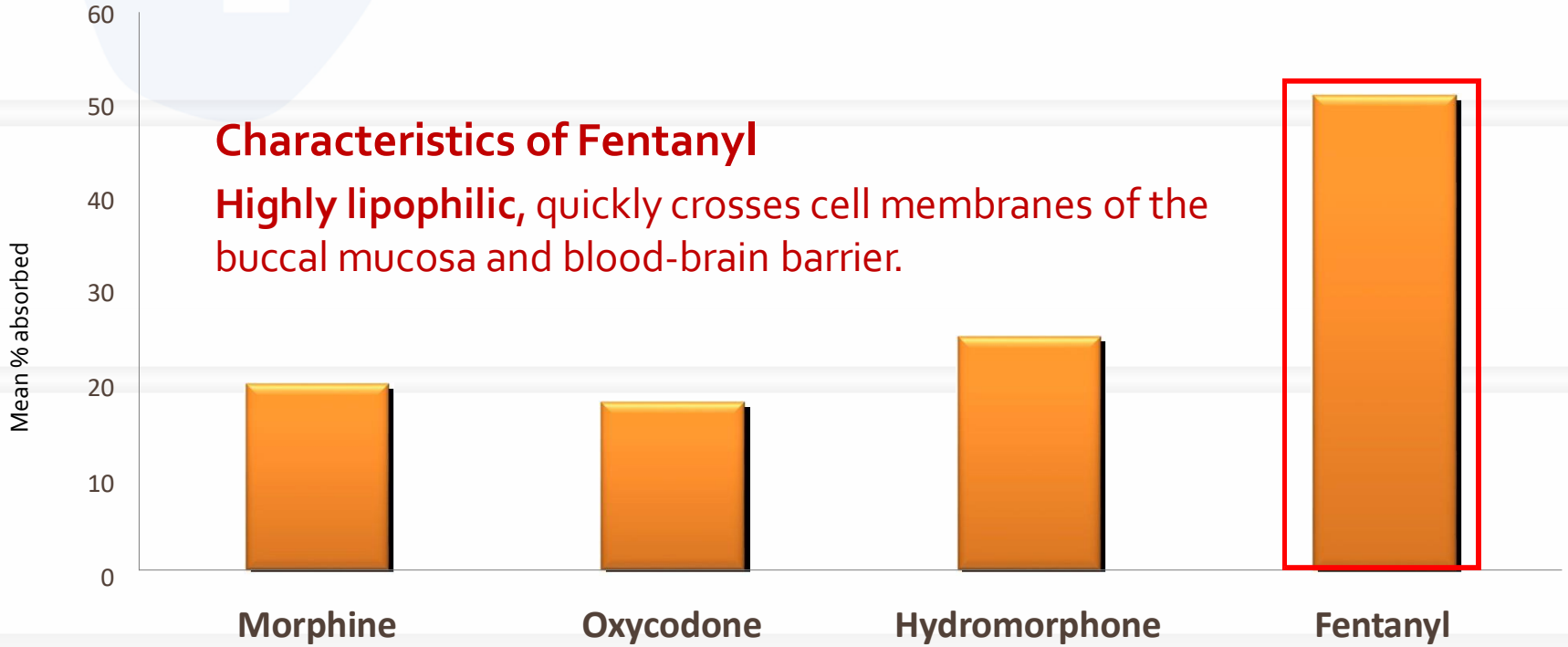
- Large surface area
- Uniform temperature
- High permeability
- Well vascularized



Advantage of transmucosal absorptions

- Rapid drug delivery to systemic circulation
- No GI degradation
- No GI motility effects (nausea) on absorption
- No hepatic first-pass metabolism
- Ease of administration and good patient compliance

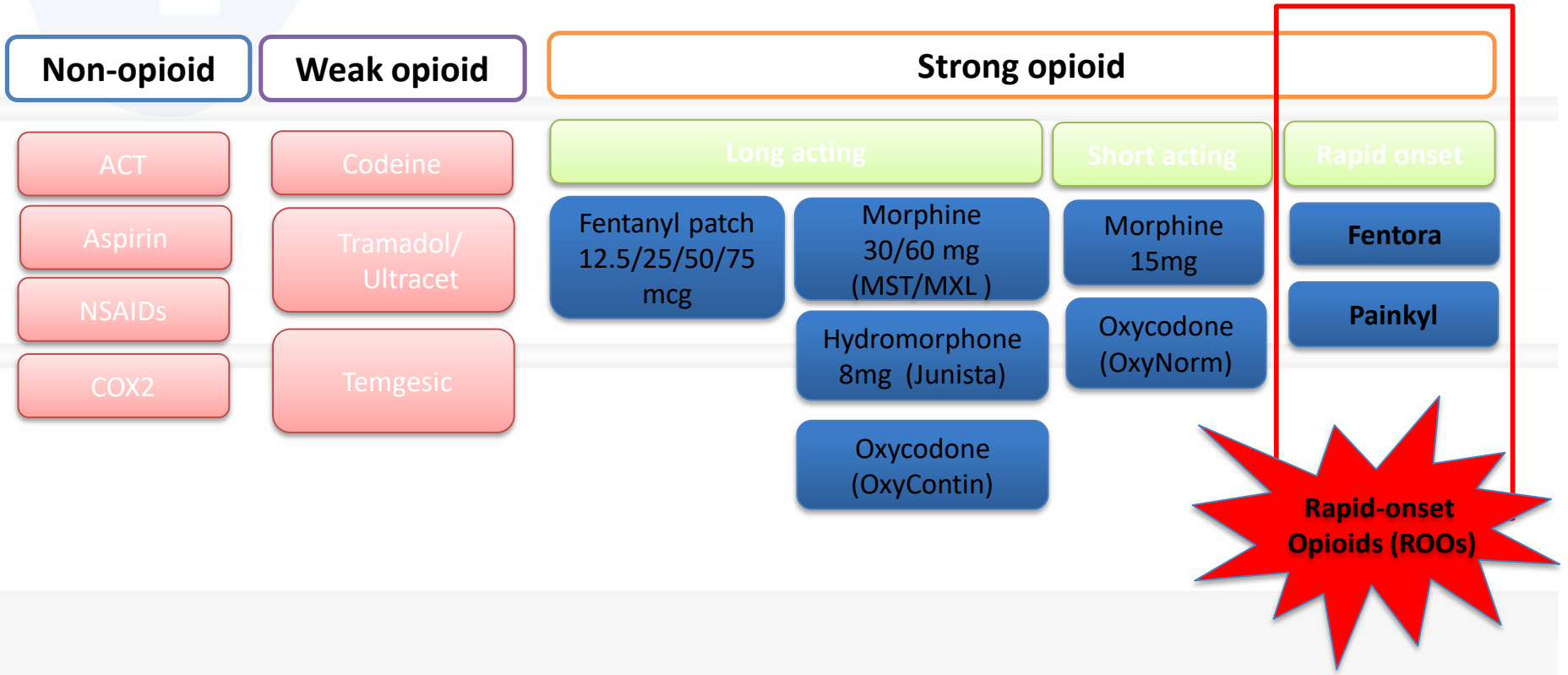
Fentanyl 非常適合經由口腔黏膜給藥 (Buccal Delivery)



	Hydrophilic			Lipophilic
Potency	1	2	4	100

Clin Pharmacol Ther. 1988 Sep;44(3):335-42.
Pain Physician 2008: Opioid Special Issue: 11: S133-S153

Rapid-Onset-Opioid
a new category of Analgesic



Adjuvant analgesics:
Antidepressants;Anticonvulsants;Corticosteroids;Bisphosphonate;GABAergic adjuvant analgesics…

Outline

1. **Characteristics of breakthrough cancer pain**
   何謂突發性癌症疼痛

2. **Breakthrough cancer pain treatment**
   突發性癌症疼痛之臨床處置

3. **New killer of breakthrough cancer pain**
   新一代癌症突發性疼痛的殺手

What Guidelines Say about Breakthrough Pain?

ESMO

- Immediate release oral morphine is appropriate to treat predictable episodes of breakthrough pain when administered at least 20 min before
- Intravenous opioids; buccal, sublingual and intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating breakthrough episodes in respect to oral morphine

NCCN

- Consider rapidly acting transmucosal fentanyl in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid

EAPC

- In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more-rapid onset of action and shorter duration of effect.

NCCN 2016; Ripamonti et al. Ann Oncol 2012; Caraceni et al. Lancet Oncol 2012

Bioavailability

	OTFC / ACTIQ®	Fentora®	Painkyl®
Buccal absorption	22%	48%	51%
GI absorption	25%	17%	20%
Absolute bioavailability	47%	65%	71%
Generation in transmucosal fentanyl	1st generation	2nd generation	3rd generation

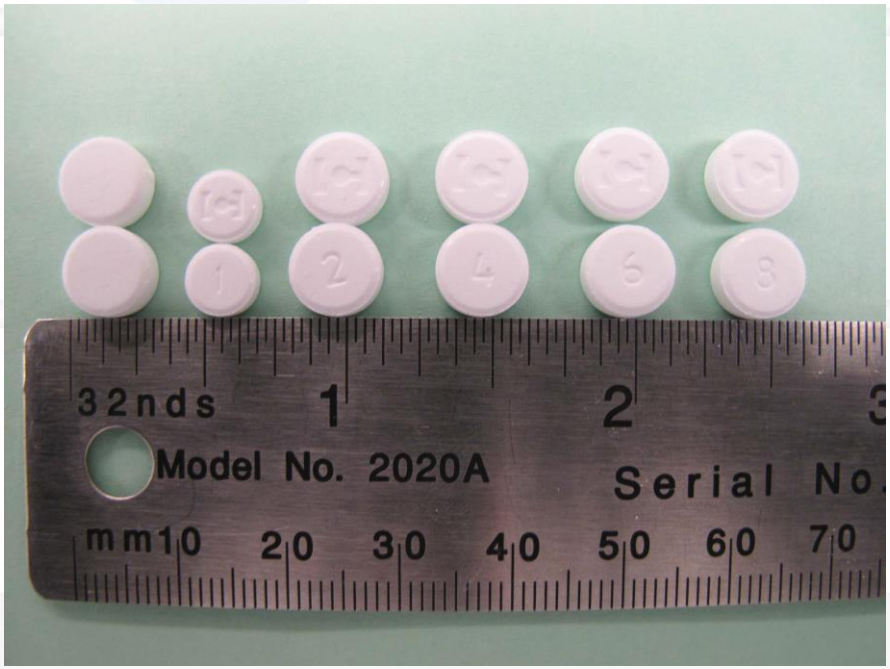
OTFC: oral transmucosal fentanyl citrate

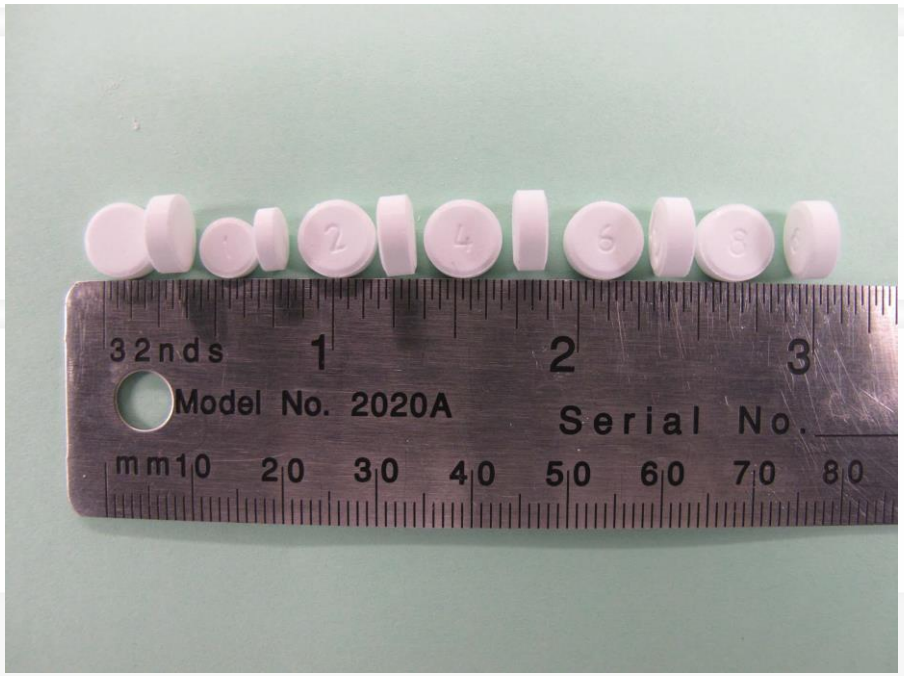
1. Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol*. 2007;47(3):343-350.
2. Vasisht N, Gever LN, Tagarro I, Finn AL. Single-dose pharmacokinetics of fentanyl buccal soluble film. Pain Med. 2010;11(7):1017-232.

