緩和安寧中之疼痛處理

Pain Control in Palliative Care

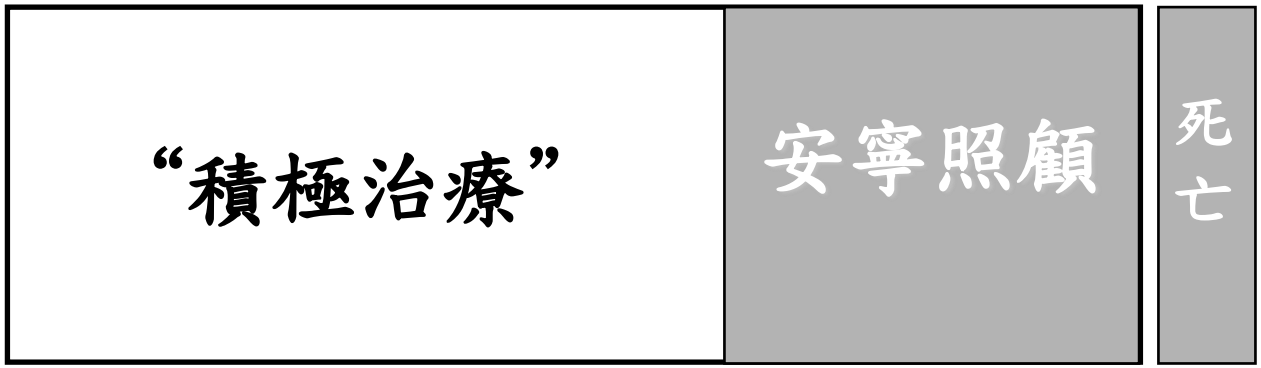
佛教慈濟綜合醫院 心蓮病房
慈濟大學 人文醫學科
王英偉

安寧緩和療護定義

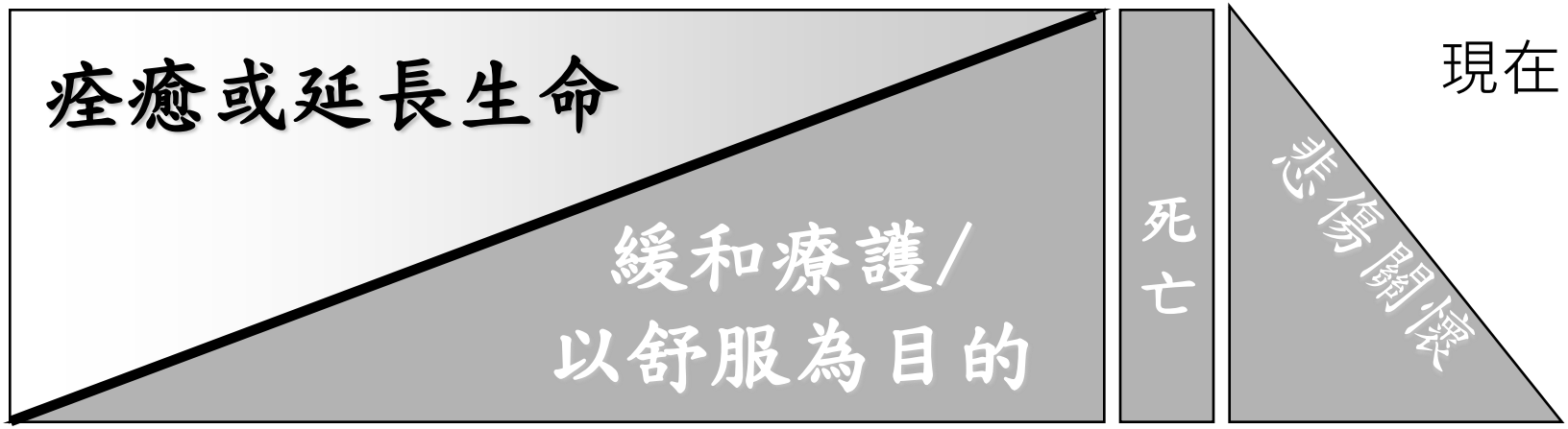
- 世界衛生組織於2002年最新定義安寧緩和照顧爲針對面對威脅生命之疾病的病人與家屬的一種照顧方式，其目標是藉由早期偵測及無懈可擊的評估與治療疼痛及其他身、心、靈的問題，預防及減緩痛苦，以達提昇生活品質之目標。此定義中强調，安寧緩和照顧以團隊照顧的方式滿足病人及家屬的需求；提供病人疼痛及其他身、心、靈痛苦症狀的緩解，幷協助家屬在病人的臨終期及病人死亡後的哀傷期（bereavement）的調適

World Health Organization. (2002). National cancer control programmes: Policies and managerial guidelines. (2nd ed.). Geneva: World Health Organization.

