

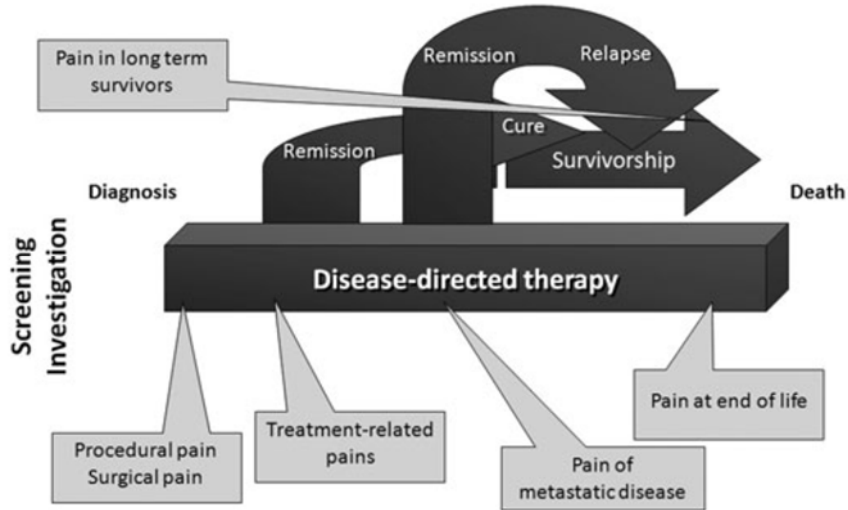
癌症疼痛之用藥近況

臺中榮民總醫院
疼痛科 吳志成醫師

Outline

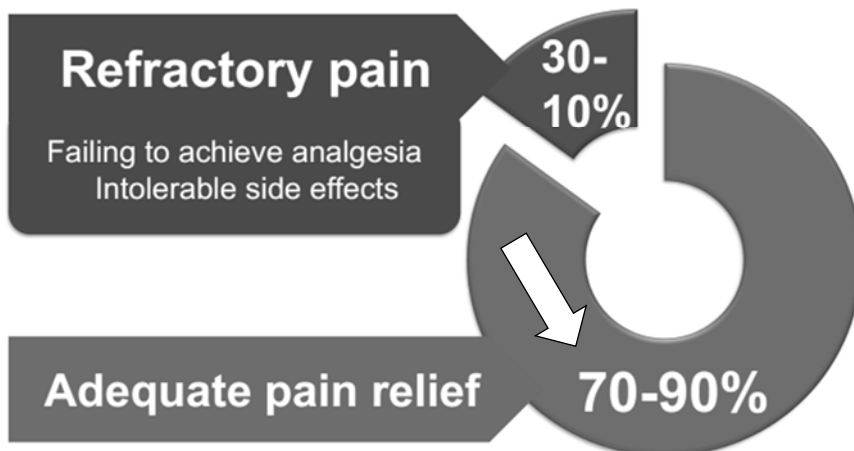
- **Pain is still an issues among cancer patients**
- General rules in cancer pain management
 - Learning from cases
- Opioids trending in Taiwan
- Take Home Message

30-40% of cancer patients had pain at diagnosis
 40-70% of cancer patients had pain during treatment
 70-90% of cancer patients had pain during the palliative care

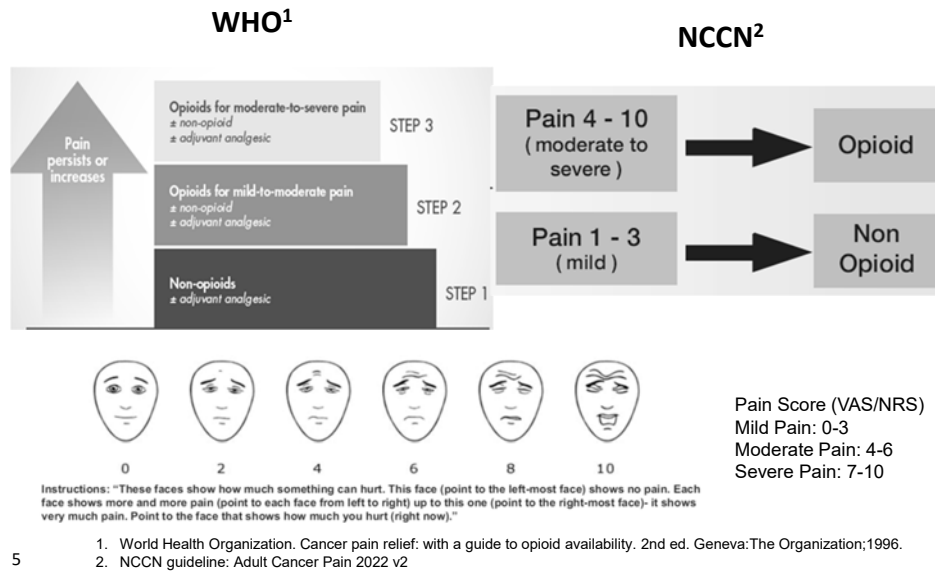


1. Raphael J, Ahmedzai S, Hester J, et al. Pain Medicine 2010; 11: 742-764
2. Pain control in cancer: recent findings and trends Annals of oncology 2007,18(suppl 9): 37-42

After Appropriate Medication



Choose appropriate opioids according to pain score



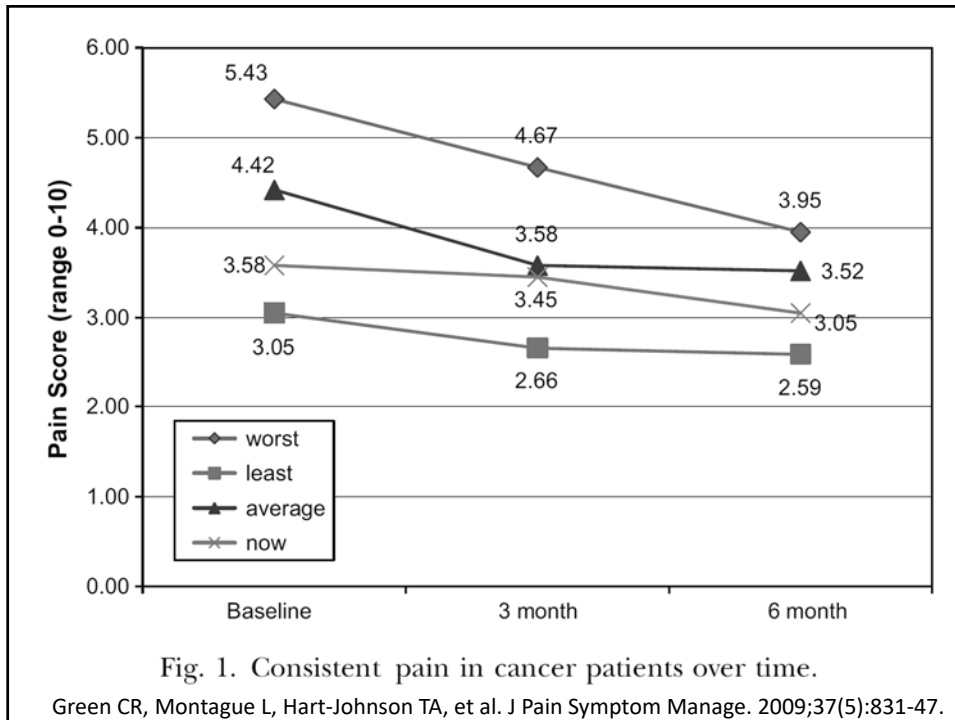
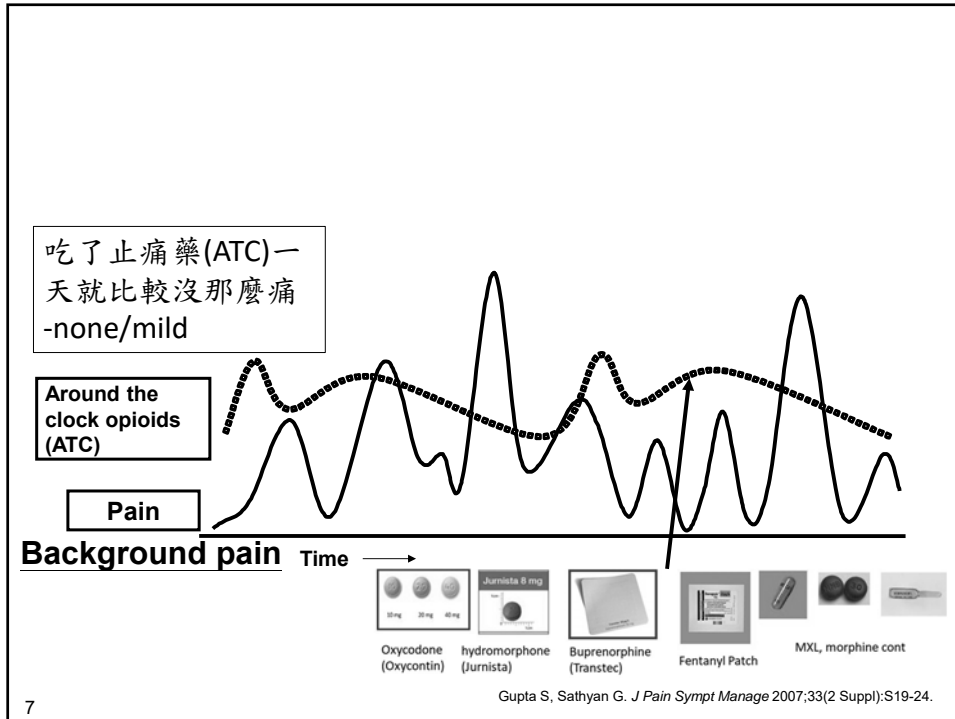
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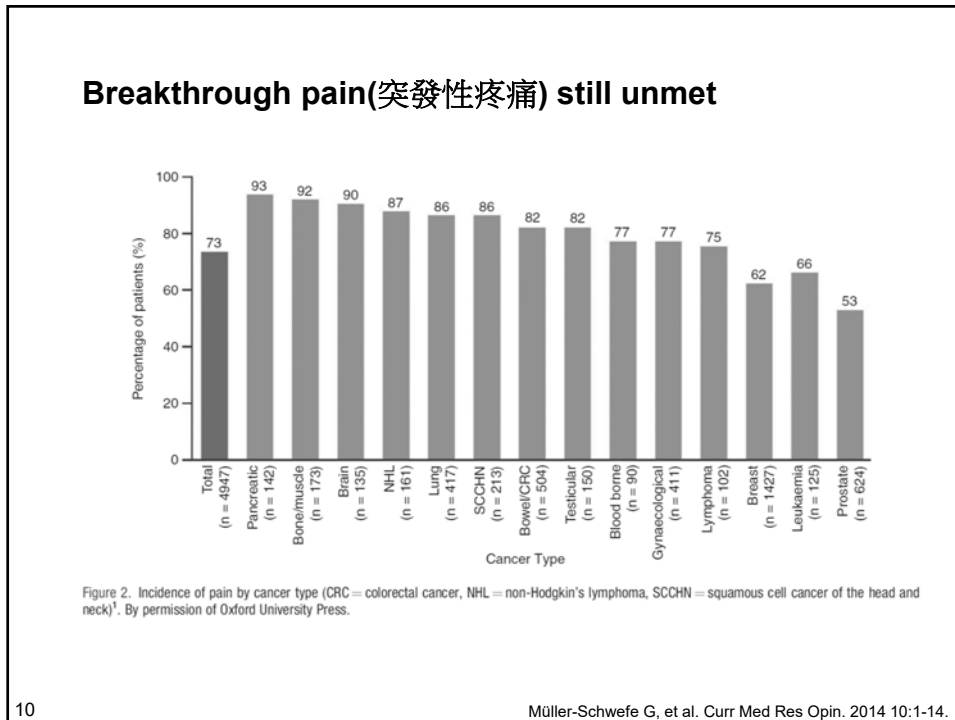
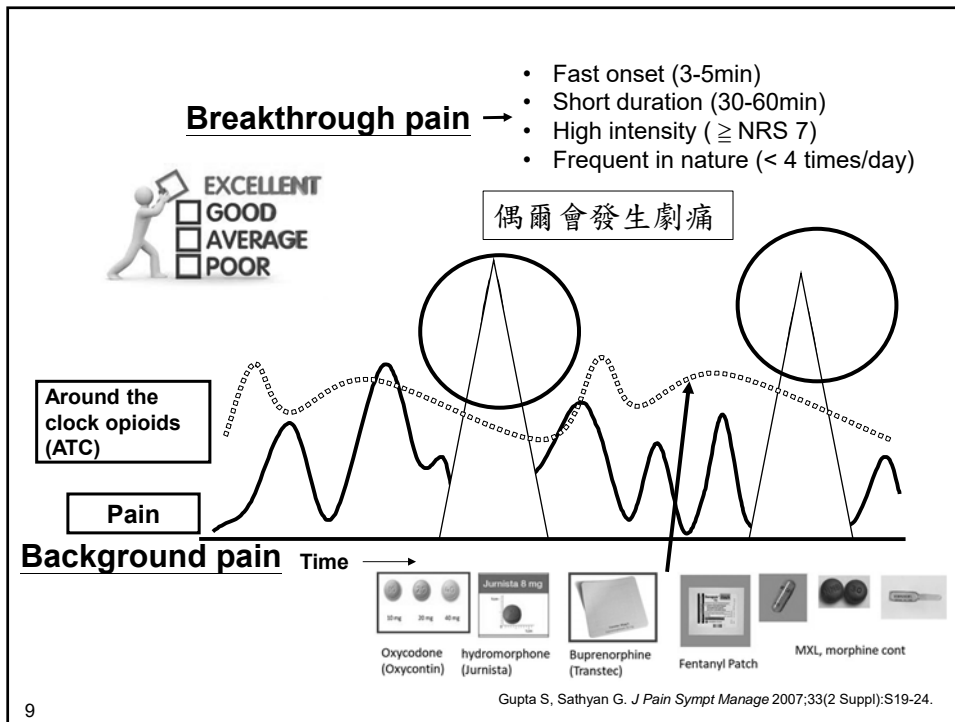
Opioid medication in Taiwan

