癌症惡病質及止痛原則

臺大醫院雲林分院虎尾院區
腫瘤醫學部
陳若白

JUNE 27 , *2015*

惡病質之機轉與影響

輔助治療的新對策

主題大綱

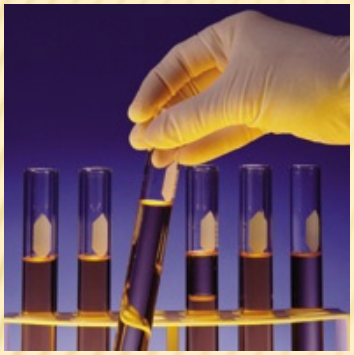
- ◆營養不良增加罹病率及致死率
- ◆惡病質之機轉與影響
- ◆輔助治療的新對策
- ◆控制體重減輕的臨床證據支持

體重減輕增加死亡的危險性

20% 的病患
是死於營養不良
不是本身的腫瘤疾病

Kondrup, AJCN 2002
De Wys et al: Am J Med 1980.
Andreyev et al: Eur J Cancer 1998

體重減輕增加死亡的危險性



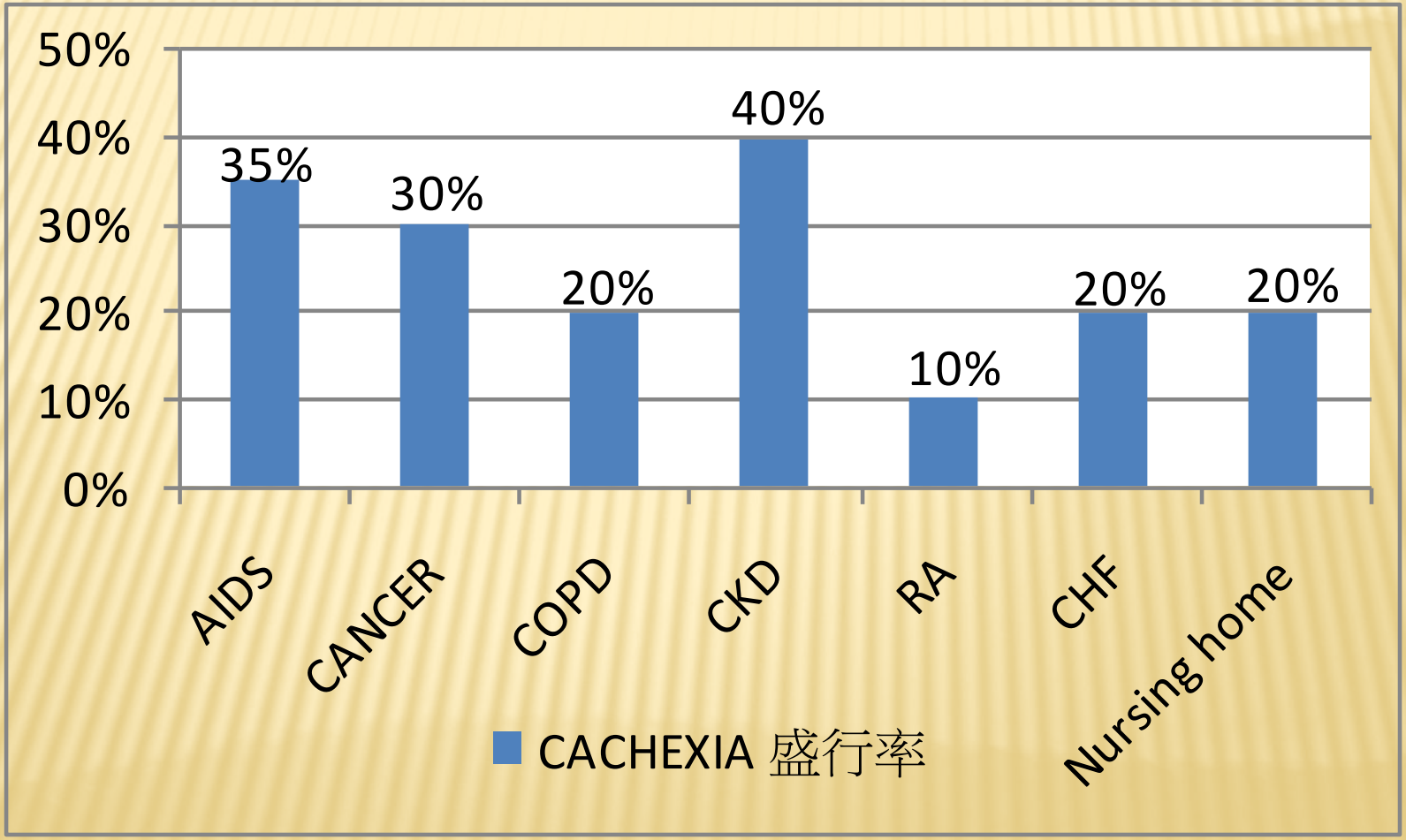
研究調查統計：

- 40-80%的癌症病患有體重減輕的危機
- 15-40% anorexia at presentation

- 因腫瘤引發體重持續減輕，造成有
- Up to 20% of patients lead to death

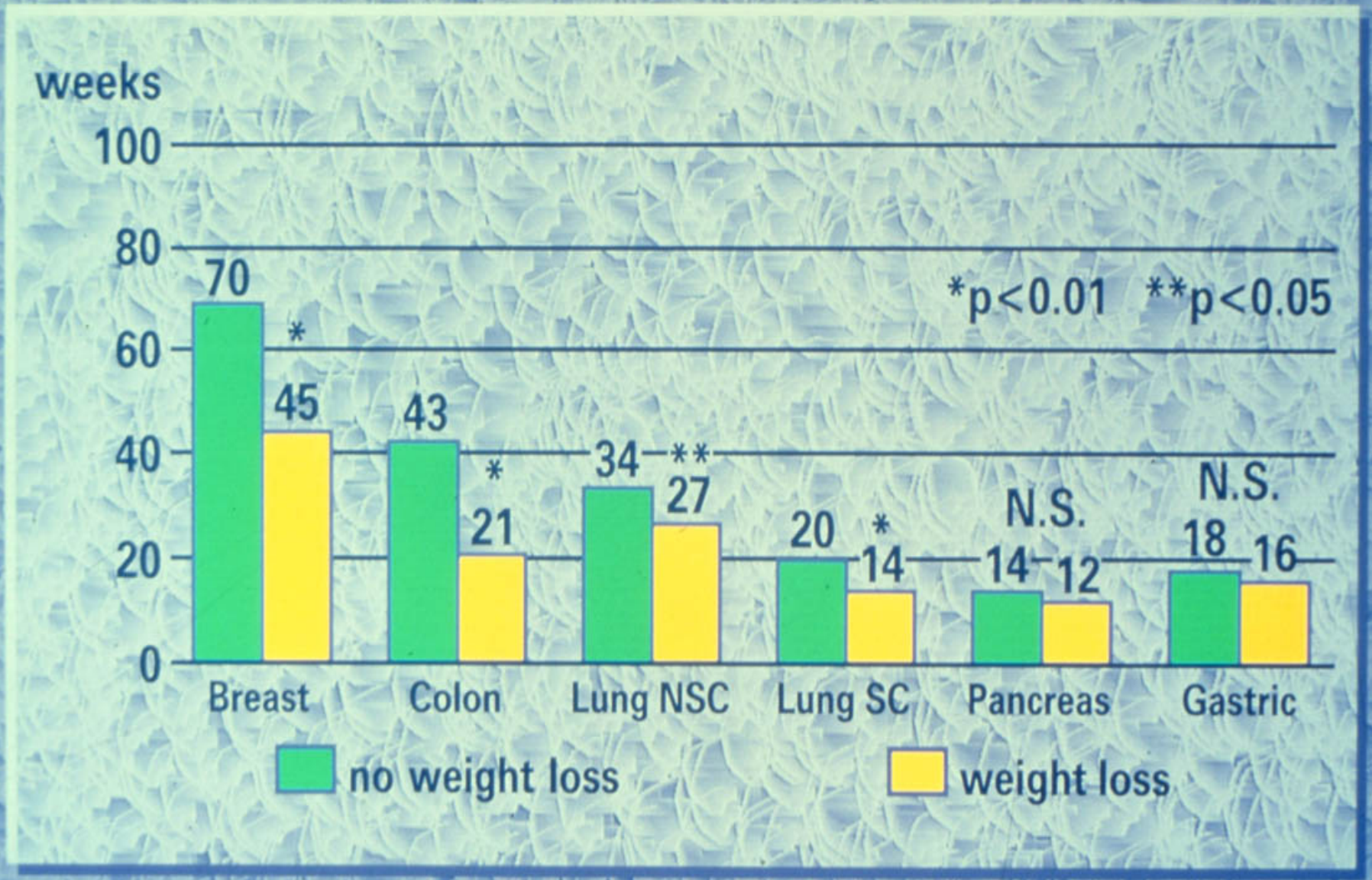
30%至50%的病患死亡

CACHEXIA 困擾著各式重症病患

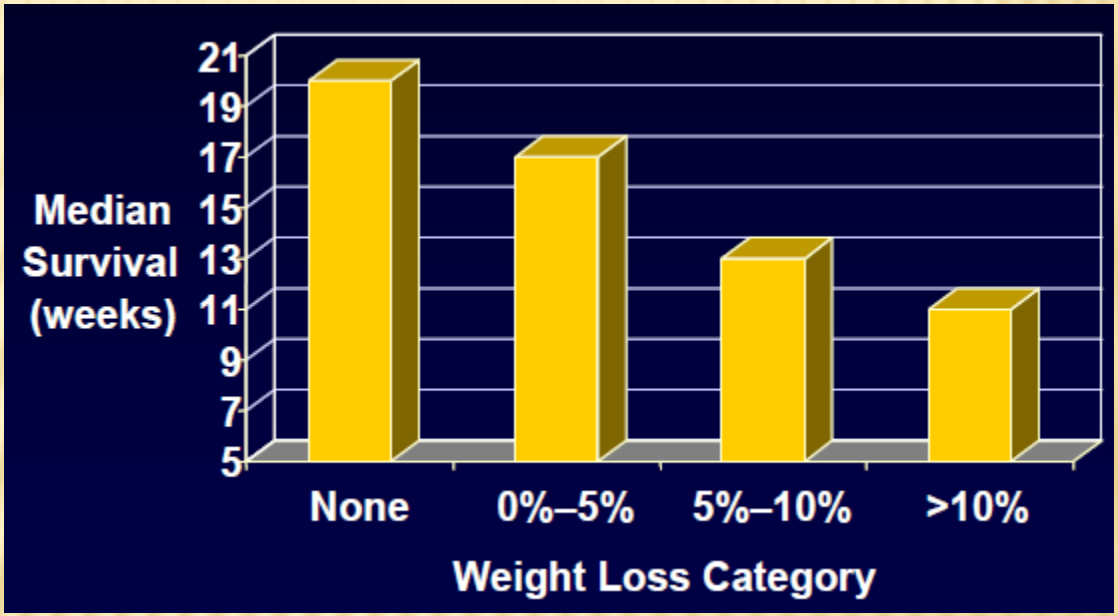


EFFECT OF WEIGHT LOSS ON MEDIAN SURVIVAL

Performance status體能狀態體重減輕與存活期之關係



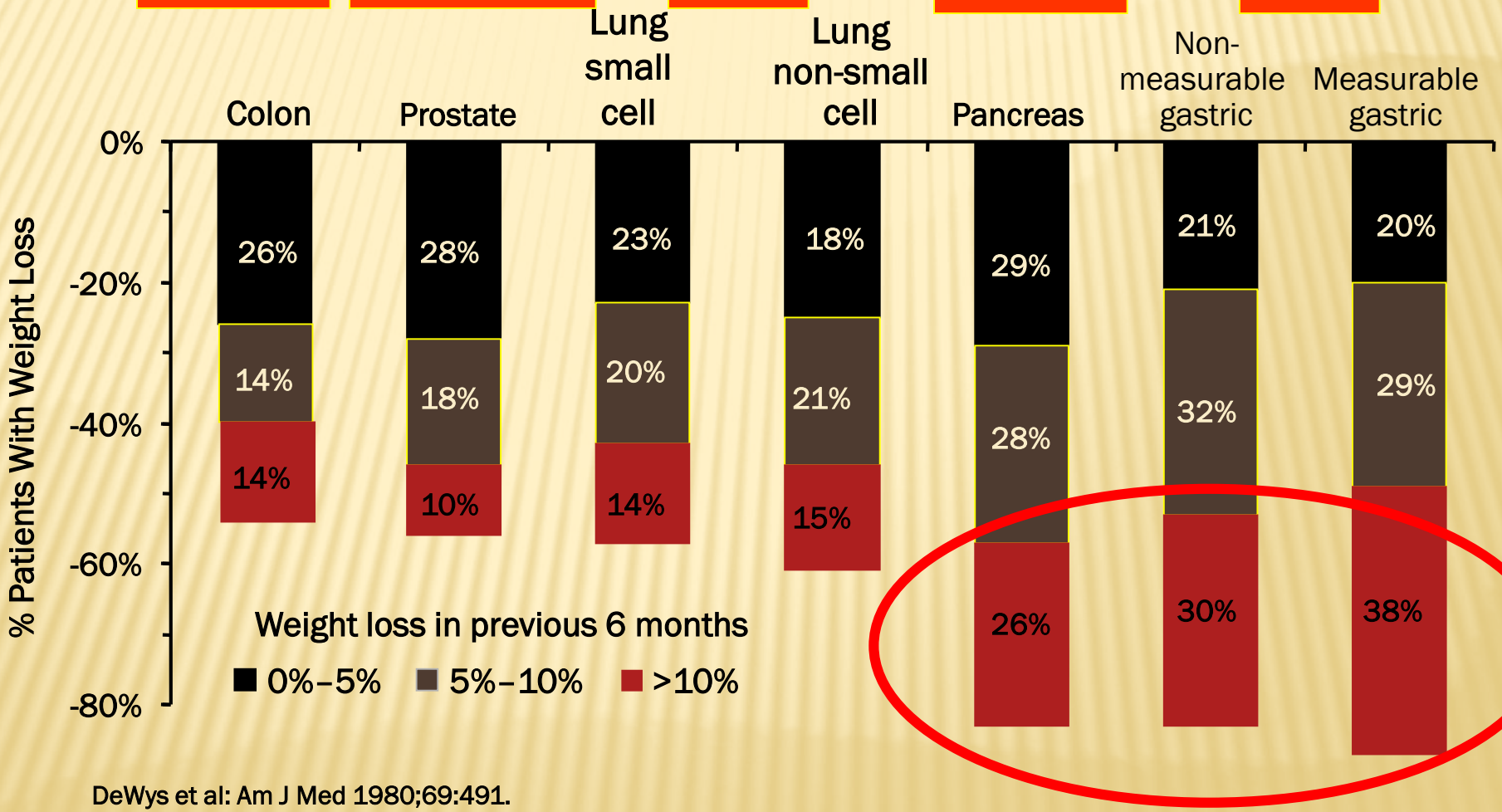
體重減輕造成癌症(NSCLC)病患存活時間下降



De Wys et al: Am J Med 1980.

各類型癌症患者體重減輕比例

結腸癌 攝護腺癌 肺癌 胰臟癌 胃癌



DeWys et al: Am J Med 1980;69:491.

各類型癌症患者體重減輕統計

- 胰臟癌Pancreatic 72%
- 食道癌Esophageal 69%
- 胃癌Gastric 67%
- 頭頸癌Head and Neck 57%
- 結腸直腸癌Colorectal 34%

Andreyev HJN et al: Eur J Cancer 1998;34(4):503.