緩和安寧療護模式的發展

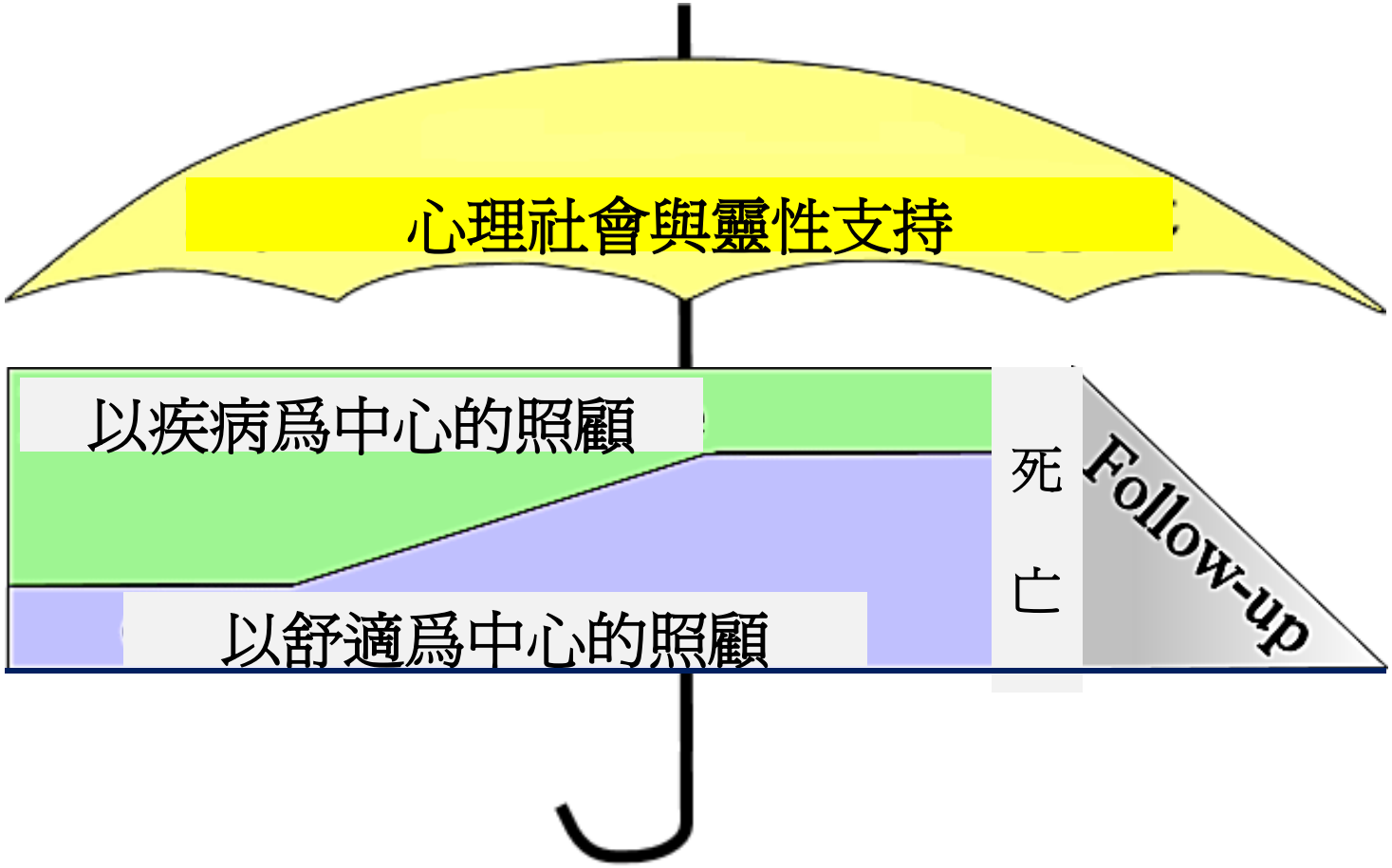


過去



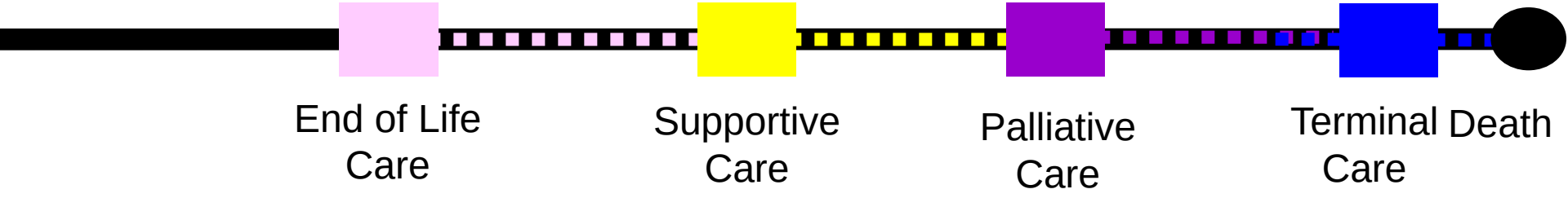
現在

非癌症末期照顧模式



觀念的澄清

- **End of Life care 末期照護**
  - *Pts living with the condition they may die from- weeks/months/ years*
  - *pts with advanced disease*
  - *3 types of pt (cancer, organ failure ,frail elderly /dementia pts)*
  - *'Ante-mortal' care like ante-natal or early life care*
- **Supportive Care 支持性照護**
  - *Helping the patient and family cope better with their illness*
  - *not disease or time specific, 'less end stage'*
  - *Preferred by some specialists- 'everyone needs supportive care'*
- **Palliative care 緩和安寧療護**
  - *holistic care (physical psychological, social, spiritual)*
  - *specialist and generalist palliative care*
  - *Some regard as overlapping or following curative treatment*
- **Terminal care 臨終照護**
  - *Diagnosing dying-care in last hours and days of life*



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.

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

end-of-life care (33% vs. 54%, P=0.05), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, P=0.02).