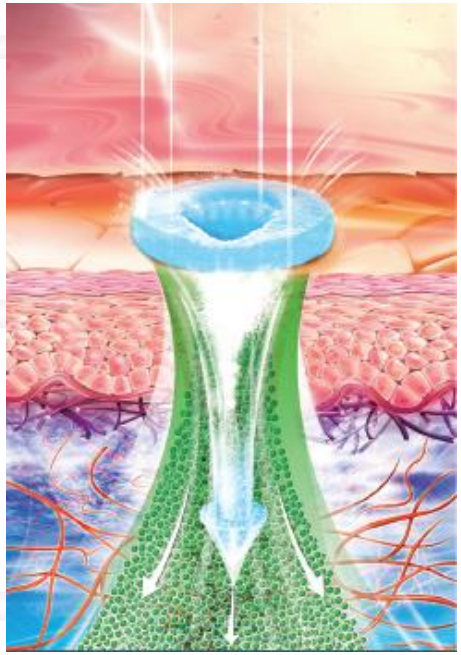
FENTORA 口頰錠 (Fentanyl Buccal Tablet)

FENTORA, which employs the OraVescent drug delivery technology, is a potent opioid analgesic intended for buccal administration. FENTORA is formulated as a flat-faced, round, beveled-edge, white tablet.

FENTORA 口颊片 (Fentanyl Buccal Tablet)







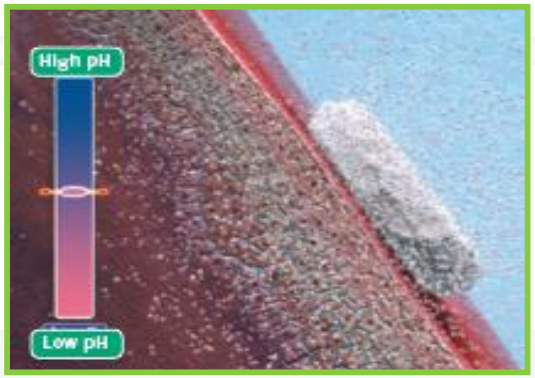
OraVescent Technology:

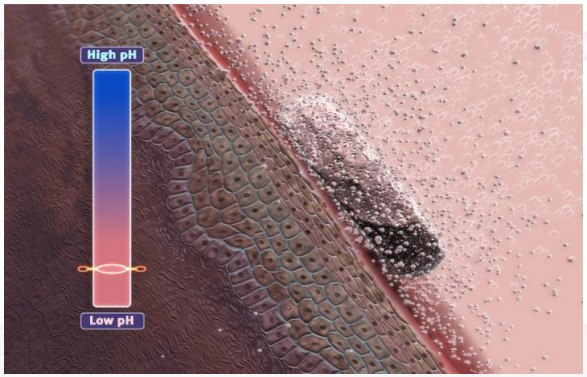
An Innovation in Drug Delivery

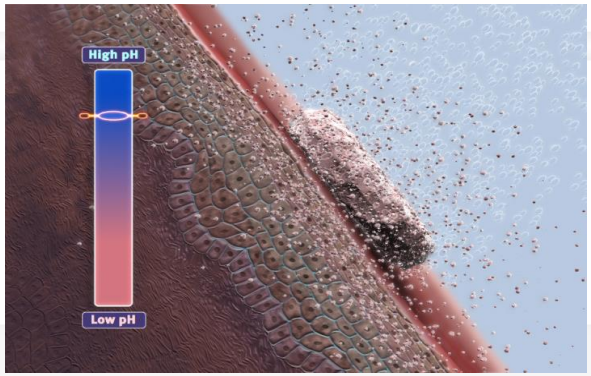
“口腔黏膜吸收專利型” 給藥技術

OraVescent® Drug Delivery Technology
“口腔黏膜吸收專利型” 給藥技術

瞬間的 pH值改變, 當pH值較低時,可使藥品的溶解度增加; 反之, 當pH值較高時則可使細胞膜的通透力增加







- ***FENTORA*** **contains citric acid, sodium bicarbonate, and sodium carbonate, which can alter pH in the oral mucosal fluid.**

增強溶解度

- When the tablet comes in contact with saliva, a combination of acid and bicarbonate forms carbonic acid

$$C_6H_8O_7 + 3HCO_3^- \longleftrightarrow 3H_2CO_3 + C_6H_5O_7^{3-}$$

citric acid + bicarbonate ⟷ carbonic acid + citrate

- This drives down the pH and may enhance the dissolution of ionized fentanyl

當pH值較低時,
可使藥品的溶解度增加

增強吸收度

- Carbonic acid dissociates into CO_2 and H_2O
  - CO_2 bubbles out of solution or is absorbed across oral mucosa

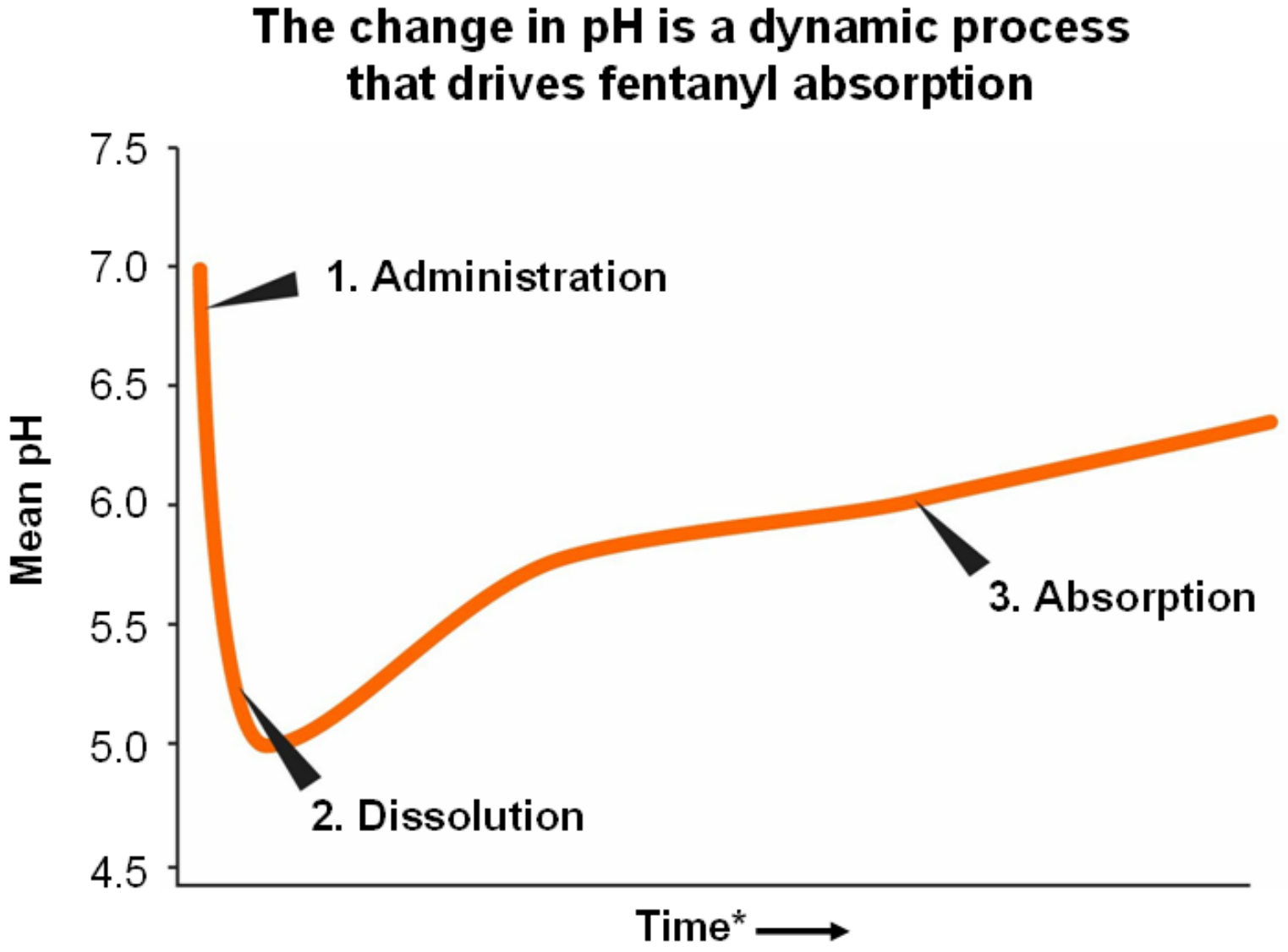
$$H_2CO_3 \longleftrightarrow CO_2 + H_2O$$

carbonic acid ⟷ carbon dioxide + water

- The loss of CO_2 results in an increa in pH, which may favor the absorpti of nonionized fentanyl

當pH值較高時則可使細胞膜的通透力增加

PH Profile of *FENTORA* (in vitro)



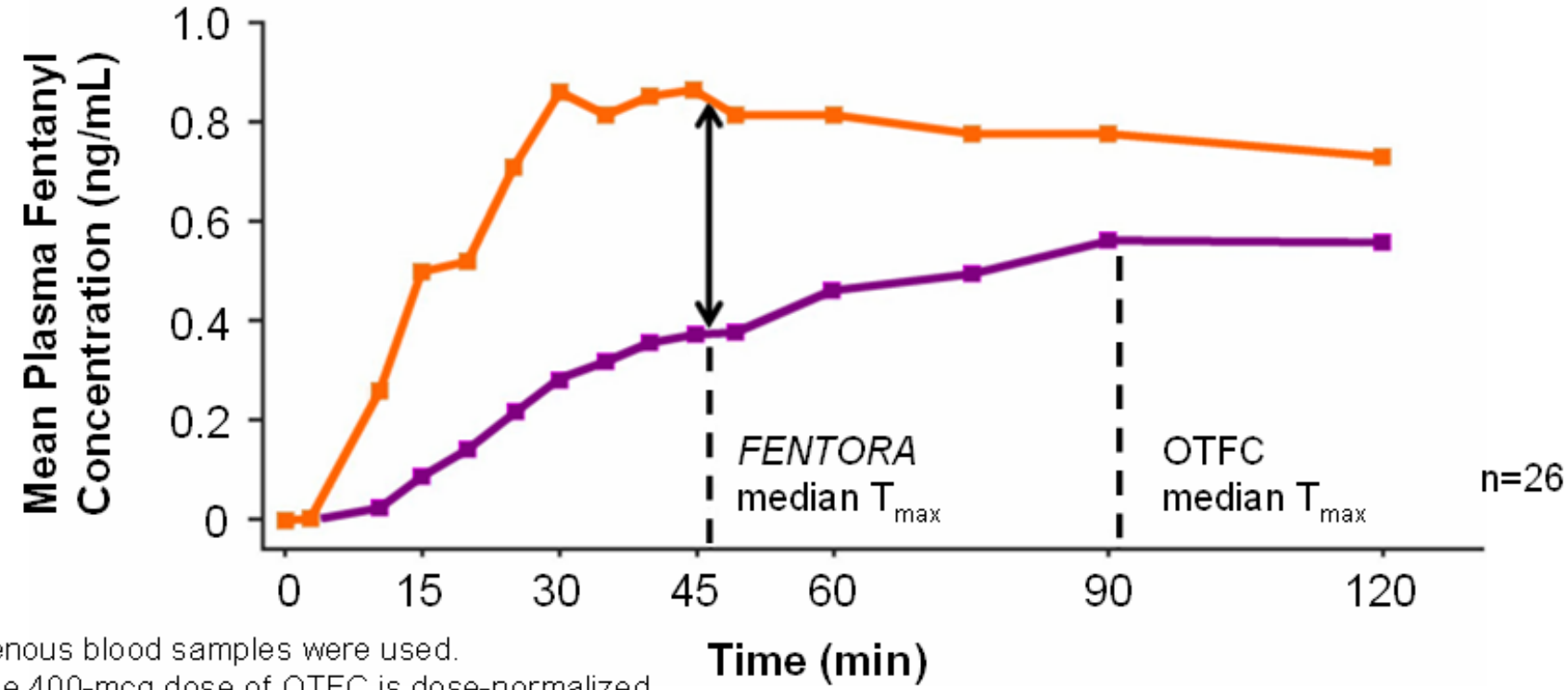
CORE

Fentanyl Absorption

FENTORA Compared With OTFC

Earlier T_{max} and Greater C_{max} and $AUC_{0\text{-}Tmax}$*

	400 mcg *FENTORA*	400 mcg OTFC†
T_{max}	46.8 min	90.8 min
C_{max}	1.02 ng/mL	0.63 ng/mL
$AUC_{0\text{-}Tmax}$‡	0.40 ng·h/mL	0.14 ng·h/mL



*Venous blood samples were used.