CACHEXIA/惡病質：新定義

- 《Cachexia: A new definition》
  - Clinical Nutrition (2008) 27, 793 – 799
    - The definition that emerged is: ‘‘cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders).
    - “惡病體質”是一種複雜的代謝症狀，病患處在身體不適與疲倦之中，並會伴隨著肌肉流失和脂肪可能性的流失。

惡病質(Cancer Cachexia)

- 造成維生素與礦物質缺乏
- 蛋白質、熱量營養不良
- 免疫功能不佳
- 延遲傷口癒合
- 病症治療療程受阻

良好的營養支持

- 增進臨床癌症治療的效果
- To Broaden spectrum of therapeutic option
- 延長病患的存活率

惡病質(CACHEXIA)

導因

- ✓ 化學治療
- ✓ 放射治療
- ✓ 手術
- ✓ 老化
- ✓ 腫瘤生長
- ✓ 慢性疾病
- ✓ 情緒憂傷

常見症狀

- 噁心,嘔吐
- 黏膜損傷
- 腸胃功能障礙
- 生化代謝改變
- 食慾改變
- 體重明顯下降

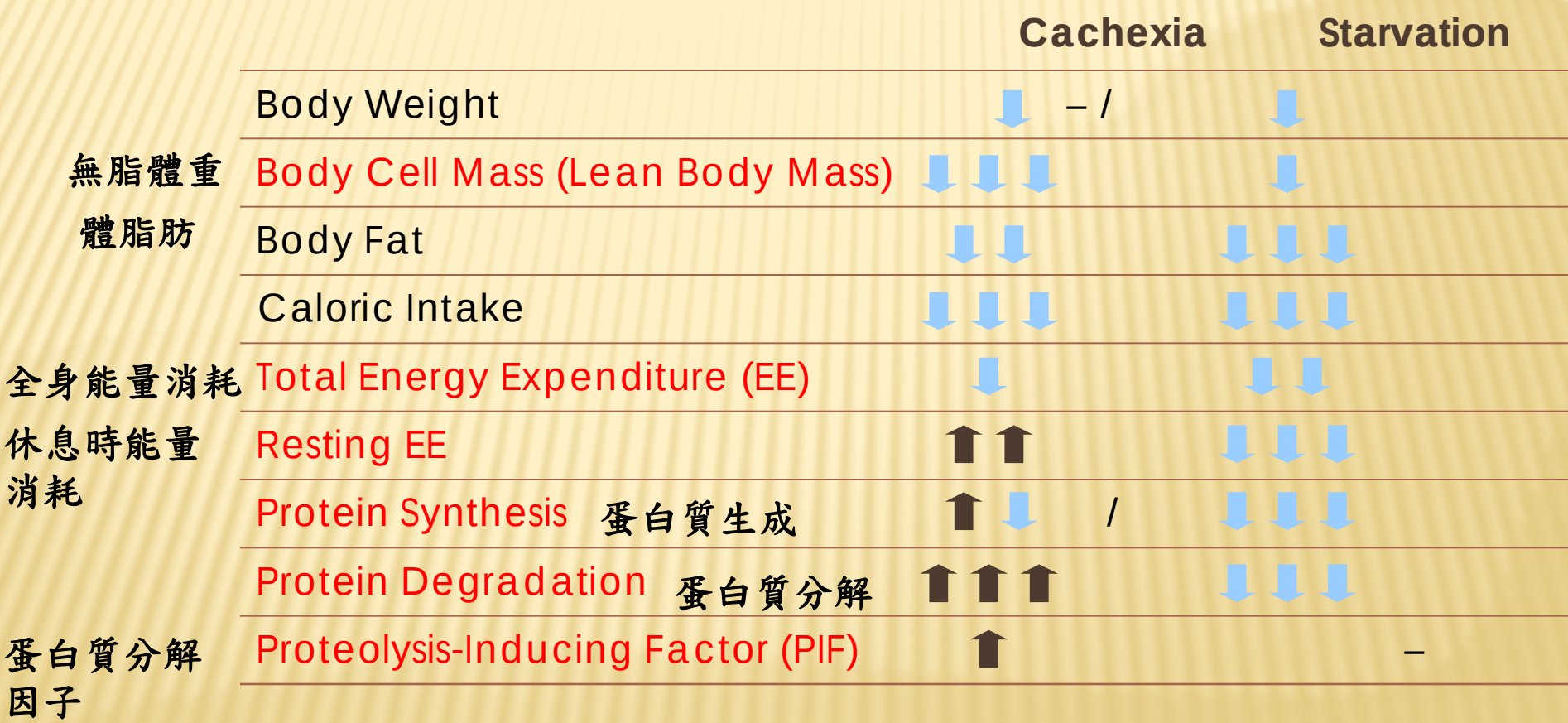
惡病質之臨床表現

- Warren於1932年報告2/3病人有癌症惡病質
- ECOG提出體重減輕者存活期較短
- 胰臟癌及胃癌體重減輕最嚴重
- 大腸癌,攝護腺癌,肺癌為中度體重減輕
- 淋巴癌,乳癌及淋巴球血癌(ALL),肉癌體重減輕最少
- 病人在腫瘤根除後仍舊無法增加體重者,必須懷疑有轉移或復發的可能

惡病質與缺乏免疫能力

- 增加疾病感染
- 缺乏特殊抗體的生成
- 免疫調節細胞的缺乏
  (Cell-mediated immunity defects)
- 缺乏巨噬細胞功能
  (Phagocyte function defects)
- 補體活動力缺損
  (Complement activity defects)
- 低白蛋白血症Hypoalbuminemia
- 低免疫球蛋白症(Hypogammaglobulinemia)

CACHEXIA VS. STARVATION (飢餓狀態)



Adapted from Kotler DP. 2000. Ann Intern Med. 133:622

營養不良與體重減輕

- 惡病質(Cancer cachexia)耗損
  - 肌肉質量與體重的耗損
- 飢餓狀況(蛋白質熱量攝取不足)
- 心理因素
- 攝食障礙

Rivadeneira et al. 1998. CA Cancer J Clin. 48:69

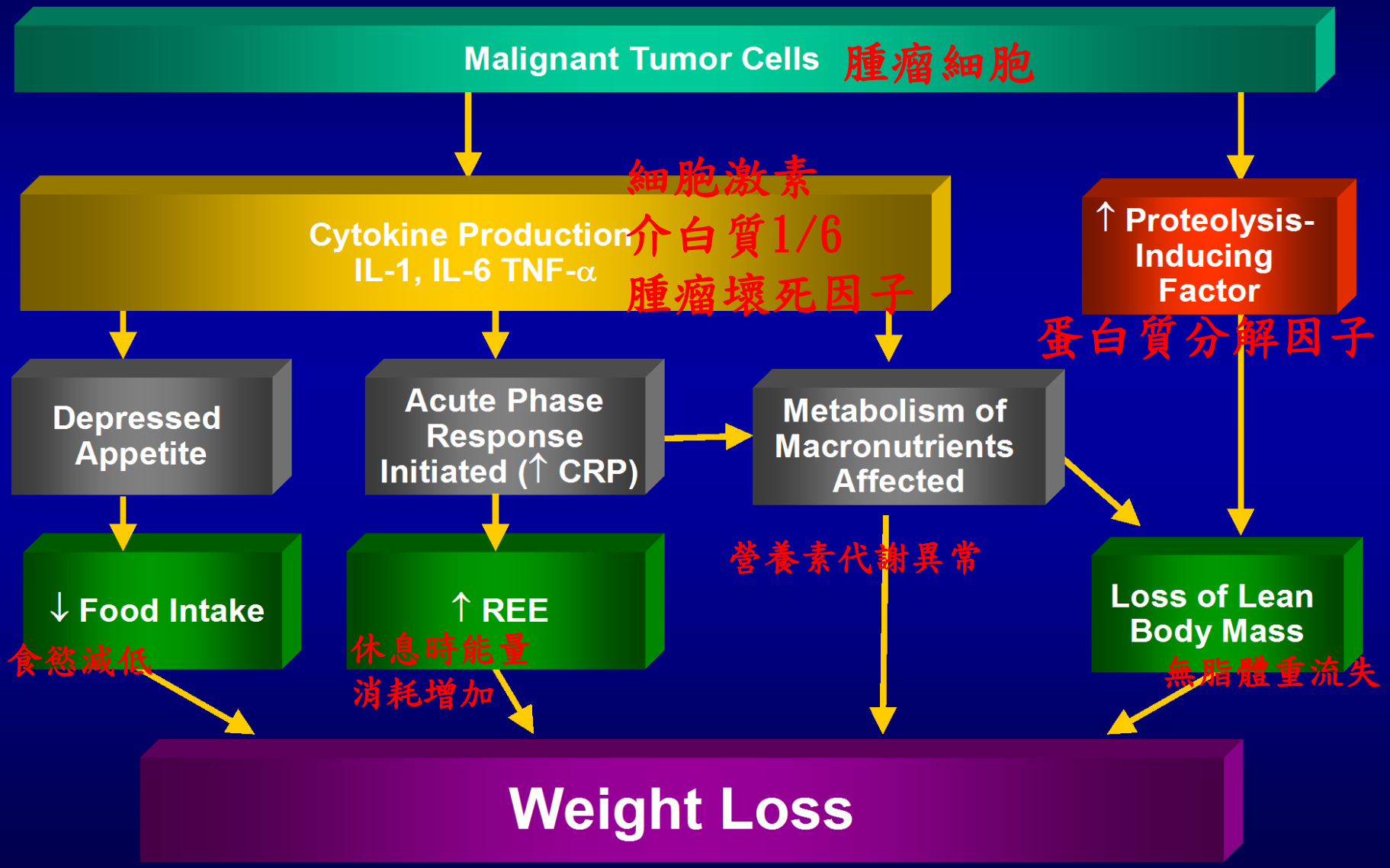
營養不良與體重減輕

惡病質
(Cachexia)

放射或化學治療
身體影響

體重減輕

Mechanism of Action

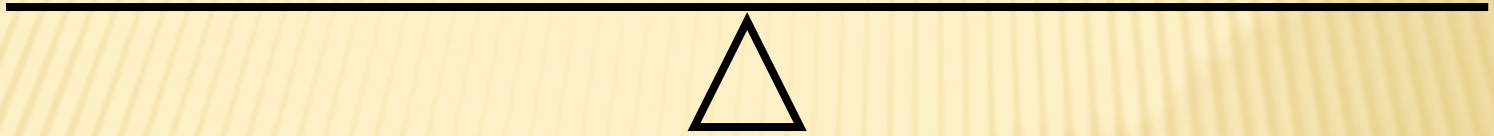


我們的對策為何?

STRATEGY FOR TREAT OFCACHEXIA

Increases food intake
增加食物攝取

Normalize metabolism
代謝正常化



Pharmacological Approach	Pharmaco-nutrition	Nutritional approach
Steroids Megestrol acetate Address intake only NSAIDs Fish oil Address metabolism only	Combination therapy Address intake and metabolism	Parenteral feeding Enteral feeding Address intake only Special Nutrients: Fish oil, Leu, Arg, Met Address intake & metabolism

類固醇
黃體素

魚油(促進食慾抗發炎)
營養素

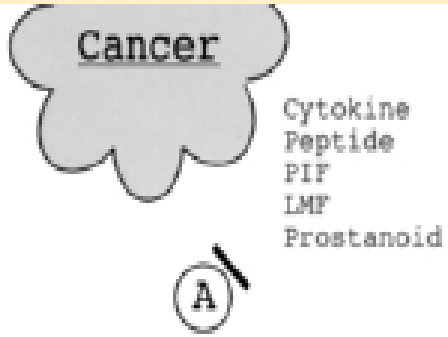
·【癌症惡病質之機轉與影響】馬偕血腫 張明志

先從增進病患食慾做起.....

食慾不振

- 食慾受serotonin, catecholamines, opiates的強力控制
- 抑制serotonin的合成,可以增進進食量
- 味覺與嗅覺的改變
- 喪失對大部分食物之胃口
- REE(休息期能量消耗)增加,導致氮及卡路里之負平衡

常用增加食慾的藥物



The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome. Agents were classified as those est (First-line) or those unproven/investigational (Second-line), depending on their site or mechanism of actions. (A), inhibitors of production/re cytokines and other factors; (B), gastroprokinetic agents with or without antinausea effect; (C), blockers of Cori cycle; (D)(E), blockers of muscle tissue wasting; (F), appetite stimulants with or without antinausea effect; and (G), anti-anxiety/depressant drugs. These agents sh selected on an individual basis according to the cause of cachexia or the state of the patient.

First-line treatments

- Glucocorticoids (F) (A)
- Progesterones (F) (A)

類固醇
黃體素

Second-line treatments

- Cannabinoids (F)
- Cyproheptadine (F)
- Branched-chain amino acids (E) (F)
- Metoclopramide (B) (F)
- Eicosapentanoic acid (D) (E) (A)
- 5′–deoxy-5-fluorouridine (A)
- Melatonin (A)

大麻

Primperan

魚油

蝮黑激素

- Thalidomide (A)
- β2-adrenoceptor agonists (E)
- Non-steroidal anti-inflammatory drugs (A) (F)
- Others
  - Anabolic steroids (E)
  - Pentoxifylline (A)
  - Hydrazine sulfate (C)

賽得 也可抗血管

ARC=Arcuate nucleus of the hypothalamus; VMH=Ventromedial nucleus of the hypothalamus; DMH=Dorsomedial nucleus of the hypotha LHA=Lateral hypothalamic area; PVN=Paraventricular nucleus of the hypothalamus; CTZ=Chemoreceptor trigger zone; PIF=proteolysis-in factor; LMF=Lipid mobilizing factor.

Most Active Compound to Alleviate Cachexia By Appetite Activation

MEGEST®(MEGESTROL ACETATE)

最有效增進食慾藥物

MEGEST®

- Megestrol acetate (MA) is a synthetic progestin

1963 Synthesized in England

1964 Contraceptive.

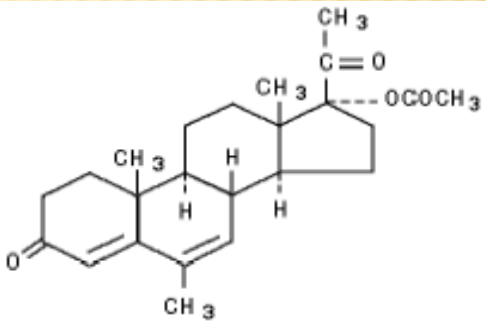
1967 Breast cancer and Endometrial cancer.

1993 Orexigenic effect

MA was approved by FDA

Indication: anorexia, cachexia, or weight loss due to unknown cause in AIDS patients.

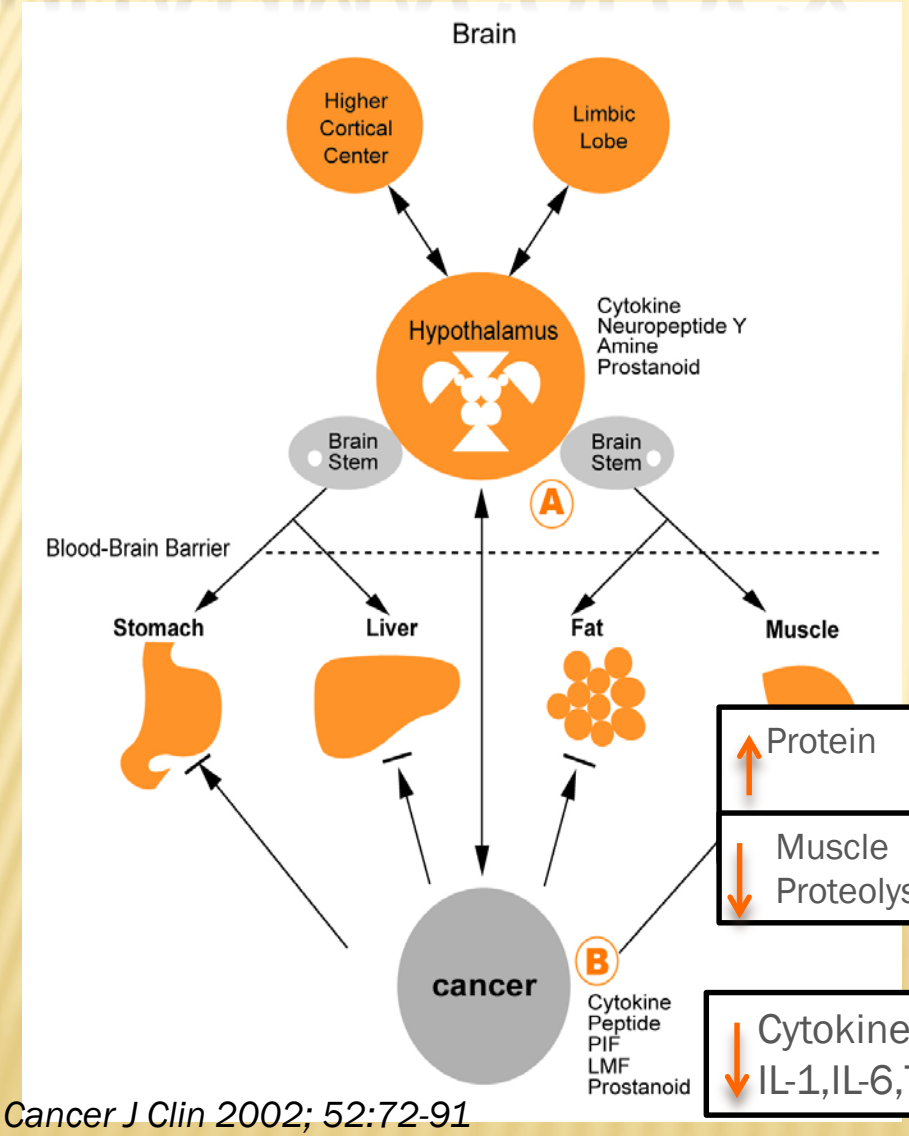
Now Majority of European countries has approved the ACS in AIDS and cancer patients



megestrol acetate, USP

40 mg/ml, 120 ml

PHARMACOLOGY



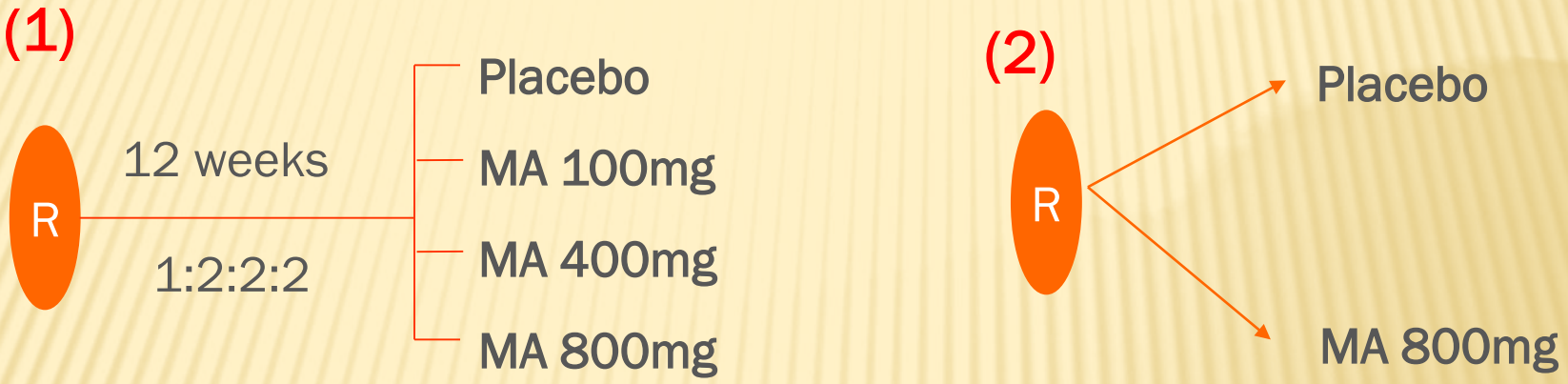
- It is related to glucocorticoid activity and similar to corticosteroids.
- It may stimulate appetite via Neuropeptide Y in CNS
- It may down-regulating the synthesis and release of pro-inflammatory cytokine, eg: TNF-a, IL-1, IL-6...