世界衛生組織四個要點 Palliative for All

適當的政策

足夠的藥物

對大眾及決策者觀念的推動

執行

+

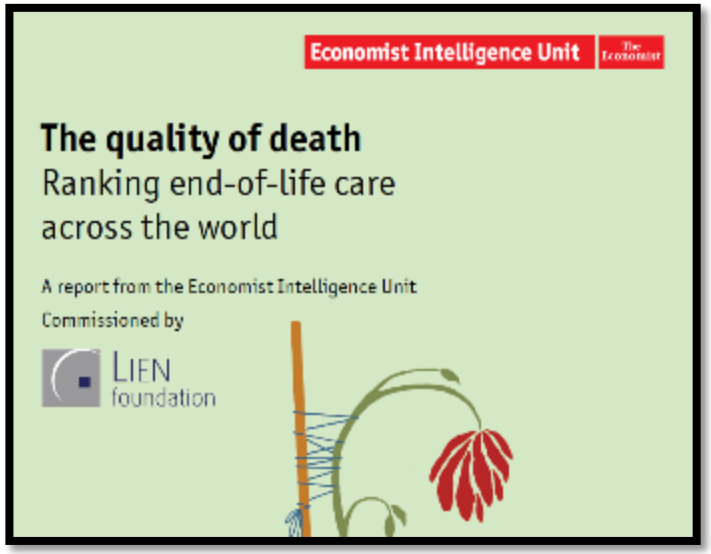
對社區結合

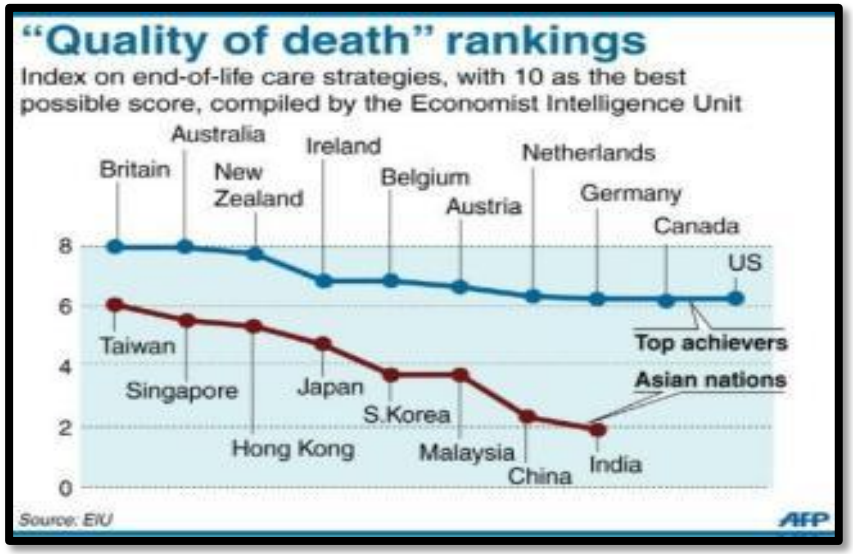
PALLIATIVE CARE FOR ALL:

BY THE PEOPLE, **THROUGH** THE PEOPLE AND

FOR THE PEOPLE

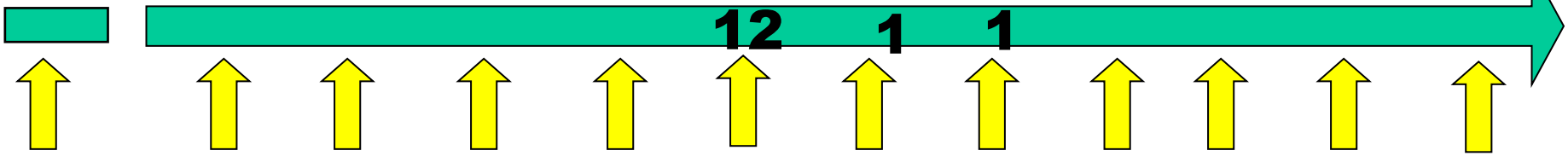
生命末期照顧質量全球比較 2010





全球「死亡品質」排名　臺灣第14，亞洲第一 (2010)

安寧療護規劃緣起



- 72年 民間團體推廣安寧療護理念
- 79年 國內成立第一家安寧療護病房
- 84年 衛生署規劃安寧療護業務
- 85/7 安寧居家納入健保給付試辦
- 89/7 安寧住院納入健保給付試辦
- 91/12 公告「安寧緩和醫療條例」
- 92/1 安寧緩和醫療條例一次修法
- 93/1 醫療機構安寧療護推廣計畫
- 93/5 調高健保安寧居家給付費用
- 98/9 建立安寧共同照護模式及試辦
- 100/ 非癌末期病患健保給付
- 102/1 安寧緩和條例二修：末期撤除
- 安寧緩和條例三修：末期「維生醫療」撤除

新的模式

重點在解除疼痛

-> 治療傷害、疾病

重點在對疼痛預先處理

-> 預防或緩解所有的疼痛

Symptoms	CANCER	AIDS	HEART DISEASE	*COPD	RENAL DISEASE
Pain	35-96	63-80	41-77	34-77	47-50
Depression	3-77	10-82	9-36	37-71	5-60
Anxiety	13-79	8-34	49	51-75	39-70
Confusion	6-93	30-65	18-32	18-33	?
Fatigue	32-90	54-85	69-82	68-80	73-87
Breathlessness	10-70	11-62	60-88	90-95	11-62
Insomnia	9-69	74	36-48	55-65	31-71
Nausea	6-68	43-49	17-48	?	30-43
Constipation	23-65	34-35	38-42	27-44	29-70
Diarrhea	3-29	30-90	12	?	21
Anorexia	30-92	51	21-41	35-67	25-64

Solano JP, Gomes B, Higginson IJ . A comparison of symptom prevalence in far-advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease (COPD) and renal disease, Journal of Pain and Symptom Management. 2005.

不同癌症疼痛發生率
Incidence of pain by primary site of cancer

% with pain	Site
>80	bone, pancreas, esophagus
71-80	Lung, stomach, hepatobiliary, prostate, breast, cervix, ovary
61-70	Oropharynx, colon, brain, kidney/bladder
51-60	Lymphoma, leukemia, soft tissue

癌症疼痛的原因

腫瘤浸潤	70-80%
與治療相關	10-20%
與癌沒有相關的其他原因	10-20%
其他	10%

對嗎啡類藥物的迷思

- 害怕現在開始使用、日後一旦疼痛增加便沒有其他的藥物止痛: 實際上嗎啡類藥物沒有最高劑量限制，亦沒有天花板效應(ceiling effect), 另有研究指出，若因需要而早期使用止痛藥物，日後的疼痛反而更易控制。

- This change in thinking emerged from a new understanding that problems at the end of life have their origins at an earlier time in the trajectory of disease. Symptoms not treated at onset become very difficult to manage in the last days of life.
- People do not “get used to” pain; rather, chronic unrelieved pain changes the status of the neural transmission of the pain message within the nervous system, with reinforcement of pain transmission, and activation of previously silent pathways.

醫療專業對鴉片類的害怕
Professional Opiophobia

- 嗎啡只有在臨終時才使用
- 嗎啡會加速病人的死亡
- 嗎啡會造成呼吸壓抑
- 嗎啡沒有效果
  - 不合理的處方
  - 對嗎啡沒有效的疼痛
  - 沒有注意到病人的心理層面
- 嗎啡造成無法接受的副作用
  - 便秘，噁心，嗜睡 、混亂
- 害怕成癮，耐受性，生理或心理依賴

病人對鴉片類的害怕
Patient opiophobia

- 使用嗎啡表示我已到末期快要死亡
- 使用嗎啡後若有更痛時便沒有其他的方法
- 我會原癮
- 我對對嗎啡過敏
- 嗎啡沒有效
  - 不正確的使用
  - 沒有對突發性疼痛的處方
  - 嗎啡沒有效的疼痛
- 沒有注意到心理社會層面的疼痛
- 我無法服用嗎啡
  - 精神狀況、噁心、便秘...

