

Breakthrough pain, the horrible time bomb of cancer patients

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Outline

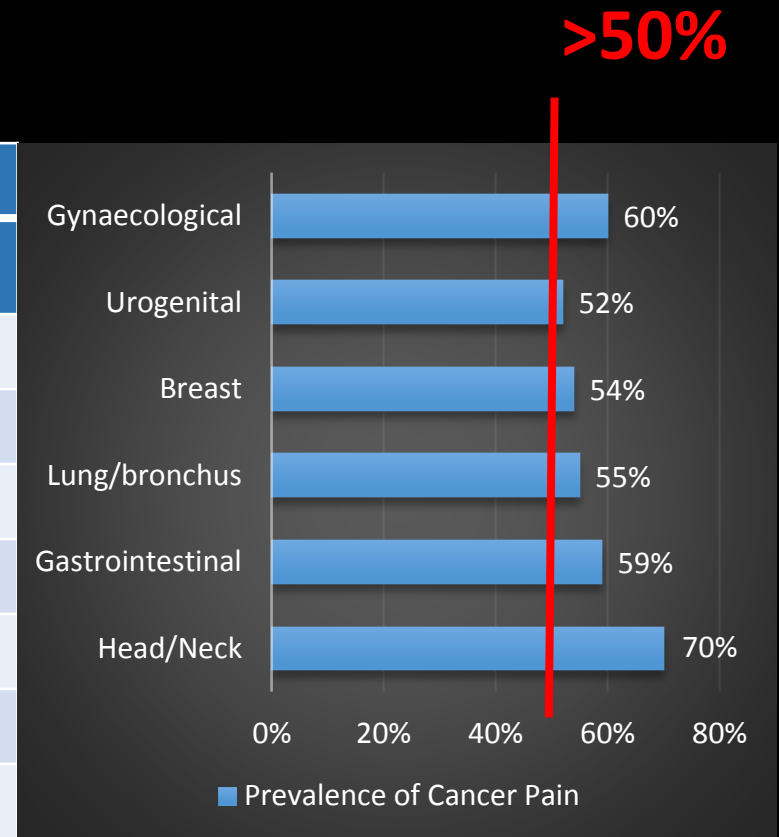
- What can we know more about breakthrough pain?
- Why do we need ROO treatments?
- What benefits could ROO bring?

More than half of the patients suffered from cancer pain

- Results of the meta-analyses:

Type of cancer	Groups 2-4		
	% Pain (95% CI)	No. of reports	No. of patients
Head/Neck	70% (51%to 88%)	3	95
Gastrointestinal	59% (44%to 74%)	9	564
Lung/bronchus	55% (44%to 67%)	7	1546
Breast	54% (44%to 64%)	7	420
Urogenital	52% (40%to 60%)	4	336
Gynaecological	60% (50%to 71%)	6	372

CI, confidence interval



'Time Lag' between BTcP suffering and treatment exists

There was a **significant lag time** between diagnosis and treatment



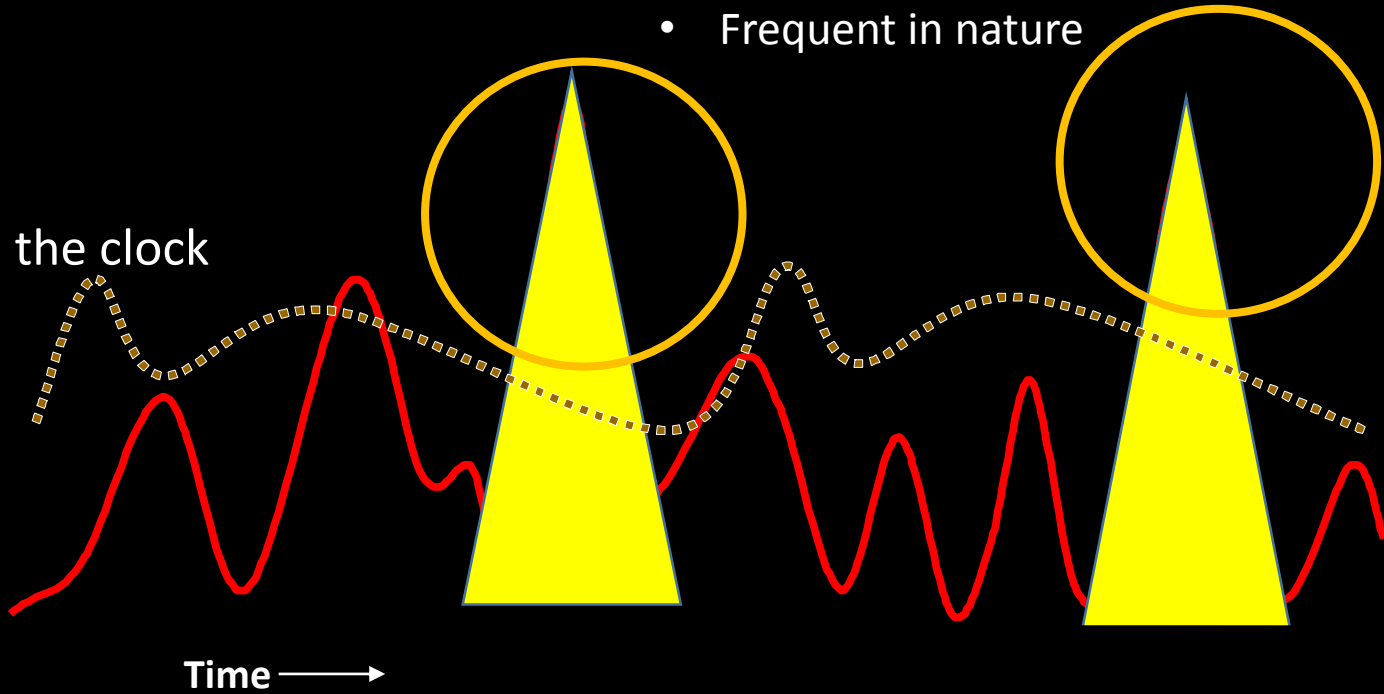
Breakthrough pain →

- Fast onset
- Short duration
- High intensity
- Frequent in nature

ATC : around the clock

Drug A

PAIN



Oxycodone (Oxycontin)

hydromorphone (Jurnista)

Buprenorphine (Transtec)

