

如何運用鴉片類藥物來
有效處理癌症疼痛？

How to effectively control cancer pain
by opioids medications

謝瑞坤 醫師



疼痛評估

Pain is always subjective

疼痛是主觀的

Believe What Patients Say
相信病人所說的

Patients

**Self-report of pain is the
gold Standard for assessment**

以病患主訴為評估標準

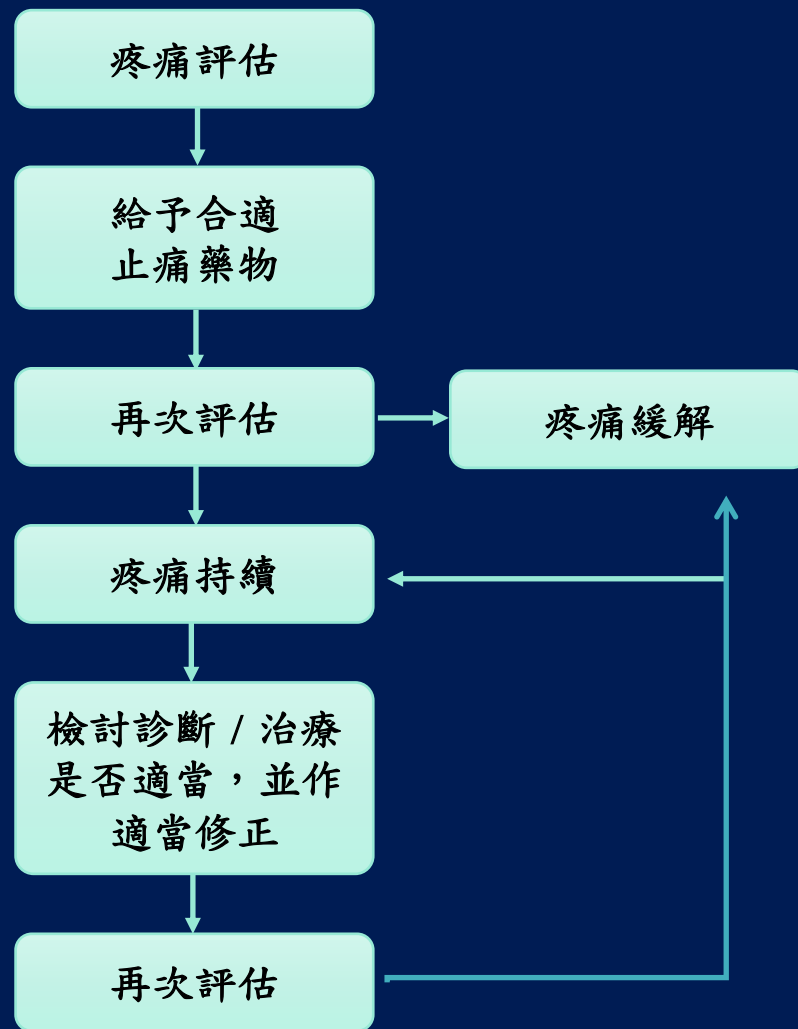
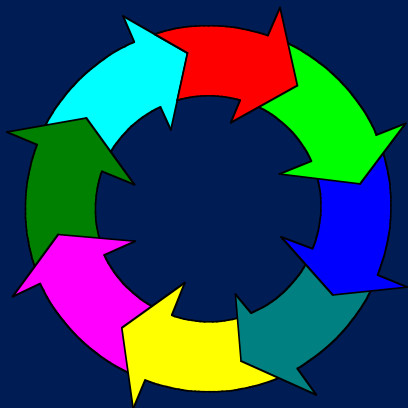
完整的癌症疼痛評估

The goal of the comprehensive pain assessment :

- To find the cause of the pain
- Assess the impact of pain
- Explore the preference of the patient
- Identify optimal therapy.

持續疼痛評估 Pain Assessment

- 評估過程包括醫護人員與患者
- 而且：
 - 開始治療後要定期評估
 - 有新的疼痛要再做評估
 - 在給藥物或非藥物治療疼痛後，在適當的觀察時間後即予評估

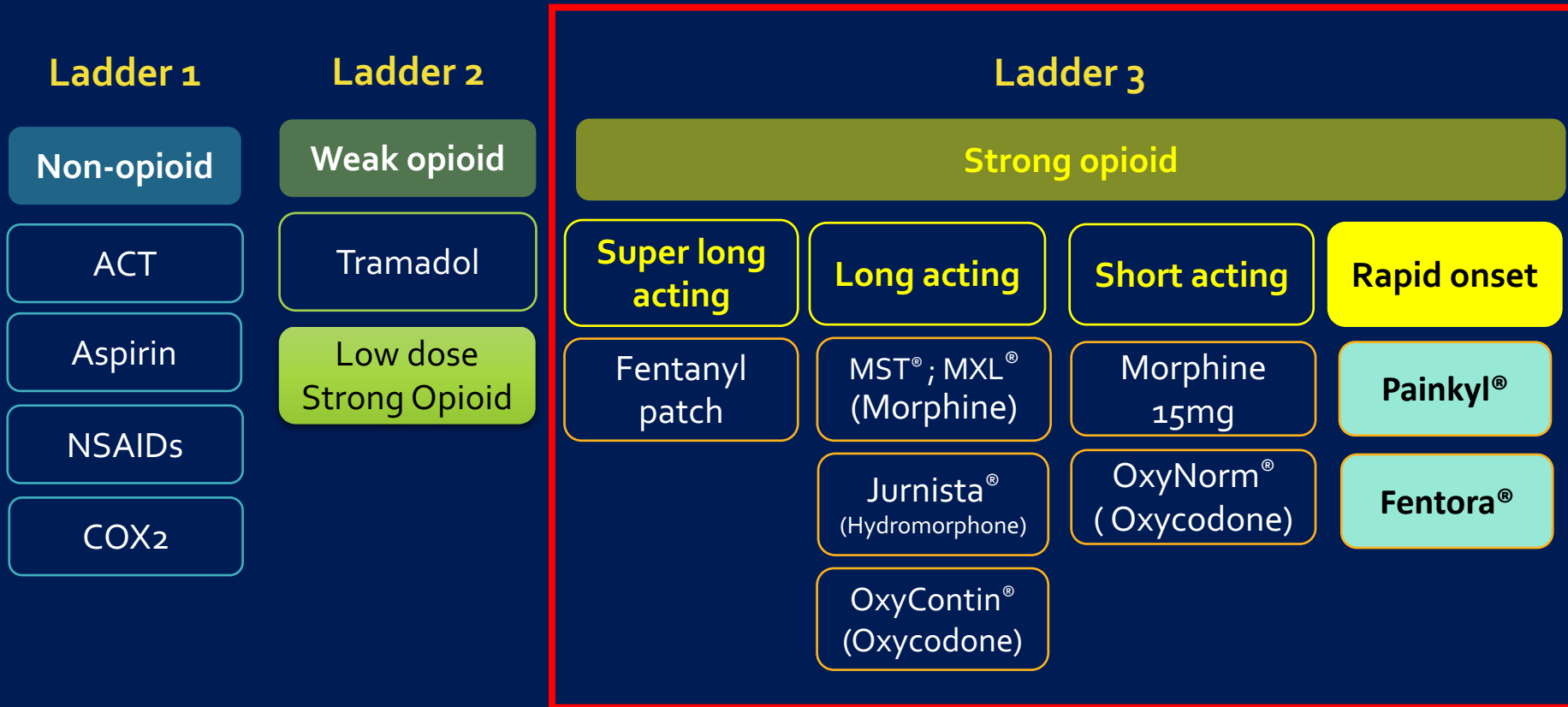


癌症疼痛藥物

使用疼痛藥物止痛應顧及：

1. **疼痛之長期、穩定控制**：以按時使用 (by the clock) 的長效性鴉片類藥物達成 (around-the-clock medication)。
2. **突發性疼痛 (breakthrough pain) 之緩解**：以按需要服用的短效性鴉片類
3. **偶發性疼痛 (incident pain)**