致命止痛貼布 傳林志玲也用【記者王慧美/綜合報導】

- 外傳林志玲在大連住院曾使用強效止痛貼Duragesic，美國食品藥物管理局（FDA）昨天發出聲明，指Duragesic自90年上市以來，至少**有120名病人在使用該款止痛貼後死亡，懷疑與藥物質量或病人誤用**有關。 林志玲在大連的主治醫師朱允濤表示，從沒有對林志玲使用過該種貼布。但林志玲的經紀人江怡蓉稍早接受訪問時曾表示：「林志玲現在已經不打針，改用止痛貼布，一片藥效有72小時。」
- FDA警告說，芬太奴止痛貼片會導致呼吸困難，這可能致命。如果病人使用後出現呼吸困難，或嗜睡、呼吸變慢、頭暈等症狀，可能就是病人用藥超用劑量。而且該貼布不適用於第一次使用麻醉劑病患，僅適用於那些身體已習慣啡或鴉片等止痛藥患者。雖然該局未要求藥廠回收，但建議這種止痛貼只適用於長期且中等至劇烈程度疼痛。
- FDA還警告說，如果使用過量止痛貼，即使貼上去後馬上撕掉，殘留在皮膚上的麻醉劑仍能維持17小時藥效，因此止痛貼要放在兒童拿不到的地方，使用後拋棄時，要把粘的一面向內折後，扔入馬桶沖走，而不是丟進垃圾筒，以免兒童拿到。
- 【2005/07/17 聯合晚報】

對適當疼痛控制的障礙

1. 迷思 :嗎啡容易成癮
2. 管理/法律層面 : 害怕非法使用
3. 制度面 ：沒有使用的指
4. 知識教育不足
5. 害怕副作用
6. 對疼痛評估的挑戰 :如何能客觀評估病人的疼痛？

有關對止痛藥觀念上的澄清

- **成癮 Addiction**：一種對藥物需求無法控制的行為，甚至瞭解無效或有害仍不能停止渴求
- **假性成癮 Pseudoaddition**： 因為疼痛無法被控制而不斷對藥物的需求，病人實際上為解除痛苦的行為
- **身體依賴 Physical dependence**： 因生理上對某種藥物已適應，若臨時停藥、減量或使用頡抗劑一可能會產生特定之戎斷症候症狀
- **藥物耐受性 Tolerance**：病人在使用某種物，藥物開始時使用有效，但其效果逐漸下降，必須使用更高劑量才能達到相同的效果

Joranson, 2000

TOTAL PAIN　整體性疼痛

・Cicely Saunders, 1976

- 整體性疼痛的觀念
- 形容病人與家屬在生命末期，臨終，死亡，傷慟時期所經歷強烈的痛苦

痛(Pain) ≠ 痛苦(Suffering)

生理

生理
心理
社會
靈性

整體性疼痛的層面

P	Physical problems	生理的問題
A	Anxiety, anger, depression	心理的焦慮、憤怒、憂鬱
I	Inter personal problems	社會問題、經濟壓力、家庭問題
N	Non-acceptance or spiritual distress	靈性問題，不肯接受問題

癌未病人疼痛的型態與特徵

疼痛型態	疼痛機轉	疼痛特缸
軀體性疼痛 (Somatic pain)	體表及深部組織之痛覺接受器(receptor)被興奮所引起	可定位的局部壓痛感，持續性穿刺痛或尖銳痛，可因移動而加劇疼痛，如骨痛
臟器性疼痛 (visceral pain)	胸腹腔的臟器被癌組織滲入，壓迫或箸脹而引起疼痛接受器（pain receptor）的活化	不易定位的絞痛，持續性鈍痛或悶痛，可伴有轉移(referred pain)及噁心嘔吐的伴隨症狀發生如胰臟癌
神經性疼痛 (Neuropathic pain)	腫瘤壓迫滲入周邊神經或脊髓而造成損傷，引起神經自發性放電，或因外科、放射治療、化學治療引起周邊神經的化學損傷	持續性鈍痛伴有間隔性抽痛，燒灼感，穿刺及壓迫性感覺異常，通常較為嚴重，對止痛藥效果較差，需合併三類藥物或抗鬱劑使用 如乳癌合併淋巴水腫

不同痛感的名詞

Neuropathic pain 神經性疼痛	Pain due to damage or dysfunction of a nerve
Nociceptive pain 體感性疼痛	Pain resulting from chemical or physical stimulation of peripheral nerve ending
Breakthrough pain 突發性疼痛	Pain occurring during the time of action of an administered analgesic
Incident pain 預期性疼痛	Pain occurring only in certain circumstances (e.g. movement, standing)