Fentanyl Patch

MXL, morphine cont

Subtypes of breakthrough cancer pain

Breakthrough pain

Sudden Onset

Gradual Onset

Spontaneous
Stimulus-Independent

Incident
Stimulus-Dependent

End-of-Dose Failure

Predictable

Unpredictable

Not precipitated
by readily
identifiable cause

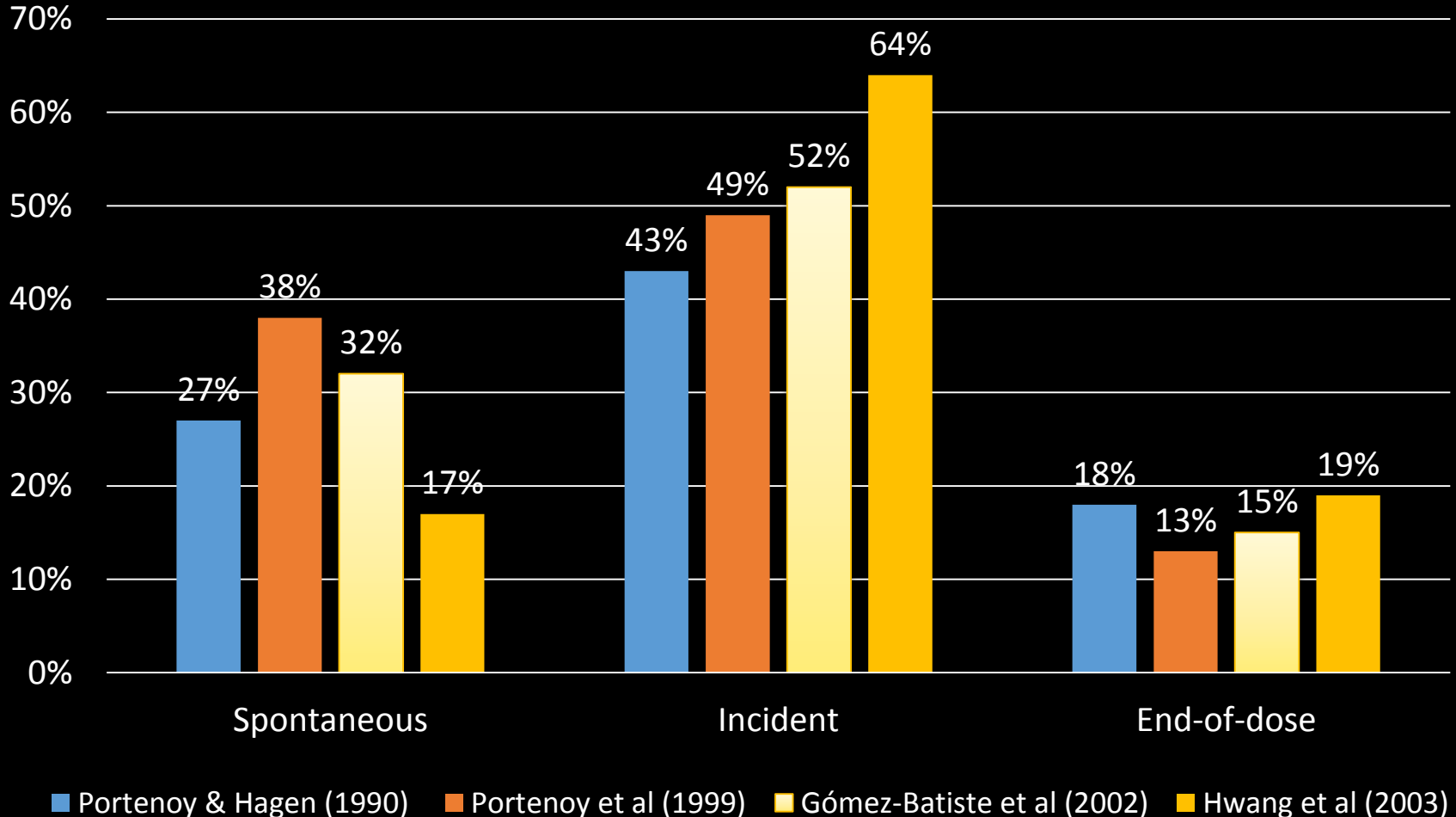
Shows consistent,
strong, temporal
relationship with
precipitating factor
(eg, movement,
procedural)

Shows inconsistent
temporal relationship
with motor activity

Presents before
scheduled dose
of ATC analgesic

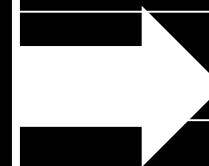
* ATC, around-the-clock

Prevalence of different types of BTcP



70%
60%
50%
40%
30%
20%
10%
0%

1. Aids of short-acting opioids or IV morphine
2. Modification of long-acting intervals

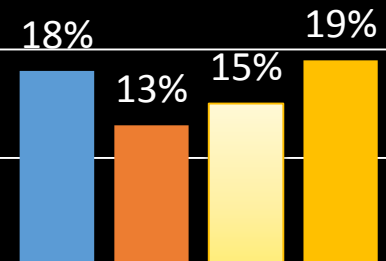


Spontaneous

Incident

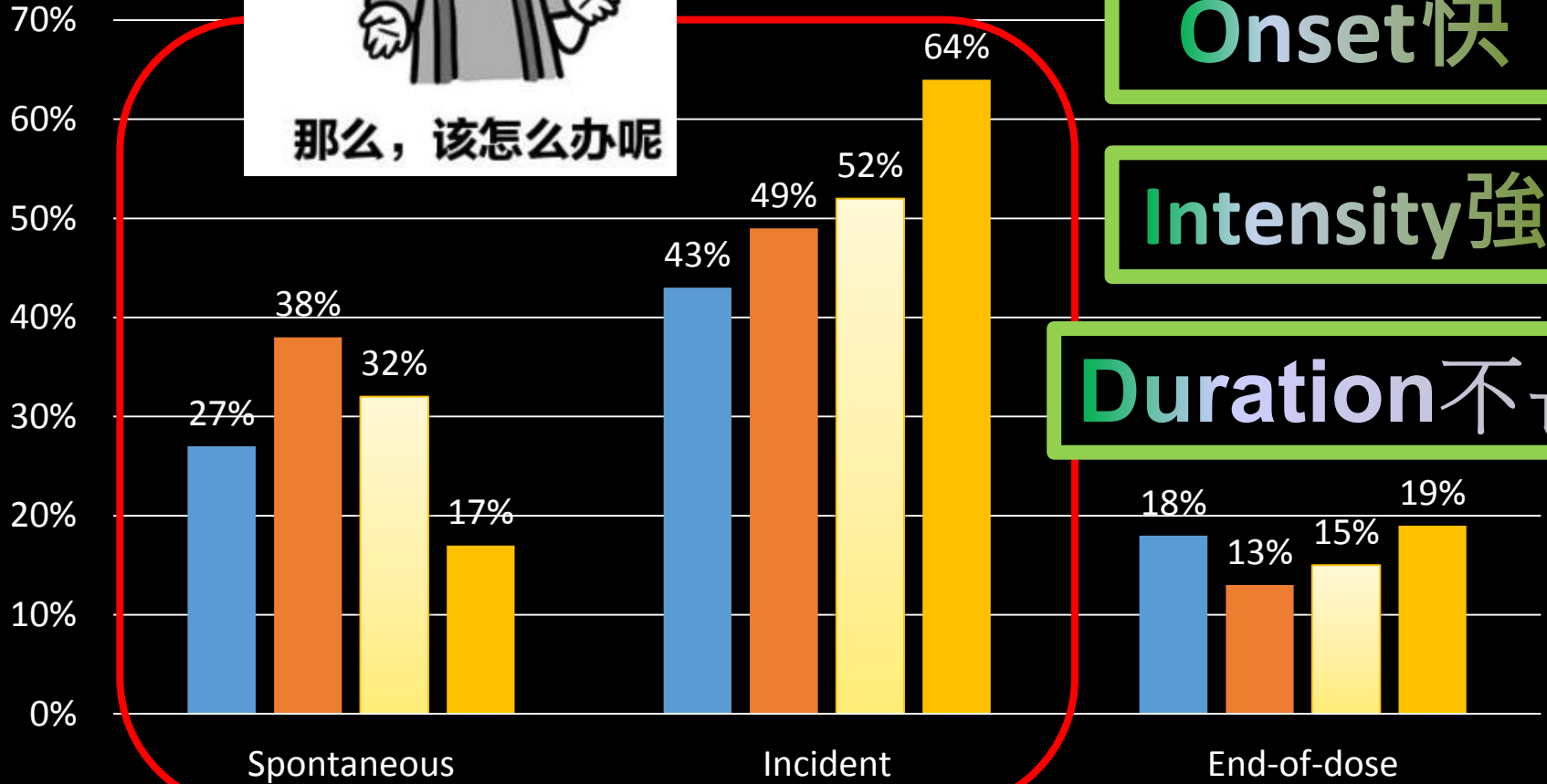
End-of-dose

■ Portenoy & Hagen (1990) ■ Portenoy et al (1999) ■ Gómez-Batiste et al (2002) ■ Hwang et al (2003)