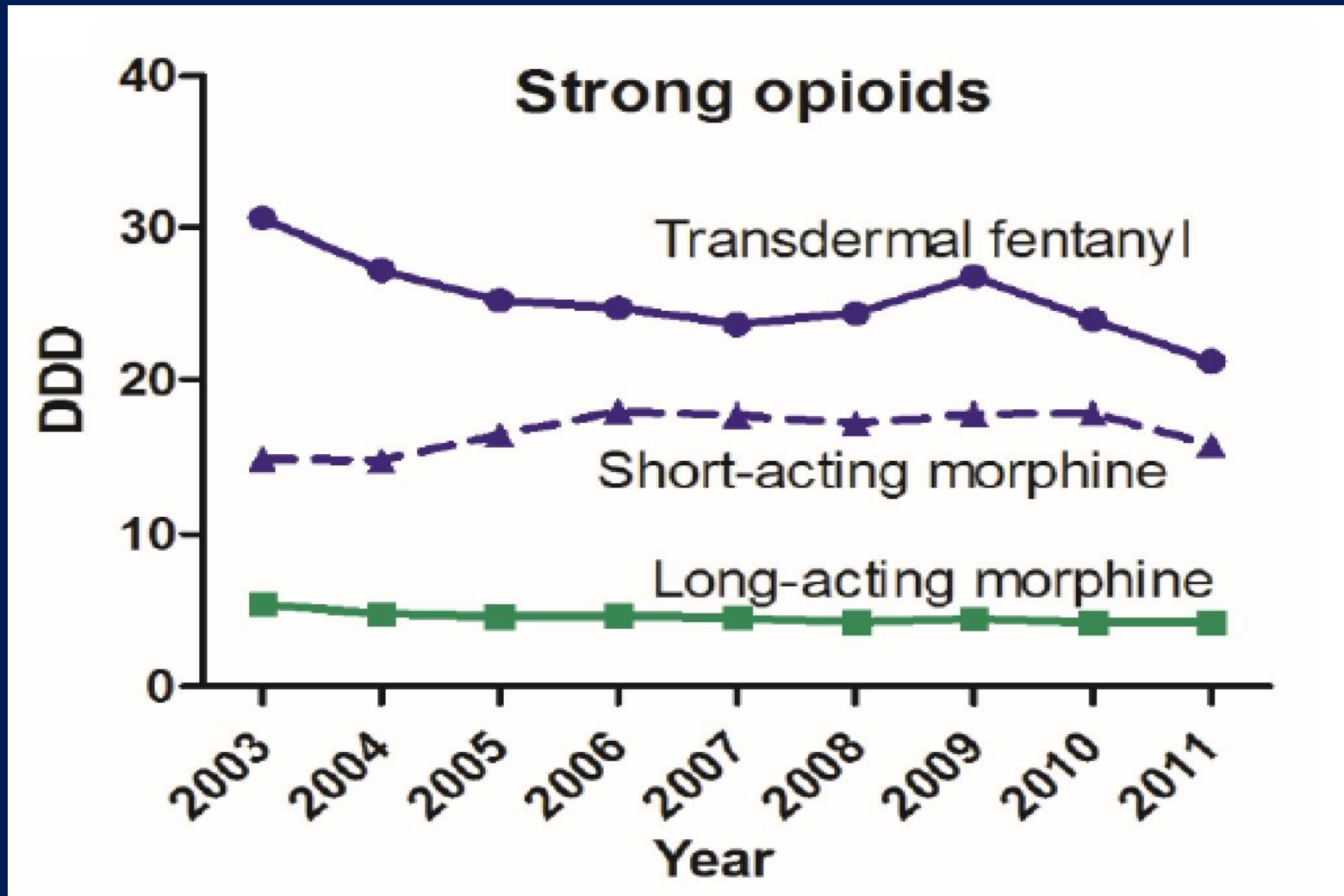
Opioid classification of WHO Ladder



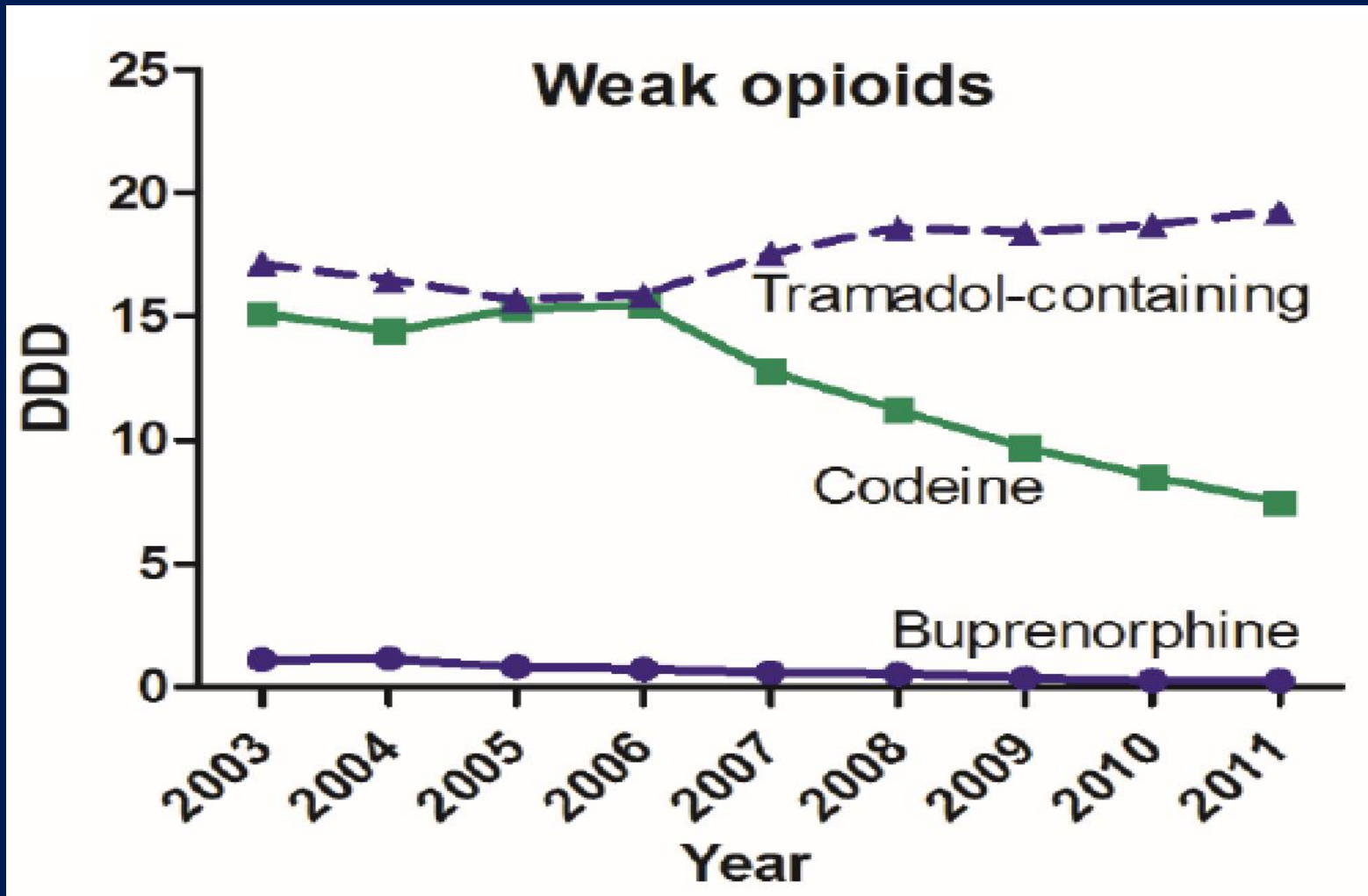
Adjuvant analgesics:

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

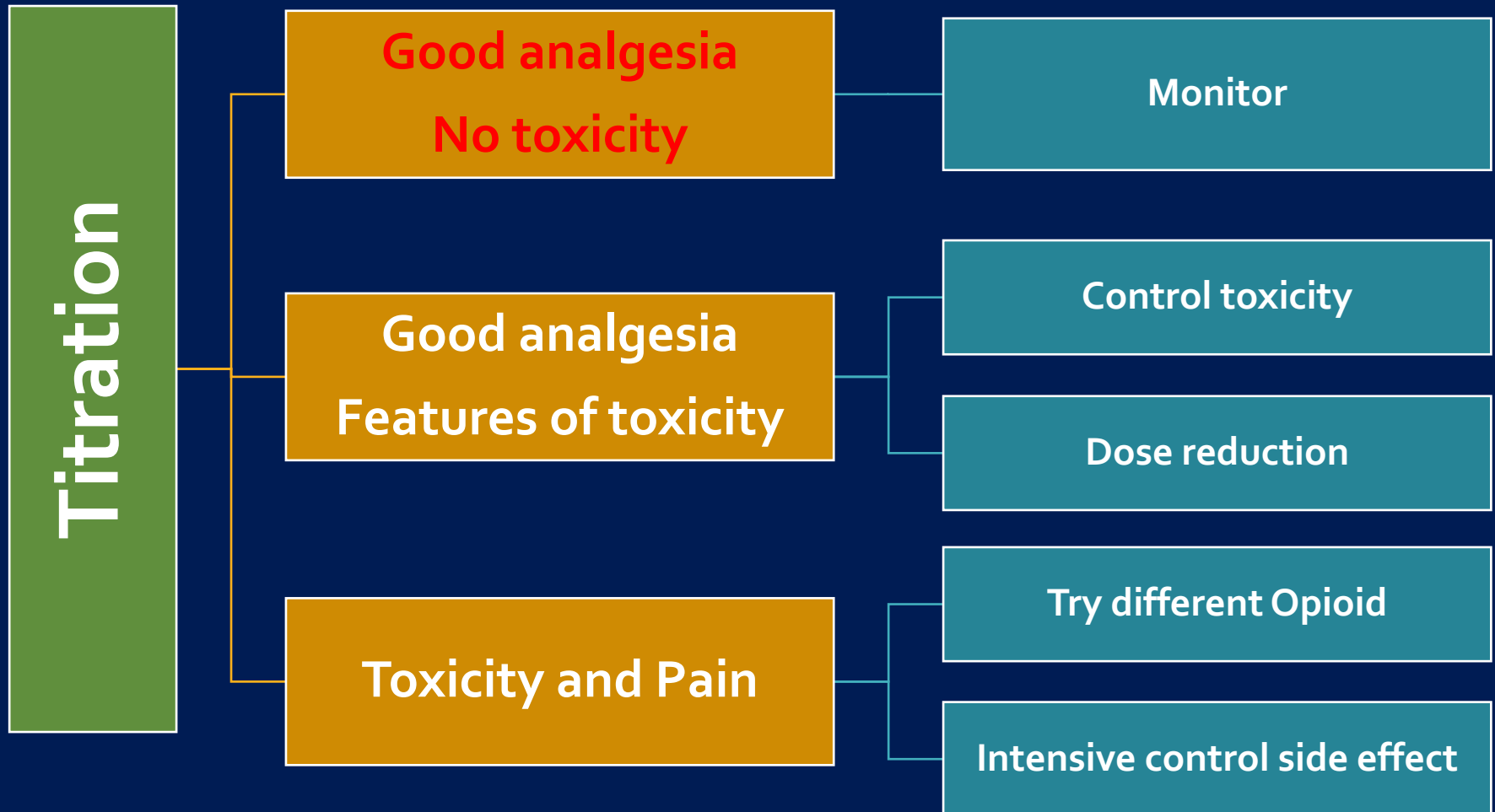
Use of Specific Strong Opioids



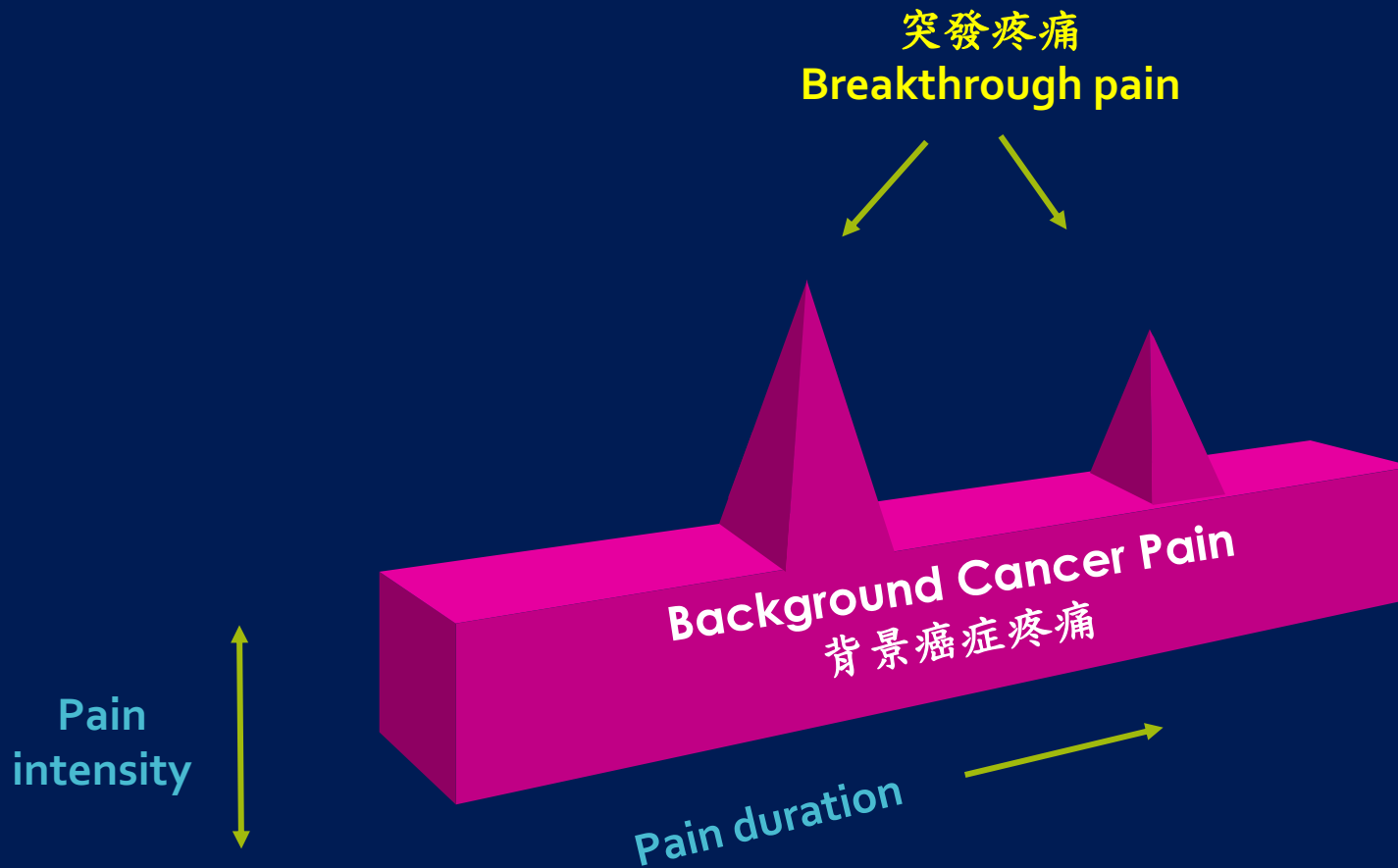
Use of Specific Weak Opioid



Opioid 劑量調整至適當劑量

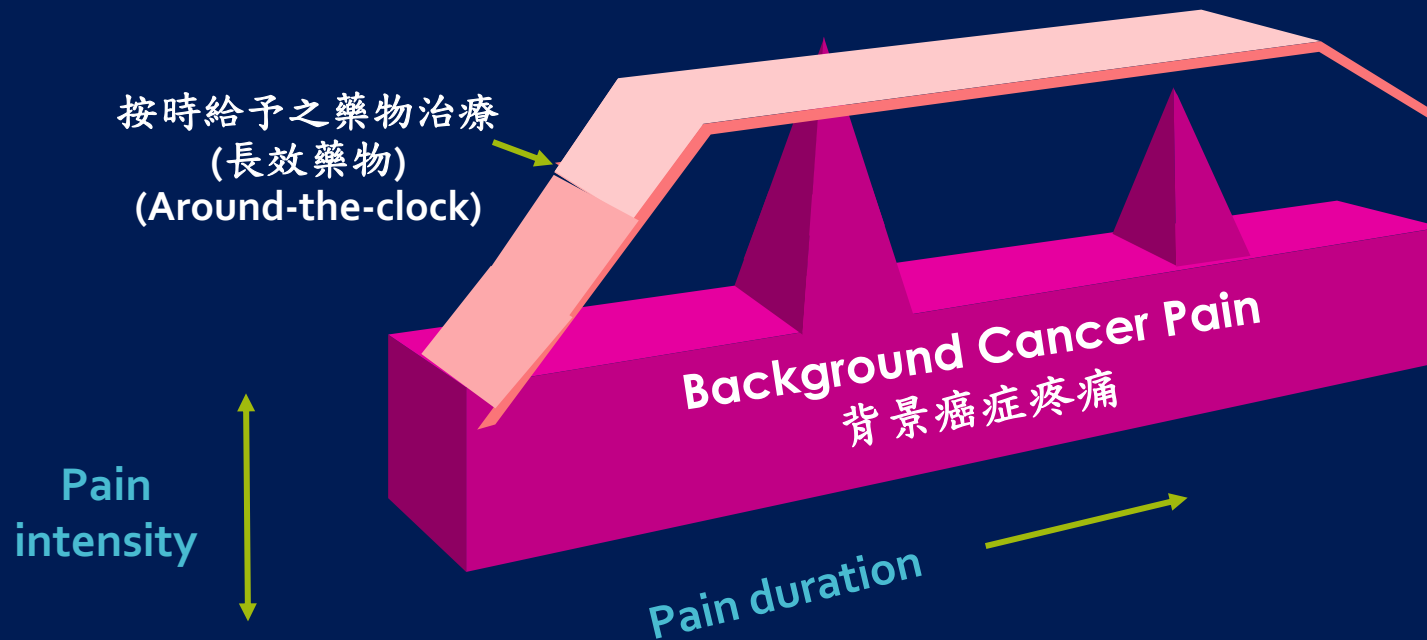


癌症疼痛



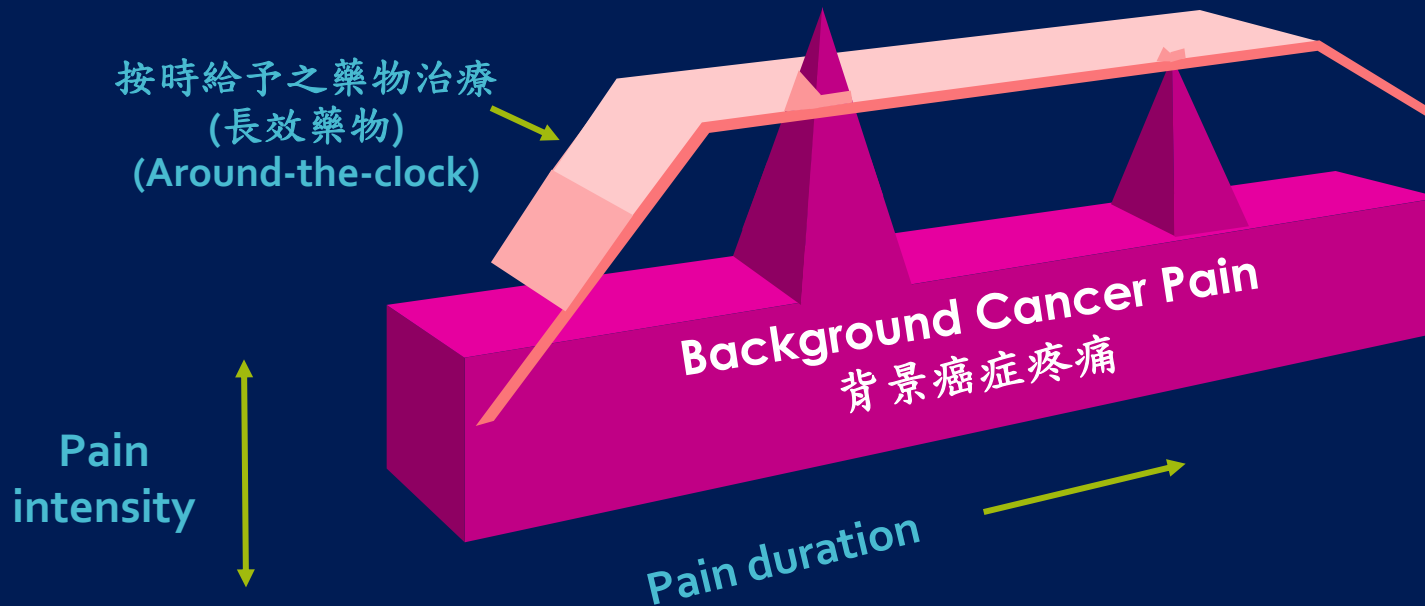
癌症疼痛的控制

No pain but Over Medication
with High Toxicity



癌症疼痛的控制

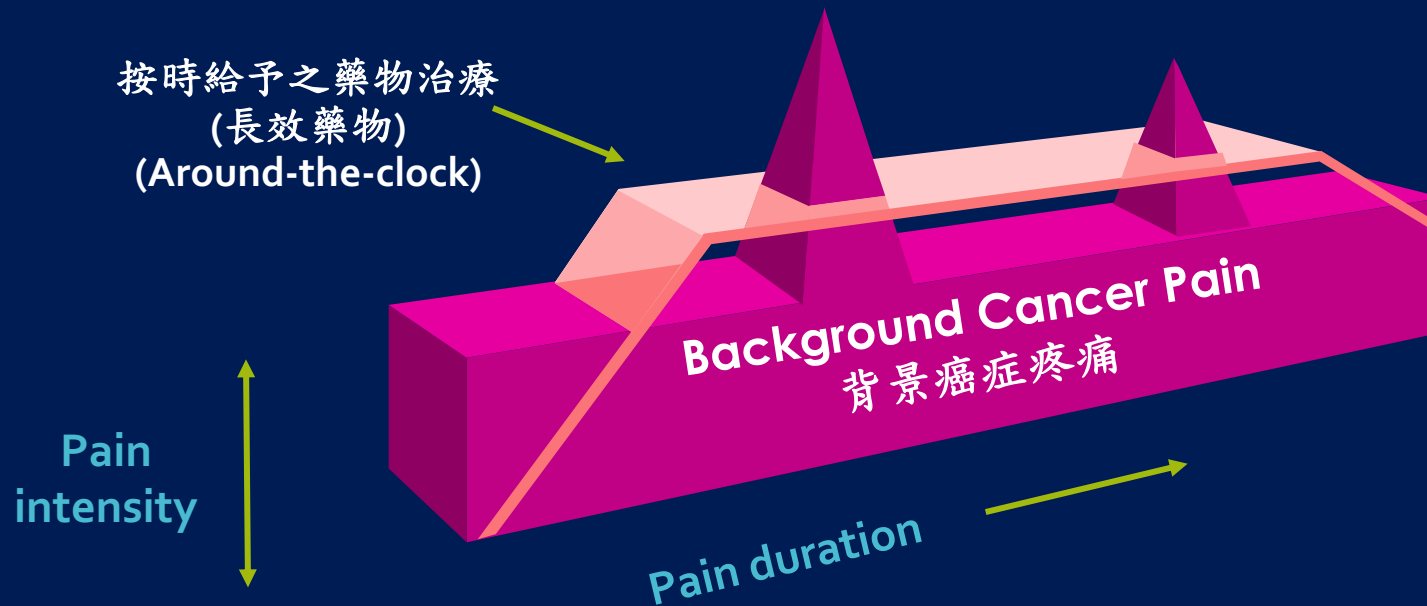
Good Pain Control with Some Toxicity
Most of the times overdose