†The 400-mcg dose of OTFC is dose-normalized.

‡$AUC_{0\text{-}Tmax}$ = AUC from time zero to the median time to C_{max} for the reference treatment regimen (400 mcg *FENTORA*).

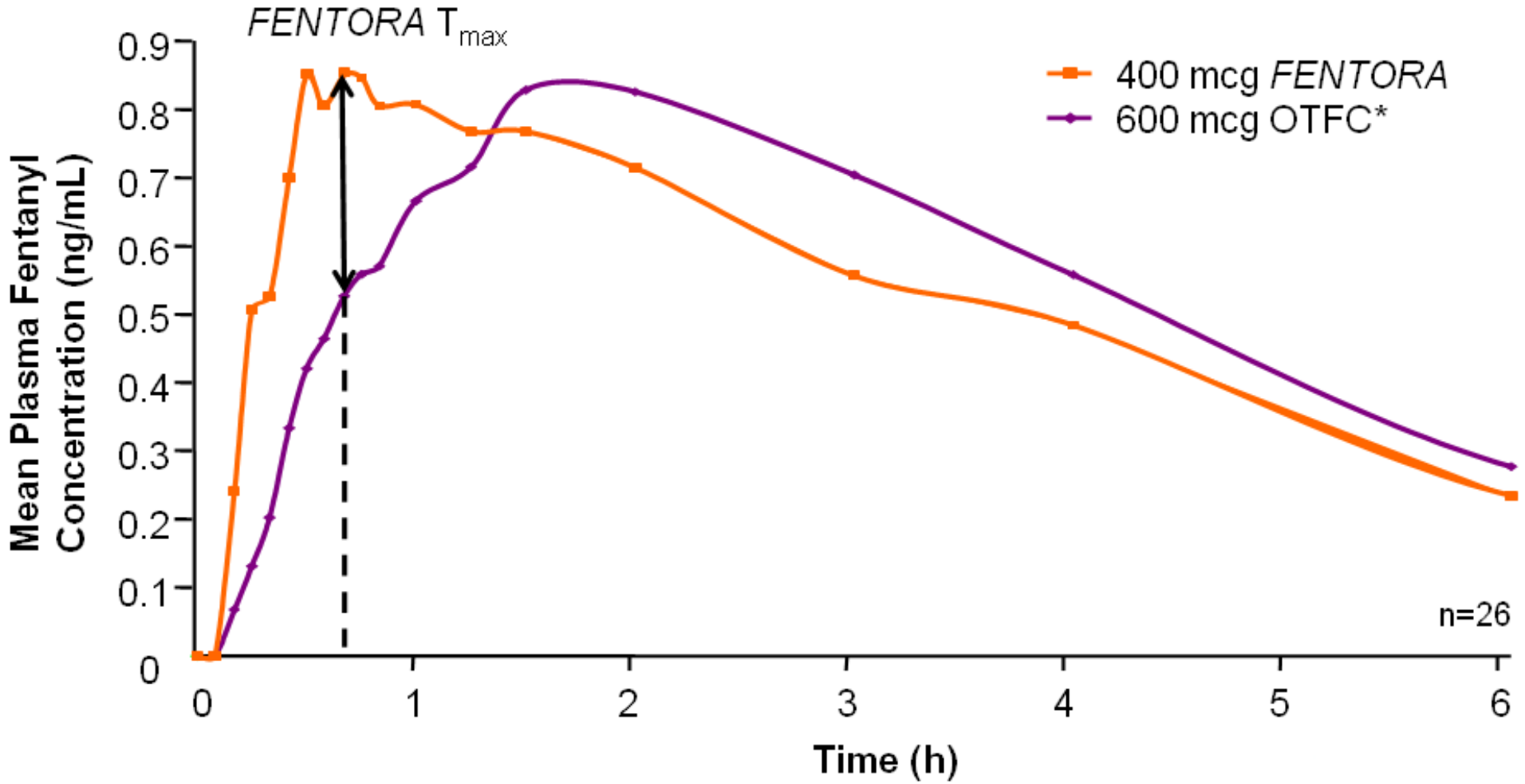
FENTORA [package insert]. Frazer, PA: Cephalon, Inc.; 2007.

Darwish M et al. Poster presented at: American Pain Society; May 3-6, 2006; San Antonio, TX.

Darwish M et al. *J Clin Pharmacol*. 2007;47:343-350.

FENTORA® fentanyl buccal tablet

Peak Concentrations
FENTORA Compared With OTFC



*The 600-mcg dose of OTFC is dose-normalized.

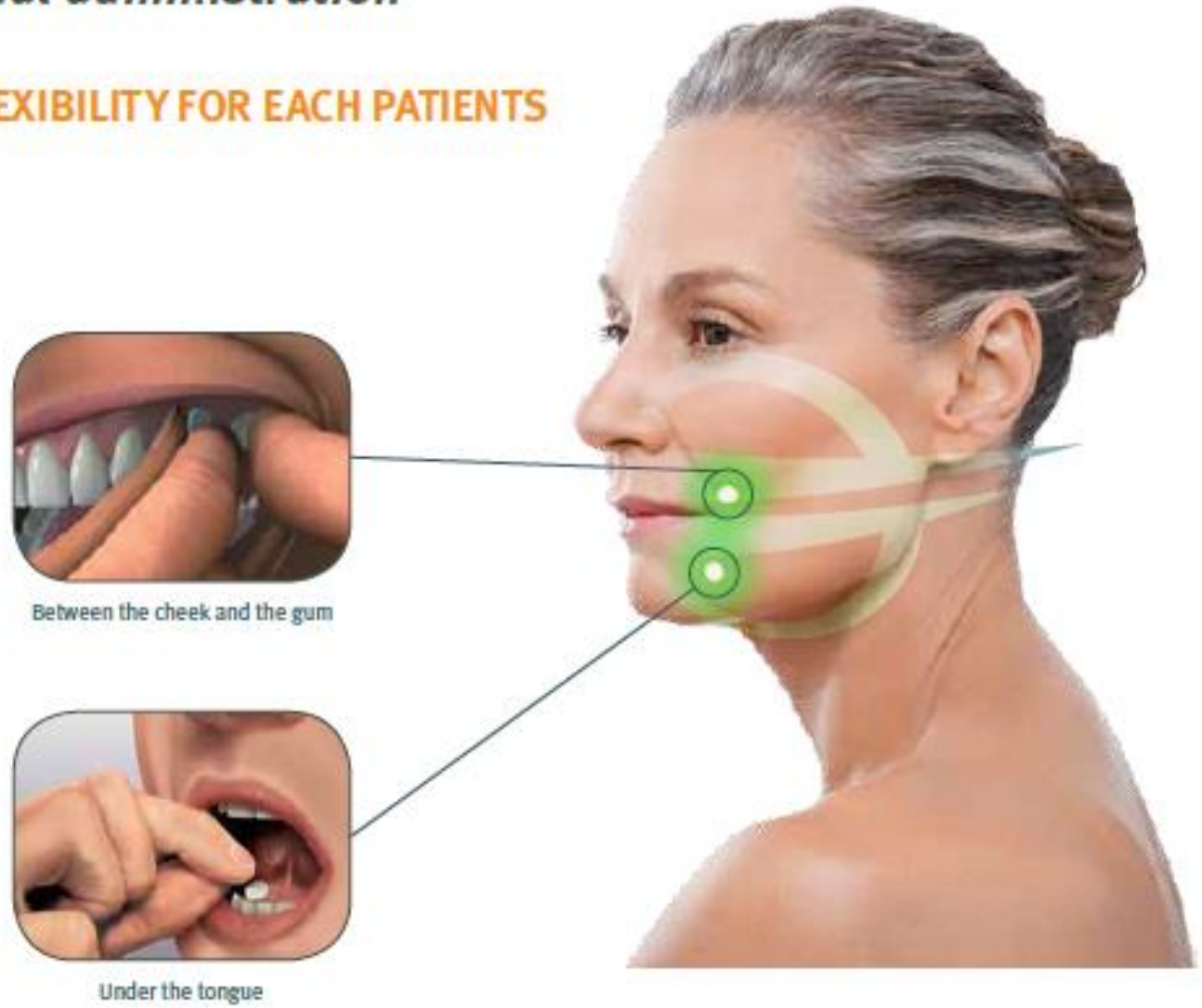
Darwish M et al. Poster presented at: American Pain Society; May 3-6, 2006; San Antonio, TX.

FENTORA. fentanyl buccal tablet

FENTORA® IS THE ONLY TRANSMUCOSAL OPIOID THAT ALLOWS BOTH BUCCAL AND SUBLINGUAL ADMINISTRATION

Buccal and sublingual administration

FENTORA® PROVIDES FLEXIBILITY FOR EACH PATIENTS



FENTORA® Prescribing Information

FENTORA Pivotal Cancer Trials

Two clinical trials were conducted to establish the efficacy and safety of *FENTORA* in opioid tolerant cancer patients with BTP