那么，该怎么办呢



Onset快


Intensity強

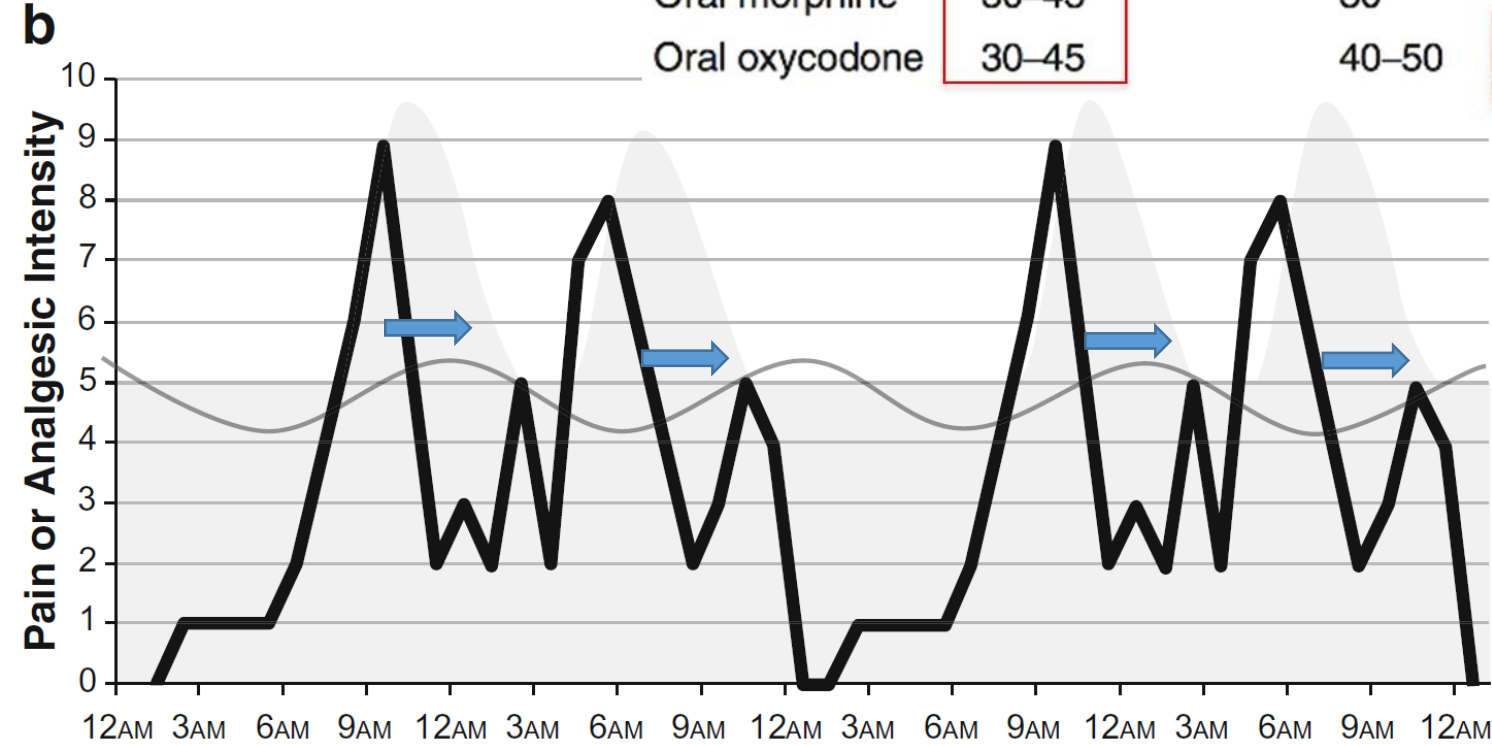
Duration不長

■ Portenoy & Hagen (1990) ■ Portenoy et al (1999) ■ Gómez-Batiste et al (2002) ■ Hwang et al (2003)

1. Portenoy RK, Hagen NA. Pain. 1990;41(3):273-81. 2. Portenoy RK, et al. Pain. 1999;81(1-2):129-34. 3. Gómez-Batiste X, et al. J Pain Symptom Manage. 2002;24(1):45-52. 4. Hwang SS, et al. Pain. 2003;101(1-2):55-64.

Table I. Characteristics of opioids used for breakthrough pain

Opioid	Analgesic onset (min)		Dwell time (min)
Oral morphine	30–45	30	NA
Oral oxycodone	30–45	40–50	NA



Oxycodone (5)

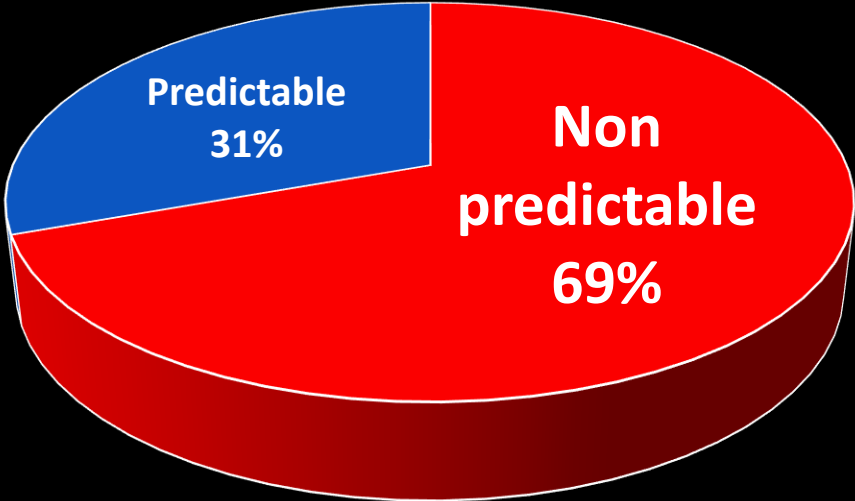


Morphine 15mg

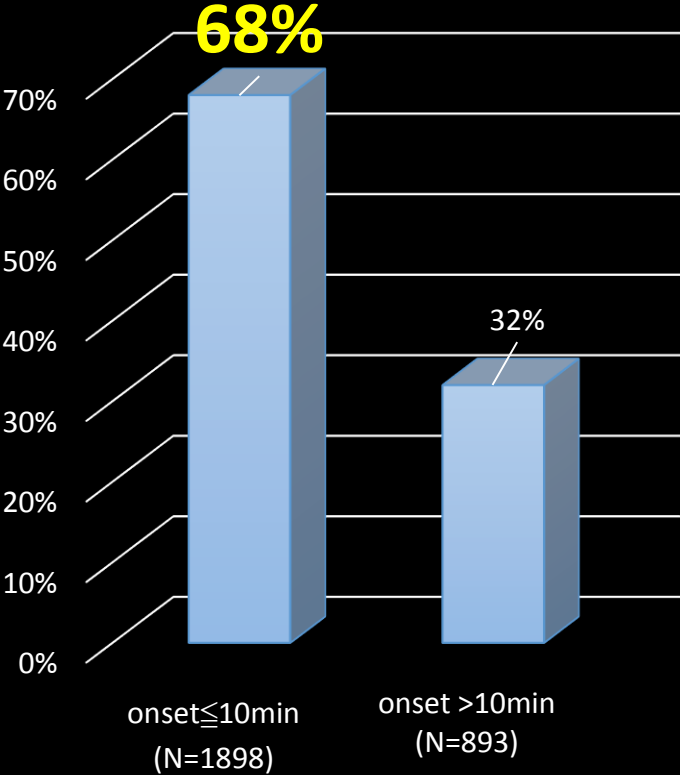
Fig. 4 Time course of cancer pain (*black line*) with various treatment strategies. The *grey shading* indicates total opioid exposure. **a** ATC every 12 h ER opioid medication (*thin grey line*). **b** Lower dosage ATC ER opioid medication, with IR opioid medication for BTP. **c** Same dosage of ATC ER opioid as in panel **b**; BTP controlled with a ROO. *ATC* around the clock, *BTP* breakthrough pain, *ER* extended release, *IR* immediate release, *ROO* rapid-onset opioid. Adapted from [5] with permission

BTP is usually unpredictable and onset less than 10 minutes

Characteristics of BTP



- : Non predictable BTP (N=2791)
- : Predictable BTP (N=1225)