Rapid-onset
Painkyl® 200mcg 600mcg
Fentora®
(transmucosal fentanyl)

Short-acting	 Tramadol 37.5mg (Acetaminophen 325mg)	 Morphine IR 15mg	 OxyNorm® 5mg Capsule	 Temgesic® 0.2mg
Long-acting	 Morphine SR 30 mg	 MST® 60 mg	 MXL® 60 mg	 OxyContin® 10/20mg
Super long-acting	 Fentanyl patch 12 mcg/hr	 Fentanyl patch 25 mcg/hr	 Fentanyl patch 50 mcg/hr	 Jurnista 8 mg
	 Transec® 35 mcg/hr	 Transec® 52.5 mcg/hr	 Fentanyl patch 80 mcg/hr	 Fentanyl patch 100 mcg/hr

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Breakthrough pain prevalence among cancer patients

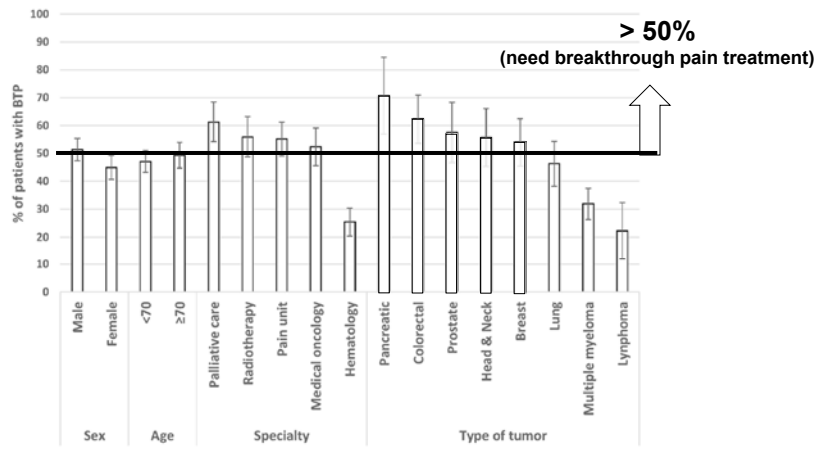


Figure 2. Prevalence of breakthrough pain by age, sex, specialty and type of tumor. Vertical bars correspond to 95% confidence intervals. BTP, breakthrough pain.

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Sci Rep. 2019 Nov 27;9(1):17701.

Breakthrough pain interferes quality of life of patients

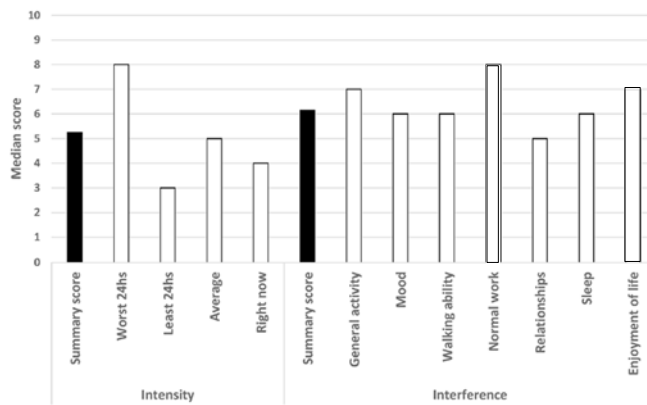


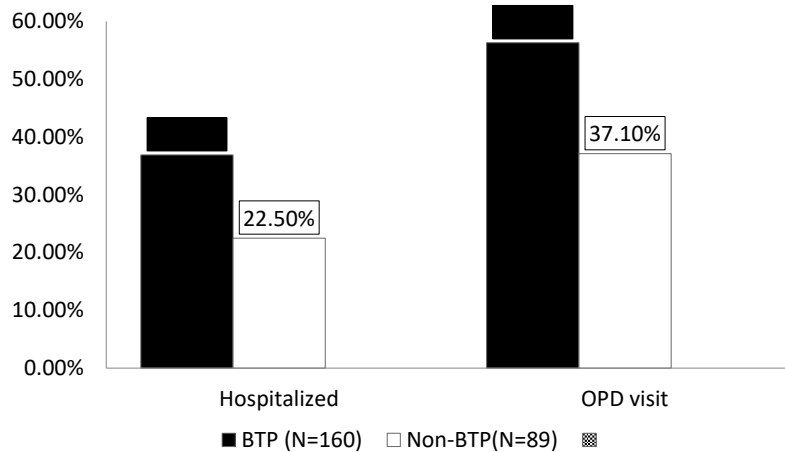
Figure 4. Pain intensity and interference in patients with breakthrough pain as evaluated with the Brief Pain Inventory.

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Sci Rep. 2019 Nov 27;9(1):17701.

Hospitalizations and OPD visit

Patients with BTcP have higher hospitalization rate and more OPD visit rate.



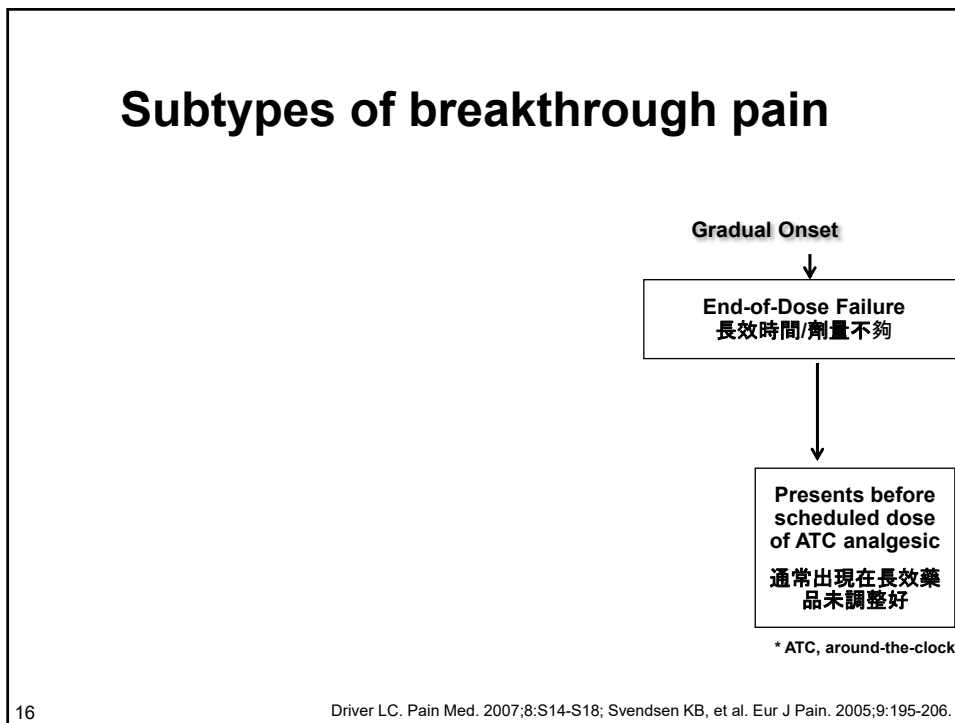
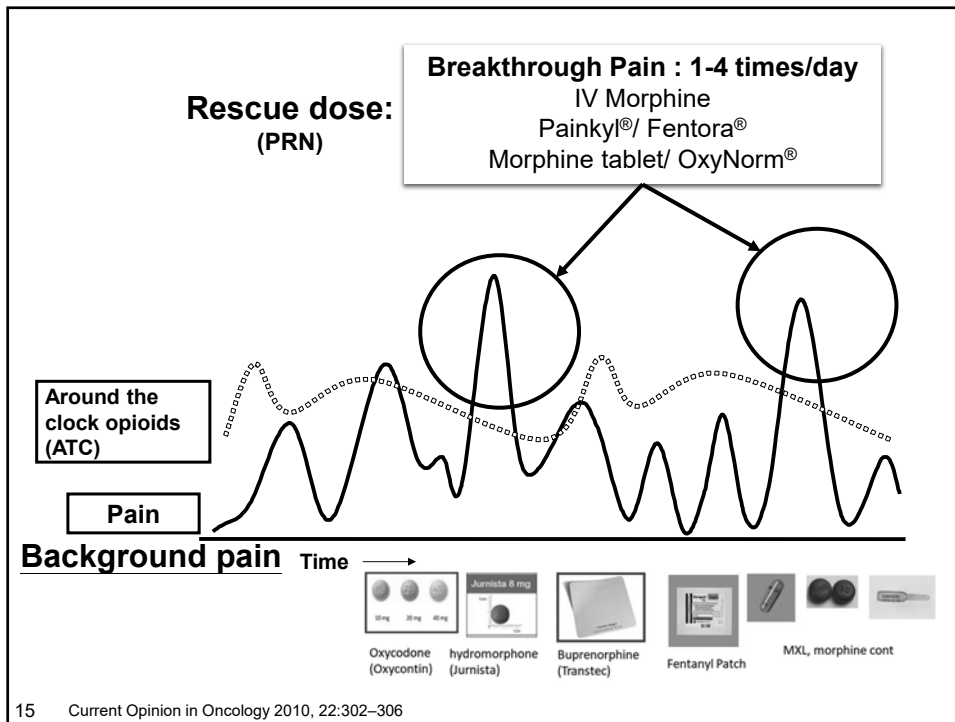
The Journal of Pain, Vol 3, No 1 (February), 2002: pp 38-44