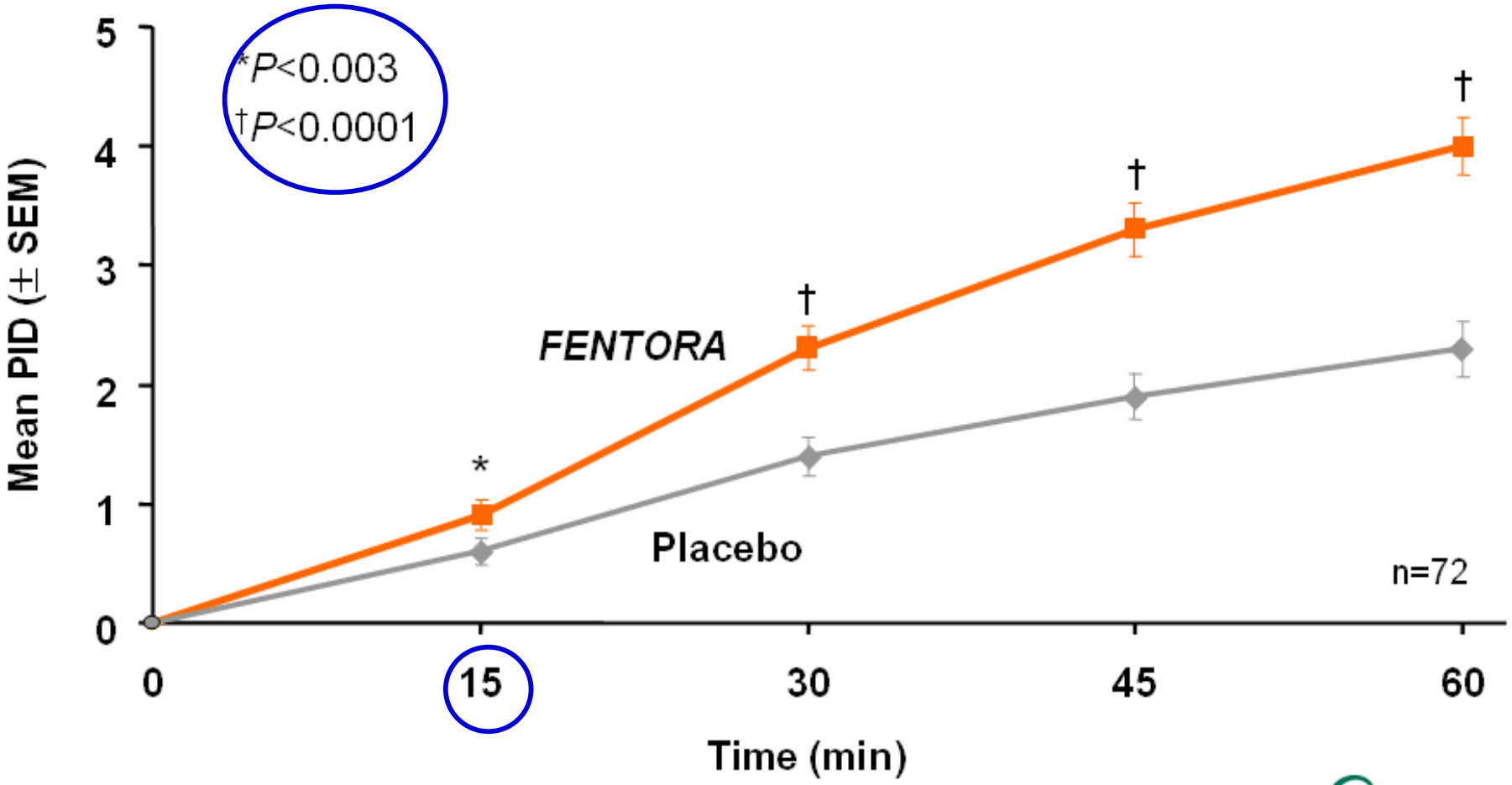
- **Initial efficacy trial (N=123) measured efficacy from 15 to 60 minutes**
- **Subsequent efficacy trial (N=125) measured efficacy from 5 to 120 minutes**

Design

- **Multicenter, randomized, double-blind, placebo-controlled study in opioid tolerant patients with cancer and BTP**
- **Inclusion criteria**
  - ✓**Initial trial: Using oral opioids equivalent to 60 mg/d of morphine or >50 mcg/h of transdermal fentanyl to control persistent pain**
  - ✓**Subsequent trial: Using oral opioids equivalent to 60 mg/d of morphine or 25 mcg/h of transdermal fentanyl to control persistent pain**
  - ✓**Experiencing an average of 1 to 4 BTP episodes per day**

Pain Intensity Difference
FENTORA Initial Trial

Greater reductions in pain observed in patients treated with *FENTORA* vs placebo

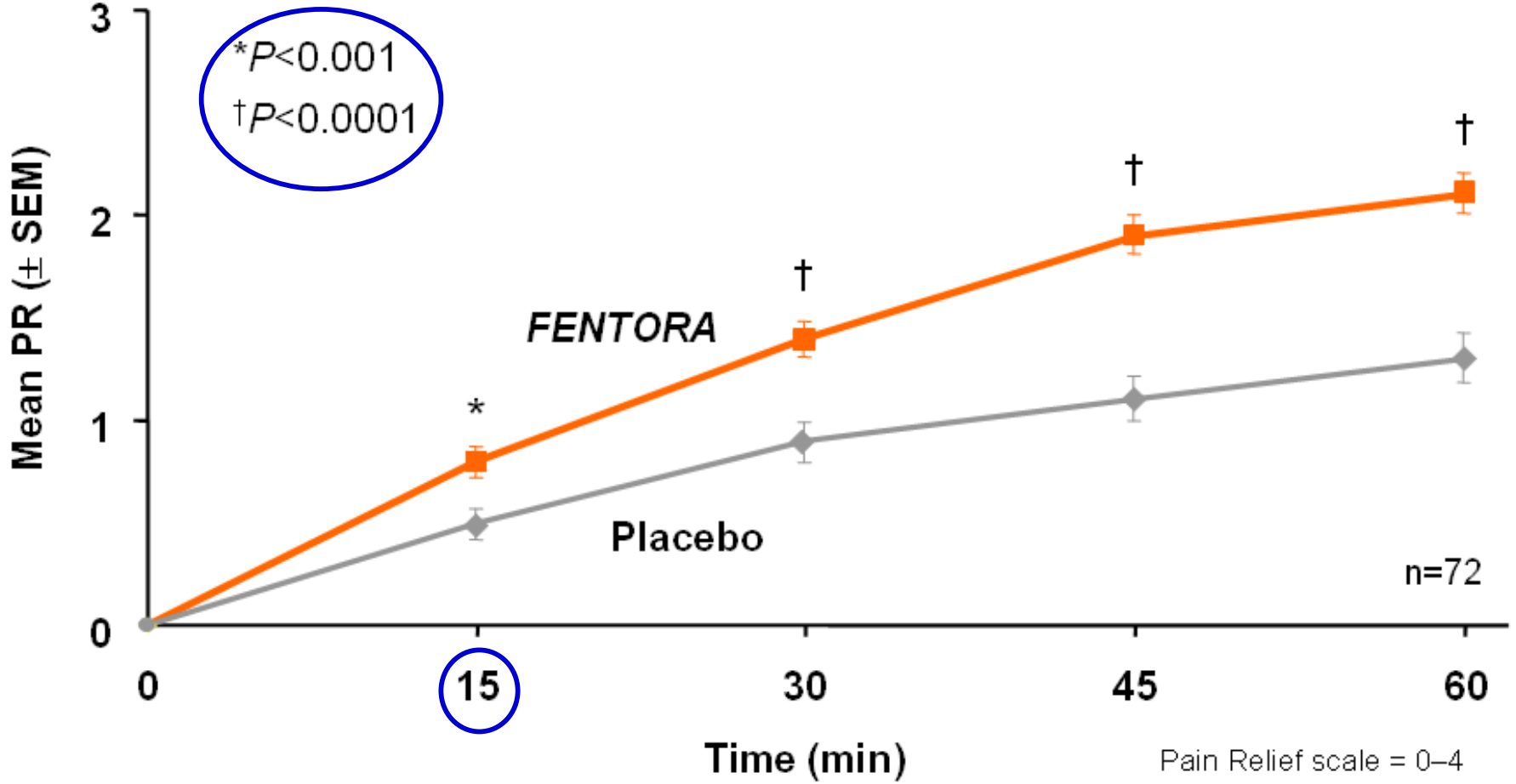


Portenoy RK et al. *Clin J Pain.* 2006;22:805-811.
FENTORA [package insert]. Frazer, PA: Cephalon, Inc.; 2007.

FENTORA fentanyl buccal tablet

Pain Relief
FENTORA Initial Trial

- **Onset of pain relief within 15 minutes**
- **Duration of pain relief up to 60 minutes (last time point measured)**



For patients with unrelieved pain, redosing may occur 30 minutes after the start of administration of *FENTORA*, using the same dosage strength.

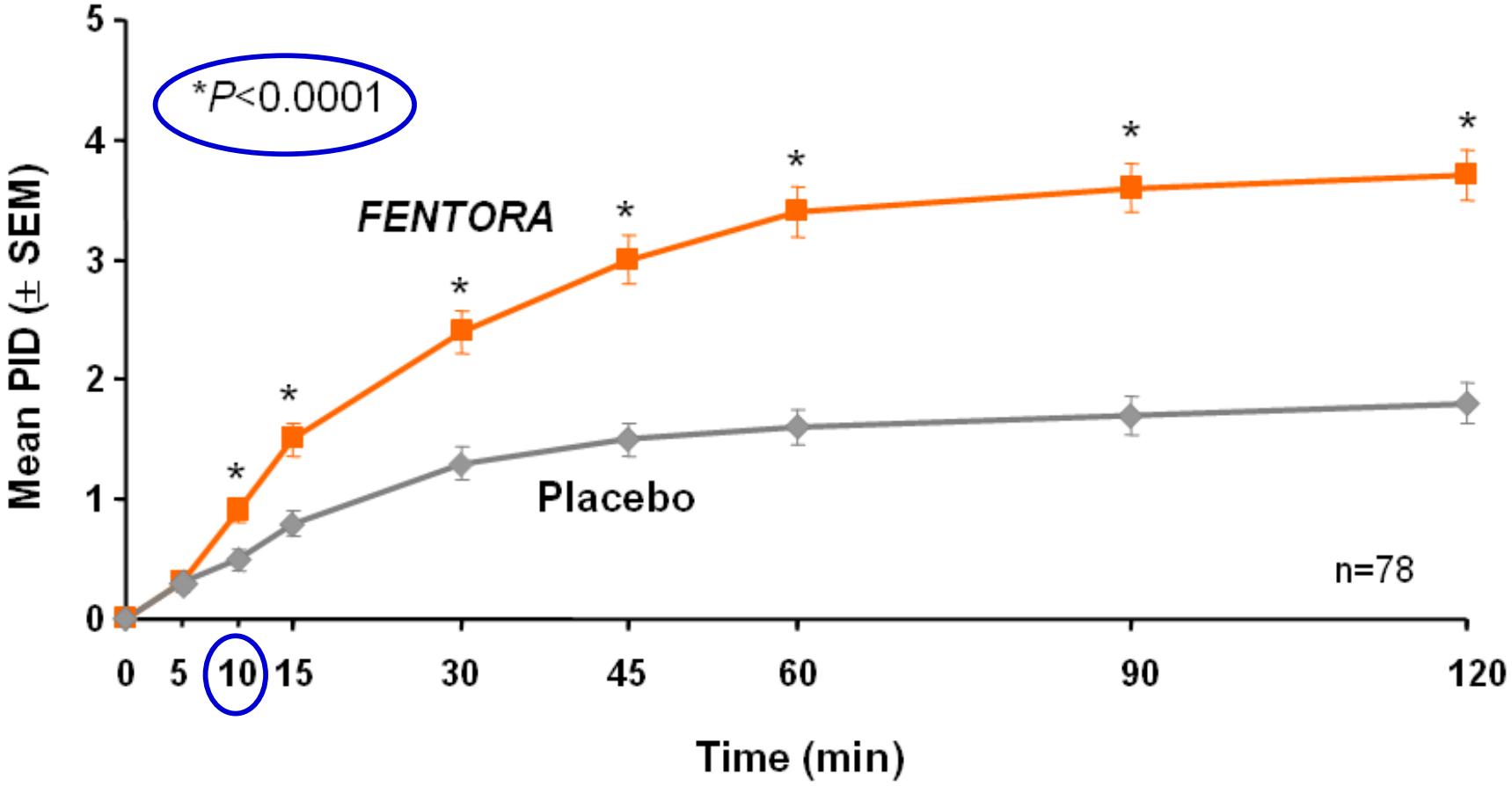
Portenoy RK et al. *Clin J Pain.* 2006;22:805-811.

FENTORA [package insert]. Frazer, PA: Cephalon, Inc.; 2007.