癌症疼痛的控制

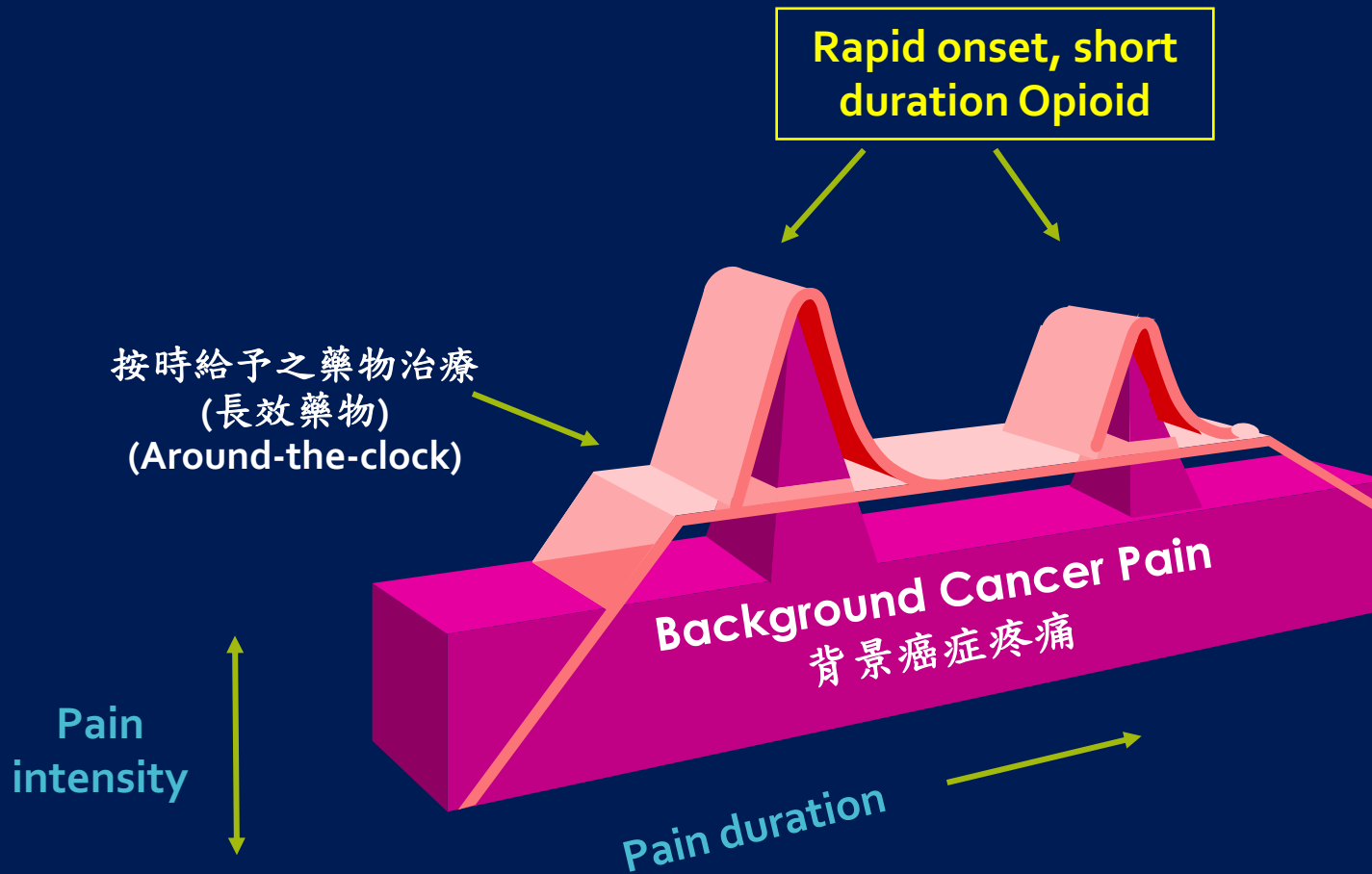
- Fentanyl patch q3d
- MXL qd
- Hydromorphone OROS qd
- MST q12h
- OxyContin q12h

Good Pain Control with No (or Low) Toxicity



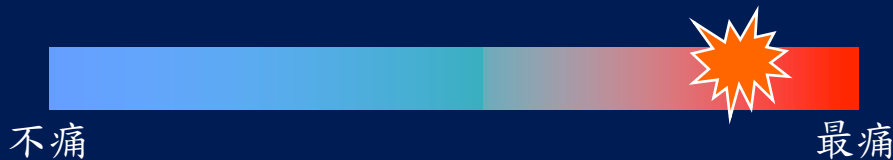
理想的癌症疼痛控制

- Morphine tablet
- Oxynorm
- ROOs



個案討論(一)

- 54 y/o 胰臟癌病患,惡病質,因為持續逐漸惡化的上腹及背痛已持續三天.
- 三個月前剛因局部廣泛性肝臟及淋巴轉移接受過化療合併局部放射線治療,當初背痛有極大的改善,治療後未定期服用止痛藥物.
- PS=3, 理學檢查發現有貧血,無黃疸現象.呼喊著希望趕快解除疼痛.
- 主訴電療前曾有類似疼痛

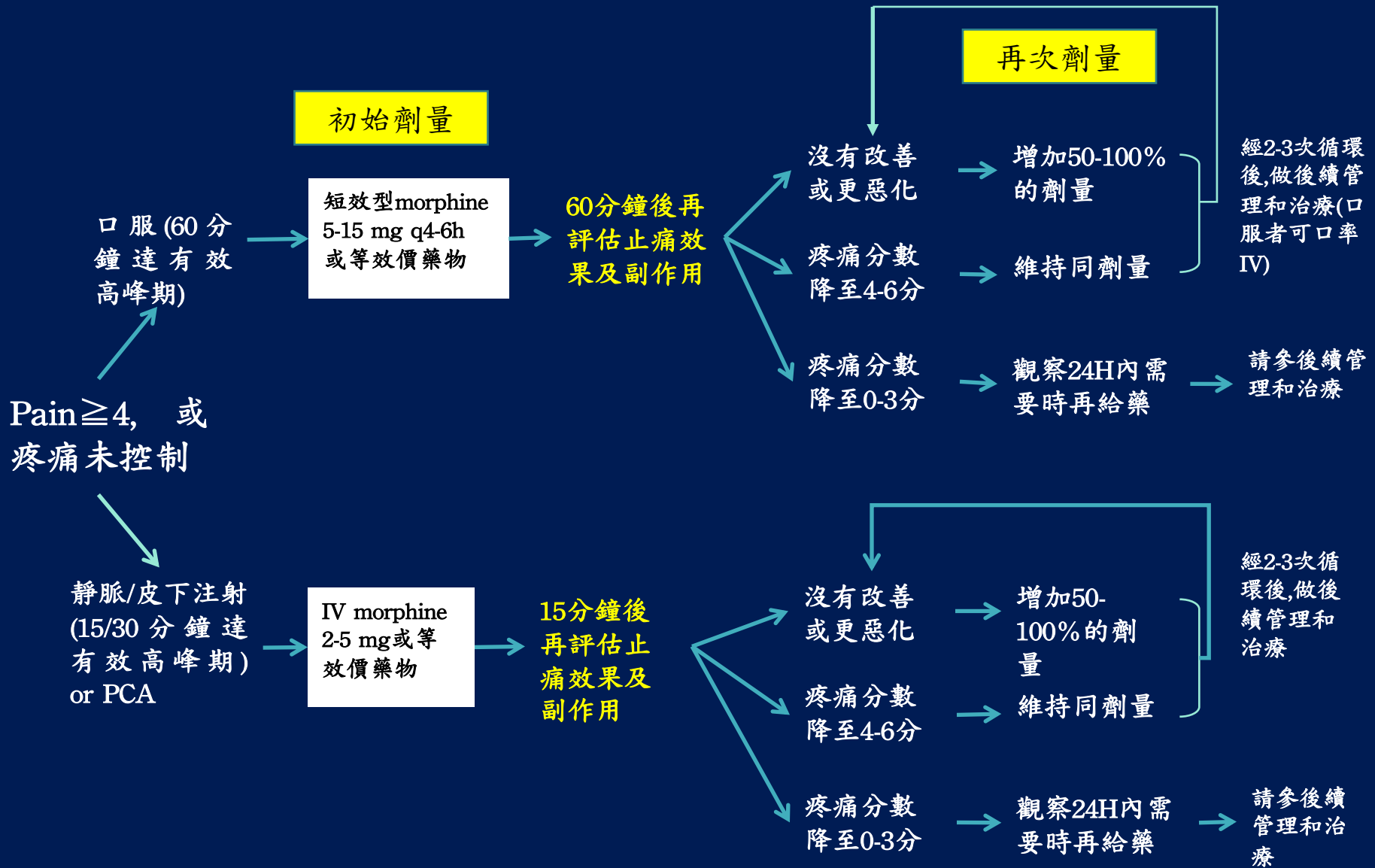


個案討論(一續)