不同痛感的名詞

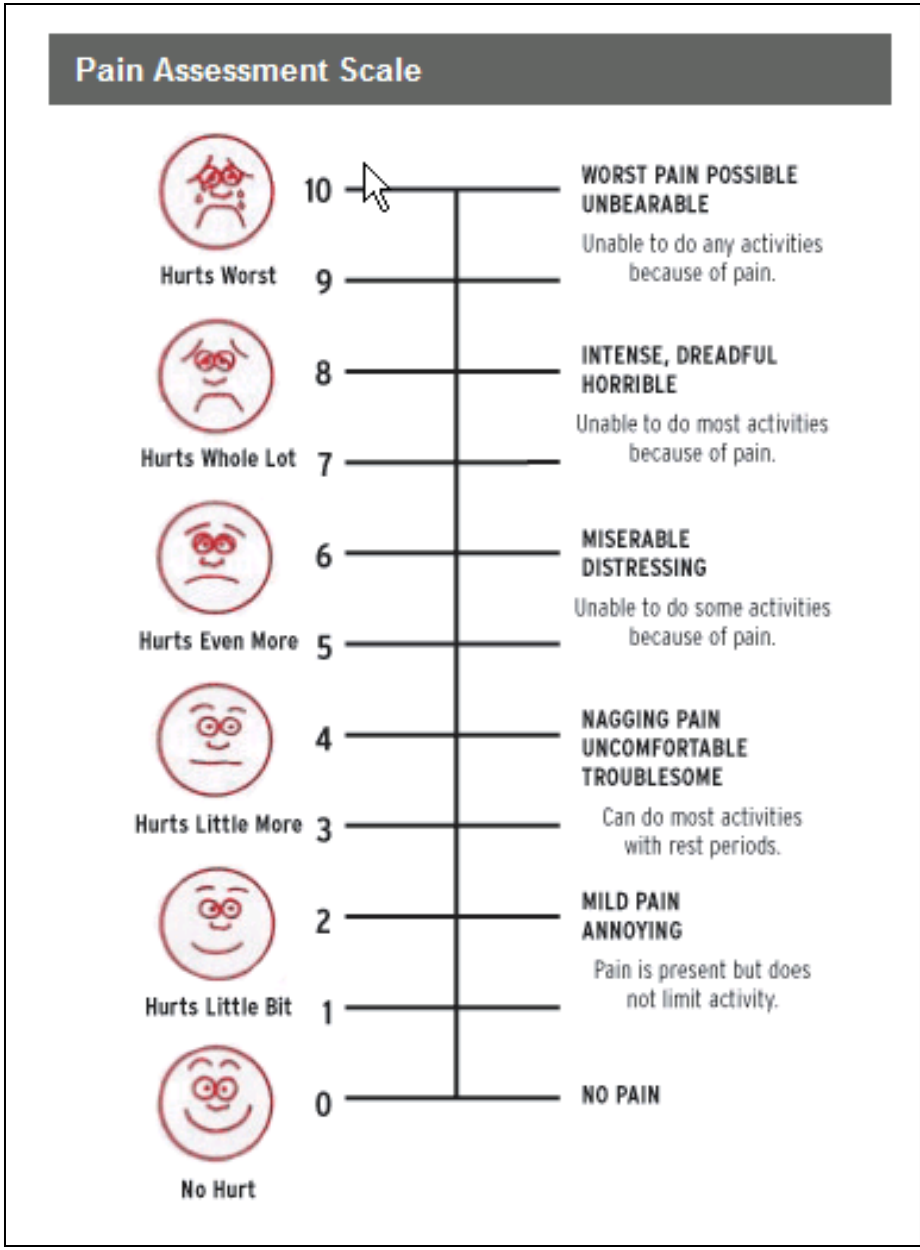
Reduced sensation 痛感下降	
Anaesthesia	Absence of sensation
Analgesia	Absence of pain in response to stimulus that is normally painful
Hypoaesthesia	Diminished sensitivity to stimulation
Hypoalgesia	Diminished sensitivity to a stimulus that is normally painful

不同痛感的名詞

Increased sensation 痛感增加	
Allodynia	Pain due to a stimulus that does not normally cause pain
Hyperaesthesia	Increased sensitivity to stimulation
Hyperalgesia	Increased sensitivity to a stimulus that is normally painful
Hyperpathia	Increase reaction to a stimulus, particularly a repetitive one

疼痛的評估

- 台灣末期病患照護的政策/指引 2014?
- 病歷記錄: 疼痛 pain score – the fifth vital sign



疼痛強度

數字量表

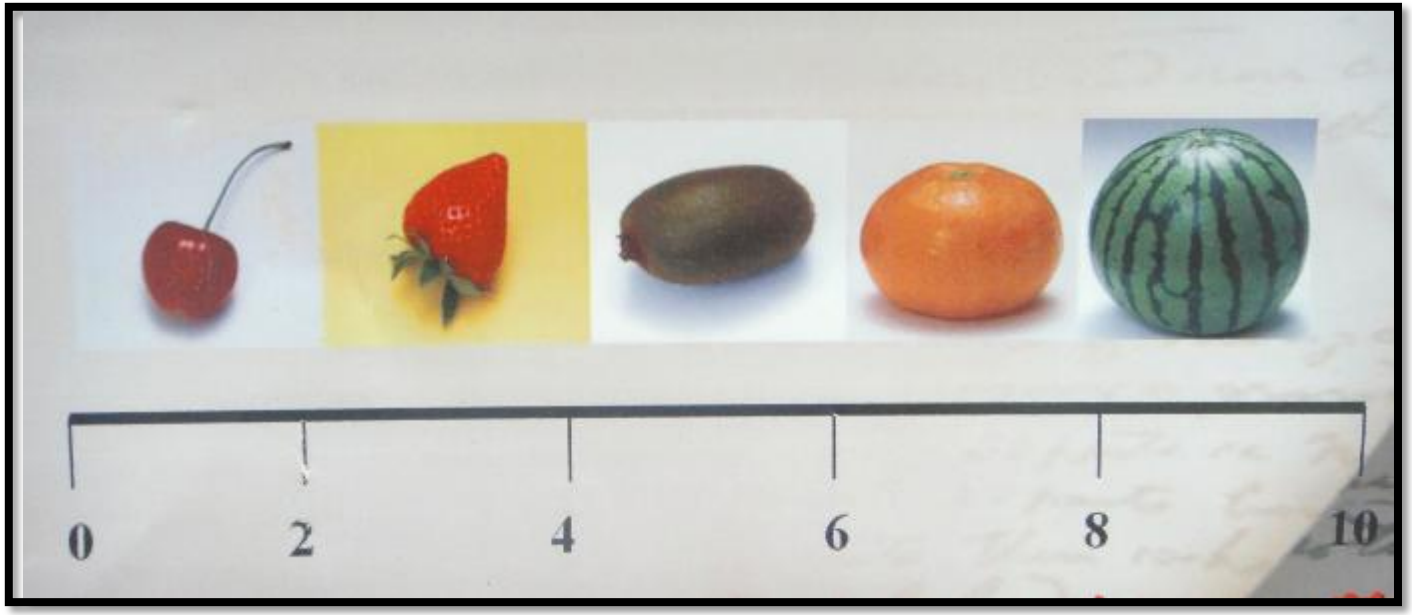
0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

無痛　　無法想像的痛

視覺主觀量表　Visual analogue scale (VAS)

無痛 ——————————————— 極痛

The Faces Pain Rating Scale - Revised[1,2]

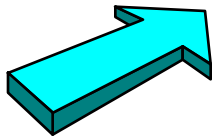


疼痛的處置

世界衛生組織建議止痛三步驟

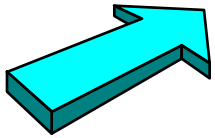
第三步

強麻醉性止痛藥物／其他非麻醉性止痛藥及幫 助性藥物



第二步

弱麻醉性止痛藥物／其他非麻醉性止痛藥及幫助性藥物



非麻醉性止痛藥物／其他幫助性藥物

疼 痛

心理
社會
靈性

生理

感覺接受性疼痛
Norciceptive pain

神經病變性疼痛
Neuropathic pain

身體性疼痛
肌肉、骨轉移

臟器性疼痛
Viceral pain

神經壓迫

神經傷害

WHO 三階
梯止痛模式

輔助療法

經及電刺
激TENS
針灸
芳香療法
藝術治療
音樂治療
…

Acetaminophen(Panadol)
非類固醇抗發炎藥 NSAID
如 Aspirin Brufen, naposin,
voltaren....)