增加食慾
減少發炎

CA Cancer J Clin 2002; 52:72-91

CLINICAL TRIAL

STUDY FOR OPTIMAL DOSAGE



- Randomized, double-blind,placebo-control trial
- **Endpoints :**
  - Primary : weight gain
  - Secondary : the changes in weight and body composition, caloric intake,sense of well-being, toxic effects and appetite.

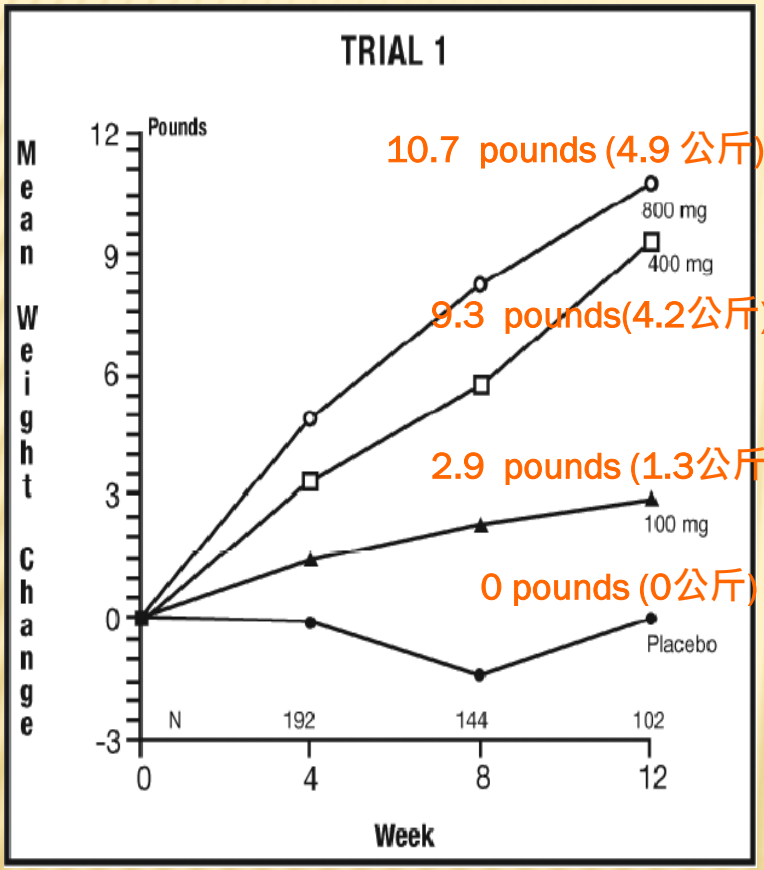
Annuals of Internal Medicine 1994; Volume 121, Number 6
Oncology 1994 ; 51 (suppl I):19-24

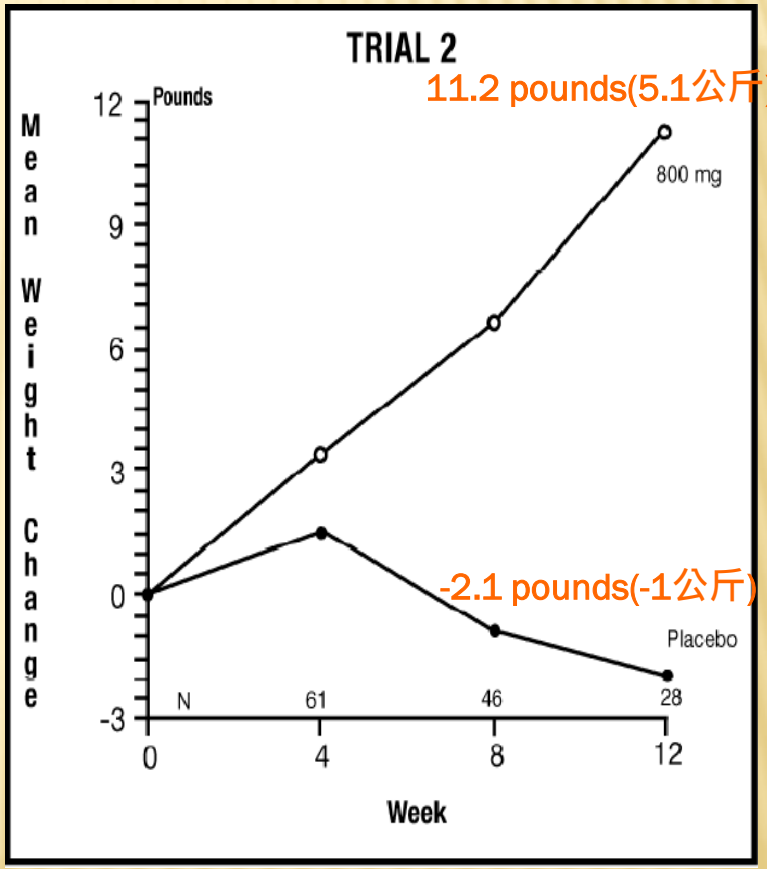
CHANGE IN APPETITE 800 mg 好

Treatment group	Patients with improved appetite at time of maximum weight change, %
Four-arm trial	
Placebo	50
Megace 100 mg	70.5
400 mg	71.7
800 mg	92.5**
Two-arm trial	
Placebo	48.3
Megace 800 mg	69.5*

Oncology 1994 ; 51 (suppl I):19-24

WEIGHT GAIN-1

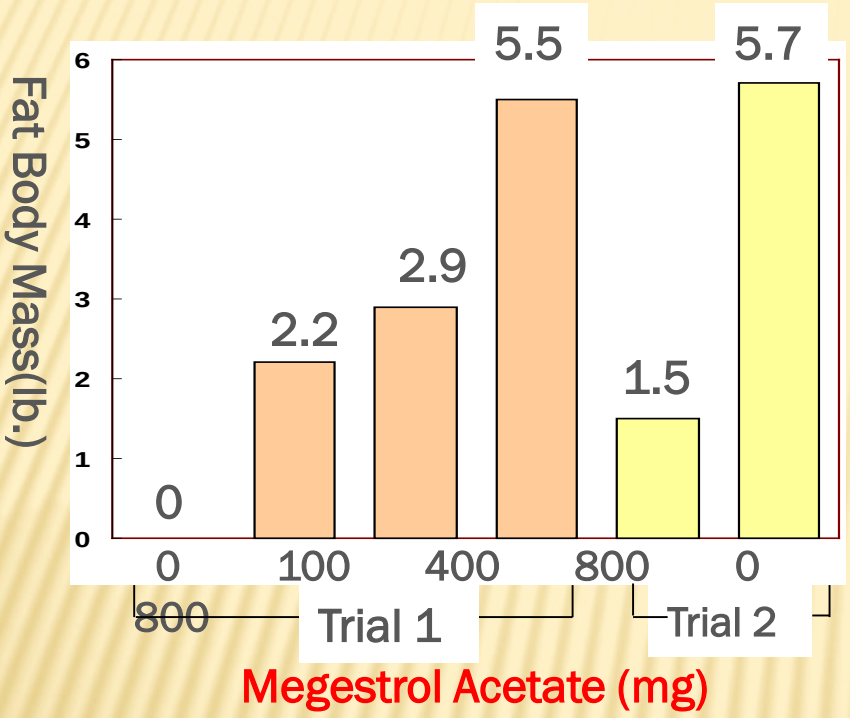


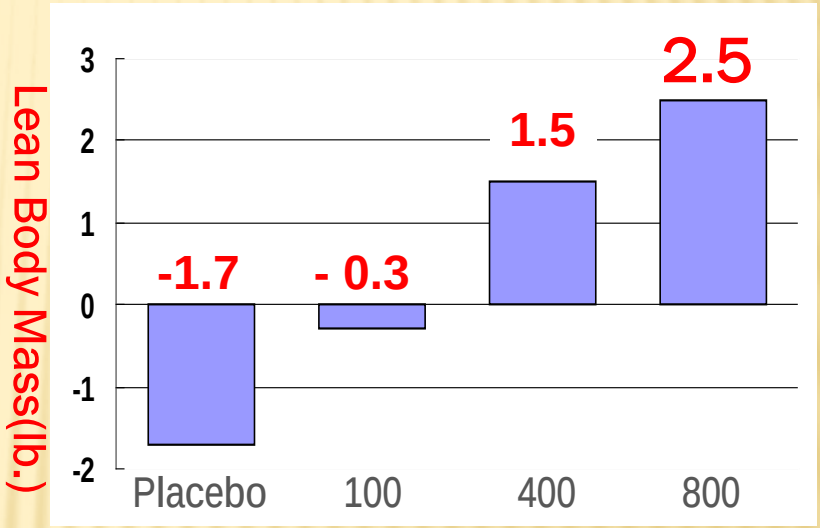


Prod Info Megace® Oral Suspension 2007 PDR®
Oncology 1994 ; 51 (suppl I):19-24

MEAN CHANGE IN BODY COMPOSITION

無脂體重也上升





	0	100	400	800	0	800
Water (liters)	-1.3	-0.3	0	0	-0.1	-0.1

No statistically significant

Prod Info Megace® Oral Suspension 2007 PDR®
Oncology 1994 ; 51 (suppl I):19-24

SAFETY 水腫跟靜脈血栓

Adverse experience	Experiences, n (%)			
	placebo	megestrol acetate, mg		
		100	400	800
	n=86	n=82	n=75	n=127
Deep-vein thrombosis	0	0	1(1.2)	0
Edema	7(8.2)	4(4.9)	9(12.0)	2(1.5)
Impotence	1(1.2)	3(3.7)	4(5.3)	11(8.7)
Rash	4(4.7)	6(7.3)	3(4.0)	9(7.1)

Values in parentheses are percentages

Oncology 1994 ; 51 (suppl I):19-24

MEGESTROL REVIEW PAPER

ORIGINAL ARTICLE

Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome – a systematic review and meta-analysis

Wiktoria Leśniak[1,2], Małgorzata Bała[1,2], Roman Jaeschke[2,3], Maciej Krzakowski[4]

1 Department of Internal Medicine Jagiellonian University Medical College, Kraków, Poland
2 Polish Institute of Evidence Based Medicine, Kraków, Poland
3 McMaster University, Hamilton, ON, Canada
4 M. Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warszawa, Poland

Objectives To review the effect of megestrol acetate (MA) in patients with ACS.
The studies were included in the review if they were randomized, enrolled patients with non-hormone-sensitive cancer and ACS and assessed the effects of MA compared with placebo, other drugs or different doses of MA.

Pol Arch Med Wewn. 2008 Nov;118(11):636-44. Review

IMPROVE APPETITE 大部分都有改善 MEGESTROL ACETATE OVER PLACEBO

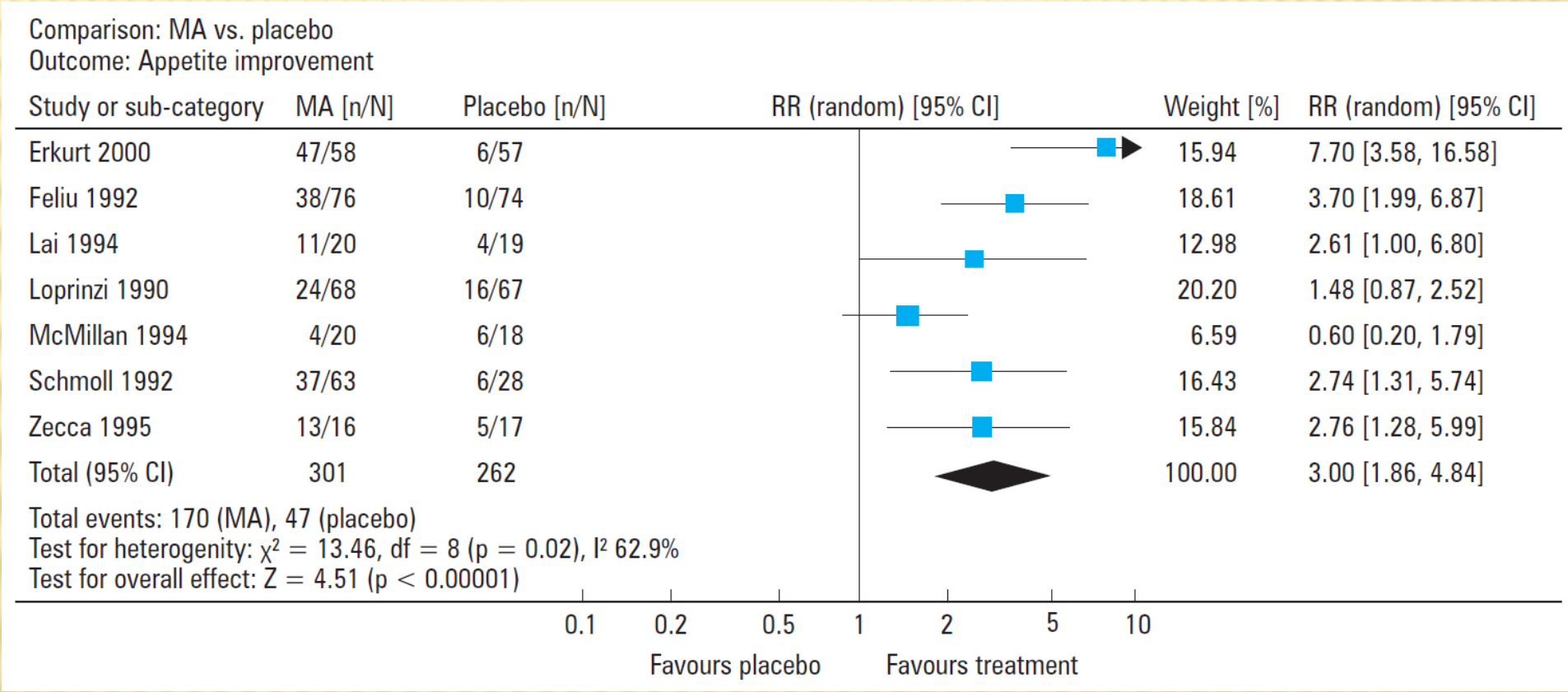


Fig. 2 The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on appetite improvement

Pol Arch Med Wewn. 2008 Nov;118(11):636-44. Review

IMPROVE WEIGHT GAIN MEGESTROL ACETATE OVER PLACEBO

大部分都有改善

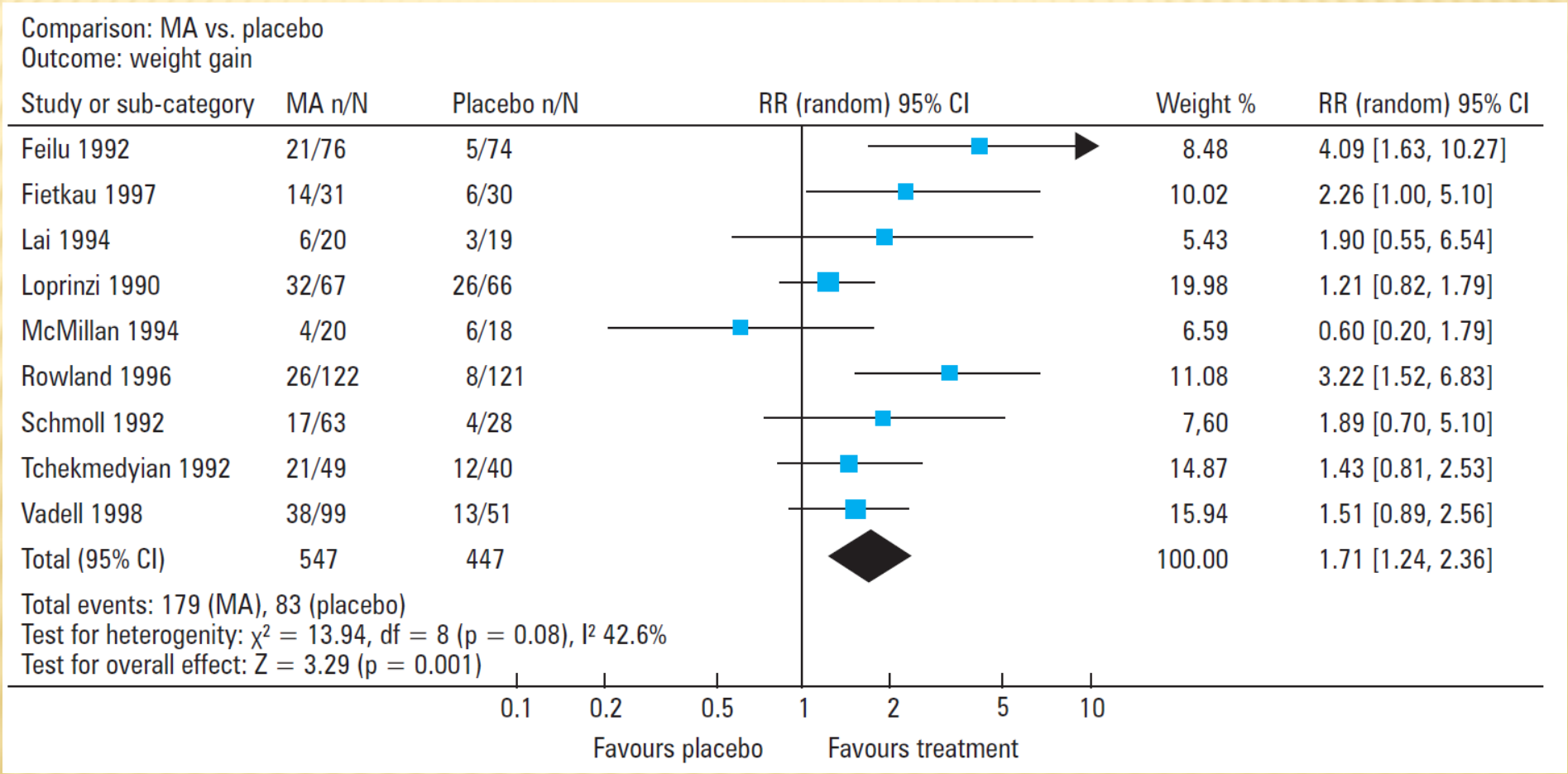


Fig. 1 The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on weight gain

Pol Arch Med Wewn. 2008 Nov;118(11):636-44. Review

優點(BENEFIT)