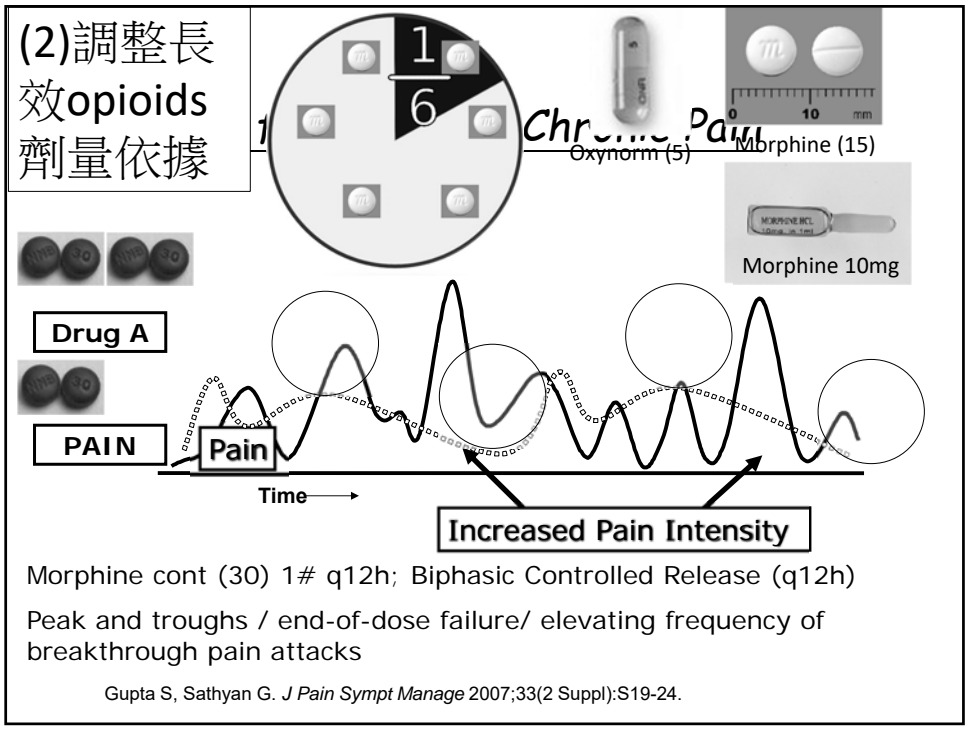
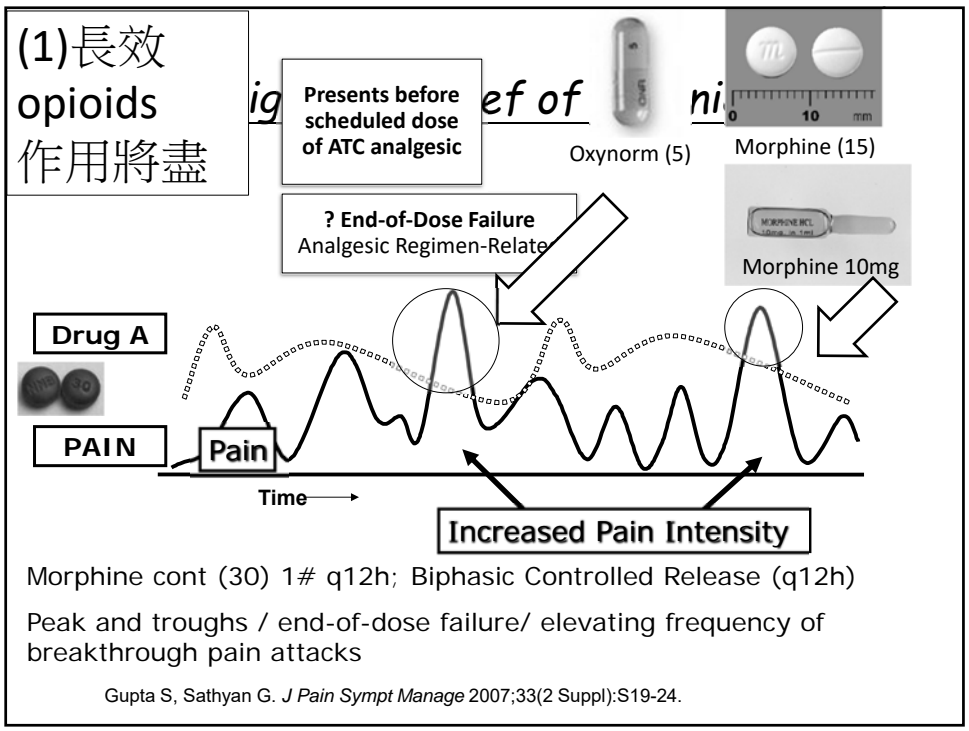
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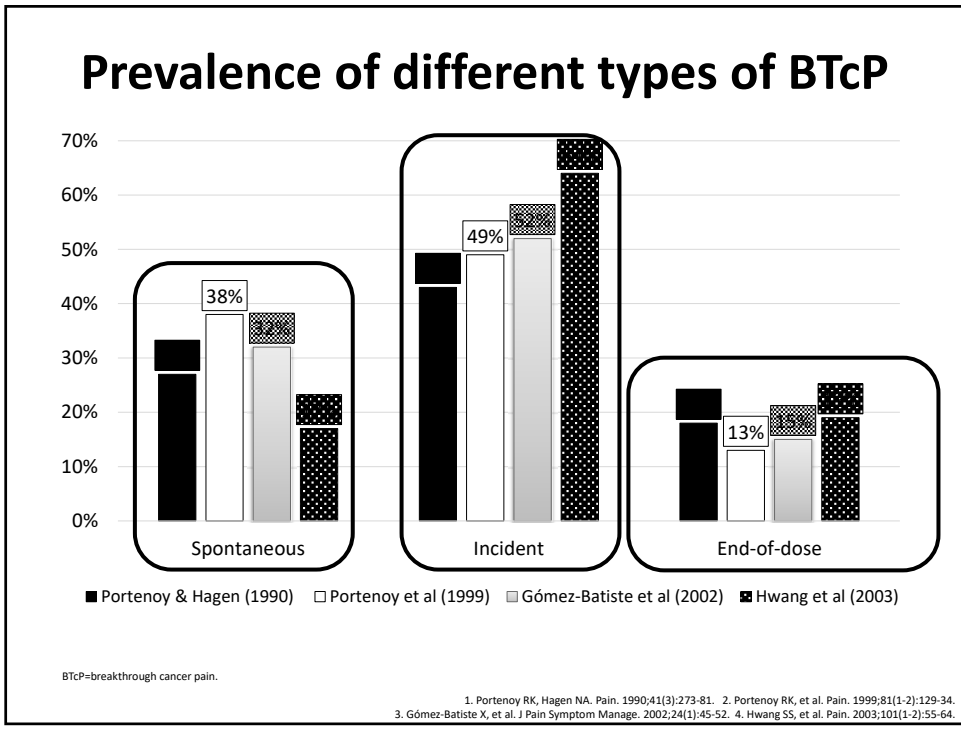
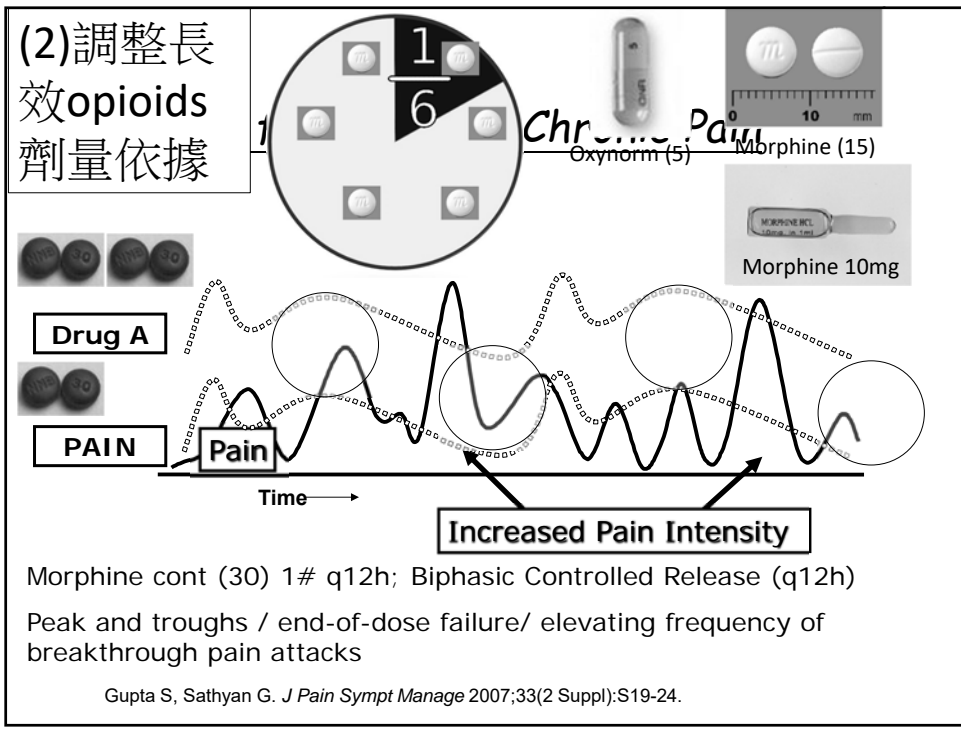
Outline

- Pain is still an issues among cancer patients
- **General rules in cancer pain management**
 - **Learning from a case : Focus on breakthrough pain**
- Opioids trending in Taiwan
- Take Home Message

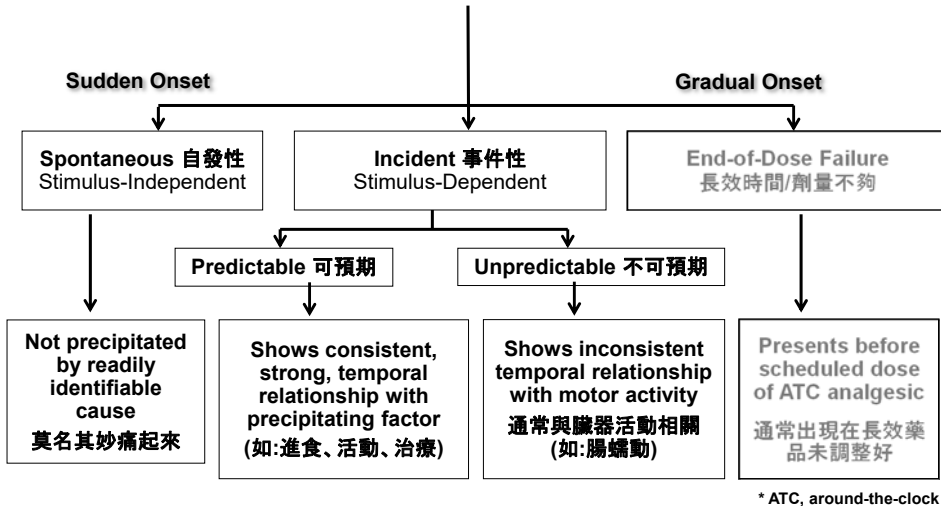
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Subtypes of breakthrough pain