Q1: 疼痛控制方面您的建議

1. Morphine 3mg sc st
2. Tramadol 100mg IM st
3. NSAID injection IM st
4. Fentanyl patch 12 micgram st
5. Morphine 15mg PO st
6. Consult the anesthesiologist for nerve block
7. Others

Titration :Opioid-Naïve Patients

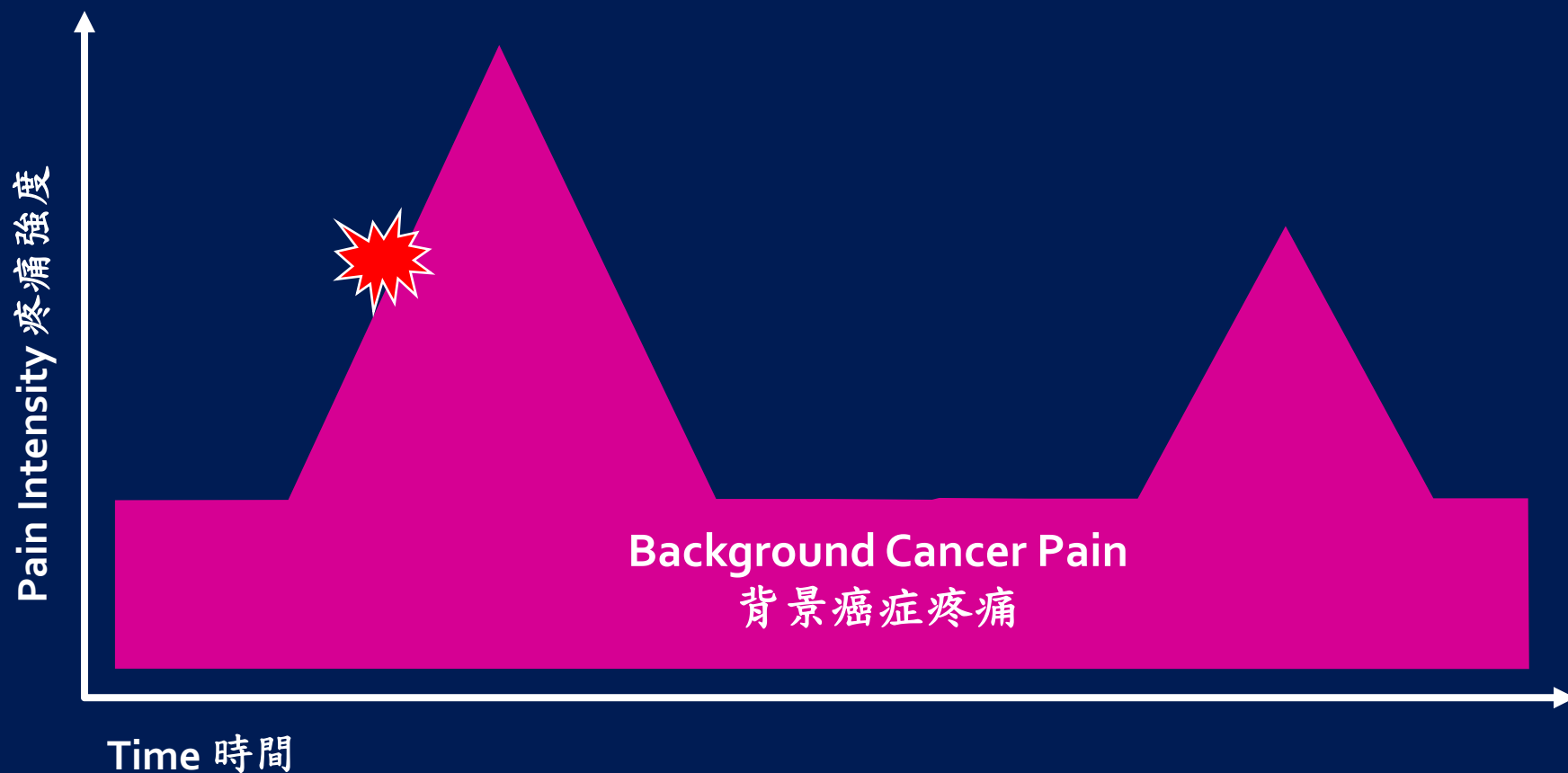


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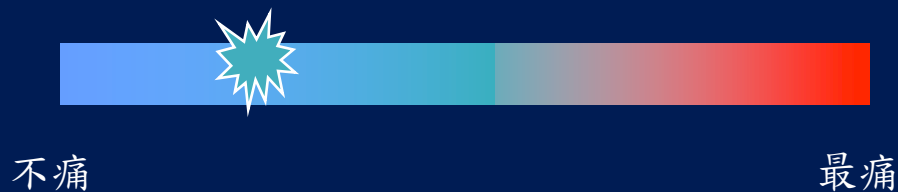
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晚期患者癌症相關疼痛常是持續的...加上偶發嚴重疼痛....



個案討論(一續)

- Morphine 3mg sc 疼痛程度主訴降為 VAS=3.
- 體檢檢查發現上腹及右上腹區域有壓痛.
- 右上腹有一大硬塊邊緣一直到肚臍上方附近



個案討論(一續)

Q1: 接續疼痛控制方面您的建議

1. Morphine 3mg q4h
2. Tramadol-SR 200mg PO qd
3. Tramadol 50mg PO q4h
4. Fentanyl 25 micogram
5. NSAIDs q4-6h
6. morphine 15mg PO q4h

個案討論(一續)

1. **Morphine 3mg q4h**
2. Tramadol-SR 200mg PO qd
3. Tramadol 50mg PO q4h
4. **Fentanyl 25 micogram**
5. NSAIDs q4-6h
6. Morphine 15mg PO q4h

其實本來有好用的 Morphine PO 10mg q4h

個案討論(一續)

- 患者在急診室觀察二日,疼痛控制大致穩定,VAS在2-3之間
- 當時使用 **Morphine 3mg SC q4h** 同時最近24小時有因疼痛額外多打了一個劑量.
- 他希望能回家.



不痛

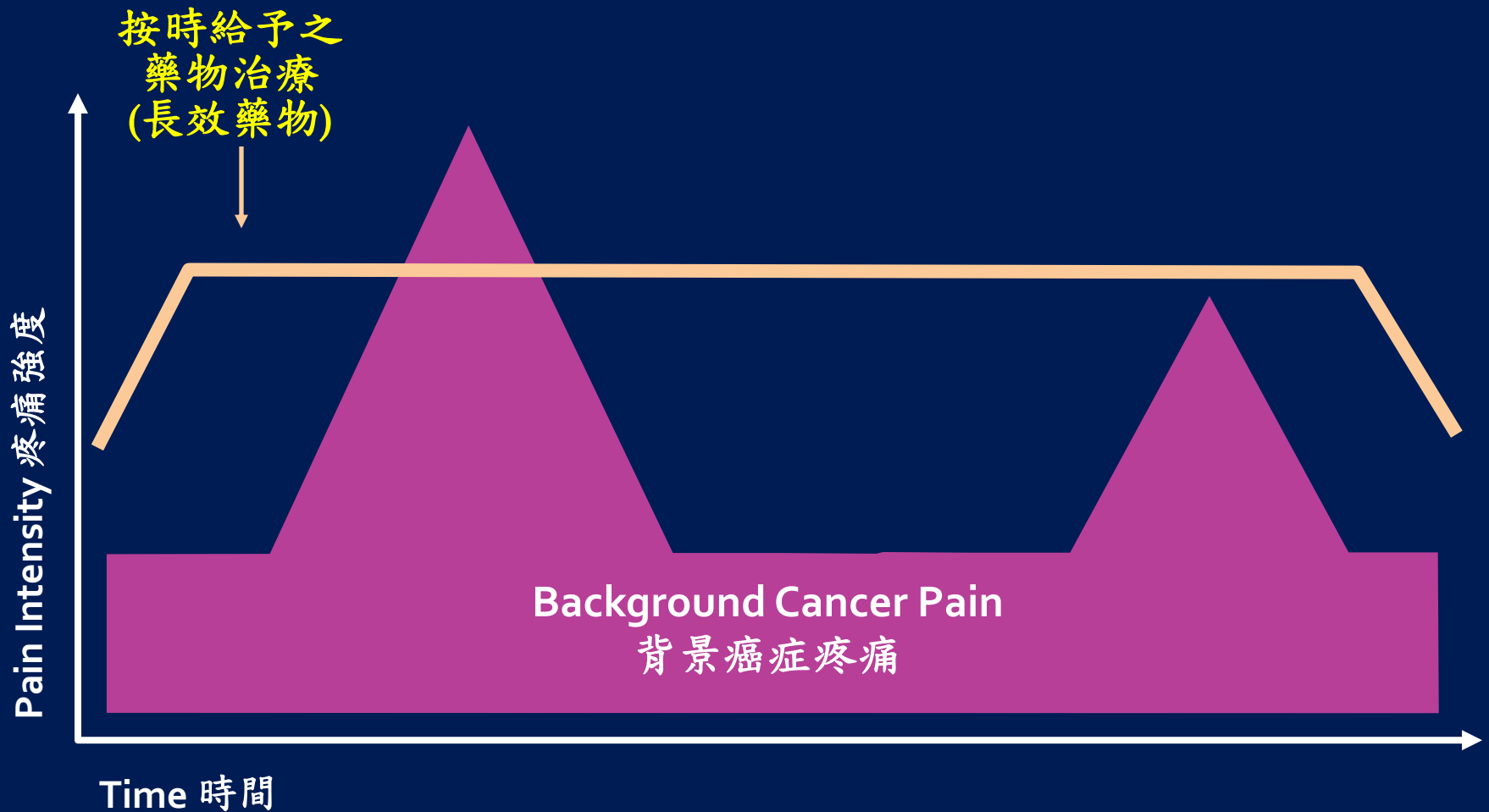
最痛

個案討論(一續)

Q4: 患者準備回家,您的疼痛控制藥物的處方?