- 口服懸液劑(oral suspension)較方便使用
- 病人順從性高 (good compliance)
- 口感佳
- 促進食慾(約兩個星期內)
- 增加體重(約一個月~三個月)
- 提升生活品質

注意事項

- 不建議使用於對Megestrol Acetate或配方任何成分過敏的患者及已知或懷疑懷孕的患者
- 以下患者需謹慎使用
  - 有血栓性栓塞病史
  - 麥格斯口服懸液劑的糖皮質類固醇作用雖然尚未經完整評估，但已觀察到腎上腺壓抑的證據。報告指出某些新的糖尿病、糖尿病惡化及欣氏症候群的臨床案例與使用麥格斯口服懸液劑有關。腎上腺功能不全的患者需謹慎評估
- 開封後請密封避光儲存於25℃以下

MEGEST ®麥格斯，120ML/瓶

- **適應症：(健保給付)**
  - 癌症患者之惡病體質引起的體重明顯減輕 。
  - 後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者之惡病體質引起的體重明顯減輕。

- **Cachexia定義**
  - Weight loss > 5% over past 6 months

  或 BMI< 20 and any degree of weight loss >2%

- **健保價：NTD: 986 /120ml/瓶**

- **國際疾病分類碼** (健保網頁公告)

ICD-10-CM...Cachexia : R64 ✧ Abnormal weight loss : R634
ICD- 9-CM...Cachexia : 799.4 ✧ Loss of weight : 783.21

* *Ref : Lancet Oncology 2011 ; 12(5) : 489-95.*

MEGEST ®麥格斯, 建議劑量

Dose adjust after 3~4 wks.

每日10cc (400mg)

Weight Loss 5~10%

10 ml / day : NT$ 83

每日4cc (160mg)

Weight Loss < 5%

自費 4 ml / day : NT$ 33

每日15cc (600mg)

Weight Loss >10%

15 ml / day : NT$ 124

每日20cc (800mg)

20 ml / day : NT$ 165

Ref : NCCN Guidelines Version 1 .2014

Megestrol acetate 400~800 mg/day

Annuals of Internal Medicine 1994; Volume 121, Number 6

Oncology 1994 ; 51 (suppl I):19-24

同類藥品比較表

	Megest®	Megejohn®/Mekei®	Farlutal®
成分	megestrol	megestrol	medroxyprogesterone
劑量	(400 		
劑型	Oral Suspension	Oral Tablet	Oral Tablet
健保價	NT$ 986 /120ml (Bot)	NT$ 38	NT$53 / (500mg)Tab.
每日藥費	NT$ 83 / day (400mg)	NT$ 114 / day (480mg)	NT$102 / day
每月藥費	NT$ 2,490	NT$ 3,420	NT$ 3,060
適應症	後天免疫缺乏症候群患者的厭食症，及後天免疫缺乏症候群患者及**癌症患者之惡病體質引起的體重明顯減輕**。	再發性或轉移性子宮內膜癌的輔助療法。 無cachexia適應症	不能手術及復發性或轉移性之子宮內膜癌之輔助療法，停經後婦女之乳癌，攝護腺癌及伴有惡病體質之末期癌症病患使用。

資料來源：中央健保局 、衛福部：Megest®仿單、Farlutal®仿單

治療重點

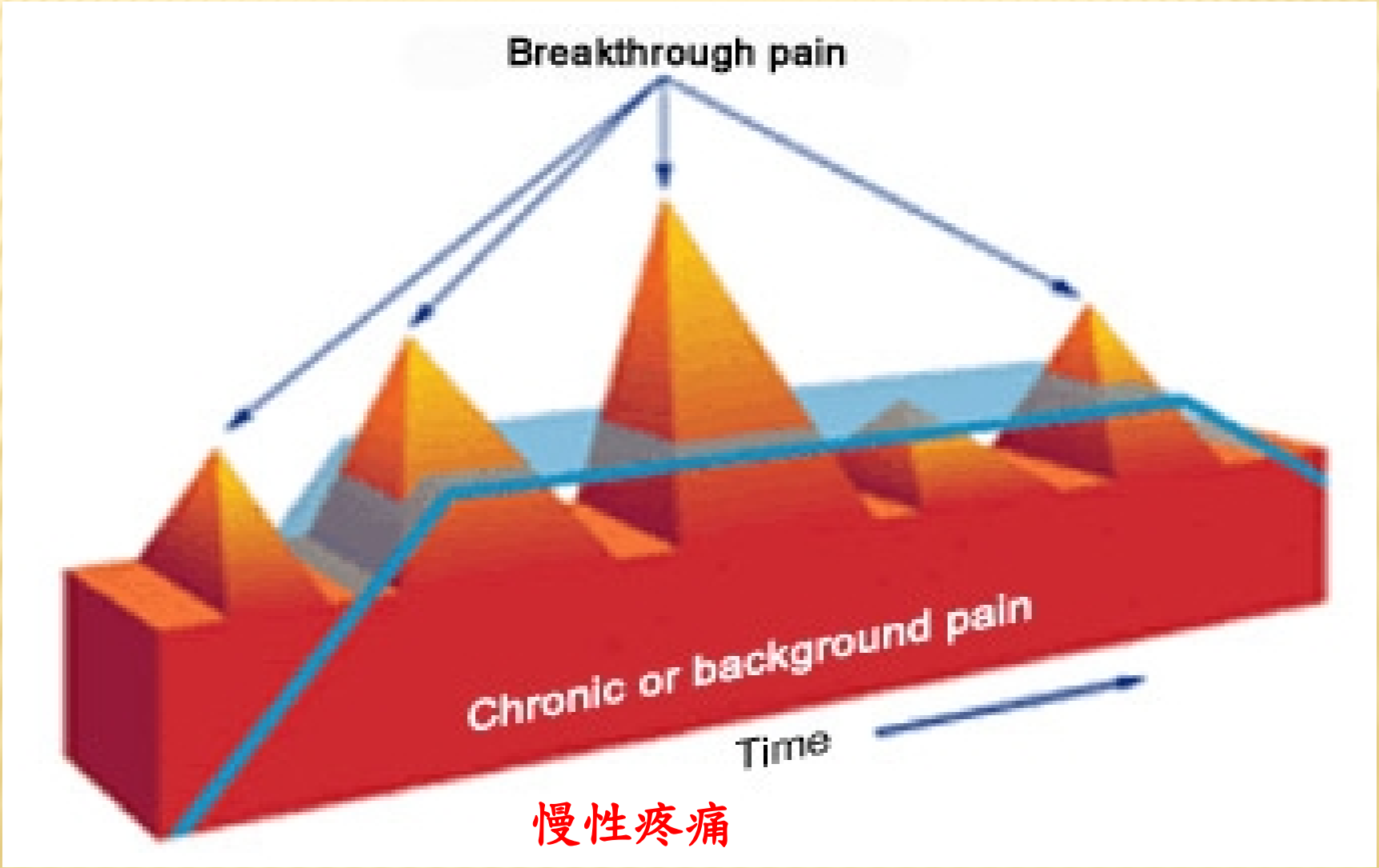
- 患者
  - 非刻意減重的老年人
  - 佔門診比例: 1.3%~8%
- 訴求
  - 罹病率及死亡率相對性增高

前瞻性的研究:
發現體重減輕的老年人
增加未來1~2.5年 9~38%的死亡率

CURRENT PERSPECTIVE OF BREAKTHROUGH（中途突發劇烈疼痛）CANCER PAIN AND FUTURE DIRECTION

What is breakthrough pain?

中途突發劇烈疼痛



慢性疼痛

BACKGROUND OF BTP(超過四次不行)

- Breakthrough pain was defined as moderate-to-severe pain that occurred at a specific site for a transitory period against a background of persistent pain controlled by the around the clock opioid regimen. The frequency averages 1-4 episodes per day
- Breakthrough pain has been reported in 64.8% of patients with cancer pain
- The presence of metastases
  - head and neck cancer (70%)
  - gastrointestinal cancer (59%)
  - lung/bronchial malignancies (55%)
  - breast cancer (54%)
  - urogenital cancer (52%)

1: Current Opinion in Oncology 2010, 22:302–306
2: Palliat Med. 2004;18:177–183
3: Drugs. 2008;68:913–924.
4:Journal of Pain Research 2012:5 559–566

BREAKTHROUGH PAIN INFLUENCE CANCER PATIENTS (生活品質低落)

- Quality of Life
  - Emotional health (in 82% of all patients),
  - Causes suffering (82%), wakens patients at least once a month(73%)
  - Influences their capacity to perform routine tasks(76%)
  - Their willingness to participate in activities(83%)

1:J Pain Palliat Care Pharmacother. 2011;25(3):252–264
2: J Pain. 2002;3(1):38–44.
3:American Pain Foundation; 2012; http://nci.nih.gov/dictionary/?CdrID=45612

TYPES OF BREAKTHROUGH PAIN

Classifications	Descriptions
Incident,	Consistent temporal causal relationship with predictable
偶發或刺激可預期 predictable	Motor activity, such as movement, defecation, micturition, breathing,
Incident,	Inconsistent temporal causal relationship with motor
不可預期之動作 unpredictable	Activity, such as sneezing, bladder spasm, or coughing
Idiopathic 疾病惡化	Not associated to any known cause, often suggests a progressive cancer
End-of-dose 下次穩定劑量前	Before a schedule or around-clock analgesic; more gradual onset and a longer duration than the incident and idiopathic BTP

1: Current Opinion in Oncology 2010;22(Suppl. 4):302e6;
2: Pain. 1999;81(1–2):129–134
3: Palliat Med. 2001;15(1):9–18

CHARACTERISTICS OF BTP

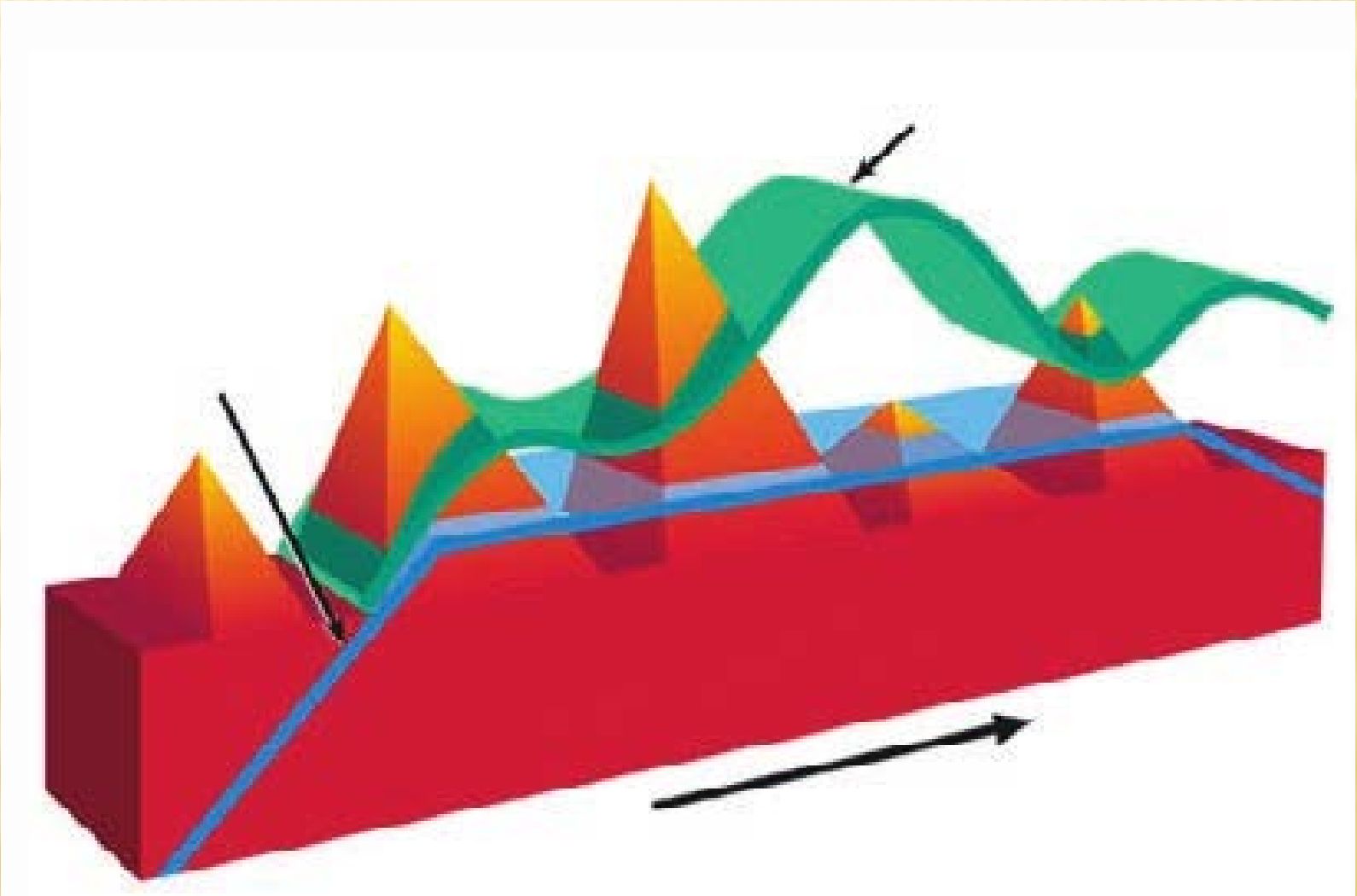
很快很痛

Characteristics	Average	Range
Time to peak severity	3-5 min	10 s- 180 min
Severity	severe or excruciating	mild to excruciating
Duration	15-30 min	1 s to more than 24 h
Number of episodes (d)	1-4	Less than 1 timee3600 times
Precipitated by event	55-60%	52-77%
Predictable	50-60%	41-81%

From “Consensus panel recommendations for the assessment and management of breakthrough pain: part 1 management” by Bennett, D., et al, 2005, Pharmacy and Therapeutic. Copyright 2005, Bennett, D., et al. Adapted with permission.