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

Onset快

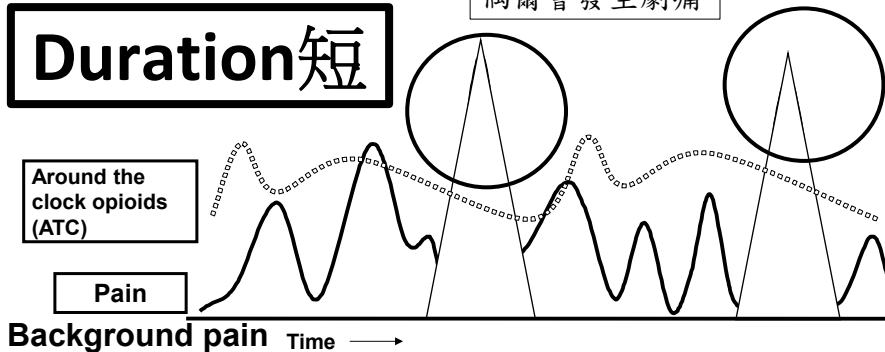
Intensity強

Duration短

Breakthrough pain

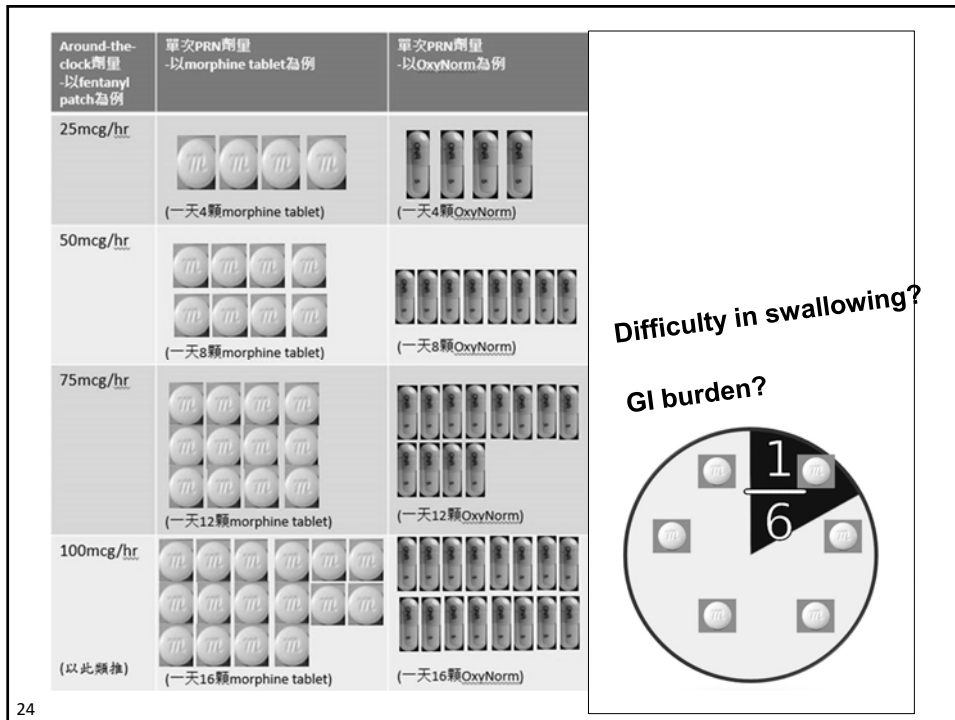
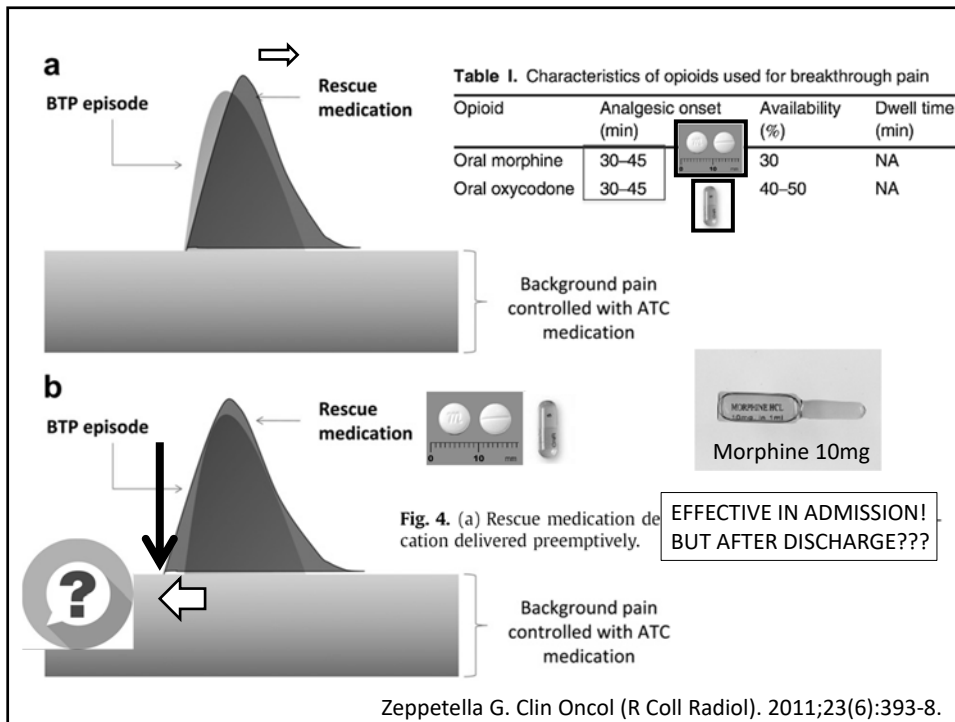
- Fast onset (3-5min)
- Short duration (30-60min)
- High intensity (\geq NRS 7)
- Frequent in nature (< 4 times/day)

偶爾會發生劇痛



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Gupta S, Sathyan G. J Pain Sympt Manage 2007;33(2 Suppl):S19-24.



Breakthrough pain medication

Onset快

Intensity強

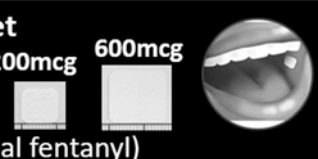
Duration短

Accessible!!!

Table 1 Characteristics of Immediate-Release Opioids Useful for Breakthrough Pain (BTP)

Hydrophilic	Immediate-Release opioid	Onset of Analgesia	Duration
↑	Morphine (oral)	30–40 minutes	4–6 hours
	Oxycodone (oral)	30 minutes	
	Hydromorphone (oral)	30 minutes	
	Methadone (oral)	~10–15 minutes	
↓	Fentanyl (transmucosal)	~5–10 minutes	1–2 hours

Rapid-onset
Painkyl® 200mcg 600mcg
Fentora®
(transmucosal fentanyl)



D — complex pharmacology, pharmacokinetics
 A — fastest onset of analgesia
 D — requires ongoing patient cooperation in use

Breakthrough pain Onset 3–5 minutes Duration 30–60 minutes

Bennett D et al. Part 2: Management. Pharm Ther. 2005;30(6):354–361.

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Canadian recommendations for the management of breakthrough cancer pain

P. Daeninck MD,* B. Gagnon MD,† R. Gallagher MD,‡ J.D. Henderson MD,§ Y. Shir MD,||
 C. Zimmermann MD PhD,² and B. Lapointe MD**

- The **cost** of transmucosal fentanyl preparations **should not impede their use**,
 - especially taking into consideration that many patients in need of those medications have a short life expectancy and that the medication will be needed for **only a brief period of time**.
- Policymakers should keep those factors in mind when making their listing recommendations.

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Transmucosal fentanyl 健保給付規範

1. 限用於突發性疼痛(breakthrough pain)，並已接受過口服 morphine 至少60mg/day、oxycodone 至少30mg/day、hydromorphone 至少8mg/day、或 fentanyl 貼片劑至少25/mcg/hr 或其他等止痛劑量之類鴉片藥物達一星期(含)以上之18歲(含)以上癌症患者。
2. 不得用於急性或術後疼痛之處置。

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Case sharing

- Opioid rotation
- With Painkyl treatment, Painkyl titration

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Case sharing

- 70 y/o male patient
- HCC , with peritoneal carcinomatosis and bone metastasis (spine, pelvic, right side acetabulum and femoral shaft)
 - Abdominal pain (dull, diffuse, frequent, 7-8/10)
 - Right hip pain (6-7/10) during standing /sitting /walking
 - Throbbing pain with numbness/ weakness at right lower extremity (intermittent, night time)

Abdominal pain (dull, diffuse, frequent, 7-8/10)

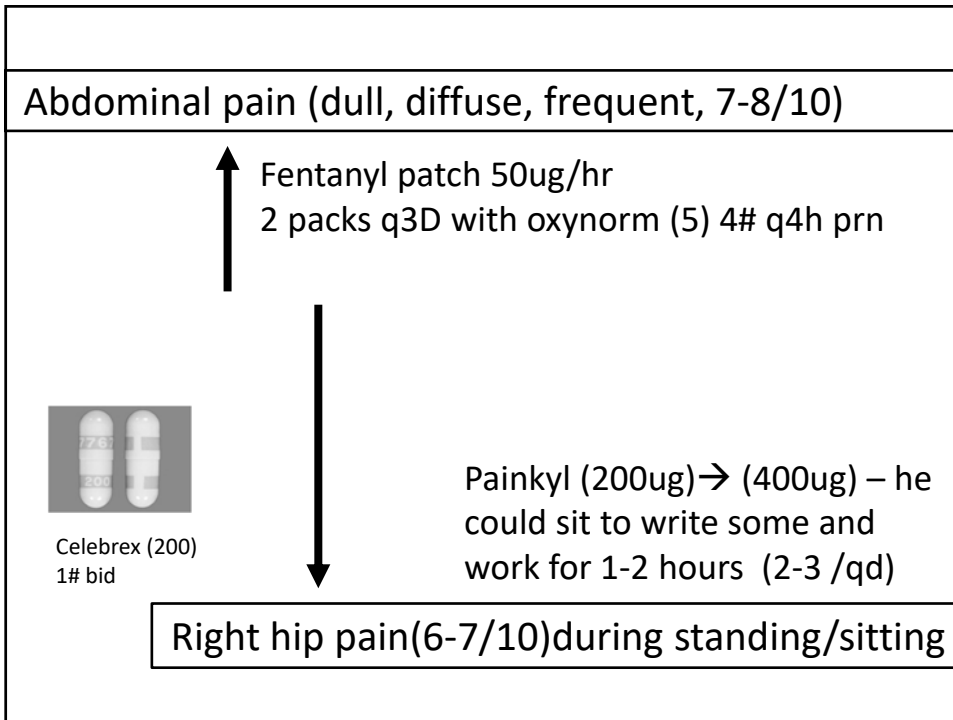
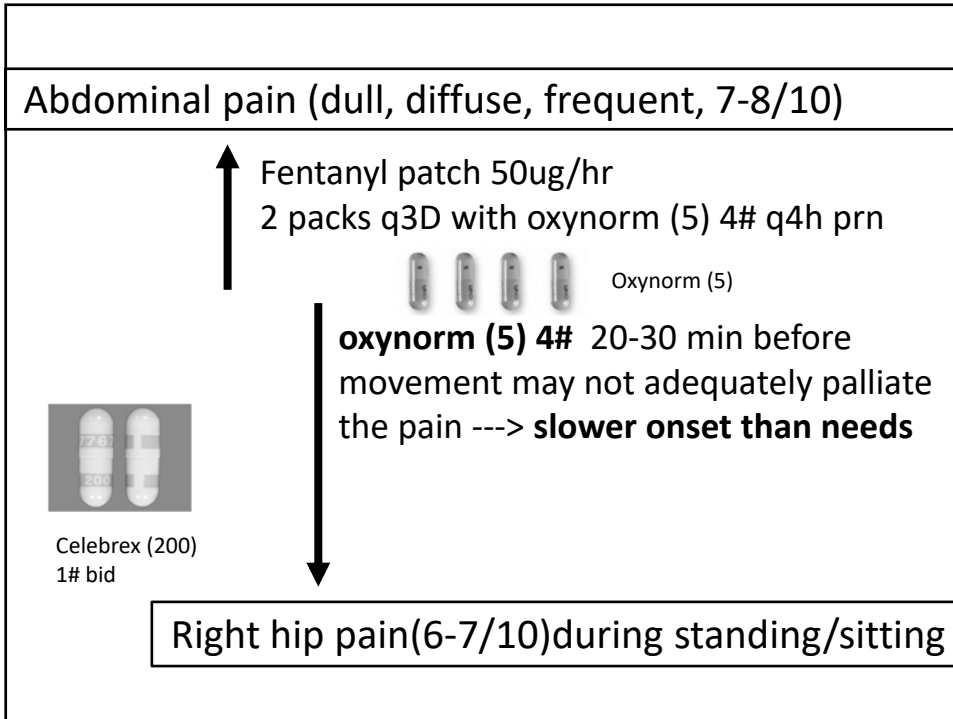
↑ Fentanyl patch 50ug/hr 1 packs q3D with
prn oral morphine tab (15) 1 --- > 2# q4h
prn (2# for 4-5 times) NRS: 6 -> 1-2/10