Non Predictable

Onset 夠快

rapid onset (incident
<5min, spontaneous
<10min to peak)

averages 3-6 episodes per day

Accessible 可近性高

moderate-to-severe pain

Efficacy 夠強

ATC : around the clock

Drug A

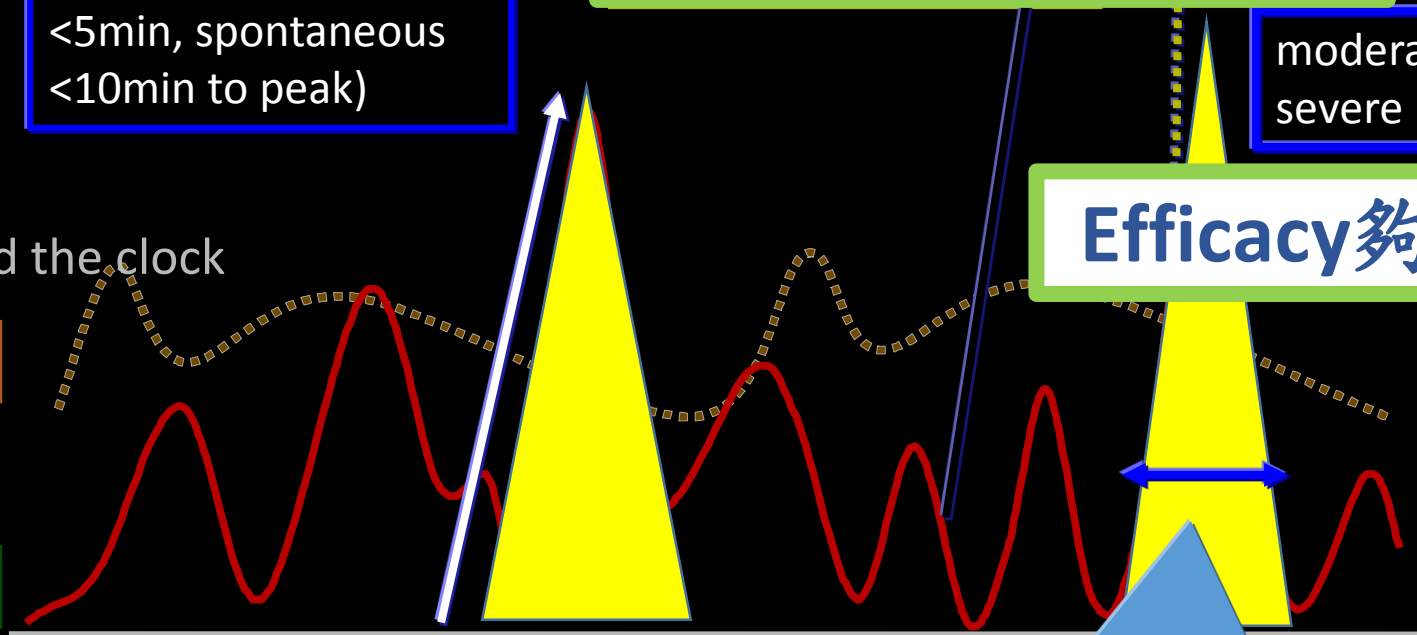
PAIN

Time →

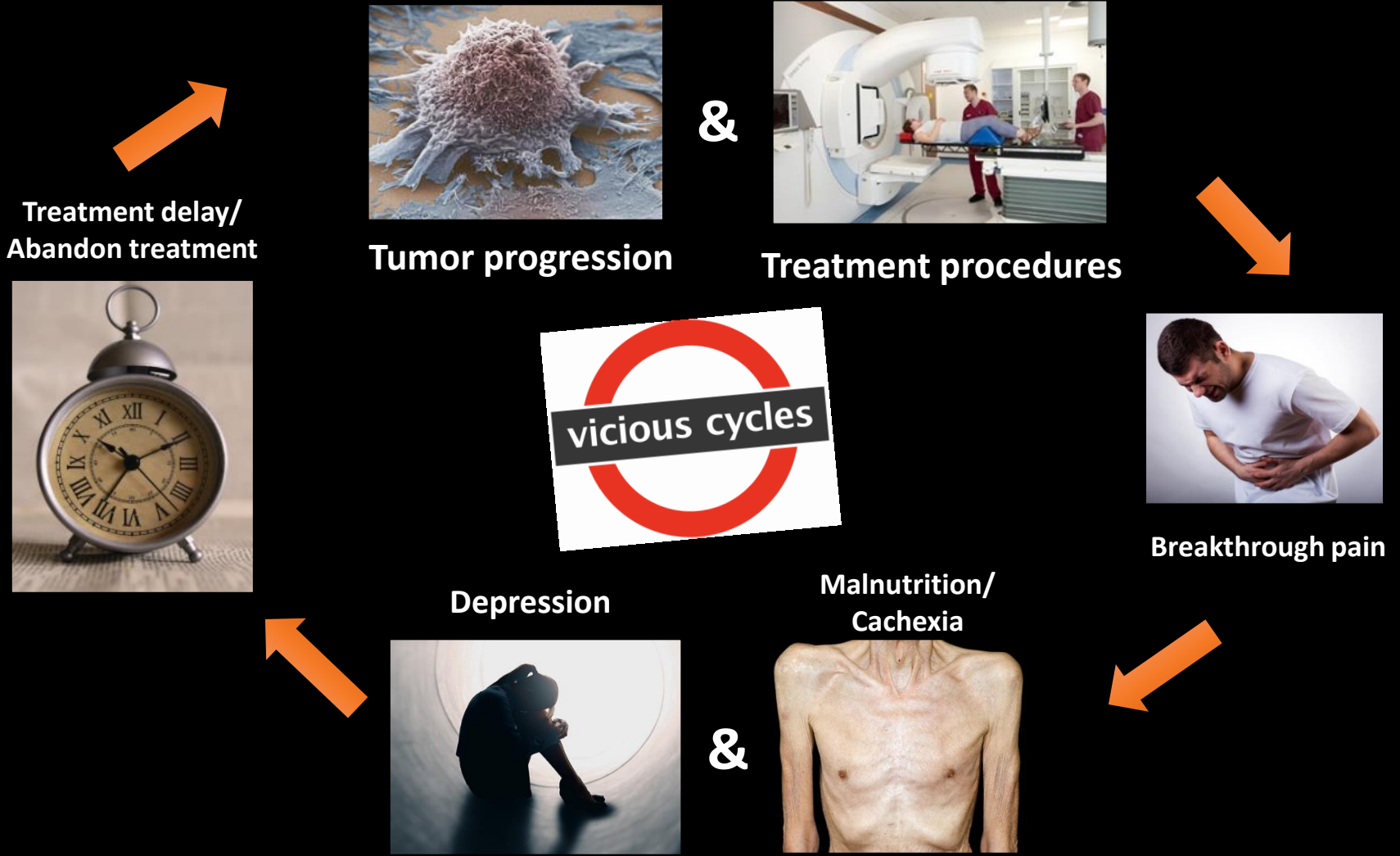
Duration 夠就好

duration of 15-30 minutes (up to 60-90 minutes)

*maximal pain intensity:3-15 minutes or even within seconds**



Vicious Cycle of Breakthrough Cancer Pain



1. Nathaniel P. Katz, Kavita L. Gajria, Alicia C. Shillington, Judith J. Stephenson & Qing Harshaw (2017), *Postgraduate Medicine*, 129:1, 32-39
2. *Clin Oncol* 2011; 23: 393-398
3. American Pain Foundation. Breakthrough Cancer Pain Survey Fact Sheet. American Pain Foundation; 2012

Different formulation of Rapid-onset-opioids

Painkyl®

**1st
Generation**



1998
Actiq® (US)
OTFC



Oral transmucosal
lozenge

**2st
Generation**



2006/2008
Fentora® (US)/
Effentora®(EU)