1. Morphine 5mg sc q4h
2. Fentanyl 25 microgram patch q3d
3. Morphine 15mg q4h, with informed way of rescue
4. MST 30mg q12h
5. MXL 60mg qd
6. Others

晚期患者癌症疼痛控制要兼顧止痛與可能副作用



Opioids Conversion table

Tramadol	Morphine			Oxycodone	Fentanyl	Hydromorphone SR
PO	SC	IV	PO	PO (1: 1.5-2)	TTS	PO
150	10	10	30	15-20 mg	12.5 mcg/h	
200			40	20-30 mg		8 mg
300	20	20	60	30-40 mg	25 mcg/h	
			80	40-50 mg		16 mg
-	30	30	90	45-60 mg	37.5 mcg/h	
-	40	40	120	60-80 mg	50 mcg/h	24 mg
-	60	60	180	90-120 mg	75 mcg/h	
-	80	80	240	120-160 mg	100 mcg/h	48 mg
-	100	100	300	150-200 mg	125 mcg/h	

Eastern Metropolitan Palliative Care Consortium Opioid Conversion Ratios - Guide to Practice July 2008.

NCCN Guideline 2014.

Cancer 2002; 94: 832-839.

個案討論(一續)

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6. Others

劑量轉換 Daily dose 3mg sc q4h = 18mg sc/ qd
Equal to oral morphine daily requirement

$$18 \times 3 = 54\text{mg/d}$$

癌症疼痛藥物

使用疼痛藥物止痛應顧及：

1. 疼痛之長期、穩定控制：以按時使用 (by the clock) 的長效性鴉片類藥物達成 (around-the-clock medication)。
2. 突發性疼痛 (breakthrough pain) 之緩解：超短效的救援性藥物是更好的選擇
3. 偶發性疼痛 (incident pain)

突發性癌症疼痛

Breakthrough cancer pain (BTcP)

- Moderate-to-severe pain
- Occurred at a specific site
- **Background of persistent pain controlled.**
- The frequency averages 1-4 episodes per day

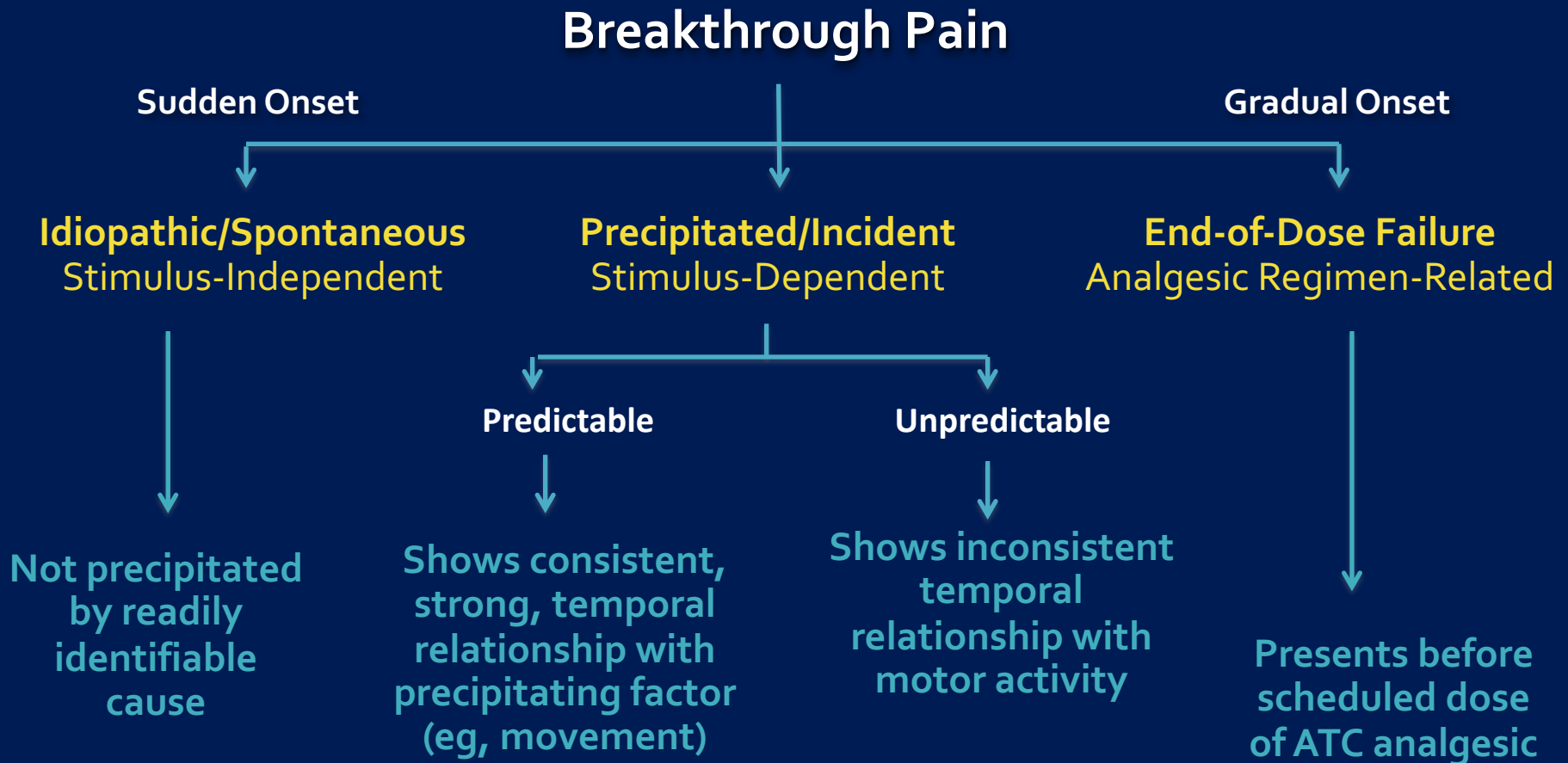
- In 1990, Russell K. Portenoy and Neil A. Hagen published a paper on a specific pain syndrome named breakthrough pain (BTP).

Current Opinion in Oncology 2010, 22:302–306

Drugs. 2008;68:913–924.

Journal of Pain Research 2012;5 559–566

Subtypes of breakthrough cancer Pain



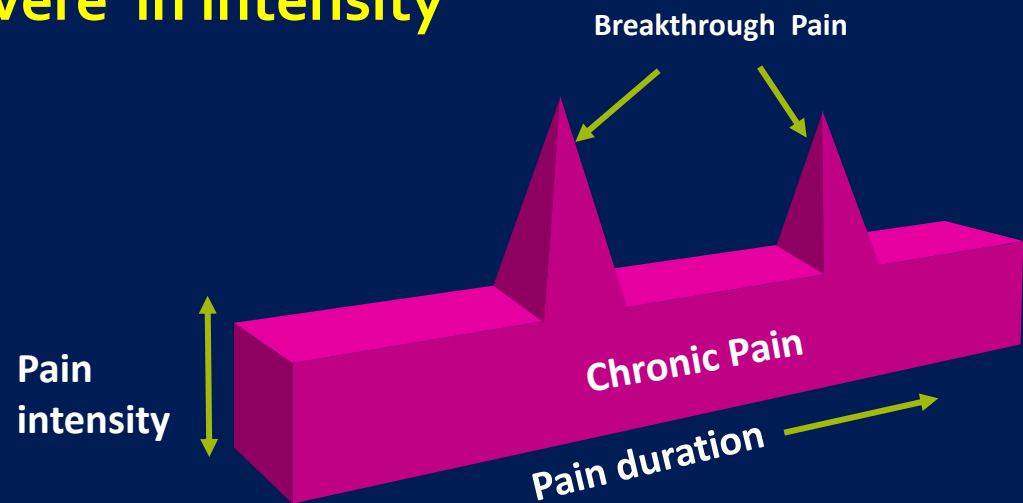
* ATC, around-the-clock.

Driver LC. *Pain Med.* 2007;8:S14-S18;
Svendsen KB, et al. *Eur J Pain.* 2005;9:195-206.

Breakthrough Cancer Pain

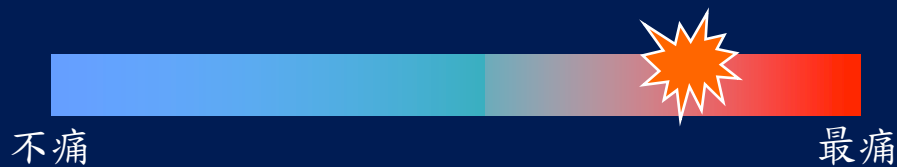
- Characteristic BTCP (Typical)

1. Rapid in Onset (Often Peaking ~3minutes)
2. Usually short in duration (Median, 30minutes)
3. Moderate to severe in intensity



個案討論(一續)

- 54 y/o 胰臟癌病患, 惡病質, 三個月前剛因局部廣泛性肝臟及淋巴轉移接受過化療合併局部放射線治療, 當初背痛有改善, 治療後定期服用止痛藥物 MXL 60mg qd
- 偶而會有突發疼痛到5-6分通常服用Morphine 15mg, 通常在二個小時後改善
- 醫院轉來電話稱說疼痛至7-8分而且口服Morphine 15mg後二小時持續疼痛