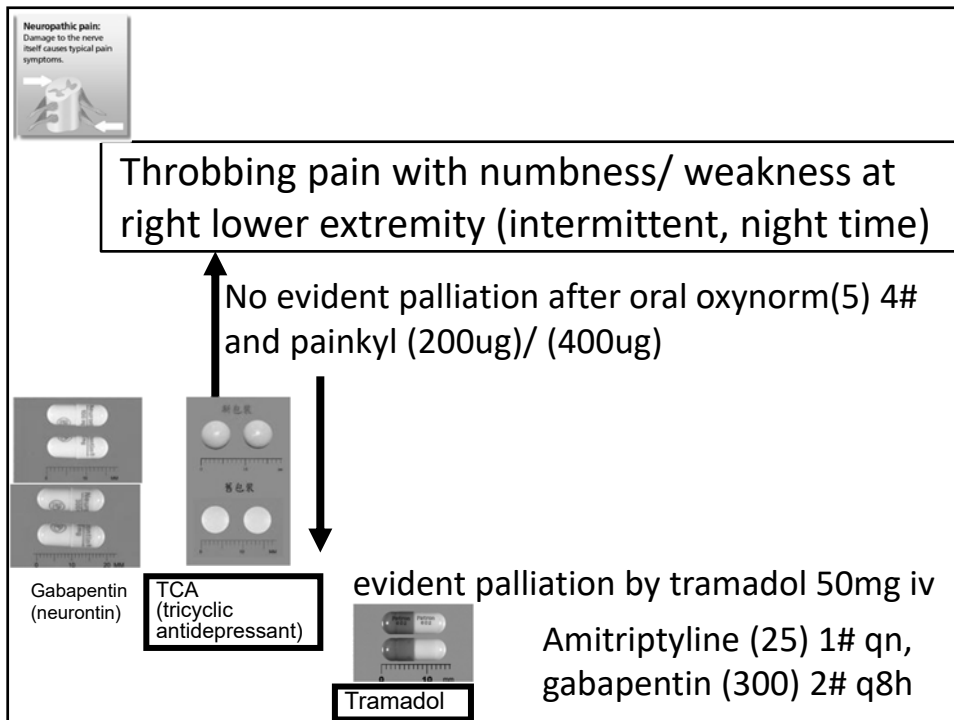
morphine=2*4*15= 120mg
-> fentanyl 50ug/hr 1 pack
PRN= 240/6= 40

⇒ Fentanyl patch 50ug/hr
2 packs q3D with oxynorm
(5) 4# q4h prn



Oxynorm (5)





Challenge from Breakthrough pain 1

- Differentiation between background and breakthrough pain

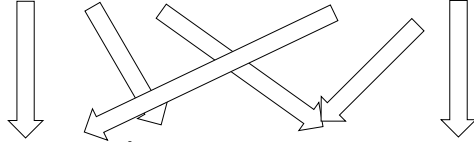
Abdominal pain (O)
Right hip pain (X)
Throbbing pain/ numbness (X)

- The same pathophysiology?

Abdominal pain - visceral
Right hip pain - somatic
Throbbing pain/ numbness - neuropathic

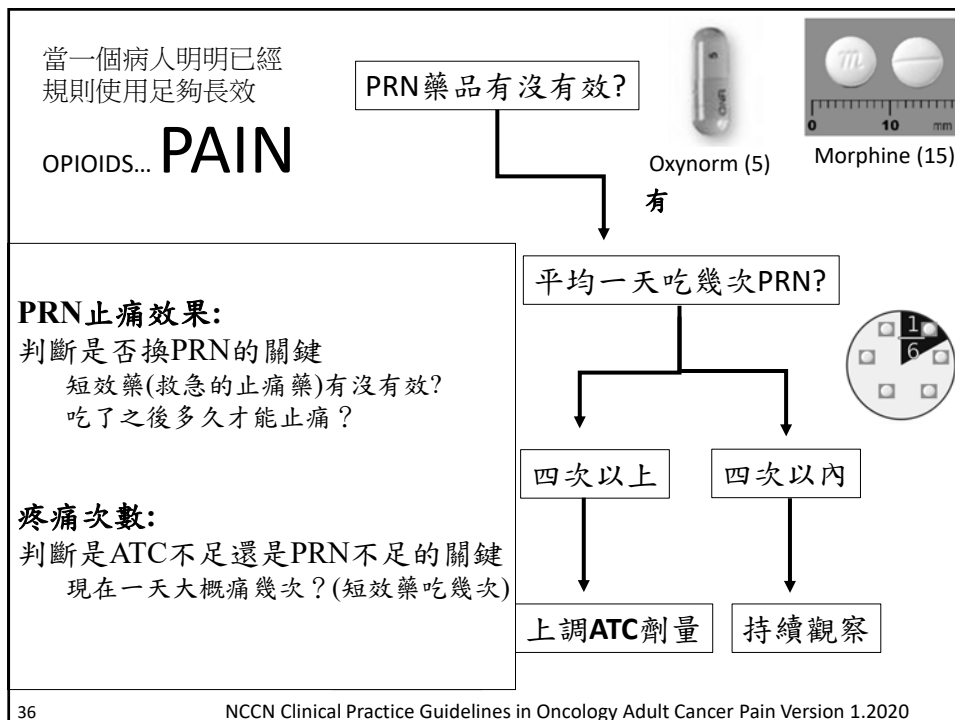
Challenge from Breakthrough pain 2

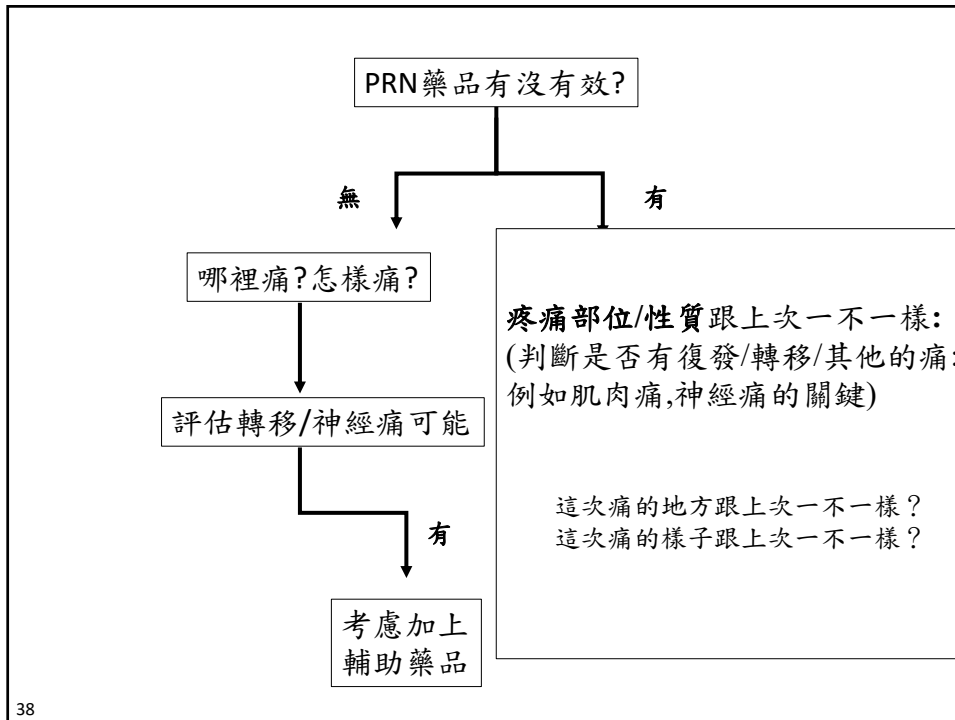
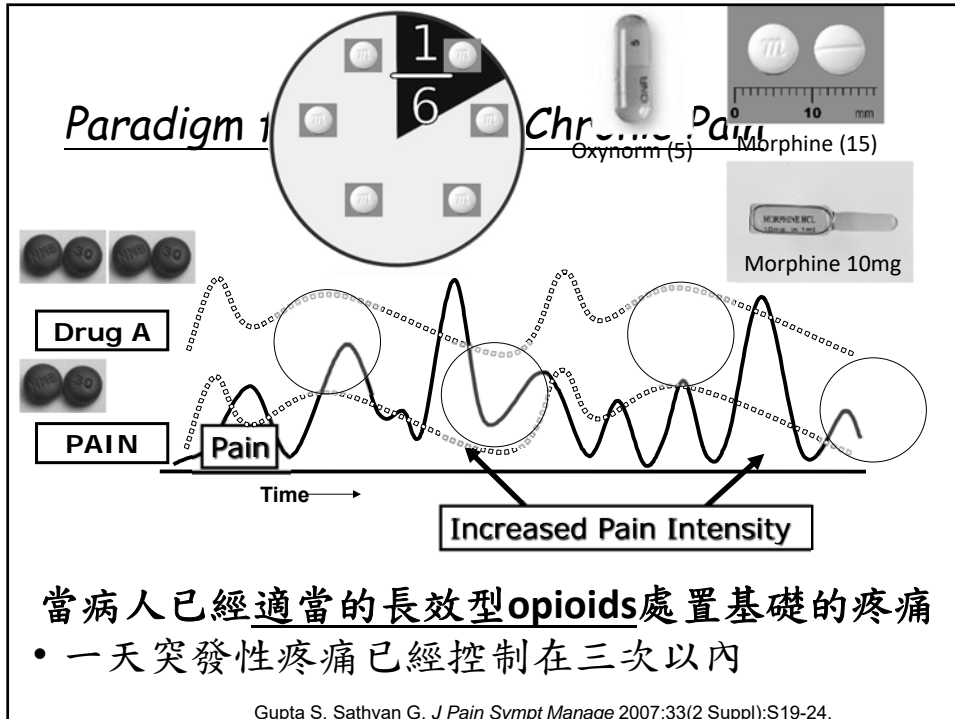
- Background and breakthrough pain