弱鴉片類＋NSAID
如 Codeine, tramadol, Depain
X...

強鴉片類＋NSAID
如 Morphine, Fentanyl,
Methadone...

輔助藥物
療法

三環抗憂鬱劑 TCA:Amiptyline
Anticonvulsants: tegretal
局部麻醉劑 (Local anaesthetics:
xylocaine)
類固醇: Dexamethasone
Baclon
Clonidine
Dextromethorphan (medicon)
Ketamine
…

治療原則：Treatment Modalities

- 解釋痛的原因 Explanation
- 改變痛的過程 Modification of the process
- 增加痛閥 Elevation of the pain threshold
- 阻斷神經傳導 Interruption of pain pathways
- 改變生活型態 Modification of lifestyle
- 疼痛部位固定 Immobilization

給藥原則

- 於症狀未發生時即給予
- 以足夠止痛的量與強度
- 定時給藥，如每四小時一次，不要等痛才給
- 早期處理一些可能出現之副作用
- 以病人能吸收之方式使用
- 定期調整病人的劑量

The principle of use of analgesics
止痛的5個基本原則

- By the clock 定時給藥
  - use regularly
  - use the next dose about one hour before the analgesic effect of the previous dose disappears
- By the ladder 階段給藥
  - The three-step analgesic ladder
- By the mouth 口服為主
- For the individual 針對個別調整
- Attention to detail 注意細節

世衛之三階段疼痛控制

- 可針對個別作彈性調整
- 以疼痛指數選擇開始使用的階段，如疼痛指數1-3/10 使用第一階段藥物，指數4-7/10 ，使用第二階段藥物，>7/10 開始即用第三階段藥物

世界衛生組織癌症疼痛三階段處理模式

- 過去20年只有少數的研究去辨証其論述的可靠性與效果。
- NSAID能有效減輕部分腫瘤疼痛，但並沒有足夠證明顯示NSAID對骨疼痛特別有效
- 研究中証實嗎啡在神經性疼痛的治療上仍有一定的功效
- 若依WHO的建議，於第二階段加入較弱的麻醉性藥物，對疼痛的減輕有限，但副作用則有增加

二階段? 三階段

- 當弱麻醉性止痛劑增加劑量時，此時與強麻醉性止痛劑低劑量相同，可以直接從第一階段跳至第三階段
- 跳過第二階段者有較好的止痛成效，在跳級治療組其疼痛的時間明顯較少，但相對的是跳級組所造成的副作用亦較多，必須作更積極的治療的預防
- 早期使用嗎啡組在疼痛的強度、藥物調整的次數及病人的滿意度上都較WHO組有較好的表現
- 病人因不適症狀住院，須要馬上提供症狀控制，可利用嗎啡靜脈注射作快速調整 (Rapid Titration)
  - 以每十分鐘注射1.5 mg 嗎啡，直至病人的疼痛獲得緩解或出現頭暈副作用，此時總劑量定為病人每四小時的口服劑量[8]。

WHO step II opioids

	Characteristics and comments
Codeine	Step II drug only: use alone or in combination with paracetamol; daily doses ≥360 mg not recommended
Tramadol	Step II drug only: use alone or in combination with paracetamol; daily doses ≥400 mg not recommended
Hydrocodone	Step II drug only: used as a substitute for codeine in some countries
Oxycodone	Step II opioid when used at low doses (eg, ≤20 mg per day) alone or in combination with paracetamol
Morphine	Step II opioid when used at low doses (eg, ≤30 mg per day)
Hydromorphone	Step II opioid when used at low doses (eg, ≤4 mg per day)

*Originally classified as weak opioids.