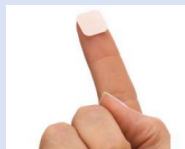


Fentanyl buccal
tablet

**3rd
Generation**



2009
Onsolis®(US)
FBSF

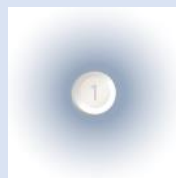


Fentanyl buccal
soluble film

Sublingual



2008
Rapinyl®/
Abstral®(EU)
SLF



Sublingual
Fentanyl

Intranasal



2009
Instanyl® (EU)
INFS



Intranasal Fentanyl
spray

Intranasal



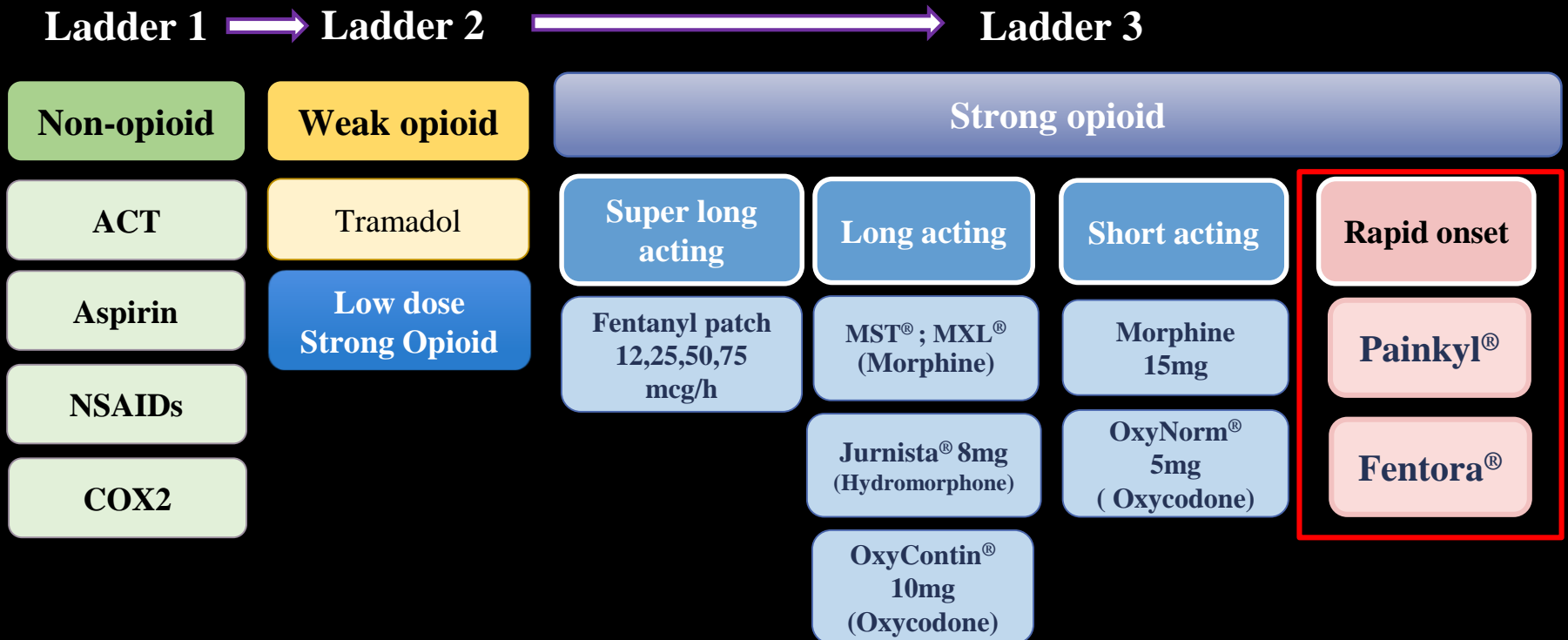
2009
Lazanda® (EU)
FPNS



Fentanyl pectin
nasal spray

BTcP=breakthrough cancer pain; ROO=rapid-onset opioid; 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. S. (2013). Journal of Pain Research 6, 189-200

A new category of strong opioids: Rapid-onset opioids

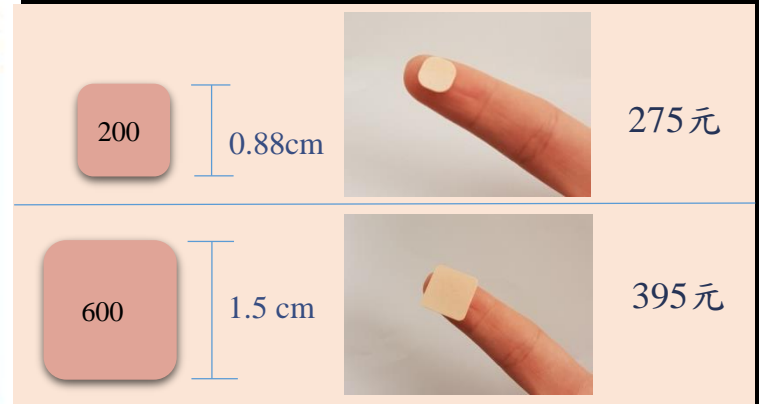
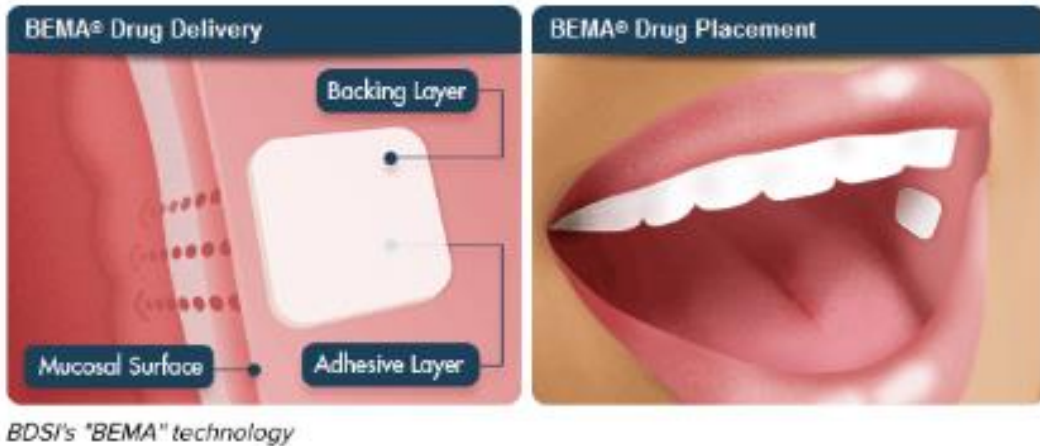


Adjuvant analgesics:

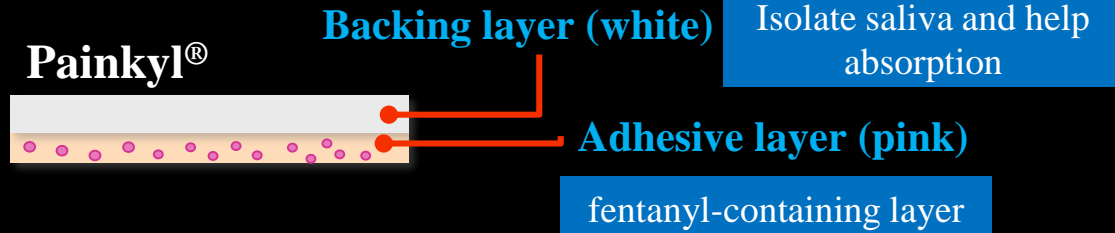
Antidepressants; Anticonvulsants; Corticosteroids; Bisphosphonate; GABAergic adjuvant analgesics.....