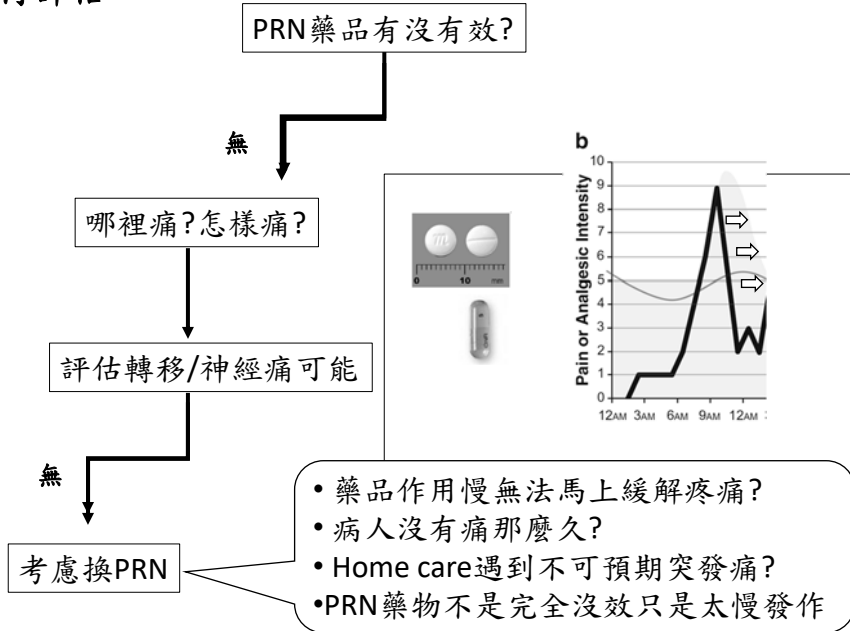
- Visceral/Somatic and neuropathic pain

- Besides Short acting opioids --- > **rapid onset opioids (ROO) ex. painkyl**





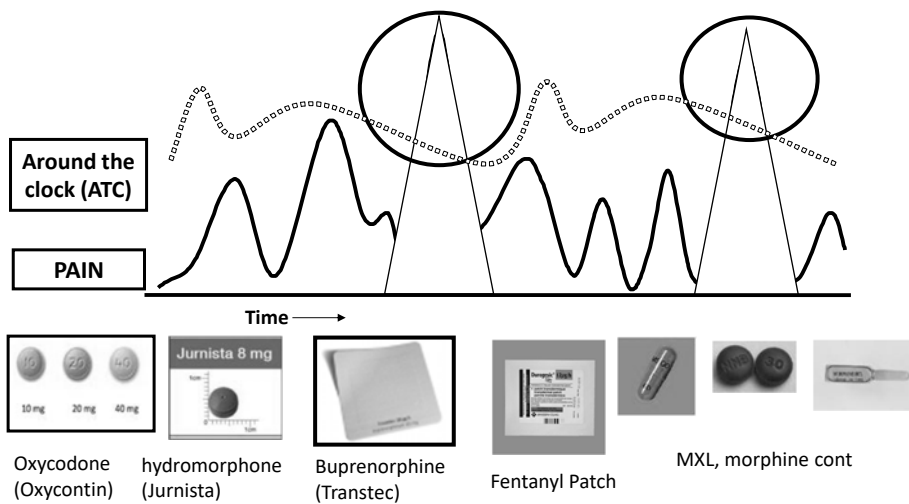
門診再評估



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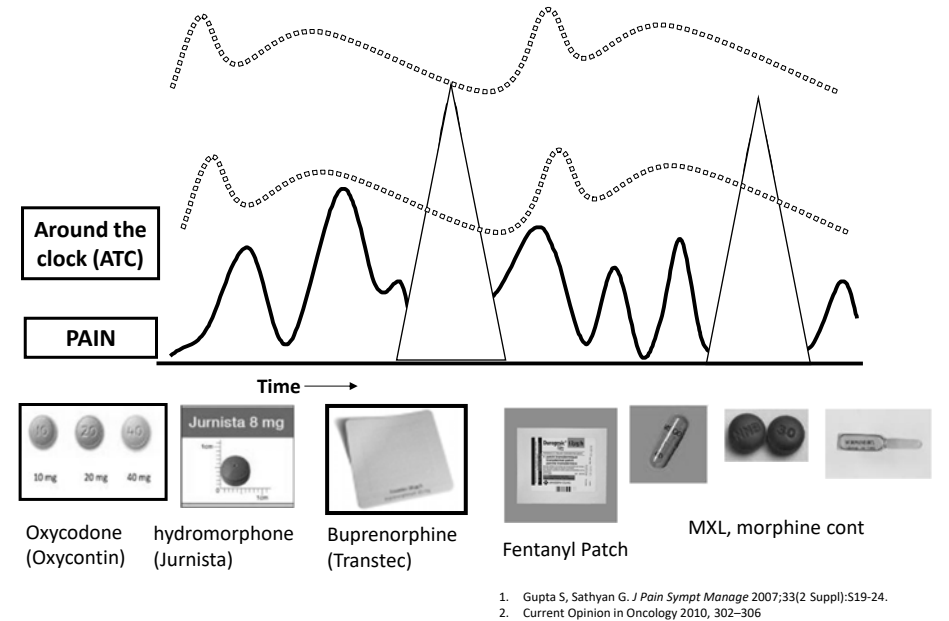
- 如果有面對較快又急的突發性疼痛
- Fast onset 來得快 (3~5分鐘達最痛)
 - Short duration 去得快 (平均30~60分鐘)
 - High intensity 強度強 (平均強度為7.3分)

Breakthrough pain (突發性疼痛)



Gupta S, Sathyan G. *J Pain Sympt Manage* 2007;33(2 Suppl):S19-24.

ATC藥品劑量墊很高，病人雖然完全感受不到疼痛，但伴隨而來的噁心嘔吐、暈眩、便秘等副作用將會變的相當嚴重，甚至有可能會產生呼吸抑制



Oxynorm (5)

In comparison with Short Acting Opioid

Morphine 15mg

Morphine (10)

	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 ^{cm}	4-6 hrs
Fentanyl buccal soluble film (paikyl®)	9 mins ² (T _{first})	1 hrs ²	1-2 hrs

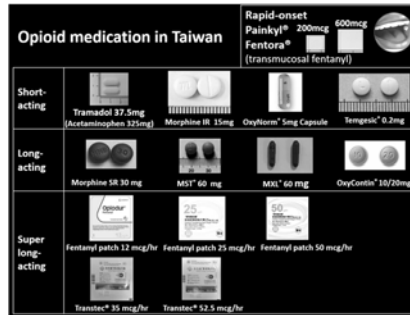
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- Pharmacokinetic Optimization of Opioid Treatment in Acute Pain Therapy Clin. *Pharmacol inet.* 1997 Sep; 33 (3); 225-244
- Formulation Selection and Pharmacokinetic Comparison of FBSF with OTFC. *Drug Investig* 2009; 29 (10): 647-654
- Pharmacotherapy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

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Outline

- Pain is still an issues among cancer patients
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- **Opioids trending in Taiwan**
- Take Home Message



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Strong opioid prescription in cancer patients in their final year of life- Taiwan NHI database 2008-2011

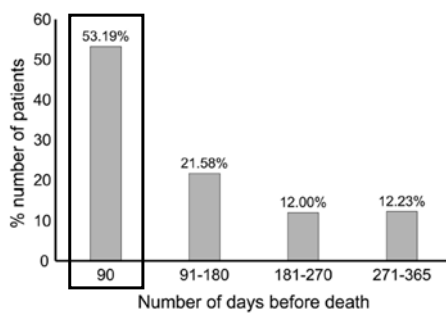
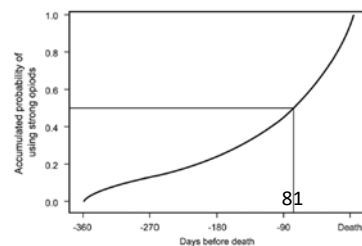


FIGURE 1 Proportion of patients who started prescribing strong opioids during 1 year prior to death



Number of patients at risk	162679	50241	43535	31543	3643
Number of events	239	55	99	191	539

FIGURE 2 Probability of a strong opioid prescription during 12 months before death among Taiwanese patients with cancer who died from cancer between 2008 and 2011

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Strong opioid prescription in cancer patients in their final year of life- Taiwan NHI database 2008-2011

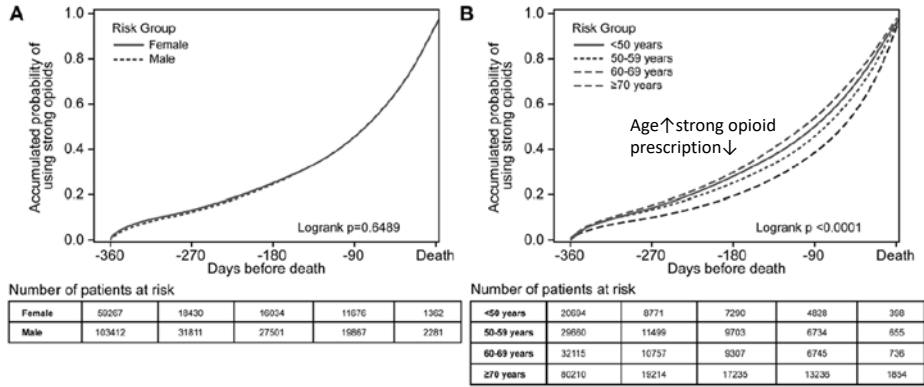


Fig.3 Probability of strong opioid prescription during 12 months before death among Taiwanese patients with cancer who died from cancer between 2008 and 2011 by key patient characteristics. (A) Sex, (B) age, (C) cancer diagnosis, and (D) hospital division

Strong opioid prescription in cancer patients in their final year of life- Taiwan NHI database 2008-2011

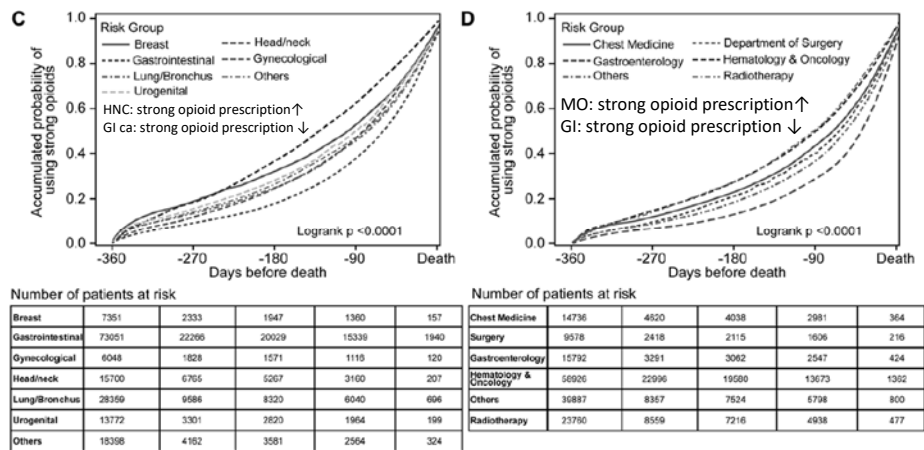


Fig.3 Probability of strong opioid prescription during 12 months before death among Taiwanese patients with cancer who died from cancer between 2008 and 2011 by key patient characteristics. (A) Sex, (B) age, (C) cancer diagnosis, and (D) hospital division

Impact of expanded strong opioid availability on opioid prescription patterns- Taiwan NHI database 2012-2017

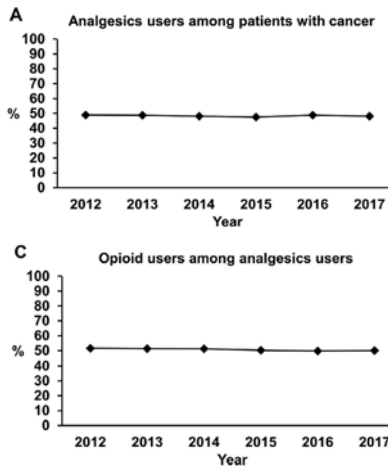


Figure 1. (A) Percentage of patients with prescriptions of analgesics among all patients with cancer from 2012 to 2017. (C) analgesic users from 2012 to 2017.

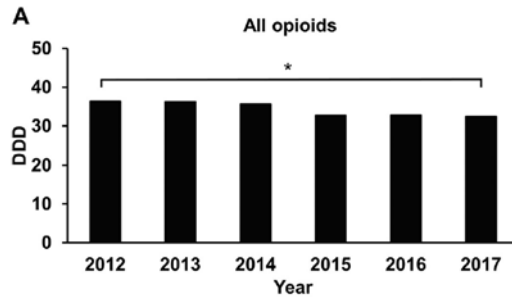


Figure 2. (A) Annual cumulative dose per patient of all opioids calculated by the defined daily dose (DDD).

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The Lancet Regional Health - Western Pacific 16 (2021) 100255

Impact of expanded strong opioid availability on opioid prescription patterns- Taiwan NHI database 2012-2017

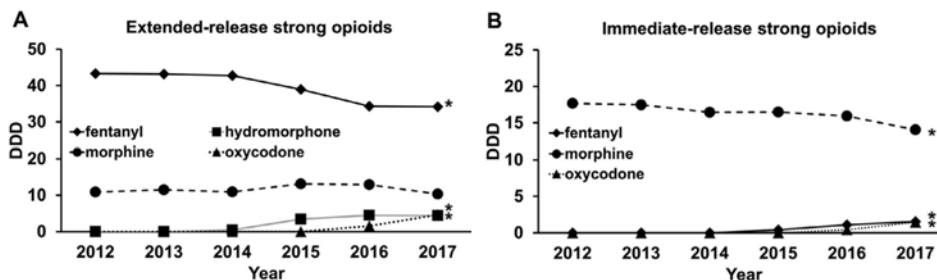


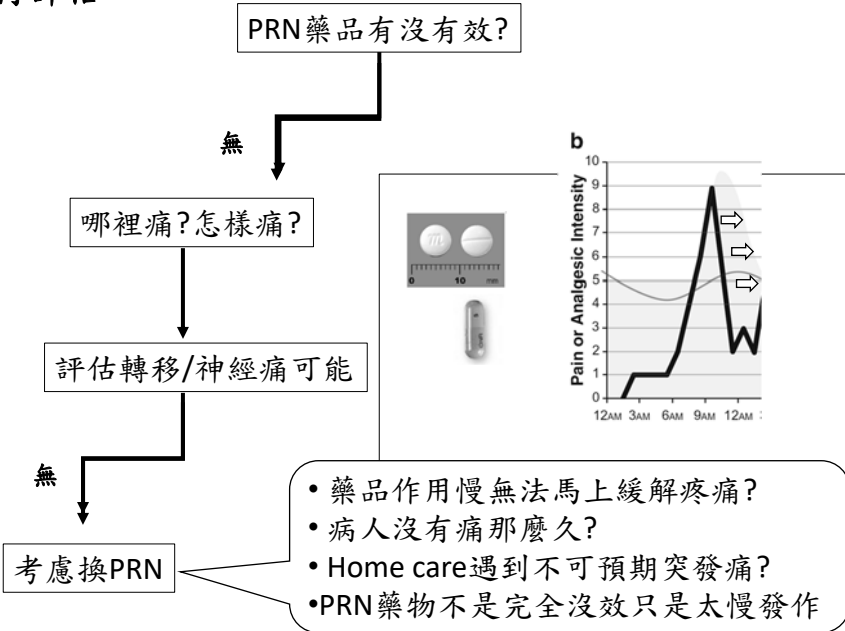
Figure 3. Annual cumulative dose of (A) extended-release strong opioids, (B) immediate-release strong opioids, and (C) weak opioids. (*: statistically significant trend with $p < .05$)

Interpretation Increased therapeutic options in strong opioid prescriptions led opioid prescription patterns to evolve towards international cancer pain management guidelines. In addition, increased accessibility to a wider range of different strong opioids may facilitate more efficient opioid titration and rotation - and thus decrease, not increase, the opioid usage.