FENTORA® fentanyl buccal tablet C

Pain Intensity Difference
FENTORA Subsequent Trial

Greater reductions in pain observed in patients treated with *FENTORA* vs placebo

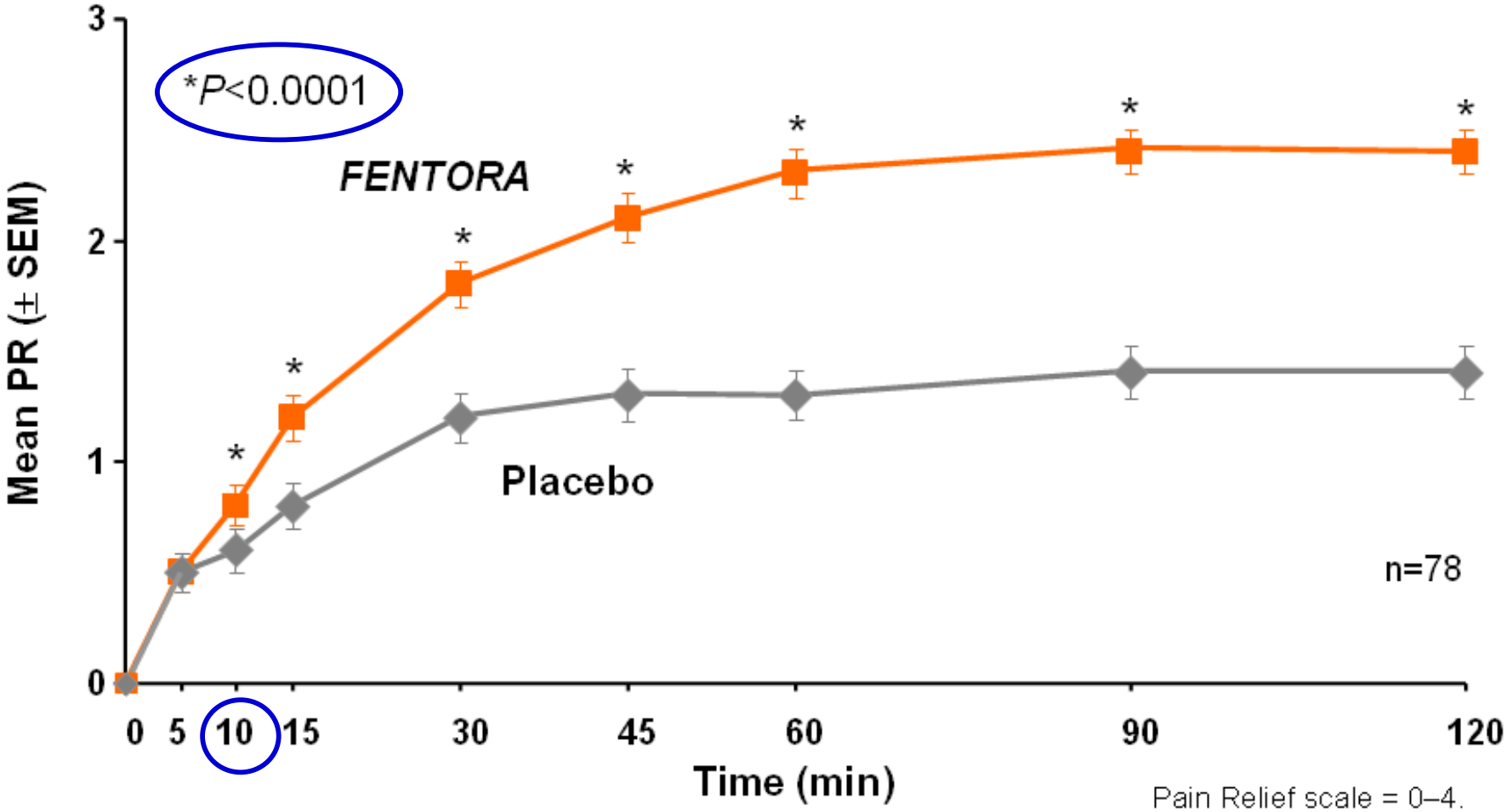


Slatkin NE et al. *J Support Oncol.* 2007;5:327-334.

FENTORA® fentanyl buccal tablet C

Pain Relief
FENTORA Subsequent Trial

- Onset of pain relief within 10 minutes in some patients
- Duration of pain relief up to 120 minutes (last time point measured)



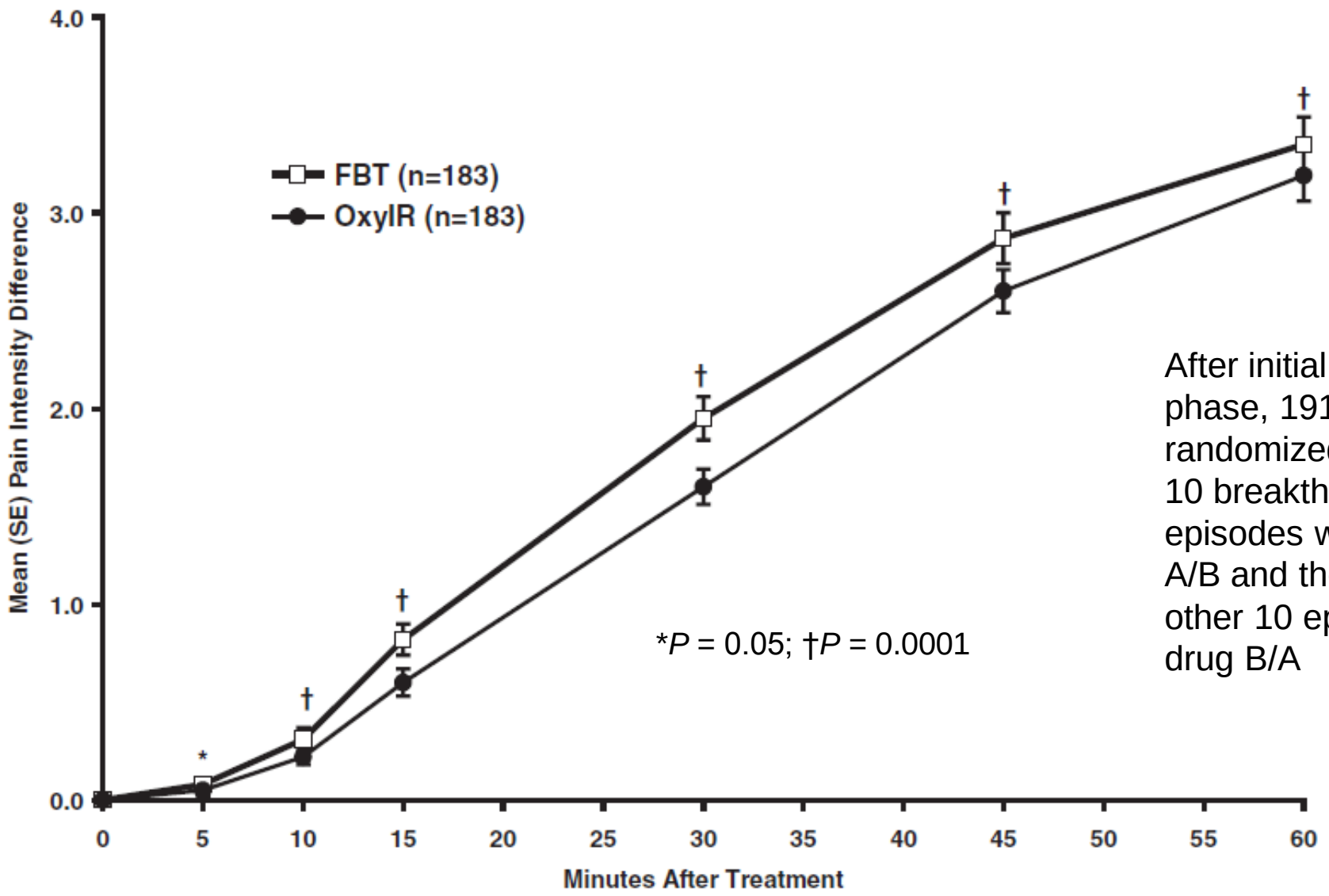
Pain Relief scale = 0–4.

For patients with unrelieved pain, redosing may occur 30 minutes after the start of administration of *FENTORA*, using the same dosage strength.

Slatkin NE et al. *J Support Oncol.* 2007;5:327-334.

FENTORA® fentanyl buccal tablet

Fentora® vs. Oxycodone Immediate-Release

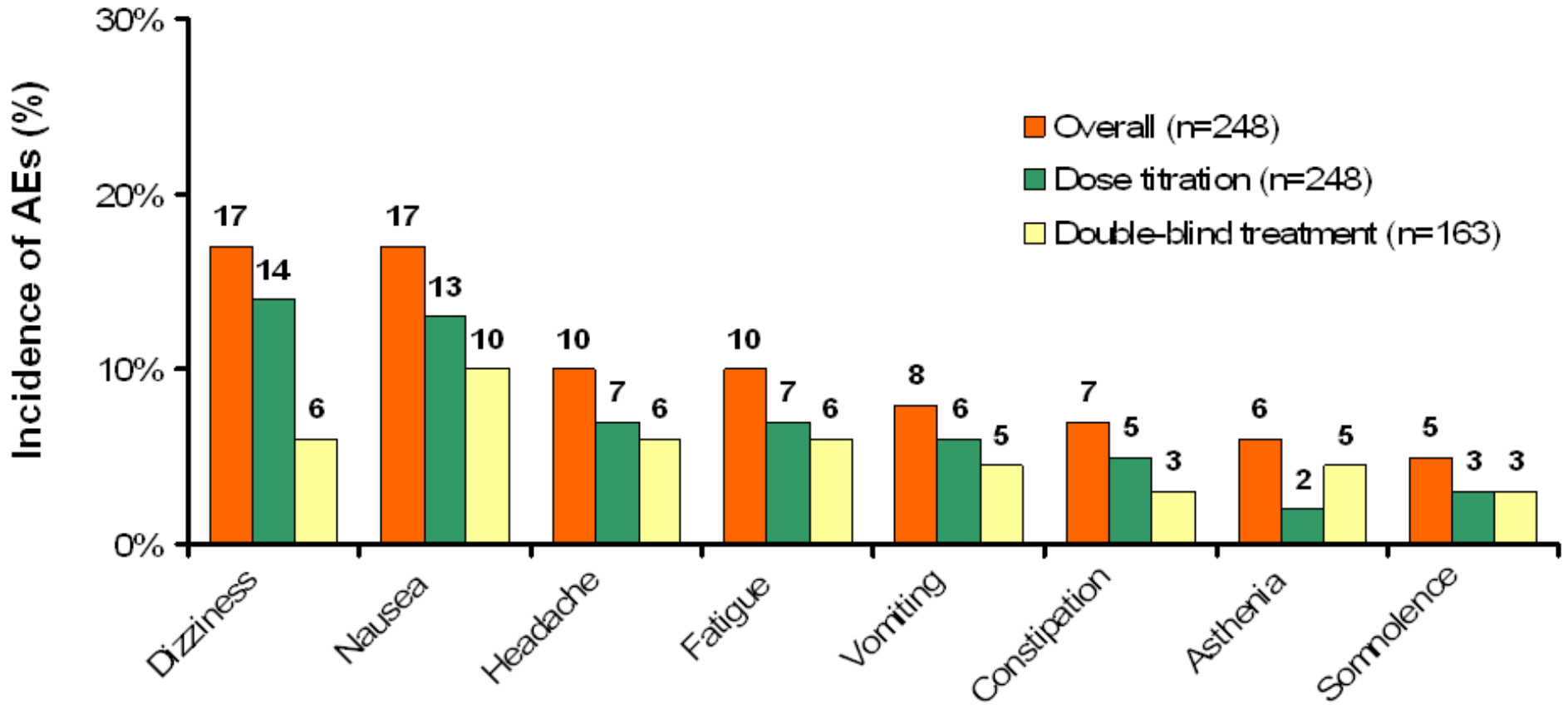


*P = 0.05; †P = 0.0001

After initial titration phase, 191 patients randomized to treat 10 breakthrough episodes with drug A/B and then the other 10 episodes with drug B/A

Ashburn et al. Anesth Analg 2011;112:693–702

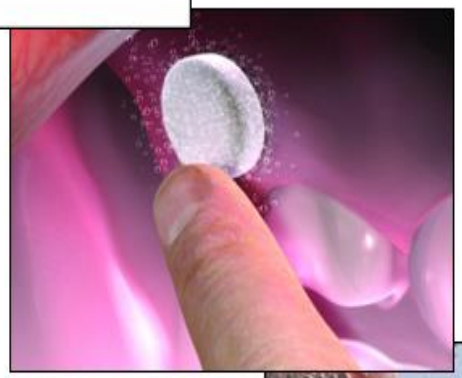
Common Adverse Events
FENTORA Pivotal Cancer Trials—Combined
AEs occurring in ≥5% of patients taking *FENTORA*



每次突發性疼痛發作時先給予一次
30分鐘後若無改善可再給予一次相同劑量

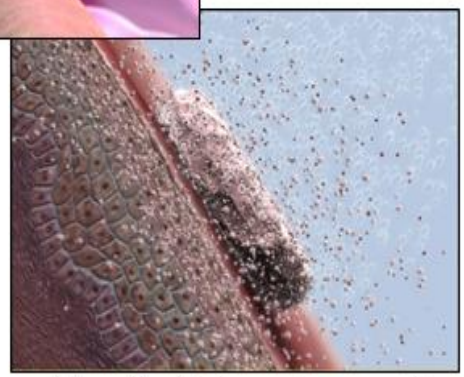
1. Peel it.