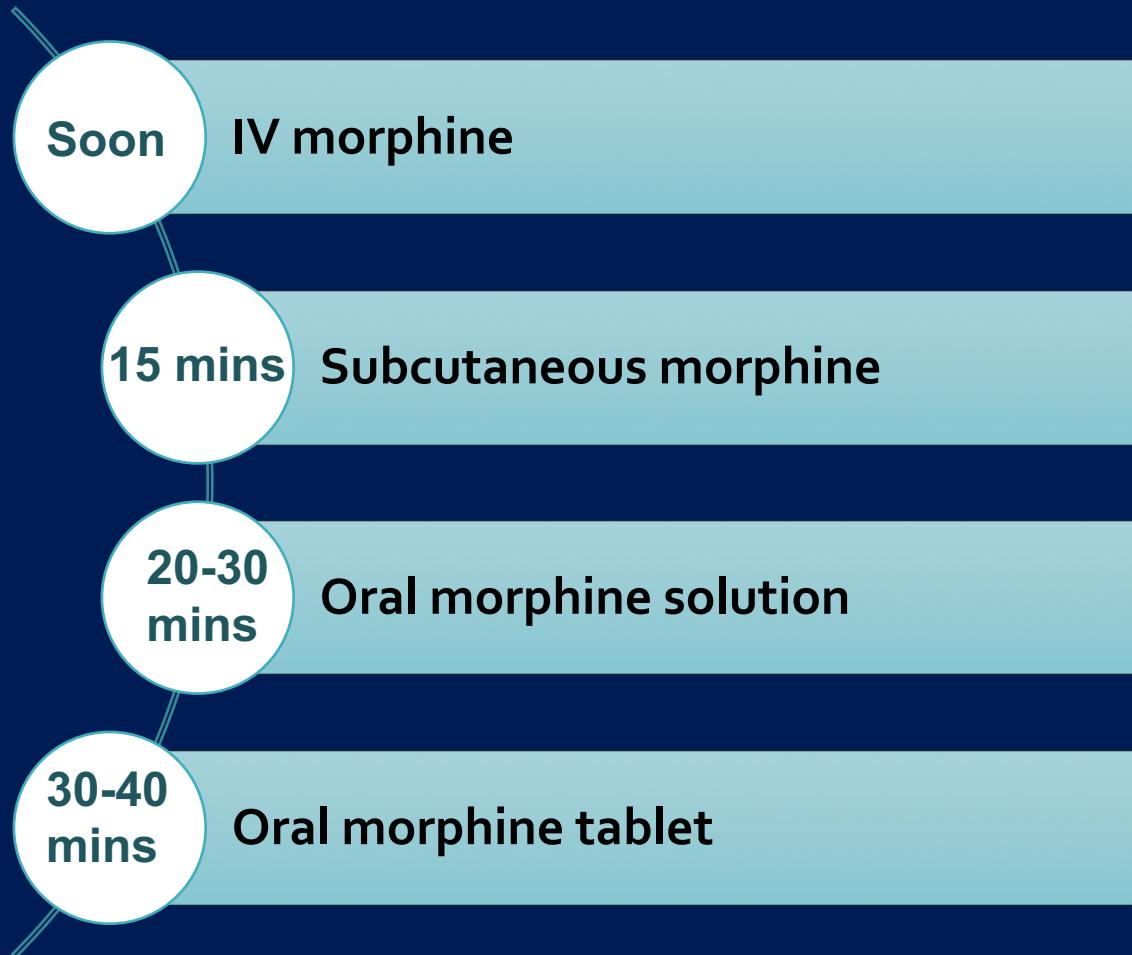
個案討論(一續)

Q2. 你的回應是?

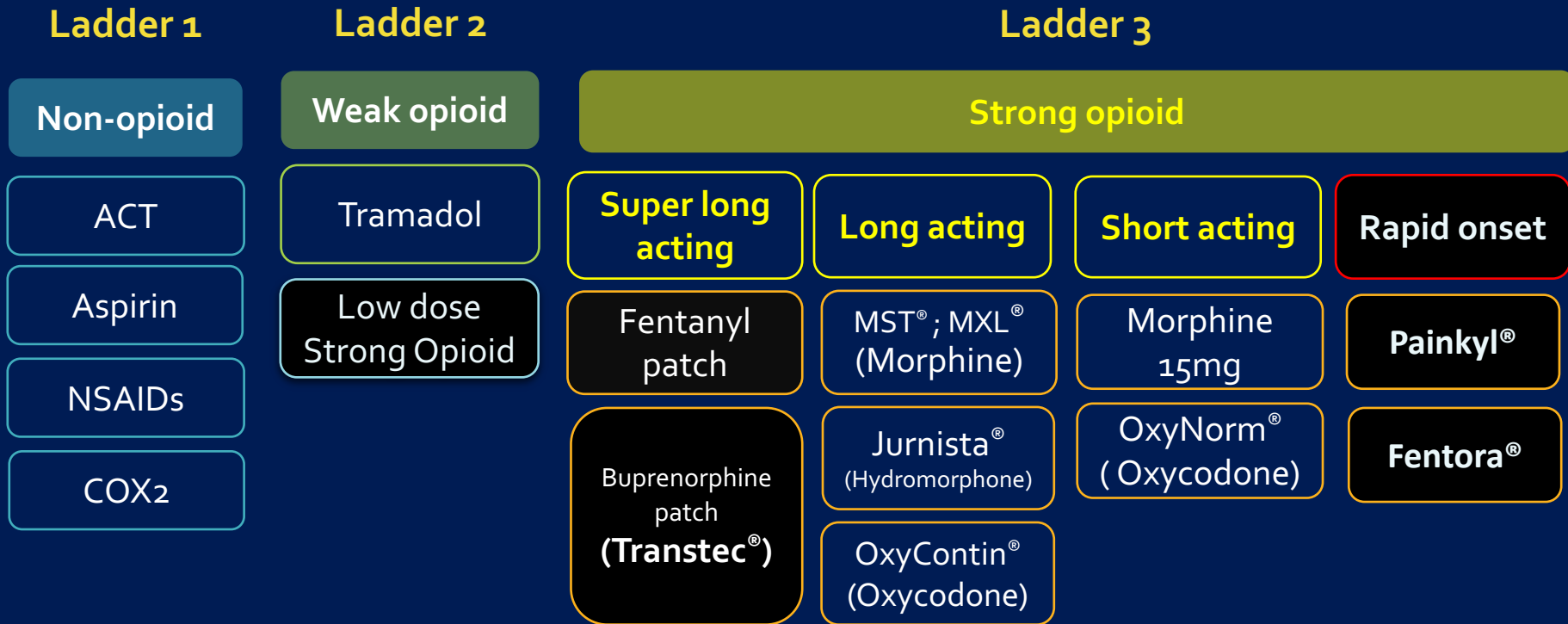
1. 請患者趕快到醫院急診接受止痛治療
2. 再吃一顆morphine 15mg觀察
3. 請他再觀察因為口服藥物還有可能作用。

Onset of Oral Morphine May Not Be Fast Enough for Breakthrough Pain

Onset



Opioid classification of WHO Ladder



Rapid-Onset-Opioid: Special formulation

1st generation in buccal



2nd generation



3rd generation



1998 OTFC/Actiq®

Oral trans-mucosal fentanyl citrate



Oral transmucosal lozenge

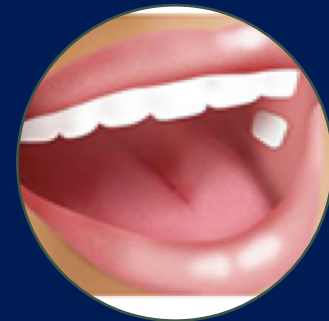


2006/2008

FBT:Fentora®(US)/Effentora®(EU)



Fentanyl buccal tablet



2009 FBSF:Onsolis®(US)

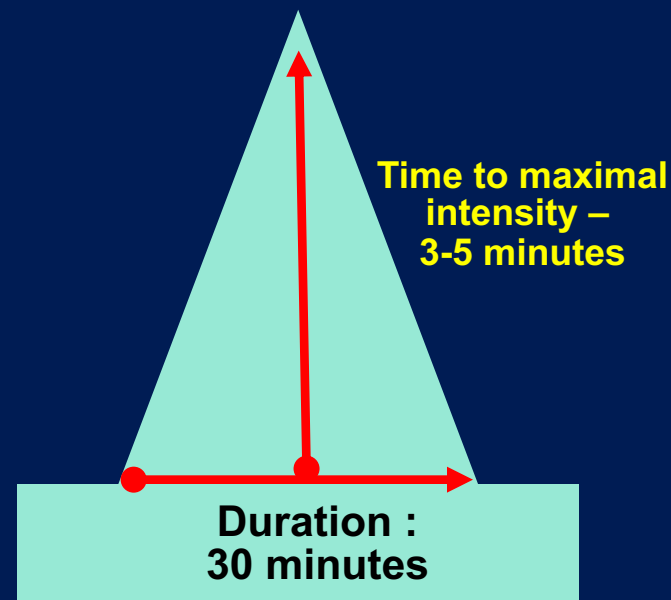
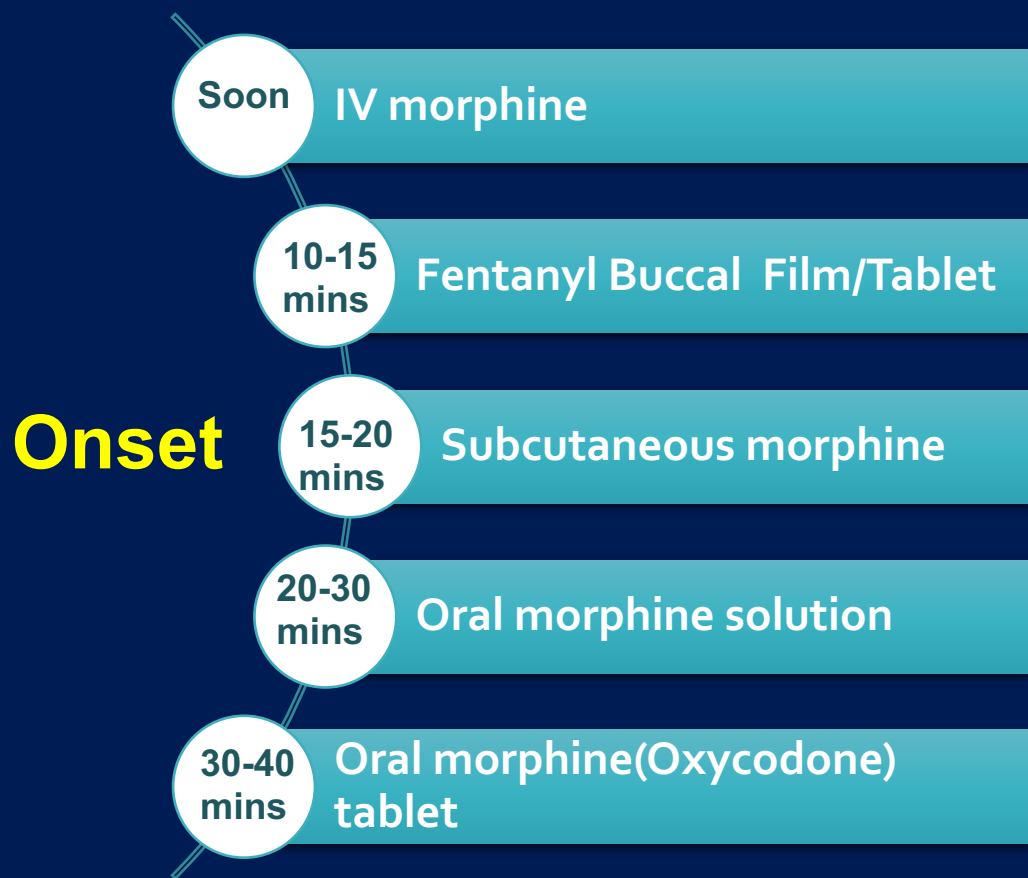
Painkyl® (TW)