The Lancet Regional Health - Western Pacific 16 (2021) 100255

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門診再評估



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Oxynorm (5)

Morphine 15mg

In comparison with Short Acting Opioid

Morphine (10)

	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 ^{cm}	4-6 hrs
Fentanyl buccal soluble film (painky!®)	9 mins ² (T _{first})	1 hrs ²	1-2 hrs

600 200

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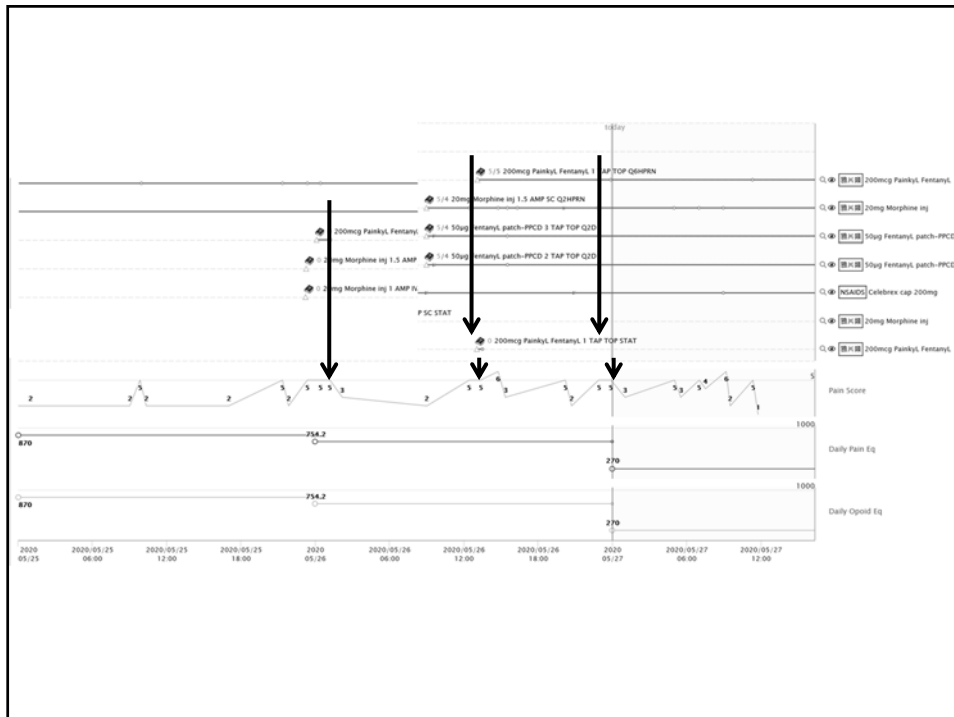
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Effective dose in Taiwanese patients

TABLE 2 Effective dose of FBSF (PP, N = 30)

Final dosage, µg	n	%
200	17	56.7
400	9	30.0
600	3	10.0
800	1	3.3
1200	-	-
	n	% (95% CI)
Requiring dose titration	13	43.3 (25.5, 62.6)

Abbreviations: CI, confidence interval; FBSF, fentanyl buccal soluble film; PP, per-protocol.



Will Breakthrough Cancer Pain Treatment through Rapid-Onset Transmucosal Fentanyl Improve the Quality of Life in Cancer Patients?

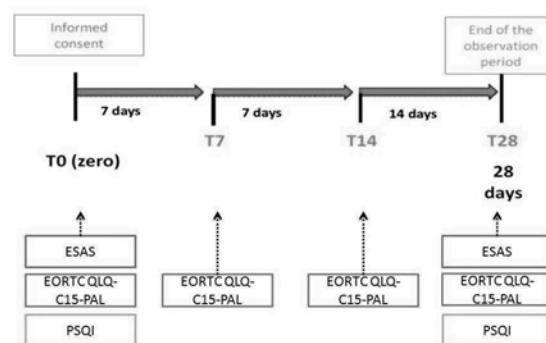


Figure 1. Study design. Legend: EORTC QLQ-C15-PAL, European Organization of Research and Treatment Quality of Life Questionnaire-Cancer 15; PSQI, Pittsburgh Sleep Quality Index; ESAS, Edmonton Symptom Assessment System.

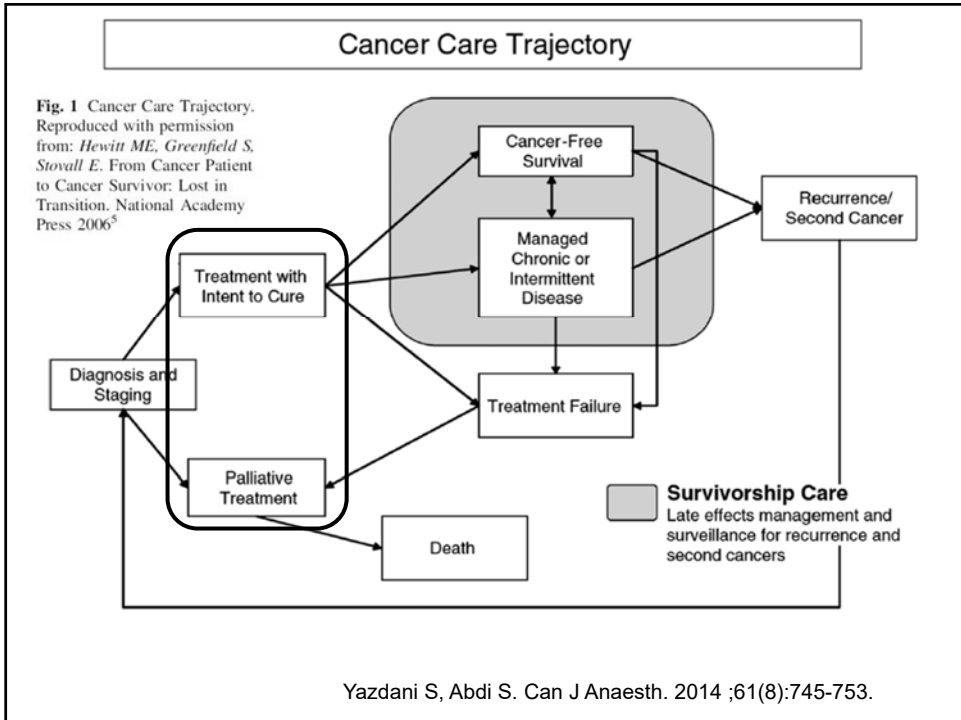
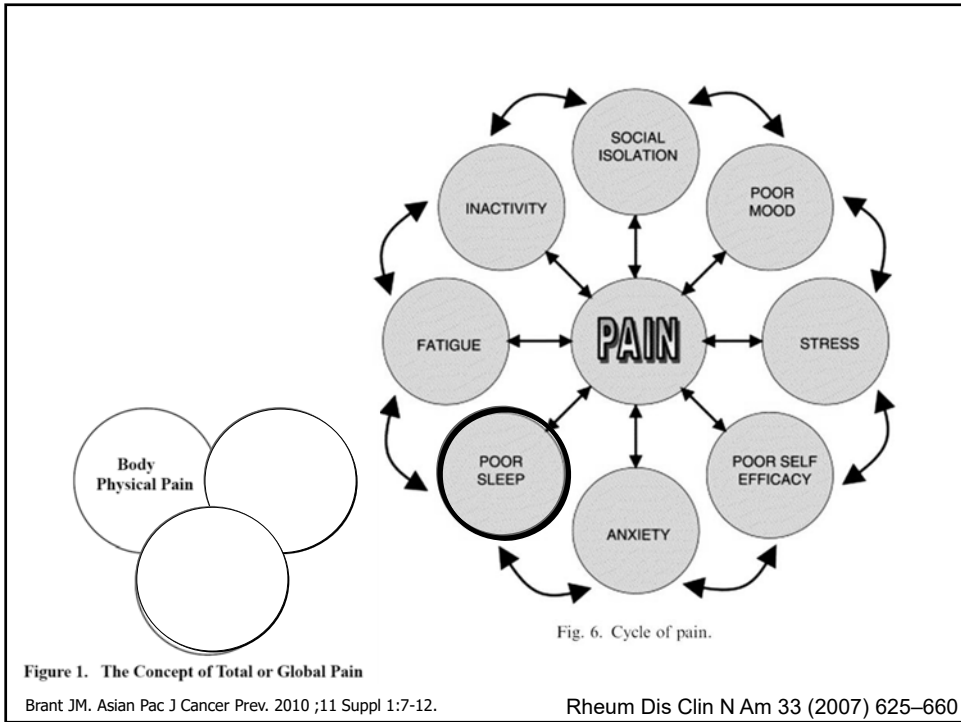
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J. Clin. Med. 2020, 9, 1003

Outline

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Opioid rotation



計算
Daily Dose

算出等量劑量

Opioid medication in Taiwan				Rapid-onset Painkyl® 200mcg Fentora® 600mcg (transmucosal fentanyl)
Short-acting	Tramadol 37.5mg (Acetaminophen 325mg)	Morphine IR 15mg	Oxyform® 5mg Capsule	Temgesic® 9.2mg
Long-acting	Morphine SR 30 mg	MST® 60 mg	ML® 60 mg	OxyContin® 10/20mg
Super long-acting	Fentanyl patch 12 mcg/hr	Fentanyl patch 25 mcg/hr	Fentanyl patch 50 mcg/hr	Transderm® 35 mcg/hr Transderm® 52.5 mcg/hr

疼痛控制不佳:
轉換 100-125%



疼痛控制良好:
減量 25-50%*

NCCN guideline: Adult Cancer Pain 2022 v2

Strong opioid prescription in cancer patients in their final year of life- Taiwan NHI database 2008-2011

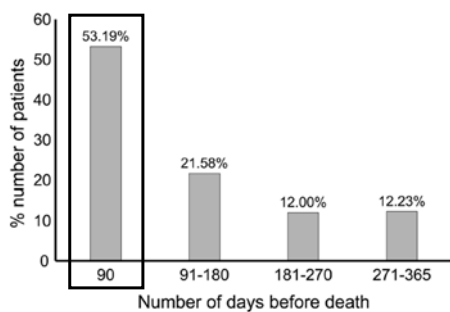
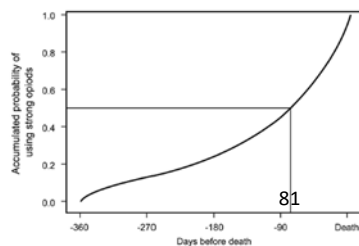


FIGURE 1 Proportion of patients who started prescribing strong opioids during 1 year prior to death



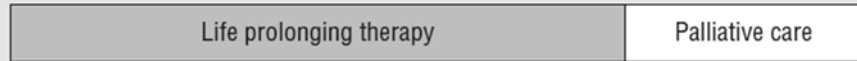
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Number of events	239	55	99	191	539

FIGURE 2 Probability of a strong opioid prescription during 12 months before death among Taiwanese patients with cancer who died from cancer between 2008 and 2011

Asia-Pac J Clin Oncol. 2018;1-7.