將口頰錠從鋁箔包裝取出



2. Place it.

立刻放置於上頰及牙齦之間
(除此之外,也可將口頰錠置於
舌下也能產生一樣的藥效)



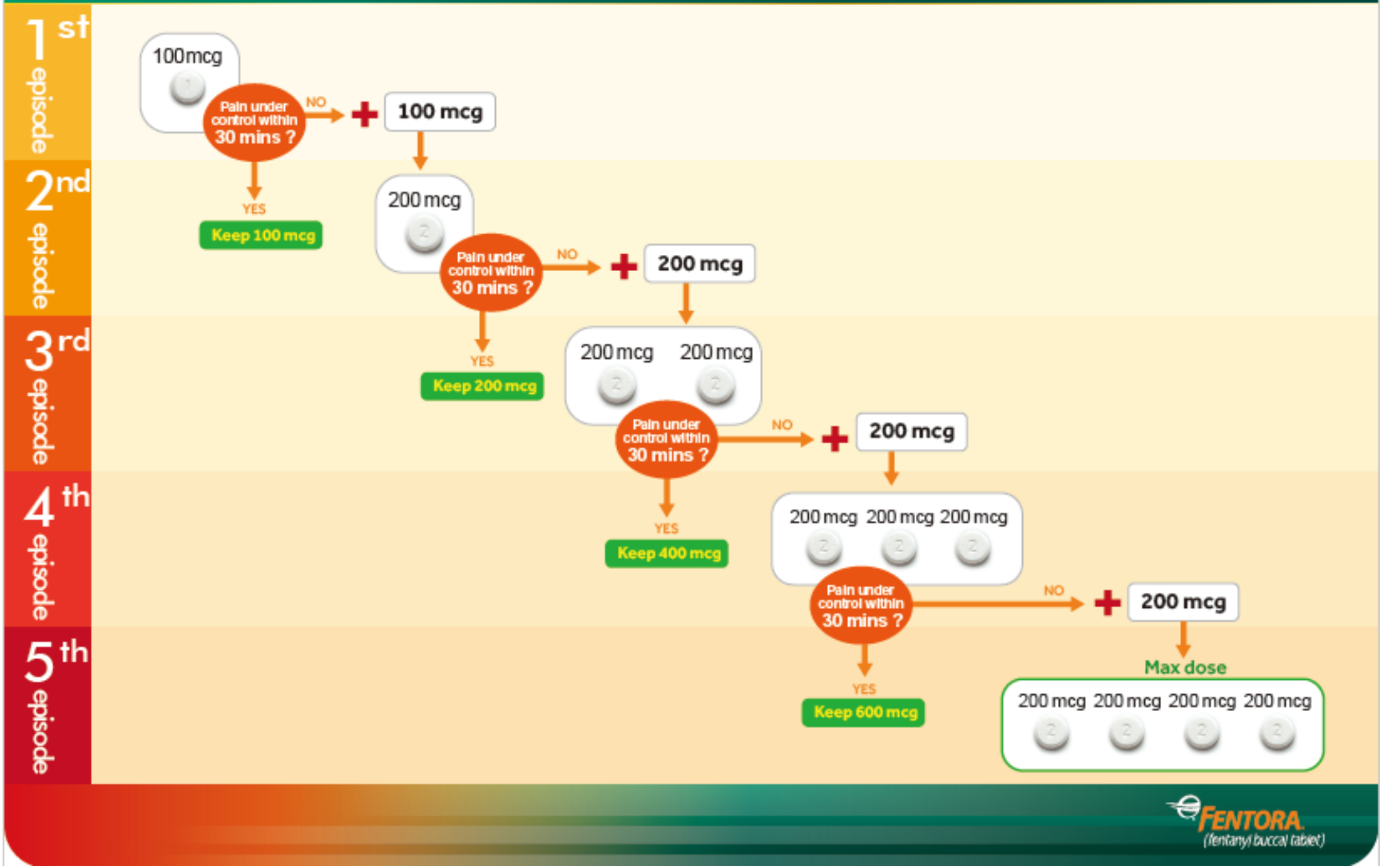
3. Feel it.

口頰錠在 10 分鐘內
即可迅速溶解產生藥效

*Tablet should not be stored once removed from the blister package, as the tablet integrity may be compromised and risk of accidental exposure to a tablet can occur.
†If remnants from the tablet remain after 30 minutes, they may be swallowed with a glass of water.
FENTORA [package insert]. Frazer, PA: Cephalon, Inc.; 2007.

FENTORA
fentanyl buccal tablet

Titration of Fentora® 100 mcg , 200 mcg , 400 mcg , 600 mcg , 800 mcg



The 1st ROO in Taiwan: Painkyl®

Fentanyl buccal soluble film (FBSF)

Rapid onset opioid—Transmucosal fentanyl	Onset of analgesia	Duration
Buccal soluble film (FBSF)	9–15 min	1-2 hrs

BDSI's "BEMA" technology

BEMA technology

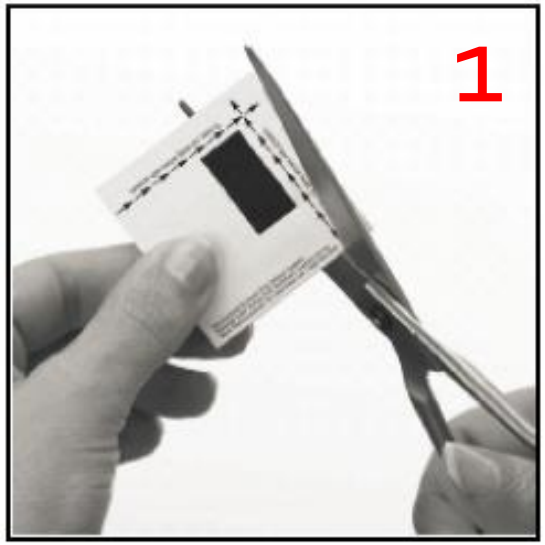
Bio **E**rodible **M**uco **A**dhesion

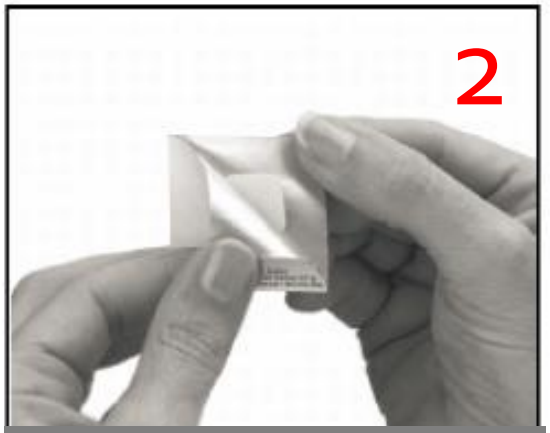
生物可溶性黏膜黏附雙層釋放技術

3rd Generation of ROO:

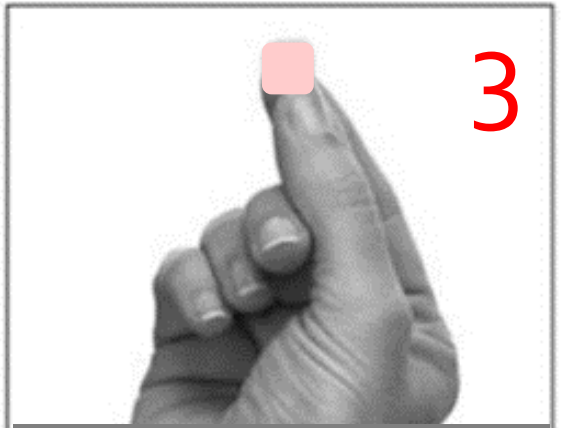
- Increase bioavailability
- Less local irritation
- Less GI absorption with less GI toxicity

The instruction of Painkyl®



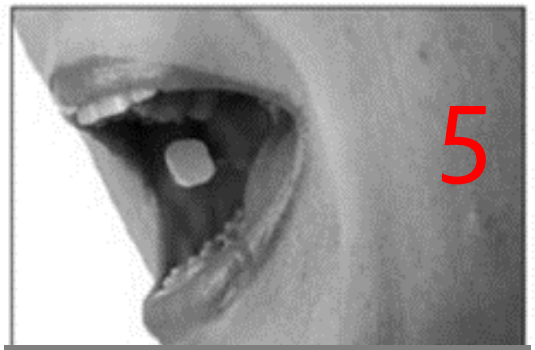


使用前用舌頭潤濕您的口腔黏膜或以清水漱口



貼片置於一清潔、乾燥的手指近指尖處，粉紅面朝上

粉紅面貼附到口腔黏膜,並按壓貼片 5 秒。



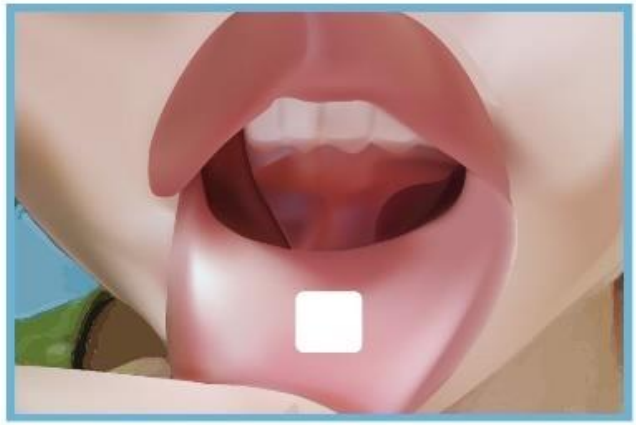
五分鐘後可以喝水或果汁,30 分鐘內會溶散。溶散前避免進食

口訣:手乾，口濕，粉紅對粉紅，按壓5秒鐘

使用部位：口頰及唇內

口頰給藥

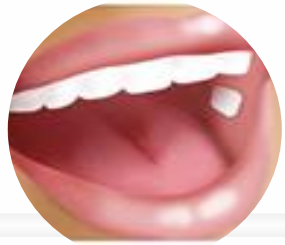
若不小心吞下，不須再補劑量，但效果會變慢及變差。



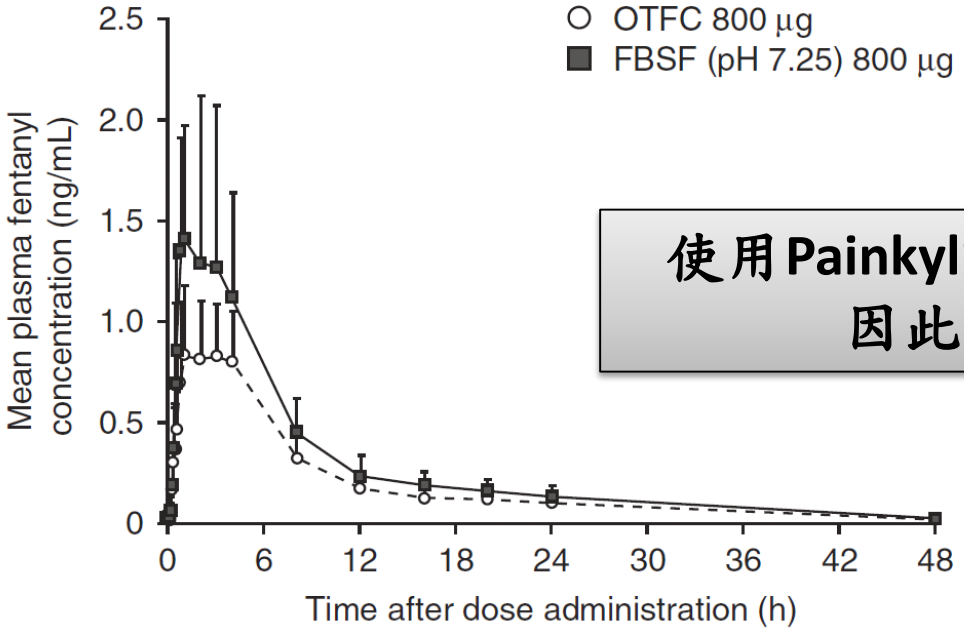
唇內給藥

針對年老病患、照護者給藥→唇內給藥

Pain relieve start in 9 mins



Comparative pharmacokinetics Painkyl® vs. Actiq®(OTFC)