The newest ROO in Taiwan: Painkyl® Fentanyl buccal soluble film (FBSF)

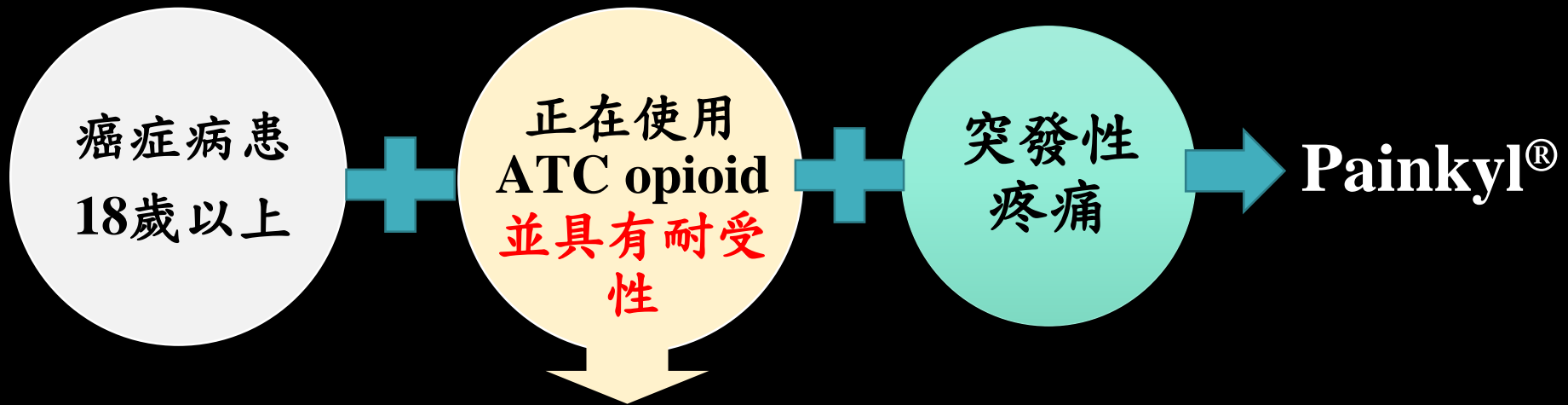
Transmucosal fentanyl	Onset of analgesia	Duration
Buccal soluble film (FBSF)	9–15 min	1-2 hrs



BEMA technology
Bio **E**rodible **M**uco **A**dhesion
 生物可溶性黏膜黏附雙層釋放技術



Painkyl[®] indication (健保)



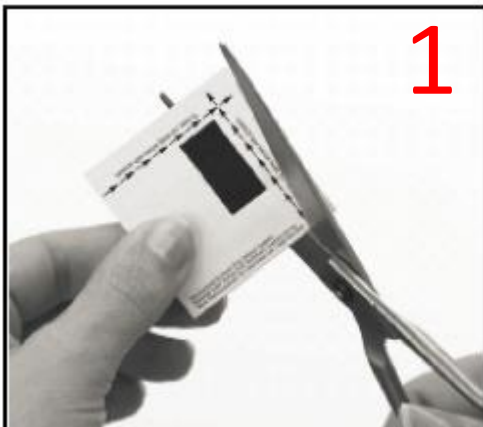
- Patients considered opioid tolerant:

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/ hour
- 8 mg oral hydromorphone/day
- 30 mg oral oxycodone/day
- 25 mg oral oxymorphone/day,

or an equi-analgesic dose of another opioid for one week or longer.

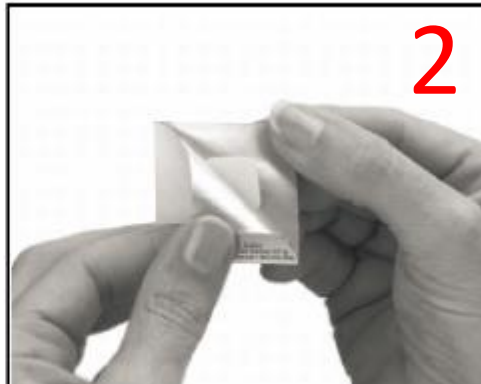
Patients must remain on around-the-clock opioids while taking Painkyl[®]

How to use Painkyl[®] correctly?



1

先用剪刀將鋁箔包裝剪開



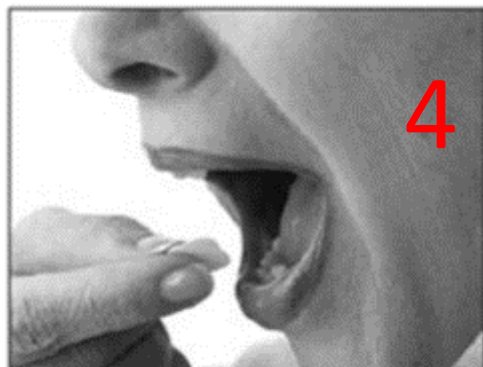
2

使用前用舌頭潤濕您的口腔黏膜或以清水漱口



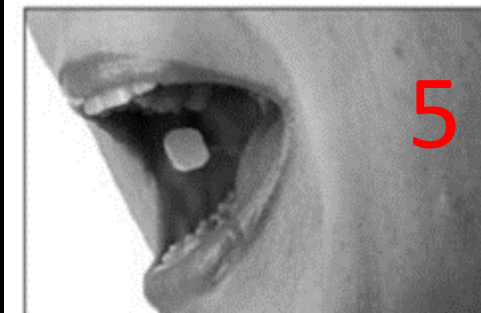
3

貼片置於一清潔、乾燥的手指近指尖處，粉紅面朝上



4

粉紅面貼附到口腔黏膜，並按壓貼片5秒。



5

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



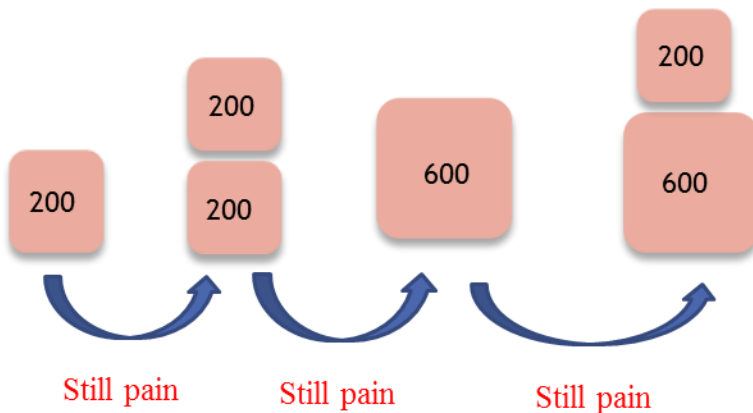
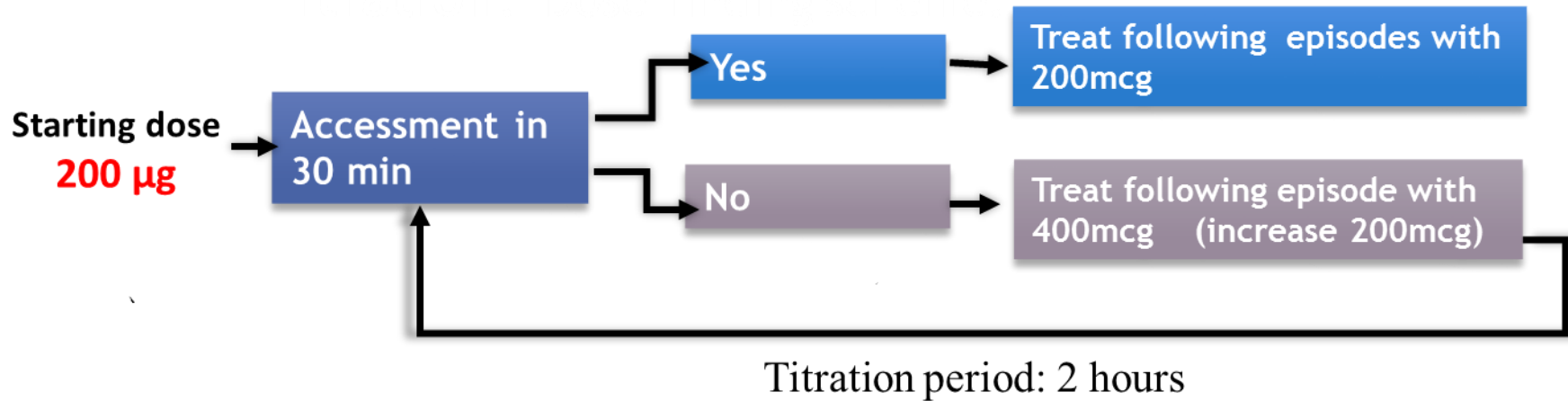
口頰給藥