Current Opinion in Oncology 2010;22(Suppl. 4):302e6

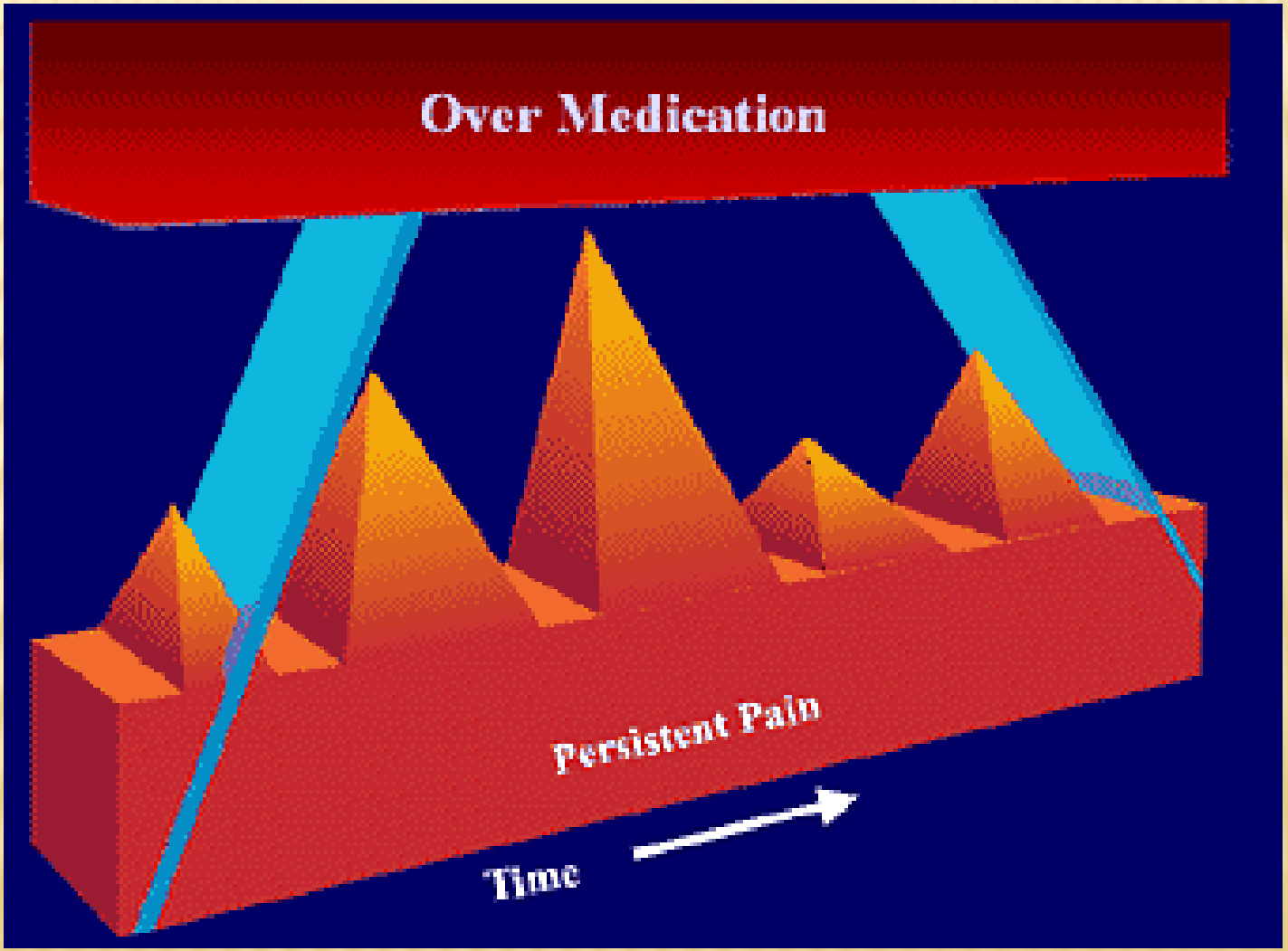
CURRENT BTP MEDICATION



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

INCREASED DOSE OF SLOW RELEASE OR ATC LEADS TO OVER-MEDICATION

增加穩定止痛
可能增加毒性



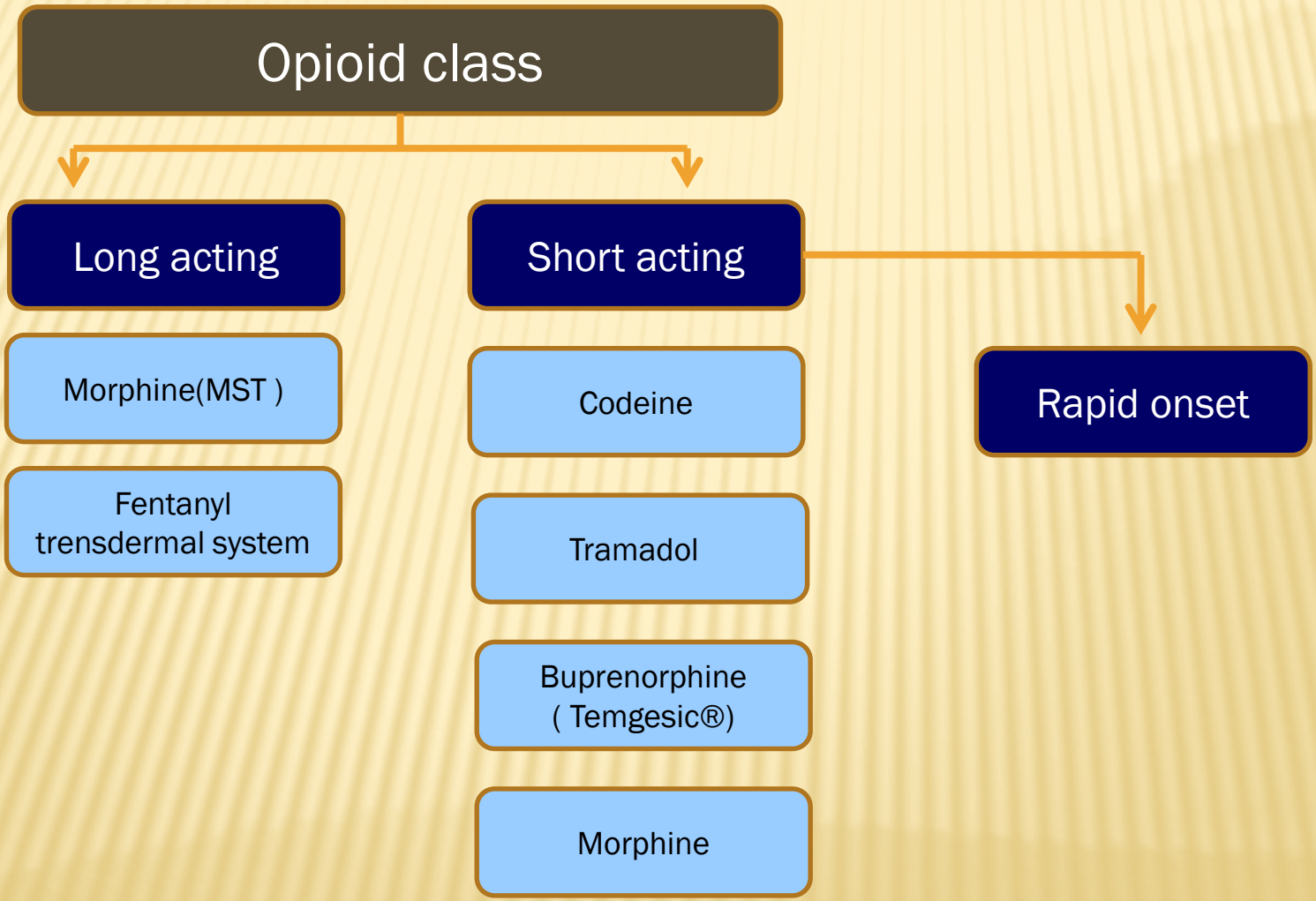
Medscape

IDEAL BTP MEDICATION

ication

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

OPIOIDS BY CLASS



CNS Drugs **26**(6): 509-535.

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.

用快的

Rapid-onset Opioids (ROOs)

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

BTP MEDICATION IN THE OVERSEA

	Immediate-release opioids	Onset of analgesia	Duration of effect	Advantages (A)/Disadvantages (D)
Hydrophilic	Morphine (oral)	30- 40 min	4h	A: available in multiple dosage forms, liquid concentrate
				D: slow onset of analgesia for idiopathic BTP
	Oxycodone (oral)	30 min	4h	Same as morphine
	Hydromorphone (oral)	30 min	4h	D: no liquid concentrate, slow onset of analgesia for idiopathic BTP
	Methadone (oral)	~10-15 min	4- 6h	A: faster onset of analgesia in one small study
				D: complex pharmacology, pharmacokinetics
Lipophilic	Fentanyl (transmucosal)	~5-10 min	1-2 h	A: fastest onset of analgesia lipophilic
				D: requires ongoing patient cooperation in use

經黏膜快

Pharmacy and Therapeutic 2005;30(Suppl. 6):354e61

THE GOLD STANDARD TREATMENT FOR BTP

1. Rapidly effective (bioavailability) 快 方便 簡單 少毒性
2. Easy to use (no injection)
3. To avoid accumulation and long-lasting side effects:

   rapid elimination
4. Well tolerated
5. Easy to take, even in case of bowel occlusion
6. Associated with few side effects
7. Superior to conventional treatments

Current Opinion in Oncology 2010, 22:302–306

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.

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 (ROOS) 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.

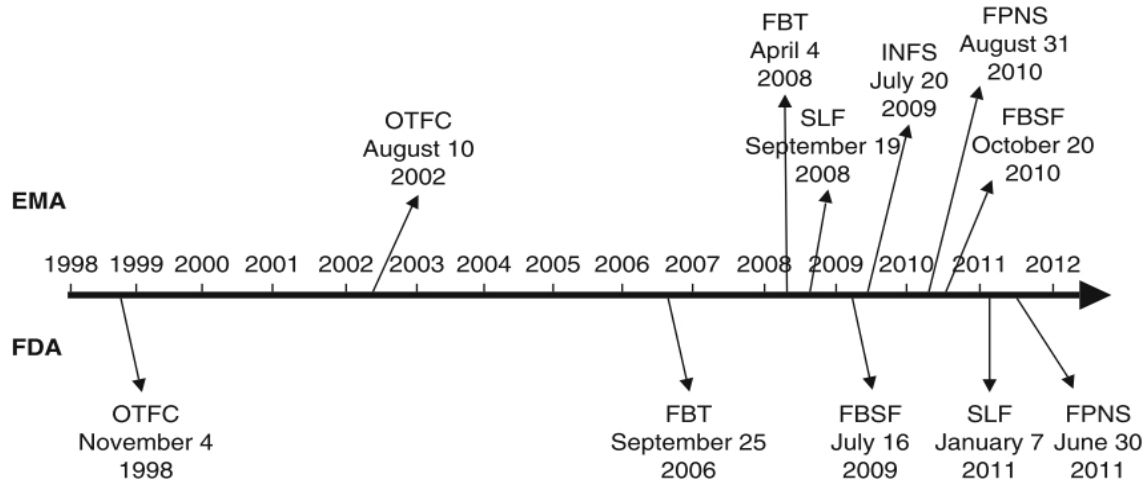


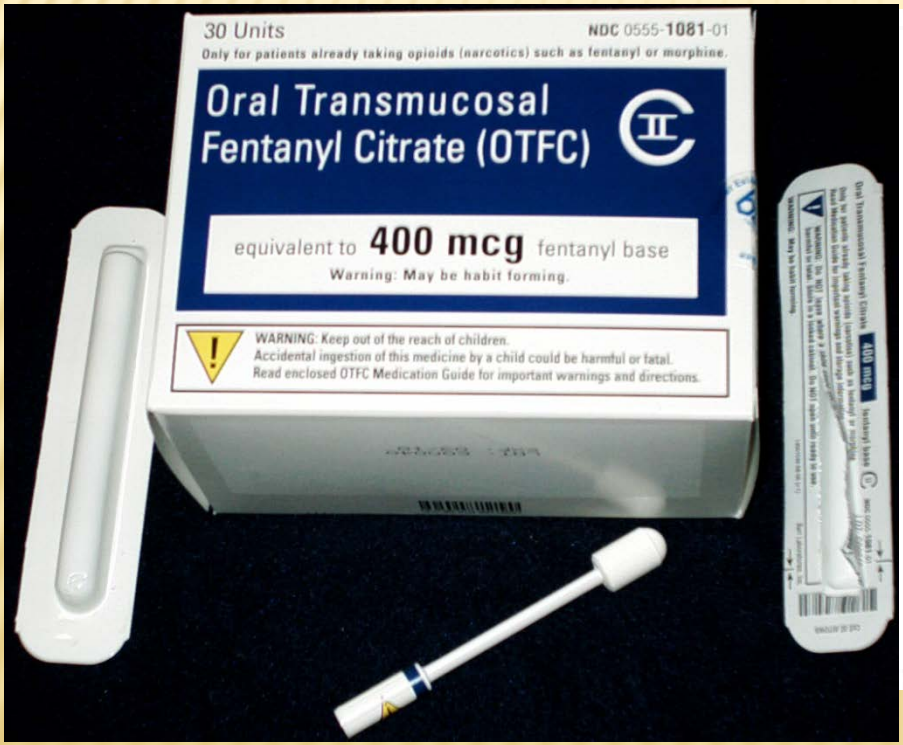
Fig. 2. Timeline of rapid-onset opioid approval in the US and EU. **EMA** = European Medicines Agency; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **OTFC** = oral transmucosal fentanyl citrate;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

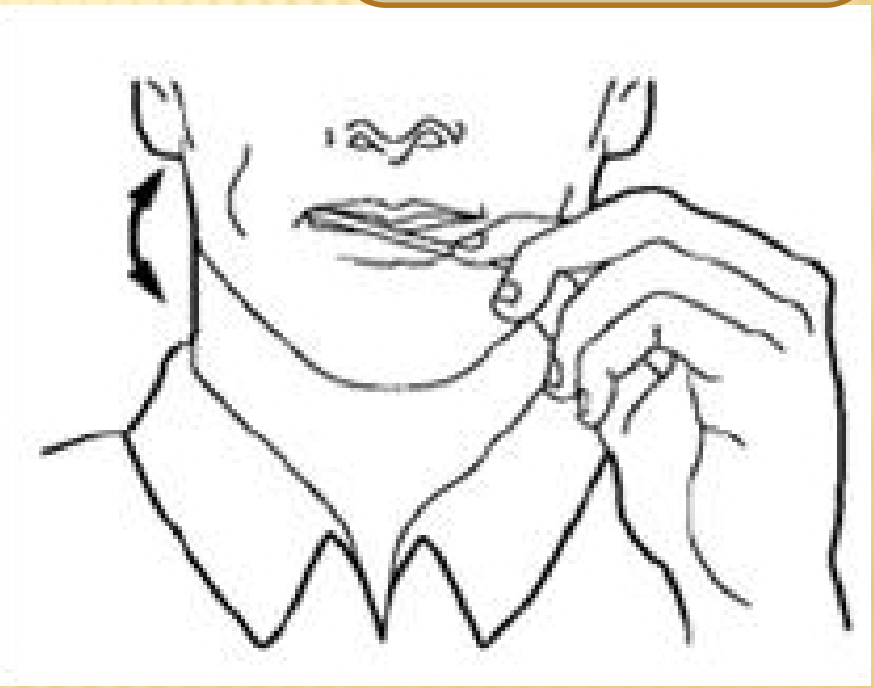
Smith, H. (2012). "A comprehensive review of rapid-onset opioids for breakthrough pain."CNS Drugs **26**(6): 509-535.

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

FENTANYL BUCCAL TABLET (FBT)

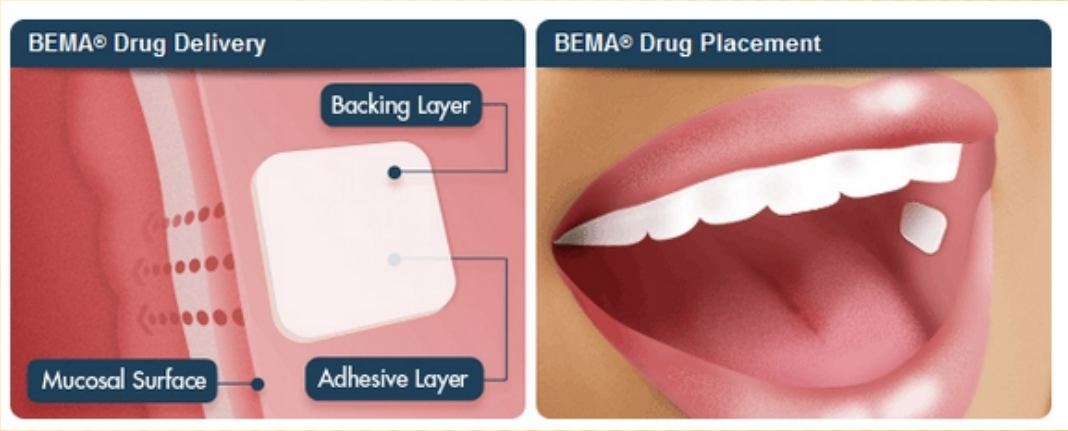
口腔黏膜壓溶

- 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)

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

Table III. Summary pharmacokinetic data[a] for fentanyl formulations

Formulation and dose (μg)	t_{max} mean (median), min	C_{max} mean, ng/mL	$t_{½}$ mean (median), h	Bioavailability, %	References
OTFC					
200	(40)	0.4	3.2		
400	(25)	0.8	6.4	40–50	51,53
800	(25)	1.6	6.4		
1600	(20)	2.5	6.0		
FBT					
100	(45)	0.3	(2.6)		
200	(40)	0.4	(4.4)		
400	(35)	1.0	(11.1)		
600	(78)	1.4	16.0	65	54,55
800	(40)	1.6	(11.7)		
1000	(84)	2.0	18.1		
1200	(96)	2.3	18.8		
1400	(60)	2.8	20.1		
FBSF					
600	60–120	1.0–1.1	9.8–12.7	71	56
800	90	1.3	19.0		
SLF					
100	40	0.2	6.1		
200	49	0.4	6.3	NA	57
400	57	0.9	5.4		
INFS					
50	23 (15)	0.4	3.2		
100	24 (12)	0.6	4.3	89	58,59
200	13 (15)	1.2	3.5		
FPNS					
100	20	0.4	21.9		
200	15	0.8	24.9	NA	60
400	21	1.6	15.0		
800	20	2.8	24.9		

a Results are from different studies in healthy volunteers and patients with chronic pain and therefore are not directly comparable.

C_{max} = maximal plasma concentration; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal soluble tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **NA** = not available; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl; **$t_{½}$** = half-life; **t_{max}** = time taken to achieve maximal plasma concentration.