使用Painkyl®9分鐘開始測得血中Fentanyl成分
因此病患於9分鐘疼痛開始緩解

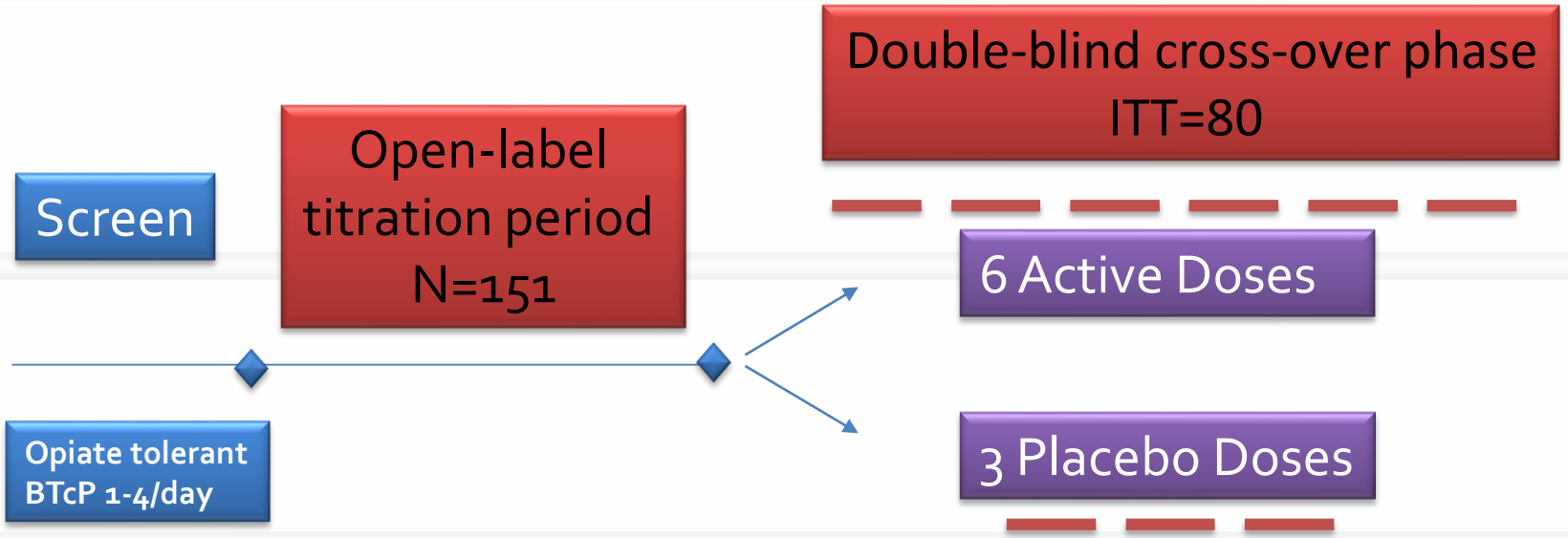
Drug and dose	t_{first} (mean, min)	C_{max} (mean, ng/mL)	t_{max} (median, h)	AUC_{∞} (mean, ng•h/mL)
FBSF 800 µg	9.0	1.70	1.0	14.5
OTFC 800 µg	13.2	1.03	2.0	10.3

F=fentanyl buccal soluble film; OTFC=oral transmucosal fentanyl citrate.
C∞=area under the plasma concentration-time curve from time zero to infinity; Cmax=maximum drug concentration in plasma;
first=time to reach the first quantifiable plasma concentration above the pre-dose concentration; tmax=time to reach Cmax.

Fentanyl buccal soluble film(FBSF) for breakthrough pain in patients with cancer

A randomized, double-blined, placebo-controlled study

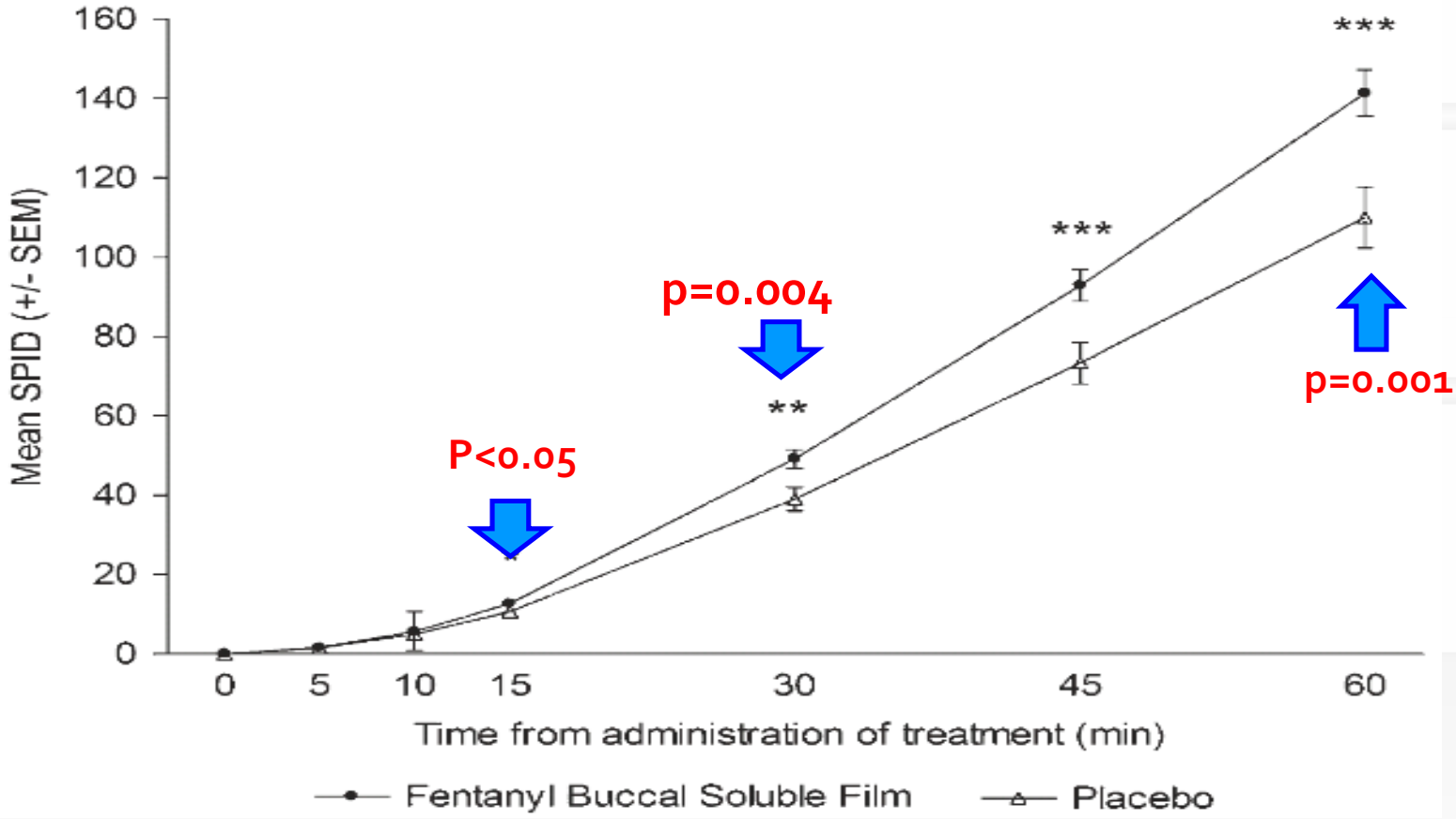
< FEN-201 study design>



Primary outcome measure: SPID30 (the weighted Sum of Pain Intensity Difference over the first 30 min postdose)

Pivotal study : FEN 201

與Placebo相比,止痛效果於第15分鐘開始有明顯的差異



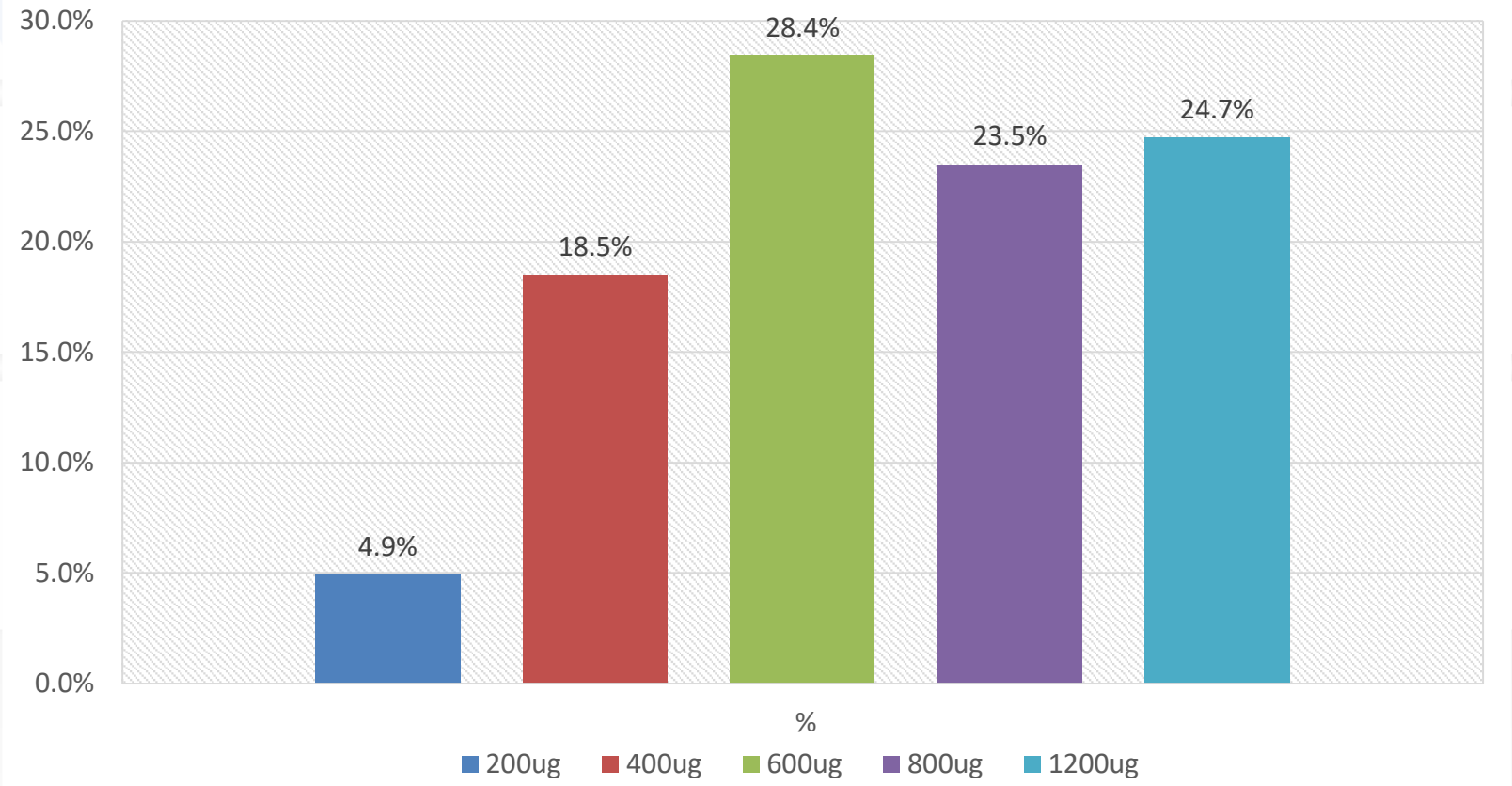
.*P < 0.05; **P < 0.01; ***P < 0.001. SEM, standard error of the mean