唇內給藥

口訣：手乾，口濕，粉紅對粉紅，按壓5秒鐘

Painkyl[®] titration to effective dose

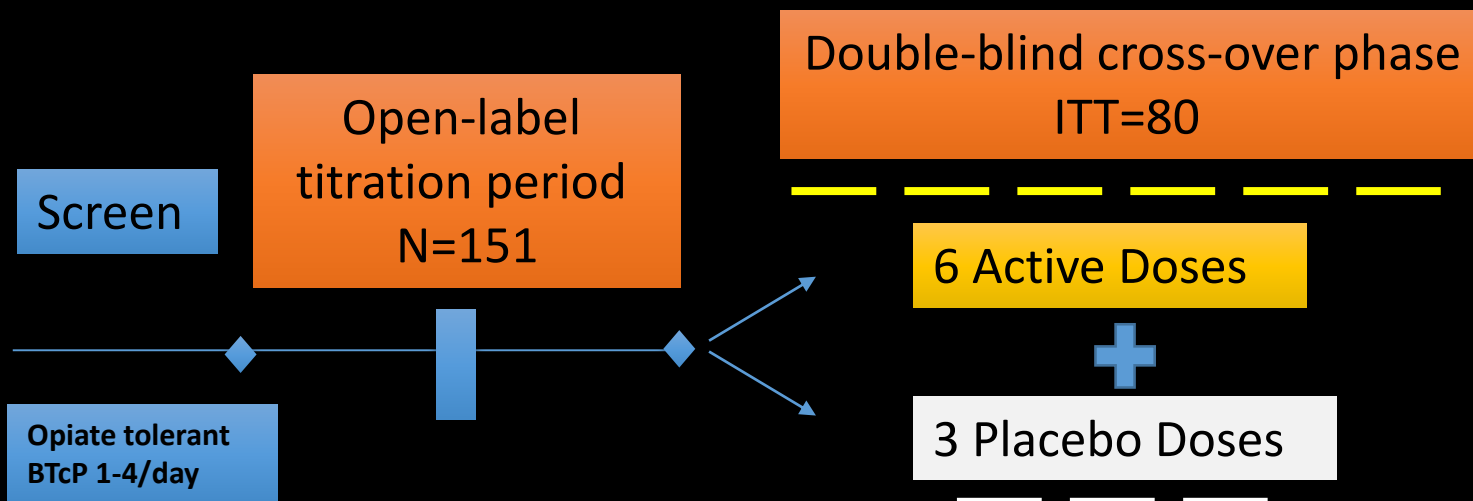


If patients experienced BTcP **more than four times** per day, considering to increase ATC dose

Fentanyl buccal soluble film for breakthrough pain in patients with cancer

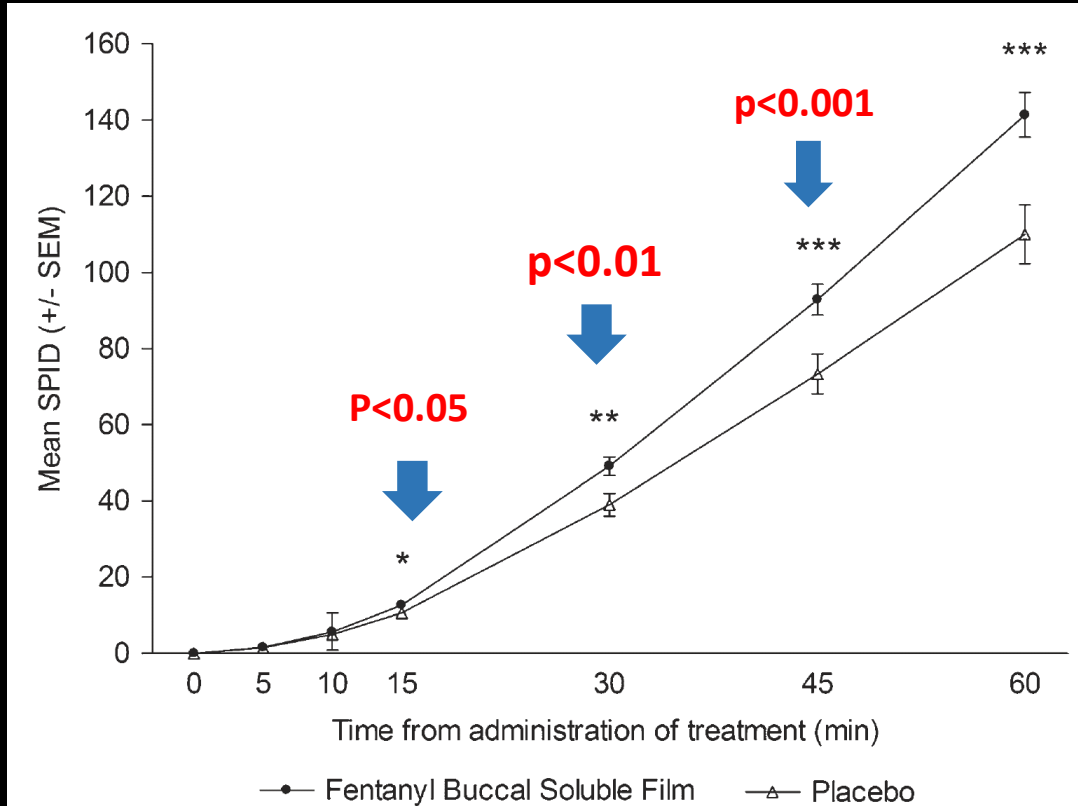
-A randomized, double-blinded, placebo-controlled study

< FEN-201 study design >



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

Pain was relieved in 15 minutes with FBSF



The least squares mean (LSM \pm SEM) of the SPID30 was significantly greater for FBSF-treated episodes of breakthrough pain than for placebo-treated episodes (47.9 \pm 3.9 versus 38.1 \pm 4.3; P = 0.004).

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

Adverse effects were \leq 6% in FEN-201

Adverse events: Painkyl[®] (n = 151)

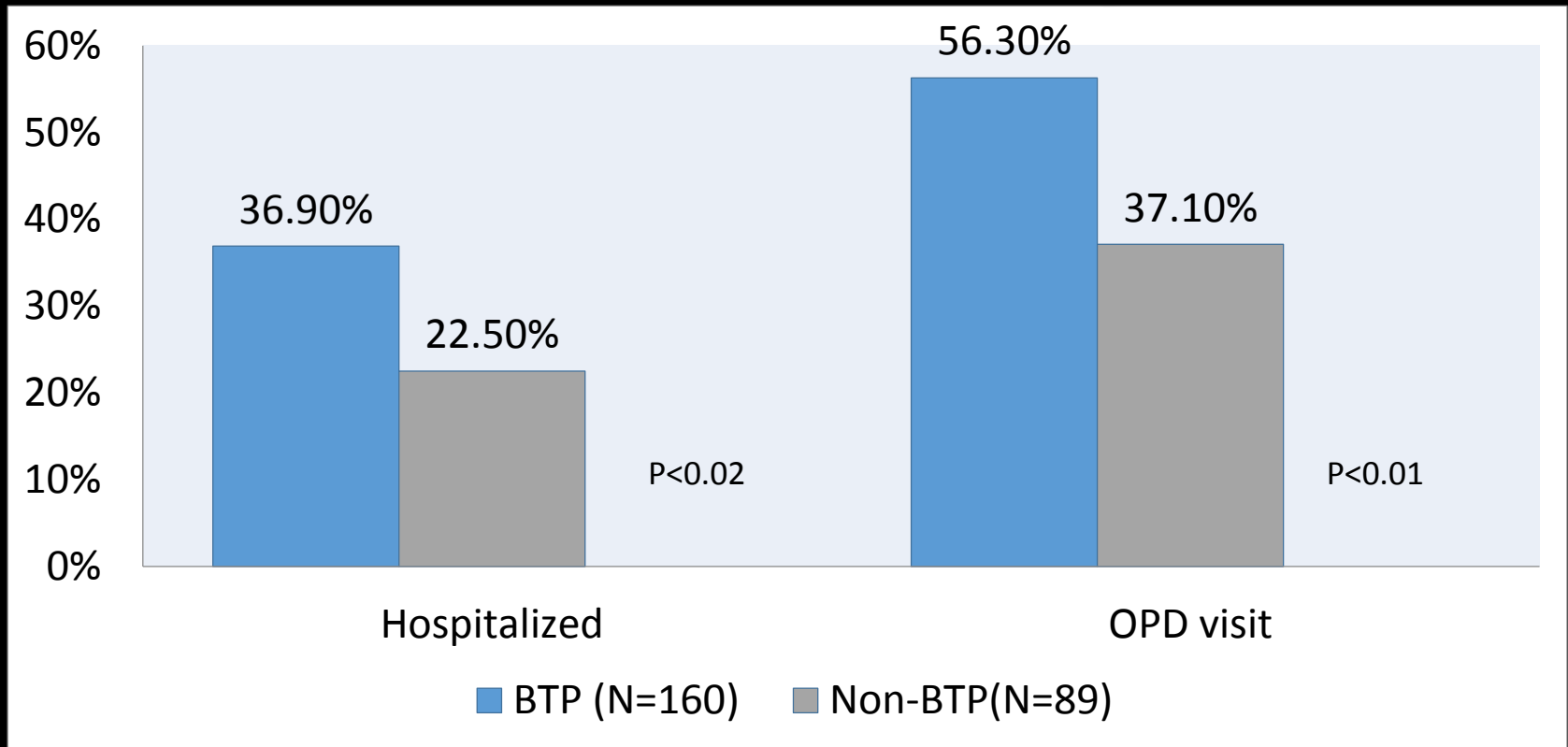
Adverse even	Incidence,n(%)
Somnolence	9(6.0)
Nausea	8(5.3)
Dizziness	7(4.6)
Vomiting	6(4.0)
Headache	4(2.6)
Constipation	3(2.0)
Dry month	2(1.3)
Dysgeusia	2(1.3)
Pruritus	2(1.3)
Confessional state	2(1.3)