Initial hospice programmes:

predominantly oncology and selected neurodegenerative diseases



Palliative care relevance, current view:

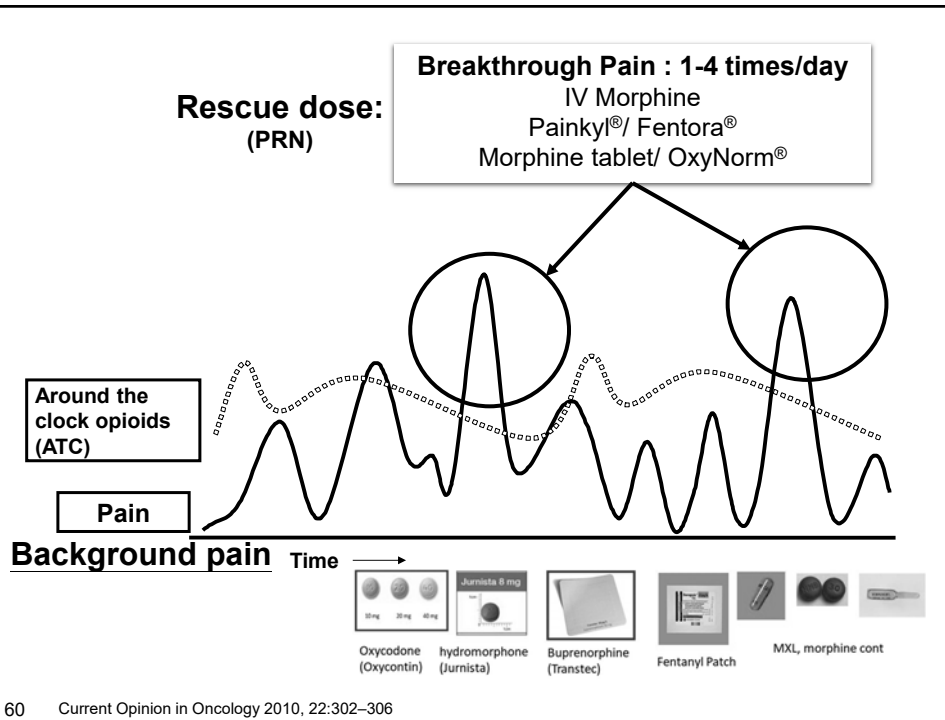
all end stage diseases and clinical settings

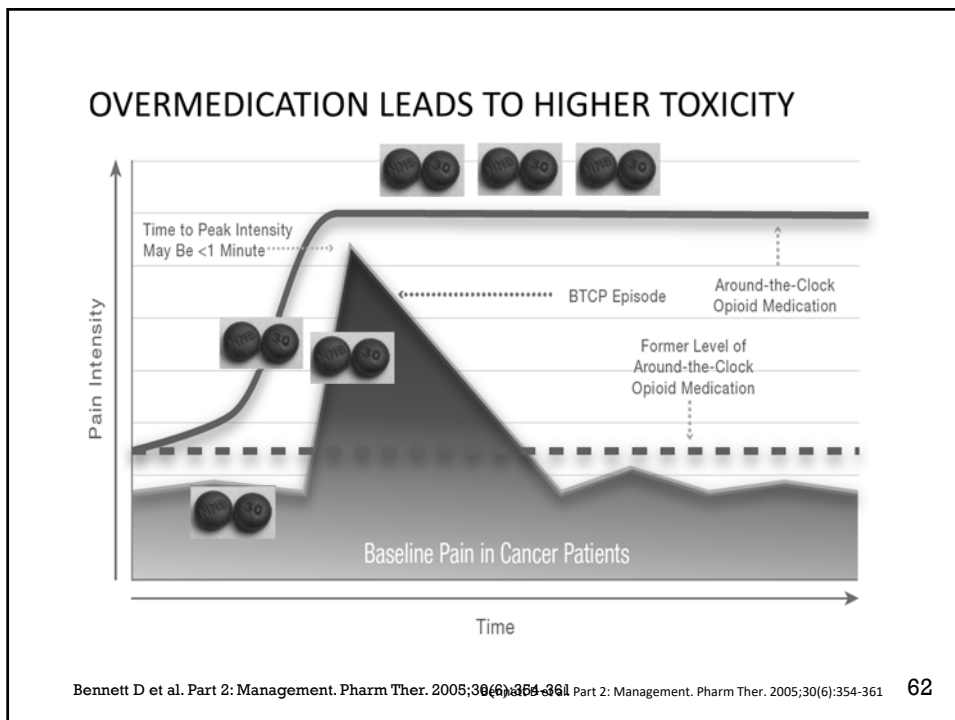
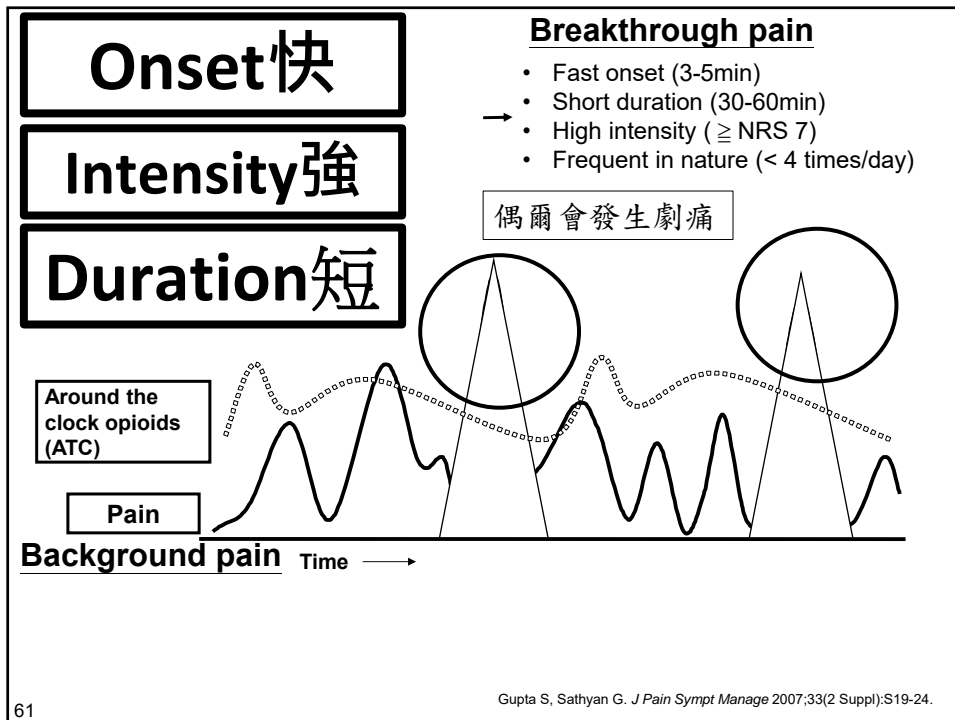


Changes in allocation of resources with the development of palliative care

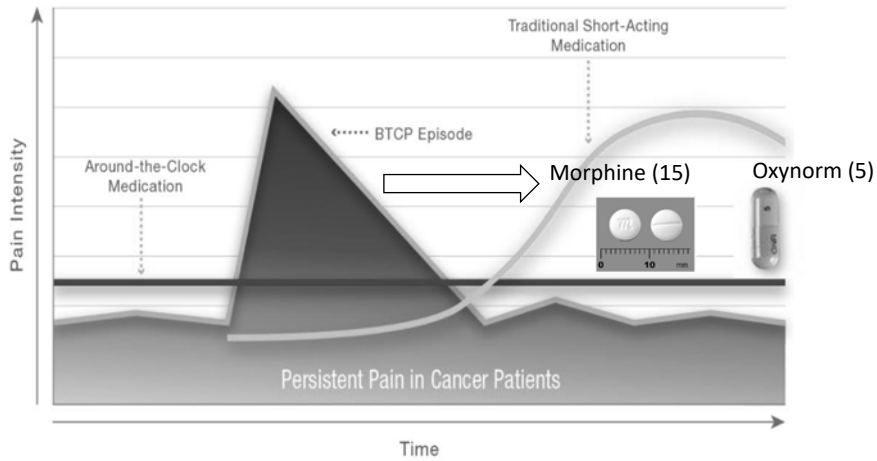
Pain management should be given only when palliative care has been planned!!!

ABC OF PALLIATIVE CARE Second Edition 2006





TRADITIONAL SHORT-ACTING OPIOIDS CANNOT RELIEVE SUCH PATTERNS OF BREAKTHROUGH PAIN PROPERLY



ROO (Rapid onset opioid)

Onset 夠快

Duration 夠就好

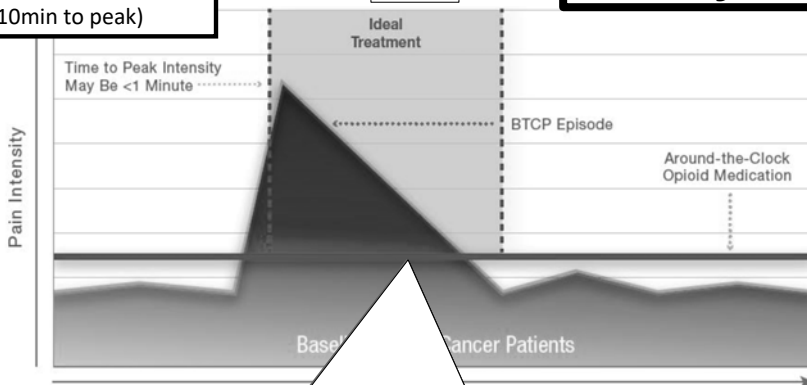
Accessible

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



Painkyl[®]
200mcg/
600mcg

Efficacy 夠強



duration of 15-30 minutes (up to 60-90 minutes)
*maximal pain intensity:3-15 minutes or even within seconds**

Transmucosal fentanyl 健保給付規範

1. 限用於突發性疼痛(breakthrough pain)，並已接受過口服 morphine 至少60mg/day、oxycodone 至少30mg/day、hydromorphone 至少8mg/day、或 fentanyl 貼片劑至少25/mcg/hr 或其他等止痛劑量之類鴉片藥物達一星期(含)以上之18歲(含)以上癌症患者。
2. 不得用於急性或術後疼痛之處置。

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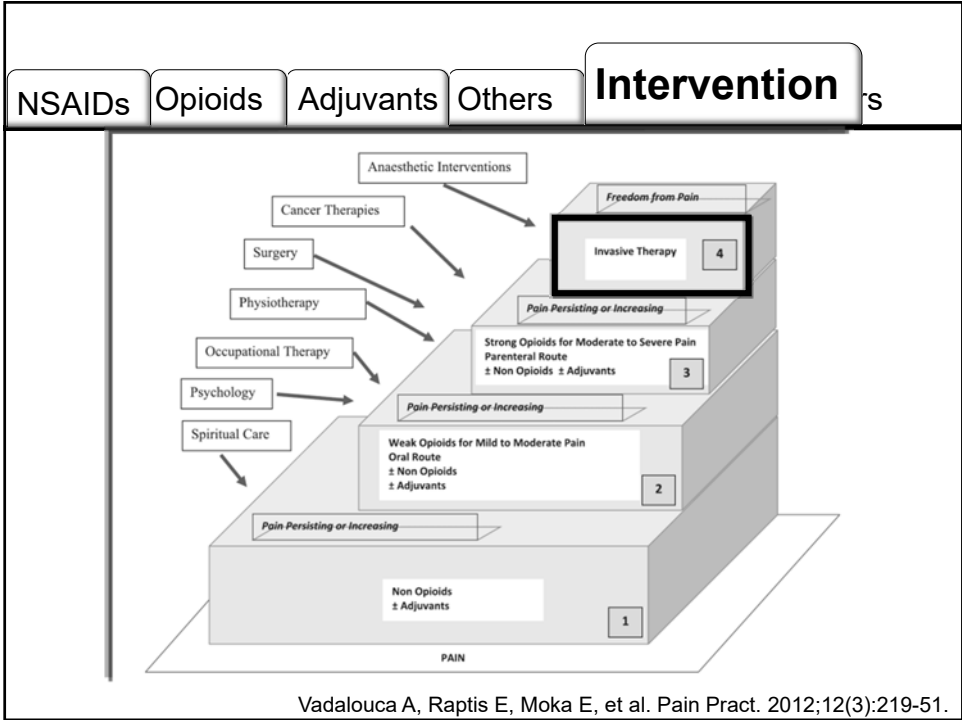
- Morphine ≥ 60 mg/day
- Oxycodone ≥ 30 mg/day
- Hydromorphone ≥ 8 mg/day
- Fentanyl ≥ 25 /mcg/hr
- 或其他等止痛劑量之類鴉片藥物
- 其他等止痛劑量之類鴉片藥物
- ≥ 60 Morphine Milligram Equivalents (MME)
- 達一星期(含)以上
- 18歲(含)以上癌症患者

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After Appropriate Medication



Adopted for Dr. Zhou, NTUH, 2018



Vadalouca A, Raptis E, Moka E, et al. Pain Pract. 2012;12(3):219-51.

Thanks for your listening!