What is fentanyl buccal soluble film? (FBSF)

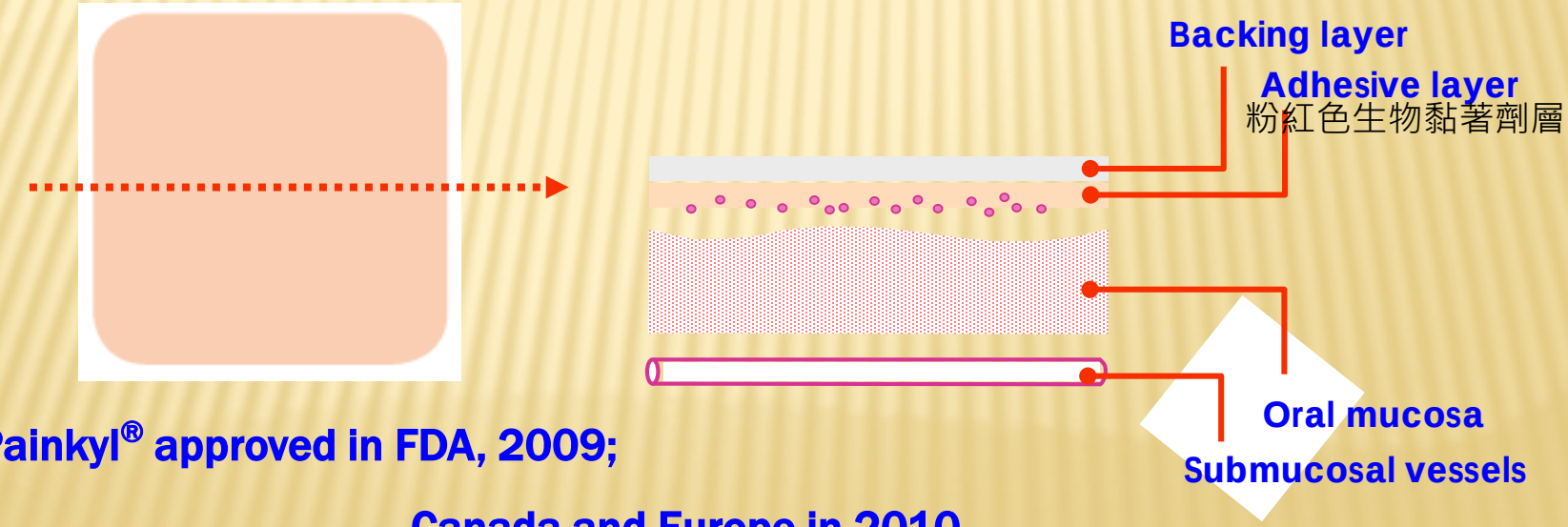
BEMA technology

Bio
Erodible
Muco
Adhesion

生物
可溶性黏膜黏附
雙層釋放技術

隔絕唾液,避免唾液與生物黏著劑層,有助吸收

白色非活性層

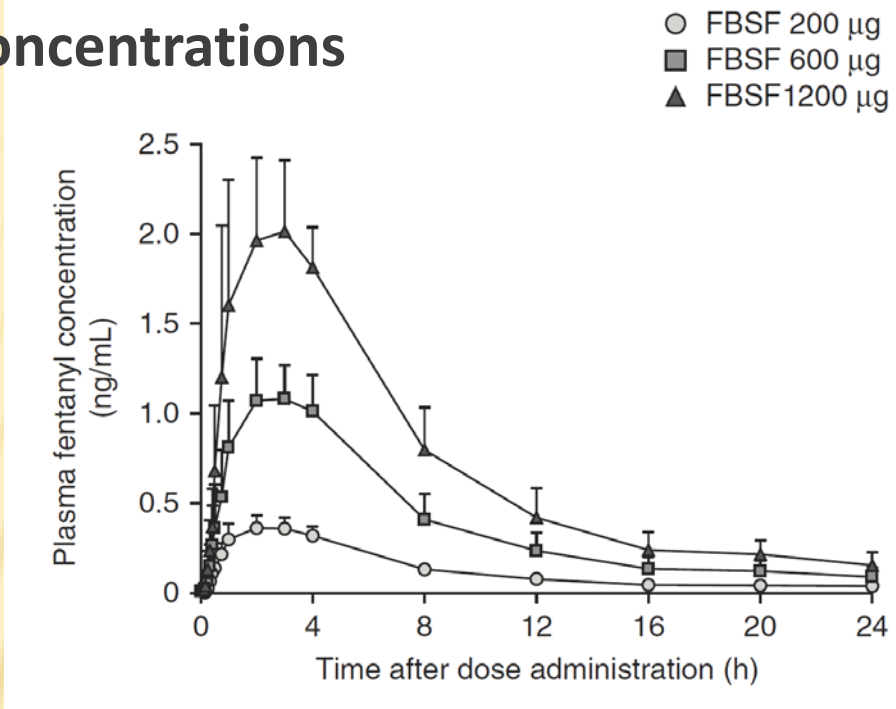


Painkyl® approved in FDA, 2009;

Canada and Europe in 2010

DOSE PROPORTIONALITY / LINEARITY

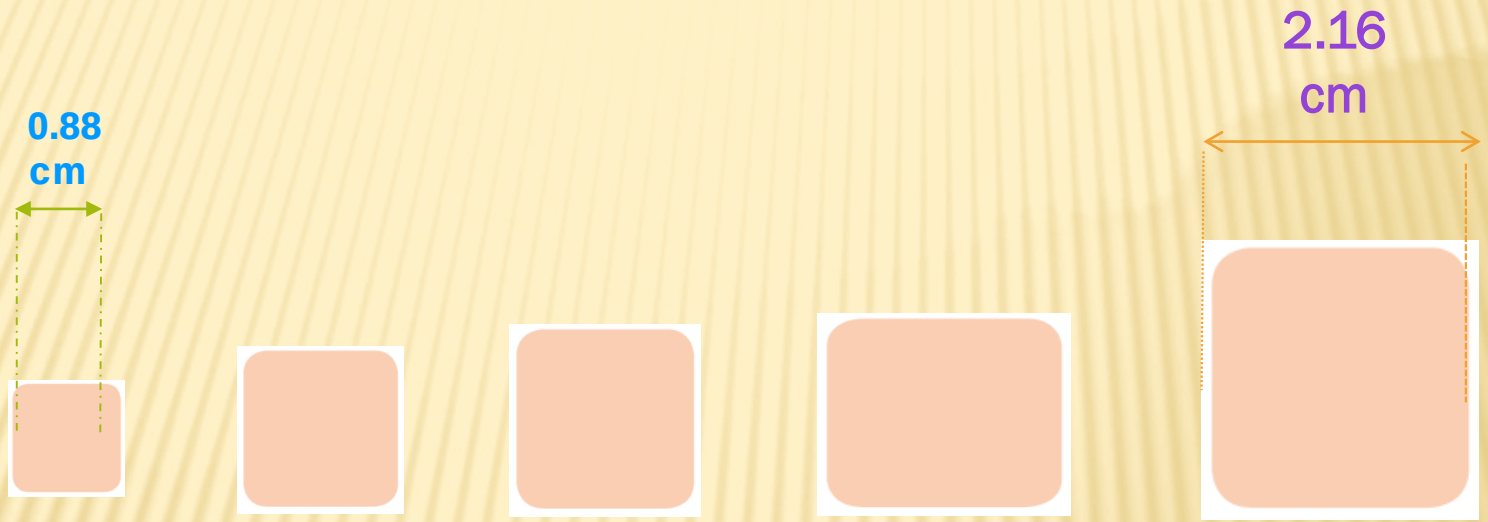
Plasma Fentanyl Concentrations



Drug and dose	FBSF 200ug	FBSF 600ug	FBSF 1200ug
T first [h]	0.28 ± 0.10	0.22 ± 0.06	0.20 ± 0.05
C max Mean ng/mL	0.383 ± 0.0746	1.16 ± 0.189	2.19 ± 0.538
AUCinf（hr·ng／mL）	3.46 ± 0.72	11.72 ± 5.29	20.43 ± 4.52

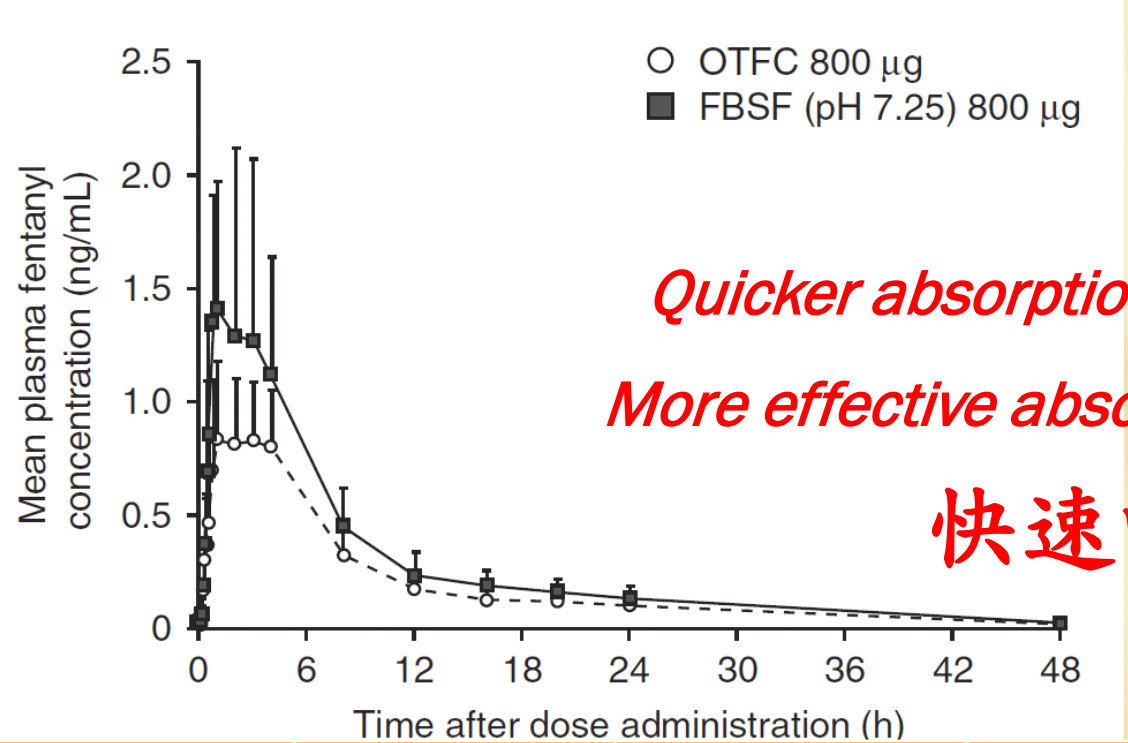
Clin Drug Investig 2012; 32 (1): 63-71

Painkyl® dosage



200 μg 400 μg 600 μg 800 μg 1,200 μg

Comparative pharmacokinetics Painkyl® vs. OTFC



Quicker absorption with Painkyl® !

More effective absorption with Painkyl® !

快速吸收

Drug and dose	T first Mean (min)	C max Mean ng/mL	T max Median (h)	AUC inf Mean h•ng/mL
Painkyl® 800µg	9	1.67	1	14.46
OTFC 800µg	13	1.03	2	10.30
	31% shorter	62% higher	50% shorter	40% larger

Clin Drug Investig 2009; 29 (10): 647-654

DRUG INTERACTIONS

- There are no prohibited concomitant medications
- But may need to carefully monitor those who are using the following drugs:
  - CYP3A4 Inhibitors
    - Concomitant use may result in a potentially dangerous increase in fentanyl plasma concentration, which could increase adverse drug effects and may cause potentially fatal respiratory depression
    - Strong CYP3A4 inhibitors : indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, and telithromycin, etc.
    - Moderate CYP3A4 inhibitors : aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, and verapamil, etc.
    - Weak CYP3A4 inhibitor : cimetidine
- CYP3A4 Inducers
    - Concomitant use may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Painkyl®
    - For example : arbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin

小心藥物交互作用

DRUG INTERACTIONS

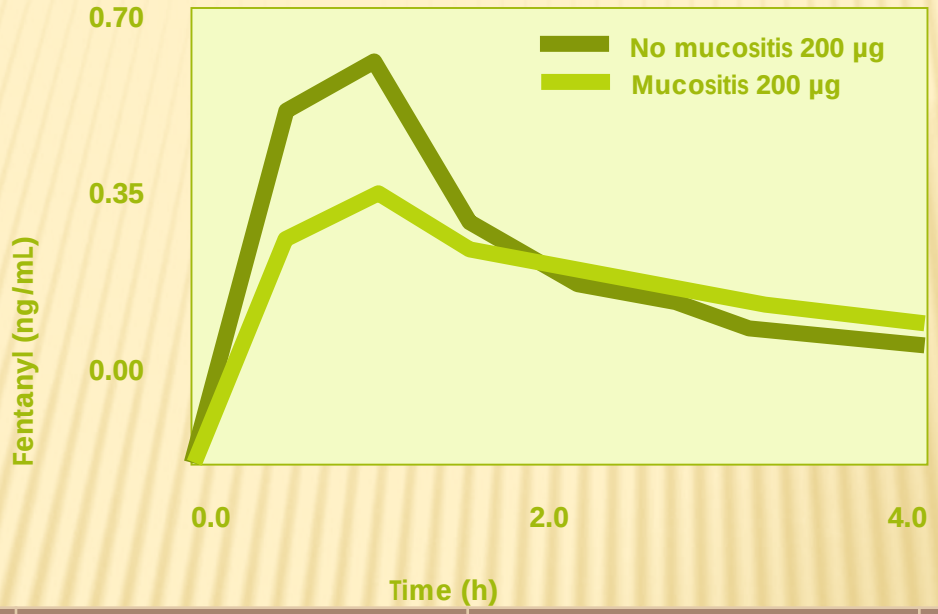
- MAO inhibitor
  - Not recommended for use in subjects who have received MAO inhibitors within 14 days, because of severe and unpredictable potentiation
- CNS depressants
  - May produce increased depressant effects, such as hypoventilation, hypotension, and profound sedation
  - Including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages
  - Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks

ELIMINATION(排除由尿)

- Fentanyl >90% eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.
- Less than 7% of the dose is excreted unchanged in the urine
- Only about 1% is excreted unchanged in the feces.
- The metabolites are mainly excreted in the urine, while fecal excretion is less important.
- The total plasma clearance 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg).

PK in special patient: Mucositis (Grade I)

- Phase I, open-label, single-dose study in patients with cancer



黏膜發炎會影響吸收

Patients status	C_{max} （ng／mL）	T_{max} （hr） *	AUC_{0-4} （hr·ng／mL）
Mucositis	0.47 ± 0.32	1.00 (0.50 – 4.00)	1.14 ± 0.71
No mucositis	0.69 ± 0.54	1.00 (0.50 – 1.50)	1.29 ± 0.87

* Data for Tmax presented as median (range); other data are presented as mean ± SD

Journal of Pain Research 2011:4 245–251

original article

Annals of Oncology 21: 1308–1314, 2010
doi:10.1093/annonc/mdp541
Published online 25 November 2009

Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study

R. Rauck[1], J. North[1], L. N. Gever[2], I. Tagarro[3] & A. L. Finn[4*]

Placebo-controlled study

↓

Open-label : Titration period ;N=151

↓

Double-blind phase: cross-over phase ; ITT=80

↓

Placebo X 3 times & FBSF x 6 times

- Primary endpoint: $SPID_{30}$ (The mean sum of pain intensity differences(SPID) at 30 min after dosing)

Annals of Oncology 21: 1308–1314, 2010

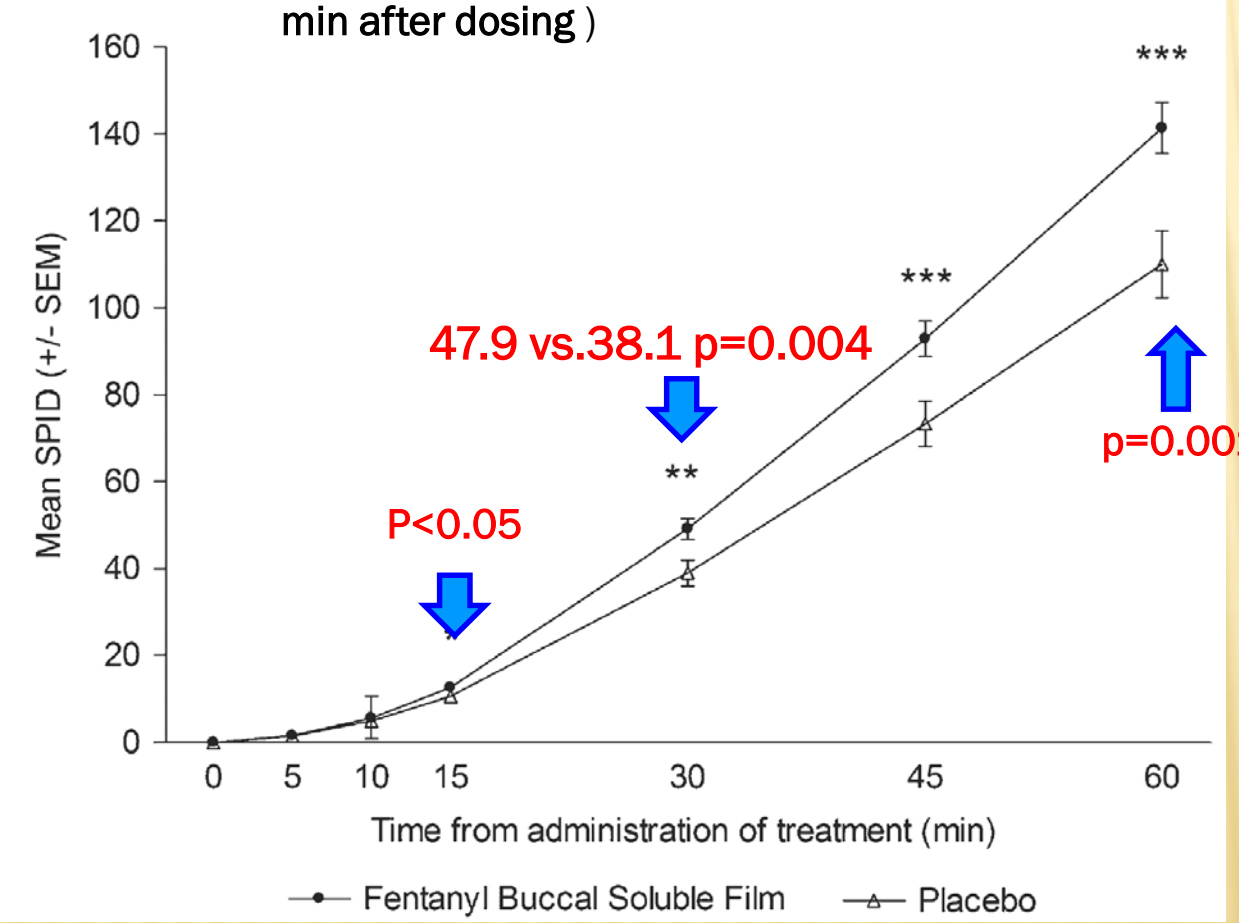
EVALUATION OF IMPROVEMENT IN BTP

- Statistically significant improvements of pain vs. clinically meaningful changes in efficacy assessments
  - **Pain intensity difference (PID) (2000):** defined as a decrease of > 33 % from base line within 30 minutes of administration
  - **30分鐘內改善1/3**
  - **PID of 33 % and 50 % improvements** (2008)
  - **≧2-point reduction in absolute pain intensity** (0-10 scale)
  - **Pain relief scores of ≧ 2** (on a 5-point categorical scale where 0 = no pain relief and 4 = complete pain relief)
  - **Global medication performance score of ≧ 2** (on a 5-point categorical scale where 0 = poor and 4 = excellent).