***Table 1:* WHO step II opioids* for moderate cancer pain in opioid-naive patients**

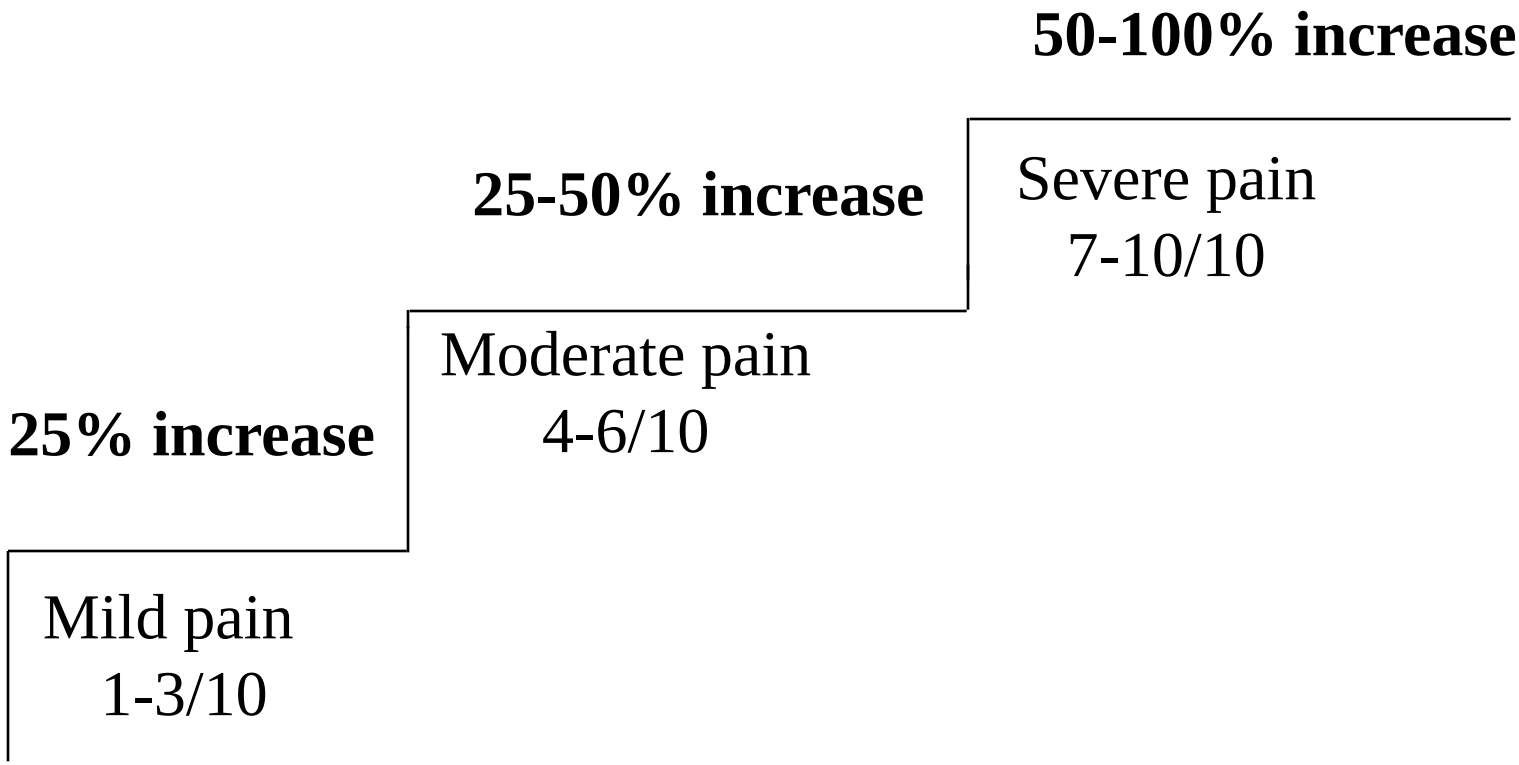
Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC Lancet Oncol2012; 13: e58–68

口服短效嗎啡類藥物
Oral immediate release morphine

- Initial dose 開始劑量
  - Total IV/SC morphine x 3, divide by 6 for oral q4h dose
  - Convert other opioids to oral morphine, divide by 6 for oral q4h dose
  - Patient not previously receiving opioids
  - Start with 10mg PO q4h
  - If frail, elderly or with renal impairment, start with 5 mg PO q4-6h
- Frequency 頻率
  - Q4h PO , 2am dose should be given
- Breakthrough pain 突發痛
  - As often as required of 50-100% of the 4 hourly dose
- Incident pain 預期疼痛
  - Treated as breakthrough pain, 30-60 min prior if predictable
- Dose adjustment 劑量調整
  - First dose -> over-sedation, ↓50%
  - First dose -> pain , ↑50%
  - Breakthrough (mg/d) + scheduled (mg/d), divided by 6 for new q4h dose

Opioid Dose Escalation

Always increase by a percentage of the present dose based upon patient's pain rating and current assessment



PRINCIPLES OF MAINTENANCE OPIOID THERAPY

- For continuous pain: give pain medication on a regular schedule with supplemental doses for breakthrough pain.
- Add extended-release or long-acting formulation to provide background analgesia (**以長效型嗎啡作為基礎的疼痛治療**) for control of chronic persistent pain controlled on stable doses of short-acting opioids
- Initial range for converting to long-acting opioid would be 50% of the daily requirement
- When possible, use the same opioid for short-acting and extended-releases forms **(儘可能用同類的長效與短效嗎啡)**

NCCN Guidelines Version 2.2013

嗎啡的反應 Response to Morphine

- Morphine responsive 對嗎啡有反應
- Morphine semi-responsive 對嗎啡部分反應
  - bone and soft tissue metastasis
  - nerve compression
  - IICP
- Morphine resistant 對嗎啡無效
  - headache- tension, migraine
  - Cramp (muscle spasm)

鴉片類止痛劑的副作用及處理

副作用	出現頻率	與劑量相關	耐受性	處理
便秘	大多會出現	是	沒有	常規使用輕瀉劑,鼓勵病
噁惡心嘔吐				
CTZ 引起	28~30%	是 (約一星期)	有	Haloperidol
胃積滯	5%	是	無	Metoclopramide
口乾	40%	?	?	局部處理
鎮靜	20%	是	有	幾天可恢復,但需注意是藥物引起,或有高血鈣症
幻覺	<1%	是	無	向病人及家屬解釋

麻醉性止痛藥物

- 中樞及腸胃道之 Opiate receptor(mu, delta, kappa)
- 副作用
  - 神智方面：鎮靜，意識模糊...
  - 便秘
  - 噁心，嘔吐
  - 呼吸壓抑
  - 尿滯留
  - 皮痒

麻醉性止痛藥物副作用

- 早期 Initial: vomiting, drowsiness, confusion (delirum)
- 持續 Continuing: constipation
- 偶而 Occasional: dry mouth, sweating, myoclonus

	止痛效果	便秘	呼吸壓抑	鎮靜
Morphine	++	++	++	++
Codeine	+	++	+	+
Fentanyl	++	+	+	--

造成嗜睡的原因

- 長者或衰弱的病人
- 腎功能異常
- 其他同時造成中樞神經壓抑的藥物
- 初次使用嗎啡的
- 病人只有輕度的疼痛
- 病人的疼痛已被其他的方式減輕

Methylphenidate for opioid-induced sedation: RCTs

Author	N	Intervention	Outcome
Bruera	28	Methylphenidate 10 mg am + 5 mg noon vs placebo	Methylphenidate: ↓ pain score, ↓ extra dose, ↓ drowsiness
Bruea	20	Methylphenidate 10 mg am +5mg noon vs placebo	Methylphenidate: improve cognitive function
Wilwerding	43	Methylphenidate 10mg am + 5mg noon vs placebo	Methylphenidate : ↓ drowsiness