Annals of Oncology 21: 1308–1314, 2010

Pivotal study：FEN 201

病患每日長效Opioid劑量平均為:196.6 mg morphine

95 % 的病患需要使用400mcg以上的劑量



Pivotal study : FEN 201

副作用低，不超過6%，且未發生呼吸抑制之副作用

Adverse events: Painkyl® (n = 151)

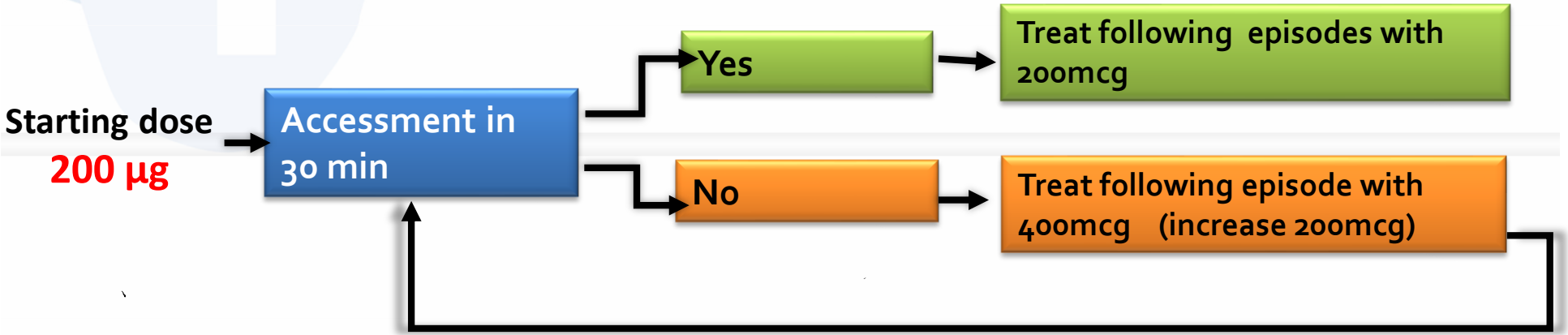
Adverse even	Incidence,n(%)
Somnolence	9(6.0)
Nausea	8(5.3)
Dizziness	7(4.6)
Vomiting	6(4.0)
Headache	4(2.6)
Constipation	3(2.0)
Dry month	2(1.3)
Dysgeusia	2(1.3)
Pruritus	2(1.3)
Confessional state	2(1.3)

There was no respiratory depression even in this study !!

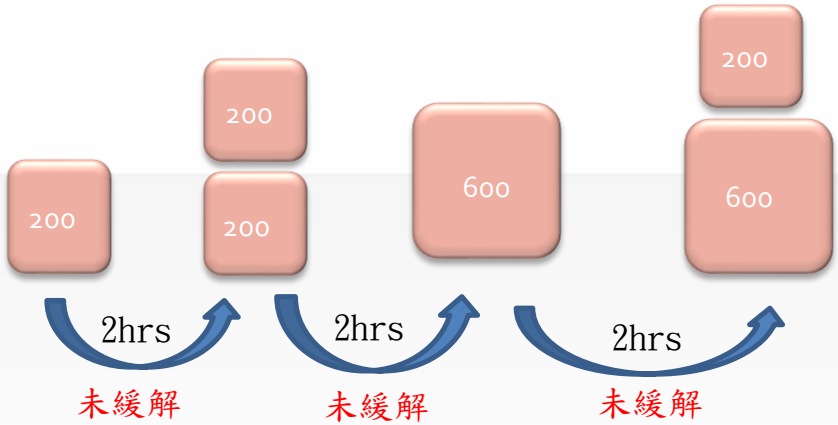
Annals of Oncology 21: 1308–1314, 2010

Painkyl® titration to effective dose

Titration: Dose-finding scheme:



兩次使用需間隔2小時



若病患每日經歷超過四次突發性癌疼痛事件，則可考慮提高治療持續性癌疼痛的日夜連續型(around-the-clock)鴉片類藥物劑量。

Difference of Painkyl and Fentora

	Fentora®（口頰錠)	Painkyl®（口頰溶片)
上市時間(FDA)	2nd generation (2006上市)	3rd generation (2009上市)
生體可用率	65%	71%
止痛速度	10-15 mins	9-15 mins
1.劑量範圍 2.沒法找到(調整至)有效劑量	100-800mcg 16%	200-1200mcg 3%
單次最大片(錠)數	4	4
健保價	220元/100 mcg	275元/200mcg
個體間差異	25~31%	7-10%
使用部位	口頰/舌下	口頰 / 唇內
容易使用	發泡錠要放於正確位置, 每次要更換使用部位	小貼片易放置
局部刺激	10%。感覺異常、潰瘍、出血：疼痛(4%)、潰瘍(3%)、刺激(3%)	無

1.Painkyl/Fentora仿單
2.台灣安寧緩和醫學會2017末期疾病疼痛評估與處置Chap 5. P144

適應症

癌症病患
18歲以上

＋

正在使用ATC opioid並具有耐受性

＋

突發性疼痛

→ Fentora / Painkyl

at least 60 mg of oral morphine daily,
at least 25 mcg/hr. of transdermal fentanyl,
at least 30 mg of oral oxycodone daily,
at least 8 mg of oral hydromorphone daily,
at least 25 mg oral oxymorphone daily,

Patients must remain on around-the-clock opioids while taking Fentora/Painkyl

Outline

1. **Characteristics of breakthrough cancer pain**
   何謂突發性癌症疼痛

2. **Breakthrough cancer pain treatment**
   突發性癌症疼痛之臨床處置

3. **New killer of breakthrough cancer pain**
   新一代癌症突發性疼痛的殺手

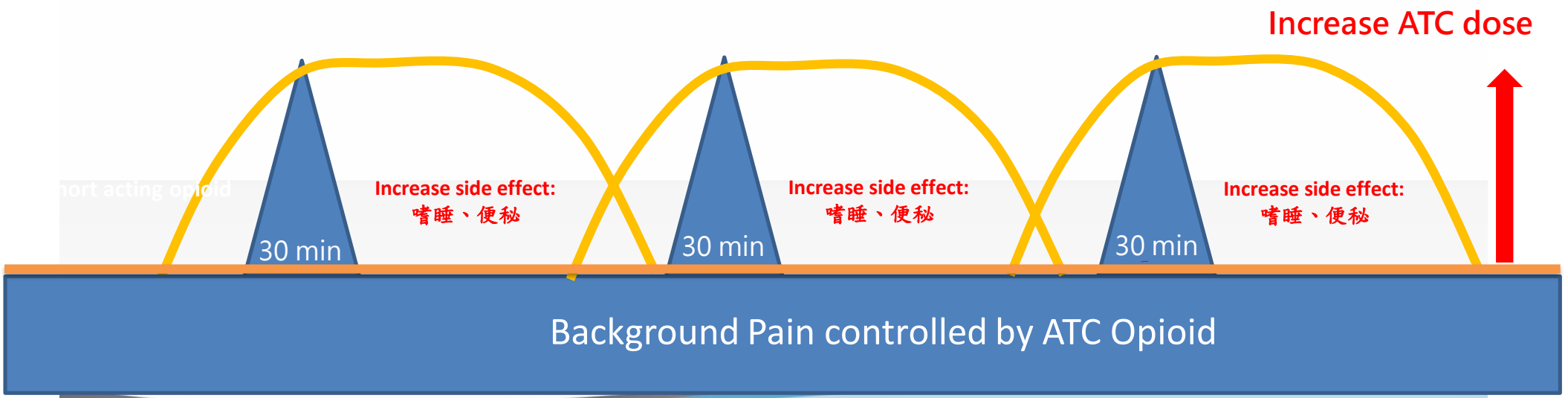
Need 3-4 times PRN medication:

頭頸癌病人RT治療下，用餐時劇烈疼痛
骨轉移病人，3-4次下床及活動中之疼痛

Oral short acting opioid- Onset :30-40 mins /Duration: 4-6 hrs

→每天3-4次口服短效Opioid= 增加ATC劑量

→副作用增加



Need 3-4 times PRN medication:

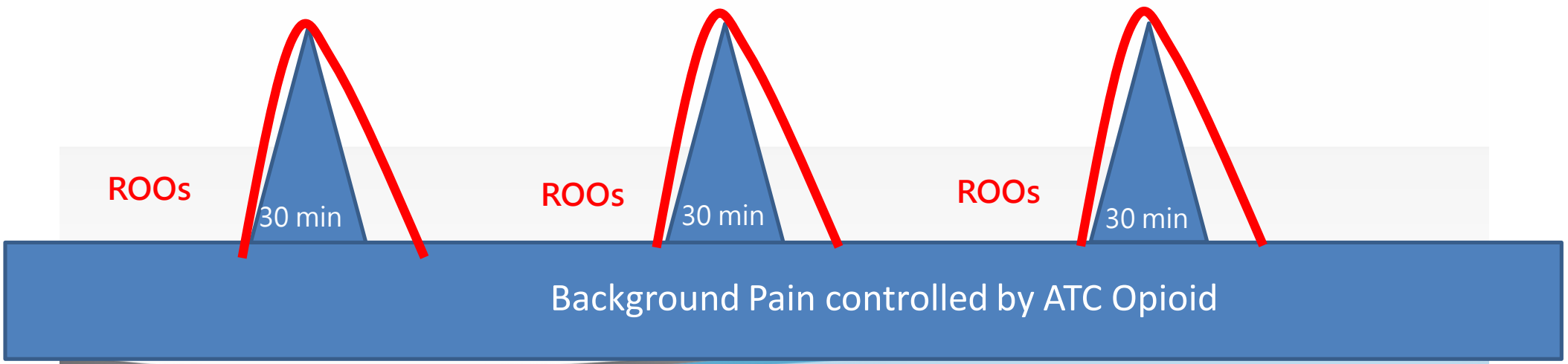
頭頸癌病人RT治療下，用餐時劇烈疼痛
骨轉移病人，3-4次下床及活動中之疼痛

→快速止痛、副作用不累積。
→不須增加ATC 劑量、維持病患生活品質

Rapidly onset with

Rapid elimination

Low side effect



Take home message

- **ROOs can rapidly release Breakthrough cancer pain within few mins.**
  - Reduce the overall medical cost (hospital days/ER and OPD times decrease)
  - Improve patients' QOL
  - Less GI toxicity.
- **ROO dose is proportional to ATC dose**
  - Patients with high ATC dose need higher ROOs dose to release BTcP.
- **Do not use ROO drugs in non-opioid tolerant patients:**
  - Risk of respiratory depression