Farrar JT et al. Pain 2000; 88 (3): 287-94
Dworkin et al. J Pain 2008; 9 (2): 105-21

EFFICACY: PAINKYL® VS. PLACEBO

- Primary endpoint: $SPID_{30}$ (The mean sum of pain intensity differences(SPID) at 30 min after dosing)



明顯改善

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

Annals of Oncology 21: 1308–1314, 2010

SECONDARY EFFICACY : PAINKYL® VS. PLACEBO

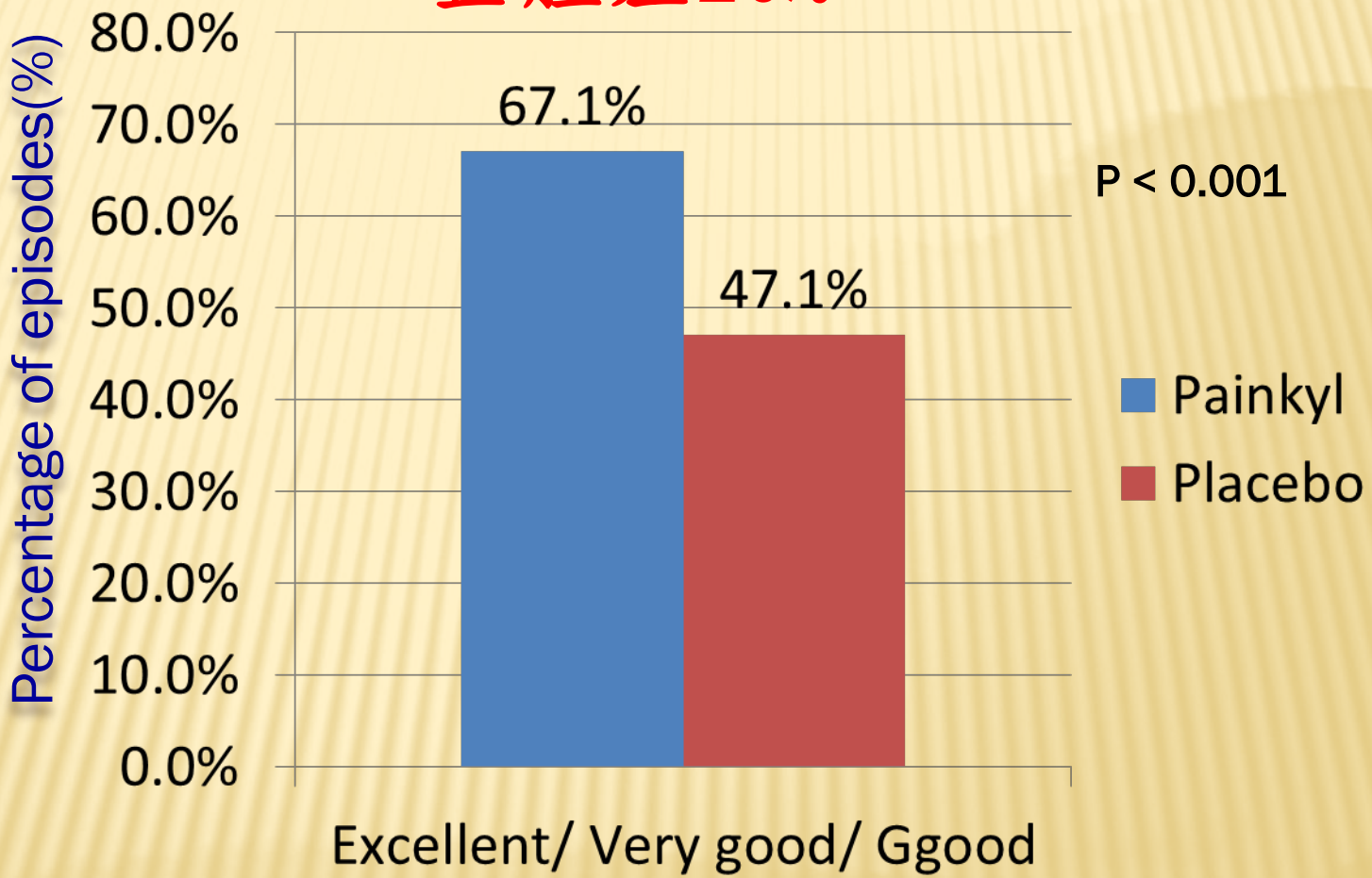
其他指標也都明顯改善

Outcome measure	Treatment/ N	30 min post-dose (mean)	p-value
PID (pain intensity difference)	Painkyl® (n=79)	2.5	0.015
	Placebo (n=77)	1.0	
PR (pain relief)	Painkyl® (n=79)	1.7	0.002
	Placebo (n=77)	1.3	
TOTPAR (total pain relief)	Painkyl® (n=79)	36.1	0.002
	Placebo (n=77)	29.5	
% episodes ≥33% decrease in pain	Painkyl® (n=79)	47.3	0.009
	Placebo (n=77)	38.2	
% episodes ≥50% decrease in pain	Painkyl® (n=79)	32.8	0.002
	Placebo (n=77)	24.1	

Annals of Oncology 21: 1308–1314, 2010

OVERALL SATISFACTION: PAINKYL®VS. PLACEBO

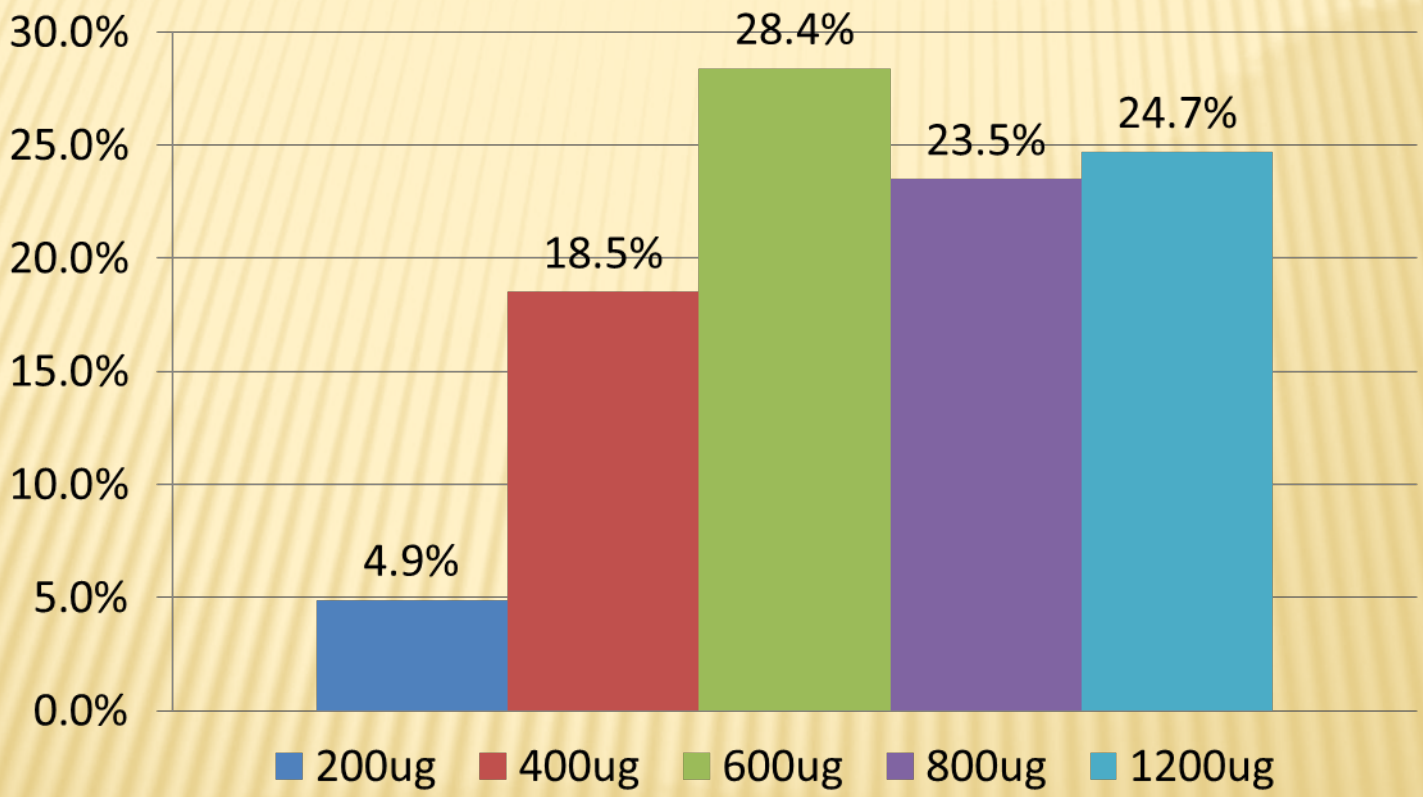
整體差20%



Annals of Oncology 21: 1308–1314, 2010

EFFECTIVE DOSE: PAINKYL®VS. PLACEBO

- **Placebo-controlled study: effective dose**



Annals of Oncology 21: 1308–1314, 2010

ADVERSE EVENTS : PAINKYL® (N = 151)

副作用

Adverse event	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 mouth	2 (1.3)
Dysgeusia	2 (1.3)
Pruritus	2 (1.3)
Confusional state	2 (1.3)

Annals of Oncology 21: 1308–1314, 2010

DEMOGRAPHICS IN THE SAFETY OF PAINKYL® USE FOR BTP

- 224 patients enrolled; 154 enrolled directly (entered the titration period) and 70 entered from FEN-201.
- 179 patients entered the open-label period.
- Mean age (safety population): 58.2 years.
- 53.2% female, 46.8% male.

毒性不高可接受可調控

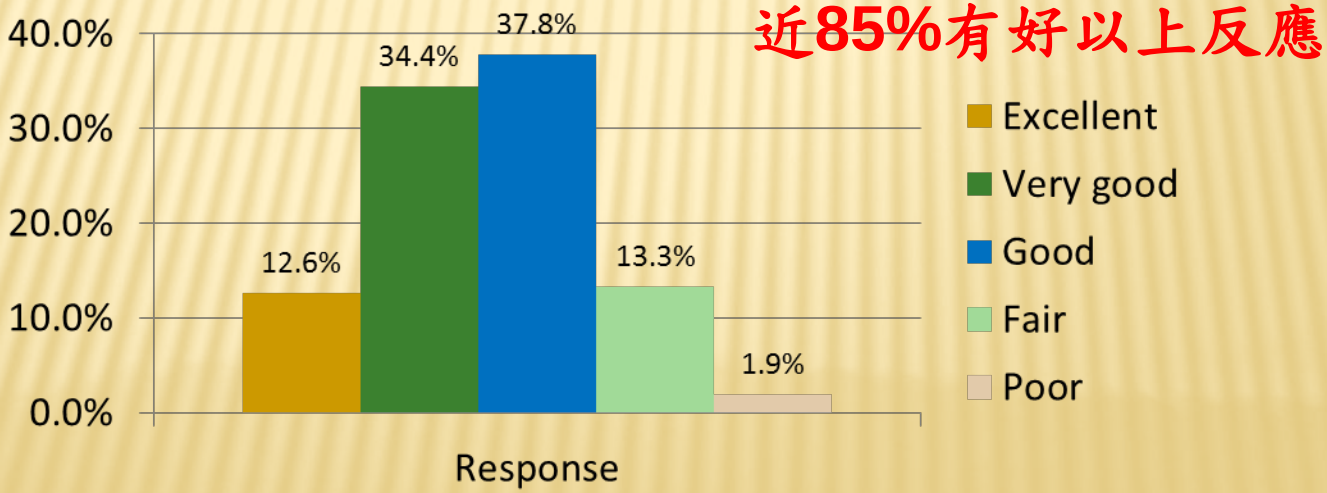
Titration Period	Number of Subjects (%)
Enrolled	224 (100)
Safety population	220 (98.2)
Discontinued[a]	37 (16.5)
Consent withdrawn[a]	10 (6.5)
Adverse event[a]	6 (3.9)
Lack of efficacy[a]	5 (3.2)
Other[a]	16 (10.4)
Open-label Period	**Number of Subjects (%)**
Entering period	179 (79.9)
Discontinued	85 (37.9)
Consent withdrawn	19 (8.5)
Adverse event	17 (7.6)
Lack of efficacy	6 (2.7)
Other	43 (19.2)

[a] Percentage based on the number of subjects entered directly (n=154)

FEN-202 study: APS 2008 Abstract #8415,Poster #190

RESULT:
GLOBAL EVALUATION OF MEDICATION PERFORMANCE

- A total of 56,718 doses were taken in the open-label period
  - Mean of 2.9 doses/subject/day for 111.9 days
- The initial effective dose was ≤1200 µg for 168/179 patients (93.9%) in the open-label period.
- Only 24 of 179 patients (13.4%) used doses above the dose range of 200 to 1200 µg at any time during the study.
- FBSF was judged to produce good to excellent response in **84.8% of BTP episodes.(220 Subjects)**



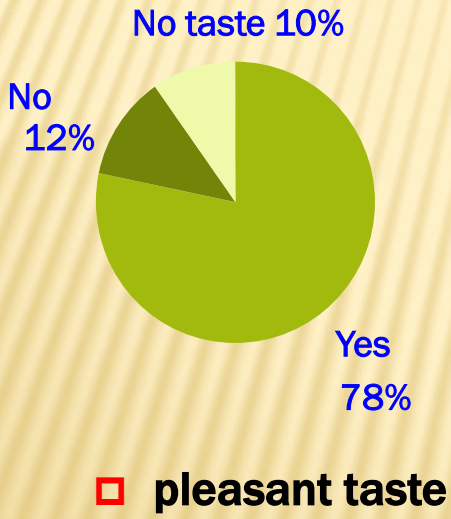
近85%有好以上反應

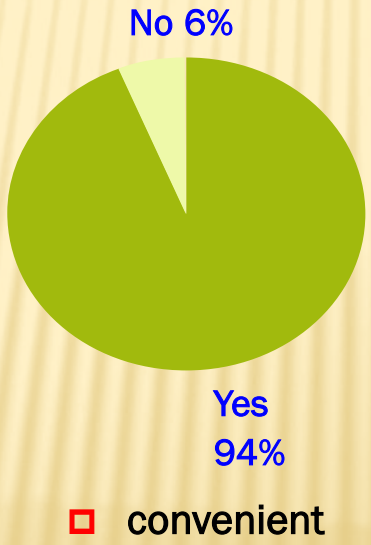
FEN-202 study: APS 2008 Abstract #8415,Poster #190

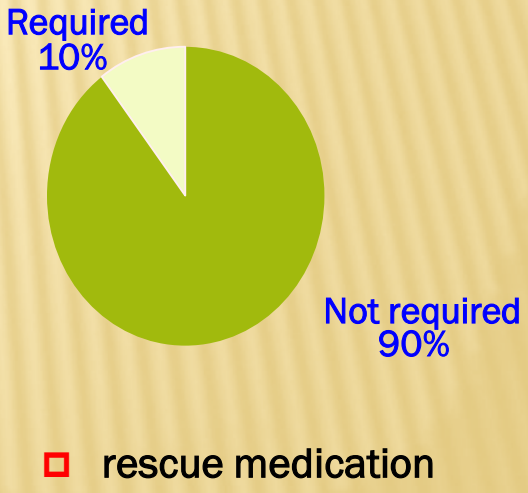
RESULT: ACCEPTABILITY IN OPEN-LABEL, LONG-TERM EXTENSION STUDY

- 88% a pleasant taste or no taste associated with FBSF
- 94% easy to use and convenient
- 10.2% required rescue medication

方便 味道可接受







FEN-202 study: APS 2008 Abstract #8415,Poster #190

CONCLUSION: THE SAFETY OF FBSF USE FOR BTP

- Interim analysis of this long-term safety study suggested FBSF is generally safe and well-tolerated in the treatment of cancer-related BTP.
- The AE profile of FBSF was consistent with use of an opioid in cancer patients with chronic pain. The most frequently reported treatment-related AEs were nausea (8.6%), dizziness (5.5%), and constipation (5.0%).
- A FBSF patient acceptance questionnaire suggested that the majority of patients found FBSF easy to use and convenient.
- FBSF was judged to produce good, very good, or excellent response in 84.8% of BTP episodes on the Global Evaluation of Medication Performance.