There was no respiratory depression event in this study!

BTcP in Hospitalization and OPD Visit

Patients with BTcP have higher hospitalization and OPD visit rate

Well control of BTcP
→不須一直住院



Correlation between place of death and ROOs therapy starting time

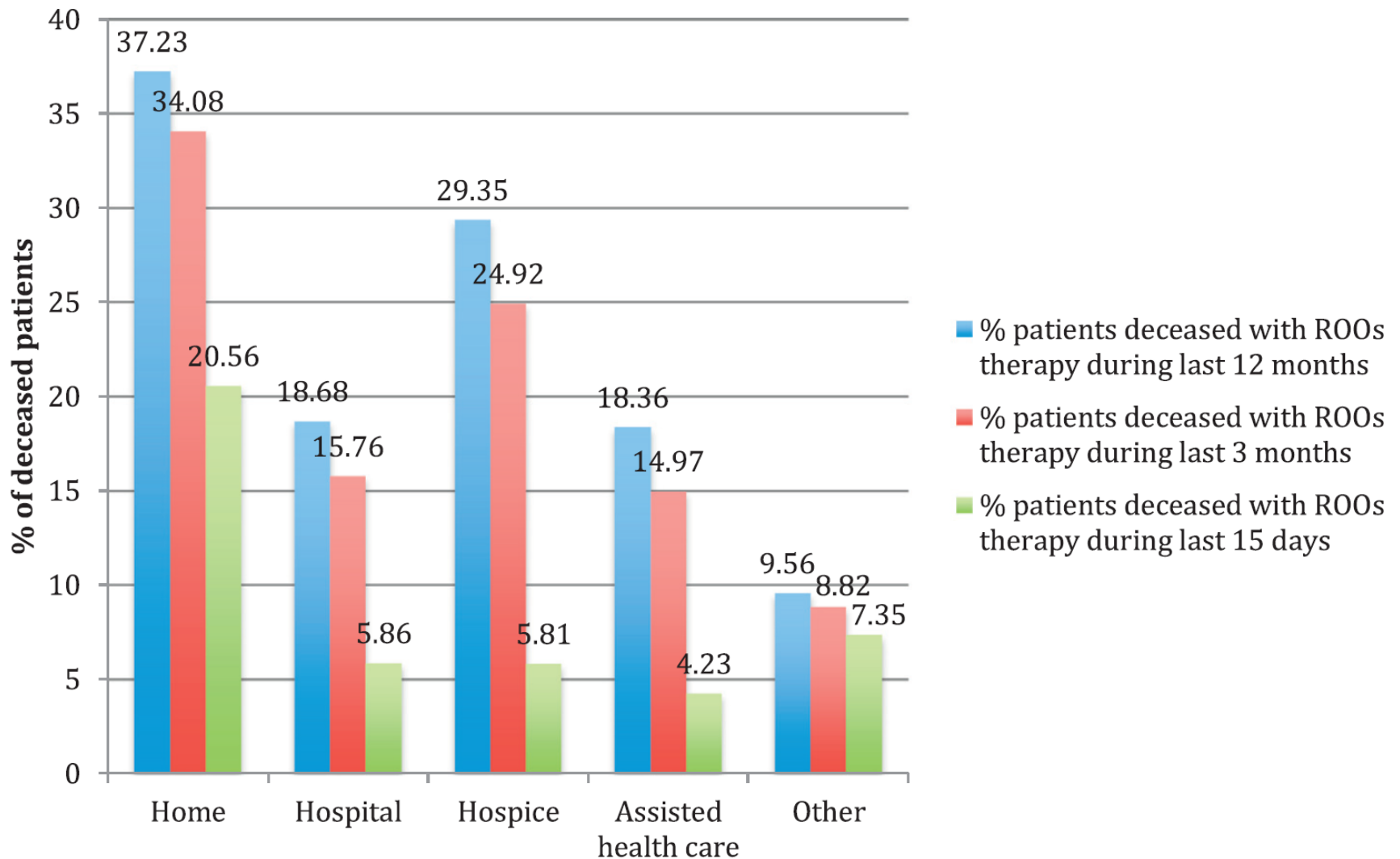
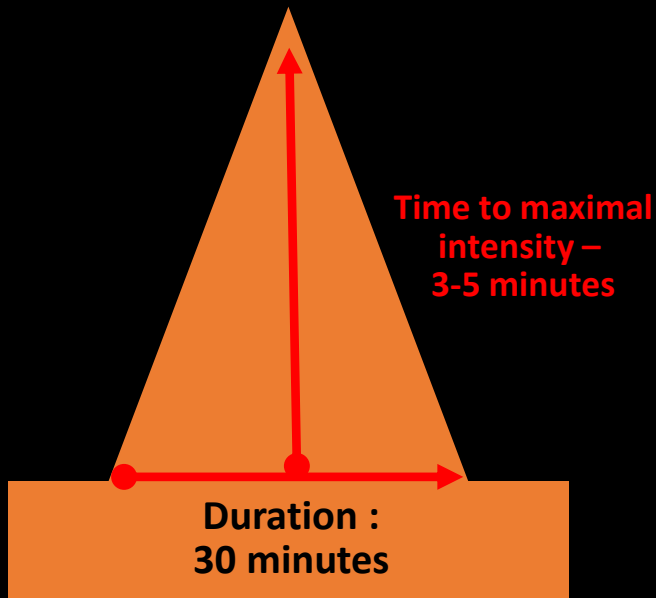


Fig. 1. Correlation between place of death and ROOs therapy starting time.

Onset

Duration

We need fast onset and short duration to avoid cumulated toxicity



Soon	IV morphine	1.5 hour
9-15 mins	Fentanyl Buccal Soluble Film	1-2 hour
15-20 mins	Subcutaneous morphine	1-2 hour
30-40 mins	Oral morphine tablet	3-4 hour
30-40 mins	Oral Oxycodone capsule	4-6 hour

1. Pharmacokinetic Optimisation of Opioid Treatment in Acute Pain Therapy Clin. *Pharmacol inet.* 1997 Sep; 33 (3); 225-244
2. Formulation Selection and Pharmacokinetic Comparison of FBSF with OTFC. *Drug Investig* 2009; 29 (10): 647-654
3. Pharmacotherapy for Breakthrough Cancer Pain. *Drugs* 2012; 72 (2): 181-190

A photograph of a single yellow flower with five petals, growing on a thin green stem. The flower is set against a background of a forest with sunlight rays streaming through the trees, creating a soft, ethereal atmosphere. The image is partially obscured by a semi-transparent grey overlay where the text is located.

Rapid-onset-opioids, **Painkyl[®]**
the intravenous morphine of outpatients
-bring them hope to leave hospitals and fulfill dreams