Fentanyl buccal soluble film



Onset of Oral Morphine May Not Be Fast Enough for Breakthrough Pain



Short Acting Opioid

	onset	T _{max}	Duration
IV Morphine	6 mins ¹	19 mins ¹	96 mins ¹
IM Morphine	20 mins ¹	48 mins ¹	110 mins ¹
Oral Morphine	37 mins ¹	82 mins ¹	139 mins ¹
Immediate-release oxycodone (OxyNorm®)	30-40 mins ³	1-1.5hrs	4-6 hrs
Fentanyl buccal soluble film (painkyl®)	9 mins ² (T _{first})	1 hrs ²	1-2 hrs

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

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- 偶而會有突發疼痛到 7-8分 在家可使用藥物的選擇

1. Morphine 15mg PO st **37 min**
2. Oxynorm 10mg st **30-40 min**
3. Temgesic sublingual 1# st **30 min**
4. **Painkyl** fentanyl mucosal patch. **9min**

EAPC, ESMO, NCCN recommendations: ROOs are preferred medication for BTcP

EAPC

- **Oral transmucosal fentanyl formulations** are more effective than immediate-release oral morphine and that intranasal fentanyl affords faster analgesia than the oral transmucosal formulation.

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.

ESMO

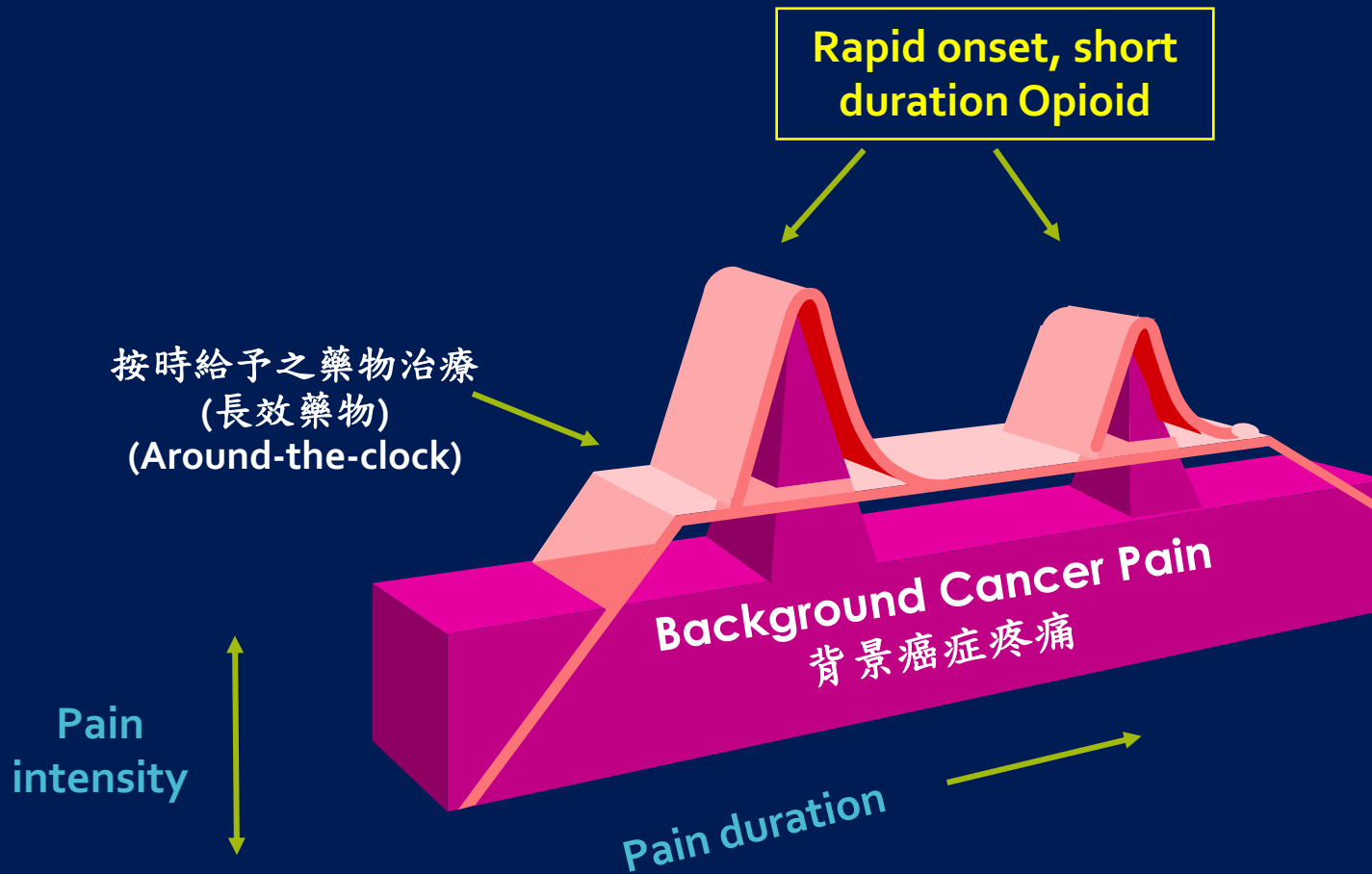
- Intravenous opioids; **buccal**, sublingual and intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating BTP episodes in respect to oral morphine.

Lancet Oncol. 2012; 13(2):e58–e68

Annals of Oncology 23 (Supplement 7): vii139–vii154, 2012
2014 NCCN

理想的癌症疼痛控制

- Morphine tablet
- Oxynorm
- ROOs



我們有的口服藥物可以幫助多數患者

- **Around The Clock:** 長效藥物 控制長時基礎疼痛

Fentanyl patch, MXL, Hydromorphone OROS, MST, OxyContin

- 運用短效藥物控制可預期的疼痛或是在睡眠時期達到不痛

Morphine tablet, Oxynorm

- 運用速效藥物處理突發性疼痛

Fentanyl submucosal patch (Painkyl)

盡早的支持治療可以延長2.7個月的存活期

Early palliative care: 疼痛控制、精神支持與相關症狀的緩解

The NEW ENGLAND JOURNAL of MEDICINE

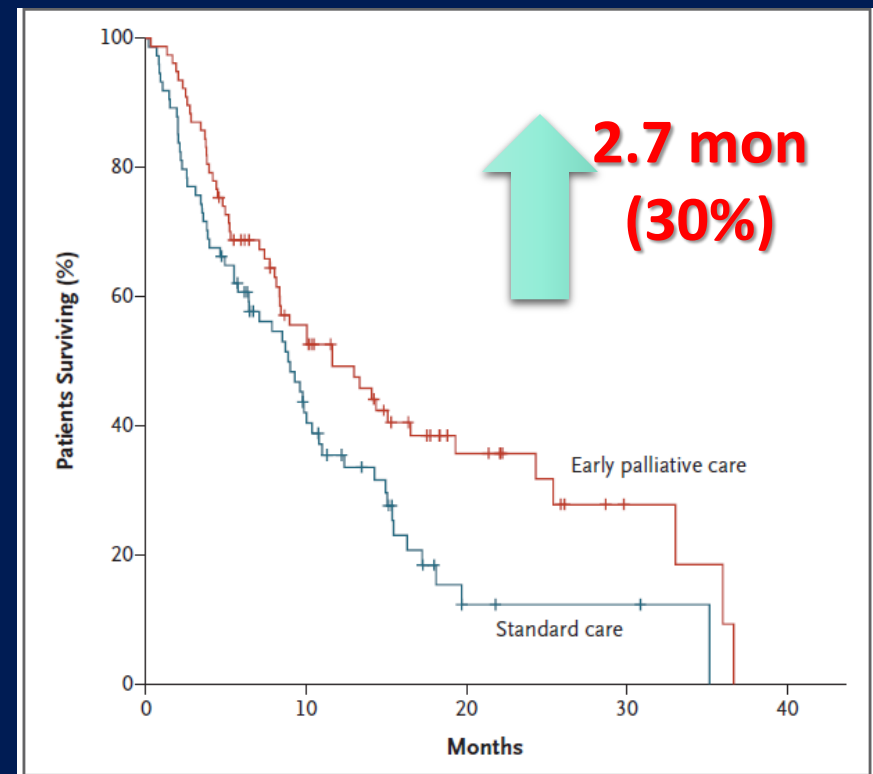
ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

	Early Palliative care with Oncologic Care	Oncologic Care	P. value
P't No.	77	74	
Median Survival	11.6 m	8.9 m	0.02

RCT: 151 patients
newly diagnosed metastatic NSCLC



N Engl J Med 2010; 363: 733-42

Take Home Message

1. Repeat Pain assessment
2. Good Pain Control : Good analgesia with Low toxicity
3. Medication : Around the Clock and choose Rapid-onset Opioid for rescue breakthrough cancer Pain
4. Avoid ER visit caused by Breakthrough cancer Pain