FEN-202 study: APS 2008 Abstract #8415,Poster #190

SUMMARY OF CLINICAL TRAIL

- Base on three study, Total enrolled 390 cancer subjects, 306 cancer subjects assessment
- > 60,000 doses & 200~2400ug have been administered
- 112 treated at least 60 days; 91 patients for 3 months; 32 patients treated more than 1 years
- Average exposure time 115 days
- Average daily doses 3(<4)
- 31.1 % of the population: aged ≥ 65 years

長期止痛

Hydromorphone(8mg 約40 mg morphine):

不同種類鴉片

一天一次

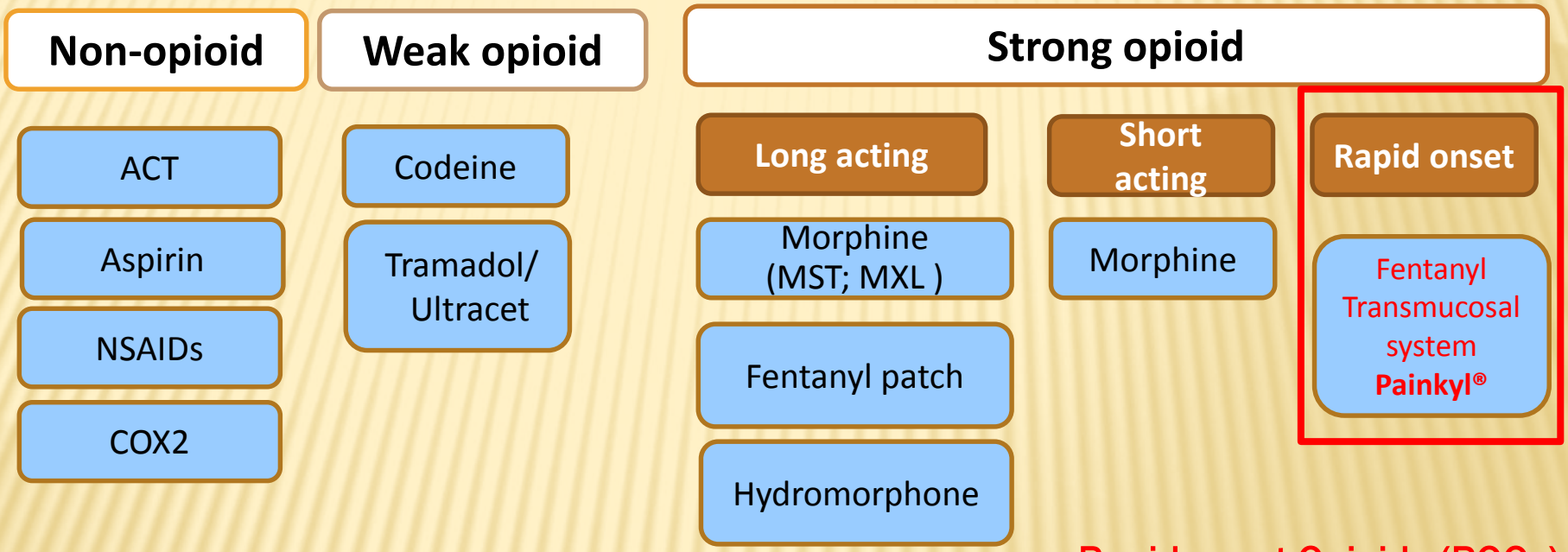
特殊崩解方式

MXL60: 長效 可NG use

PAINKYL® Q&A

THE 1ST RAPID-ONSET OPIOID OF TREATING BTCP

RAPID-ONSET OPIOID IS A NEW CATEGORY OF ANALGESICS



Adjuvant analgesics:
Antidepressants; Anticonvulsants; Corticostroids; Bisphosphonate; GABAergic adjuvant analgesics…..

CNS Drugs 26(6): 509-535.

PAINKYL®(平舒疼口頰溶片)

- Painkyl®是一種類鴉片止痛劑，僅適用於癌症病患突發性疼痛（breakthrough pain）之處置，且適用對象僅限於18歲（含）以上且正在使用類鴉片藥物治療其潛在持續性癌疼痛並具耐受性者，或其他等止痛劑量之類鴉片藥物達一星期（含）以上。
- Patients considered opioid tolerant:
  1. 60 mg oral morphine/day
  2. 25 ug transdermal fentanyl/ hour
  3. 8 mg oral hydromorphone/day
  4. 30 mg oral oxycodone/day
  5. 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

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

規則止痛要繼續

臨床常見Q&A

Q: 600mcgBTcP的量+ATC是否會有over dose的可能性？門診病人帶600mcg，病人是否容易發生危險？

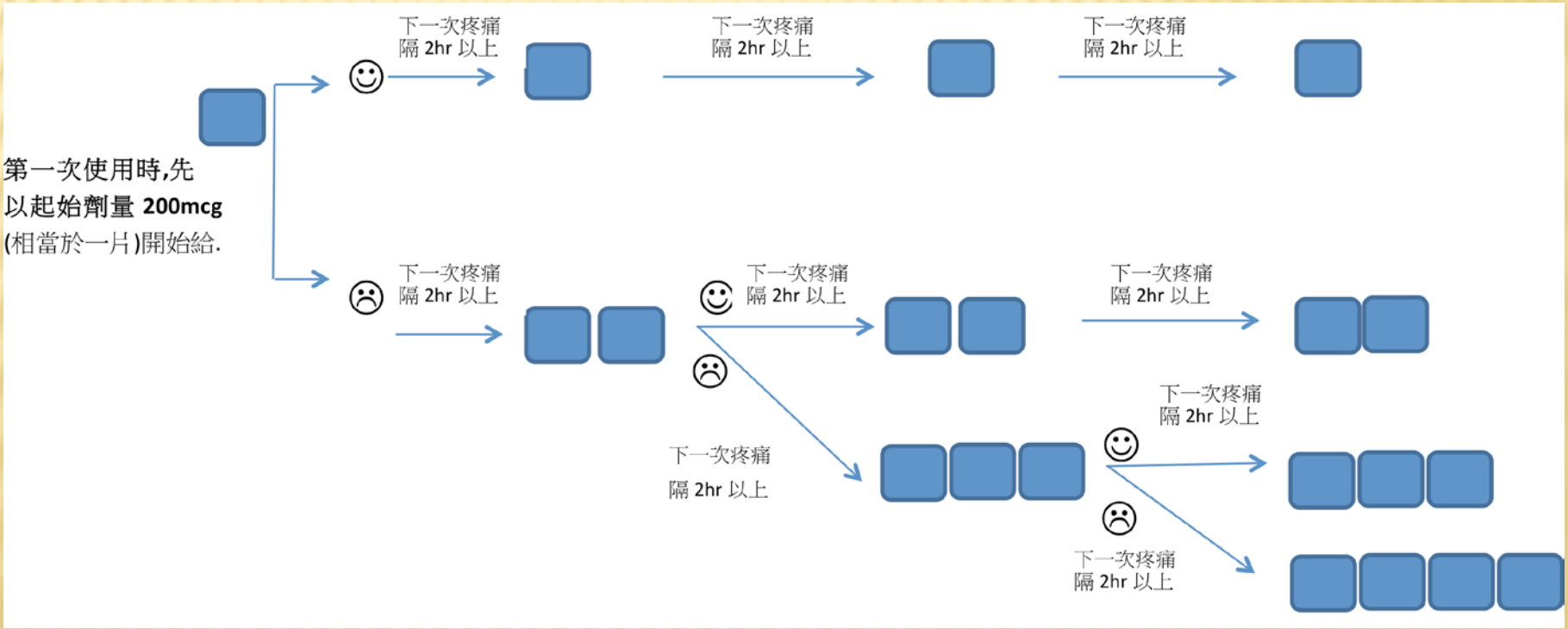
A: Painkyl®治療BTCP須titration 適合的劑量，故較無over dose的風險。

臨床上需強調titration的重要。

臨床常見Q&A

Q: 如何選擇Painkyl®使用劑量？

A: Titration:



臨床常見Q&A

Q: 每次最高劑量為何？每日最高劑量為何？

A: 每次最高劑量1200mcg
每日最高劑量4800mcg

臨床常見Q&A

Q: 是否可以使用於其他部位的黏膜？

A: 白色層需要唾液分解，若貼於別處黏膜，
白色層不易分解或排出，且也無相關資料

臨床常見Q&A

Q: 已使用3位病患,都是每次1片就能pain control,但出院時都 會再帶口服morphine 當rescue.

A: 釐清處方morphine 當rescue之用意為何？

強調morphine及Painkyl藥動學特性

若於30分鐘後rescue使用，無法及時止痛。

且容易混淆病患，以為其疼痛緩解為Morphine所致。

臨床常見Q&A

Q: 如何開立醫囑？

A:其他臨床使用方式：

- 住院→ Q2H PRN(備註：一日不超過四次)
  - → Q6H PRN(6小時內疼痛，開立STAT處方)
- 門診→Q2H PRN(提醒病患一日超過四次，提早回診)
  - → Q6H PRN(告知病人要間隔兩個小時才能再使用)

臨床常見Q&A

Q: 門診初次使用如何建議臨床處方？

A: 已確認劑量→ Q6 PRN，14 day

→ 若需自行調高一個劑量，請病人提早回診

門診titration劑量→200 mcg Q6 PRN 14day

→增加至400mcg 時→請病人提早回診

400mcg仍不夠→馬上回診

建議病患每次需自行titration增量次數不超過2次。

臨床常見Q&A

Q: 擔心是否有成癮性問題？

A: Fentanyl相較其他Opioid藥物，較無成癮性的問題

→根據統計癌症病患因為使用瑪啡類藥物而成癮機率僅有4/12000)

Duration: 2hrs

院方二級管制藥的管控嚴格

Indication 限制相對嚴格

臨床常見Q&A

Q: 是否有任何研究患者的腎功能衰竭？

A: 腎或肝功能損害之病患

- 目前所存資訊不足以針對 Painkyl®於腎或肝功能損害病患中之使用作出建議。吩坦尼主要經由人類 CYP3A4異構酵素系統代謝,而其 非活性代謝物主要經由尿液排除;因吩坦尼經由肝臟代謝且經由腎臟排除,若本藥使用於肝腎相關病患,應謹慎使用。
- 因病患已經使用ATC藥物控制其潛在持續性疼痛，對Painkyl也會有相對應之耐受性，加上Painkyl快速onset及快速排除，故對原先Opioid藥物副作用之影響小。
- Morphine 相對來說對腎臟功能的影響比Fentanyl大，此類病人更應慎用。

臨床常見Q&A

Q: Temgesic®使用起來很好，有什麼差異？

A: 1.Temgesic®其雖然快速吸收，但其止痛強度低於Fentanyl，達止痛效果時間需20-30分，

2.為agonist-antagonist agent，使用高劑量或併用其它類的Opioid，可能造成拮抗作用，產生戒斷現象。

3.半衰期長，其使用為Q6h~Q8h應定位為“快速onset之ATC藥物”。

藥品名稱(英文)	藥品名稱(中文)	成分	成分含量	單複方	價格	起迄	藥商	劑型
TEMGESIC SUBLINGUAL TABLETS 0.2MG	丁基原啡因舌下錠0．2公絲	BUPRENORPHINE (HYDROCHLORIDE)	0.2 MG	單方	22	104.04.01 | 迄今	利潔時股份有限公司	舌下錠

臨床常見Q&A

Q: 病患因使用Painkyl® 治療BTCP次數超過4次，而需調整ATC dose時，如何調整？

A: 臨床調整ATC 之標準原則為:

嚴重疼痛增量50-100%

中等疼痛增量25-50%

臨床常見Q&A

Q:Opioid劑量如何換算？

A: 1mg Fentanyl= 100 mg morphine

1mg IV morphine = 3 mg oral morphine

25 mcg/h Fentanyl Patch= 60 mg morphine

→25 mcg*24hrs = 600 mcg/day = 0.6 mg/day

→0.6 mg Fentanyl = 60 mg morphine

臨床常見Q&A

Q: 病患貼25 mcg/h Fentanyl Patch，使用Painkyl® 200mcg，因快速onset，相對原本ATC 25 mcg/h劑量，應該太高，病患會受不了！

A: **國際上針對ROO類藥物，無與其他Opioid藥物做換算之公式**，若用數學方式換算可能相當於→200mcg Painkyl®生體可用率為71% =140mcg =0.14mg →可能相當於14mg morphine

IV/SC Morphine	Oral morphine	Transdermal Fentanyl	Oral Morphine PRN for BTP
20mg	60mg	25mcg/hr	10mg
40mg	120mg	50mcg/hr	20mg
60mg	180mg	75mcg/hr	30mg
80mg	240mg	100mcg/hr	40mg
+20mg	+60mg	+25mcg/hr	+10mg

臨床常見Q&A

Q: 頭頸癌病人因為照射RT造成Buccal血流變差，加上纖維化的情形，所以使用Painkyl®效果是否會變差?

A: 目前未有針對這類病患的研究，建議使用於完整的黏膜表面，嘴唇內側之黏膜也可以使用，因為此類病人的Buccal血流變差，加上纖維化的情形，所以使用Painkyl®更需要titration，找到其有效止痛之劑量。

臨床常見Q&A

Q: 是否會被健保核刪：

A: 處方於符合健保給付之病人，無核刪之虞。
且Painkyl®為ROO類唯一藥物，Onset最快(IV之外)。

臨床常見Q&A

Q: 如果病患每次的劑量使用到很高如800mcg，而一日發生次數只有2-3次，以目前的morphine使用方式來說，隔日會將使用在BTCP的morphine加到 ATC劑量上，如果換成Painkyl要如何調整成ATC劑量？

A: 1.如果病患一日發生2-3次BTCP是不需要調整ATC 劑量的

2. 如果超過4次的BTCP，調整方式如先前所說：

嚴重疼痛增量50-100%

中等疼痛增量25-50%

Q:健保費太貴了？

COST-EFFECTIVENESS ANALYSIS OF ROO FOR THE TREATMENT OF BREAKTHROUGH CANCER PAIN

- 根據Zeppetella and Ribeiro研究， 90% 的BTCP平均發生期間為30-60 min.
- Gomez-Batiste et al.的研究表示 87% 的BTCP平均發生期間少於60分鐘，其中有31%在15分鐘後消失。

- 此試驗結果證實 ：有BTCP的病人每年花費為$12,000/year ，沒有BTCP的病人每年花費為 $2400/year.

- Cost per quality-adjusted life-year (QALYs):生活品質調整生命年數』(quality adjusted life year, QALY)表示。也就是除了延長 生命之成本之外,亦計算所延長生命之生活品質

CONCLUSION

- Fentanyl鼻噴劑提供較高的cost-effective 價值，其生活品質年數(QALY),所花費的費用較Placebo組低(€15703:€22176)

- Painkyl®相對Fentanyl 鼻噴劑藥費更便宜，增加生活品質生命年數1年所需之醫療費用更低,能減輕整體醫療成本。

Fentanyl citrate (Onsolis)	Fentanyl buccal soluble film (FBSF)	200 μg	Buccal mucosa	Buccal film	200, 400, 600, 800, 1200 μg	$25.73/200 μg NTD:772元
Fentanyl citrate (Abstral)	Sublingual fentanyl (SLF)	100 μg	Sublingual	Sublingual tablet	100, 200, 300, 400, 600, 800 μg	$16.18/100 μg
Fentanyl citrate (Subsys)	Fentanyl sublingual spray (FSS)	100 μg	Sublingual	Liquid spray	100, 200, 400, 600, 800, 1200, 1600 μg	$23.3/100 μg/spray
Fentanyl citrate (Lazanda)	Intranasal fentanyl spray (INFS); fentanyl-pectin nasal spray (FPNS)	100 μg	Intranasal	Liquid spray	100, 400 μg/spray (5 mL, delivering 8 metered sprays)	$42/100 μg/spray NTD:1260元

NTD:2520/200mcg

SUMMARY

- Fentanyl 鼻噴劑在國外這麼高的價格(NTD:1260/噴)，醫療費用上相較無使用ROO藥物的病人，在提供一樣生活品質的條件下，醫療整體花費較低(€15703:€22176)/年，主要是因其降低住院率、減少住院天數、減少急診次數及減少醫師看診次數而來。

- Painkyl®相對費用更低(美國USD 25.73 vs 84)，能帶給病患的benefit相同下，整體醫療花費更低，也能降低住院率、減少住院天數、減少急診次數及減少醫師看診次數，在今天醫護人力緊縮的環境下，可減輕臨床醫護人員的loading。

PAINKYL®

- 9分鐘快速止痛，藥效維持1-2小時
- 方便使用且即使腸胃道阻塞的病人也可以使用
- 長期使用，累積性副作用低(<8.6%)
- 增加癌症病患整體生活品質
- 減少住院次數及天數
- 減少急診次數
- 降低整體醫療成本

快速且有效緩解突發性癌症疼痛