Naloxone: treatment of narcosis and respiratory depression

Initial therapy

- Iatrogenic respiratory depression
  - RR<5/min : naloxone 0.4mg IV or SC stat
  - RR<8/min (or not rousable , or cyanosed SaO_2<90%) : naloxone 0.4mg in 10ml, 1-2ml IV or SC q3min
  - RR >8/min, rousable, not cyanosed (SaO_2>90%) : careful observation
- Known or suspected overdose
  - Naloxone 0.4-2.0 mg IV or SC q3min, up to 5 dose
- Note
  - The minimum effective dose of naloxone should be used
  - If total dose 10mg ineffective, opioid effect is unlikely

Continued therapy

- Repeat the same effective dose to maintain adequate respiration
- Continuous infusion 2/3 initial successful dose per hour

嗎啡使用的方式
Routes of Administration

嗎啡使用的方式

Oral (PO) 口服

- Requires functioning GI tract
- Convenient, noninvasive, flexible, less discomfort
- Slow onset of action, requires patient compliance

Rectal (PR) 肛門塞劑

- Insertion of suppository or solution
- Useful for patients who cannot take medications by mouth
- Absorption may be unpredictable

Berry PH, Chapman CR, Covington EC, et al. Pain: Current Understanding of Assessment, Management, and Treatments.Reston, VA: National Pharmaceutical Council and the Joint Commission for Accreditation of Healthcare Organizations; December, 2001.35

Intramuscular (IM) 肌肉注射

- Injection into large muscle
- Not recommended due to painful injections, wide fluctuations in drug levels, rapid decline in effect compared with oral administration

Intravenous (IV) 靜脈注射

- Single, repetitive bolus or patient-controlled analgesia
- Most effective for immediate analgesia, permits rapid titration
- Continuous IV infusion provides steadier drug blood levels, maximizing pain relief and minimizing side effects

Subcutaneous (SC) 皮下注射

- Infusion via butterfly needle
- Produces steady blood levels, obviates need for GI function
- Costs less than IV administration
- Slower onset and offset, lower peak effects than IV administration

靜脈注射嗎啡 Parenteral Opioids

- **IV is the route of choice if access is available**.
  - There is NO indication for IM opioids (painful, no benefit over SQ route)
  - All standard opioids can be given SQ, by either bolus dose or by continuous infusion.
- PCA (basal rate plus a patient initiated dose) is an effective and well accepted modality; either IV or SQ.

靜脈注射嗎啡 Parenteral Opioids (cont.)

- IV or SQ bolus doses have a shorter duration of action than oral doses; typically 1-3 hours.
- The peak effect from an IV bolus dose is 5-15 minutes.
- Dose escalation of parenteral opioids is the same as with oral—always by a percentage of the starting dose.

Syringe Drivers

- Persistent vomiting
- Reduced level consciousness
- Weak
- Dysphagia
- Forgets to take PO medication
- Last days of life

Alternative systemic routes of opioid administration

Recommendation for alternative systemic routes of opioid administration : three strong recommendations:

1. the subcutaneous route is simple and effective for the administration of morphine, diamorphine, and hydromorphone, and it should be the first choice alternative route for patients unable to receive opioids by oral or transdermal routes
2. intravenous infusion should be considered when subcutaneous administration is contraindicated (eg, because of peripheral oedema, coagulation disorders, poor peripheral circulation, and need for high volumes and doses
3. intravenous administration should be used for opioid titration when rapid pain control is needed.

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC Lancet Oncol 2012; 13: e58–68

Four weak recommendations:

1. intravenous and subcutaneous infusions can be used to achieve optimum pain control in patients unable to achieve adequate analgesia with oral and transdermal administration
2. techniques for patient-controlled analgesia can be adopted for subcutaneous and intravenous opioid infusions in patients who are able and willing to be in control of rescue doses
3. when switching from oral to subcutaneous and intravenous morphine administration, the relative analgesic potency is the same for both routes and is between 3:1 and 2:1
4. although rectal opioids are effective, and this route of administration should be used only as a second choice

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC Lancet Oncol2012; 13: e58–68

Fentanyl TTS 貼片之使用

- 為一強麻醉性止痛劑，其作用與一般嗎啡類相約。
- 無法用口服嗎啡控制之疼痛，亦無法以相當轉換劑量之Fentanyl 控制。
- 副作用與morphine 類似，但較少之便秘、惡心、嘔吐
- 可以用naloxone 抵抗其作用。
- 每72小時換一次，少部份病人需48 小時換一片
- 適用於無法忍受嗎啡副作用或無法口服藥物的病人，作為強麻醉性止痛劑之第二線藥物

Fentanyl TTS 貼片之使用不適用於

- 急性疼痛，特別是當病人止痛劑量還在調整當中
- 嗎啡所需劑量不超過30 mg/24h之病人。
- 當病人使用嗎啡劑量在30-60 mg/24 hr時，可能在最低Fentanyl 貼片仍會感到頭暈惡心。
- 發燒冒汗病人

Fentanyl TTS 貼片之使用方式

- 使用短效嗎啡病人：貼上Fentanyl 貼片後繼續使用口服藥物12-24 小時
- 使用長效嗎啡病人於服用最後劑量時同時貼上
- 準備短效嗎啡作為突發痛(Breakthrough pain)，在第一次使用 Fentanyl 貼片前1-3天，突發痛頻率會增加
- 預防便秘之瀉劑應減一半量
- 以每三天增加 25 ug/hr為原則
- 貼於清潔乾燥無毛的平面，一般為軀體或外上臂，病人可作淋浴，但熱水泡澡或局部加熱會增加藥物經皮吸收。

停止Fentanyl 貼片

- 當病人疼痛變化很快或病人無法忍受副作用時
- 當貼片撕除後，藥物仍會在皮膚上繼續24小時
- 若疼痛已被穩定控制：轉換相當嗎啡劑量，撕下 Fentanyl 貼片6-8小時後開始服用長效劑型嗎啡。
- 若疼痛未被控制：轉換相當嗎啡劑量後再增加30%劑量，馬上給予第一劑短效之嗎啡量，可於貼片撕下8小時後開始使用PCA。

突發性疼痛
Breakthrough Pain

Breakthrough pain

- "**transitory exacerbations** of pain that occur on a back ground of stable pain otherwise **adequately controlled by around-the-clock** opioid therap."

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC Lancet Oncol2012; 13: e58–68

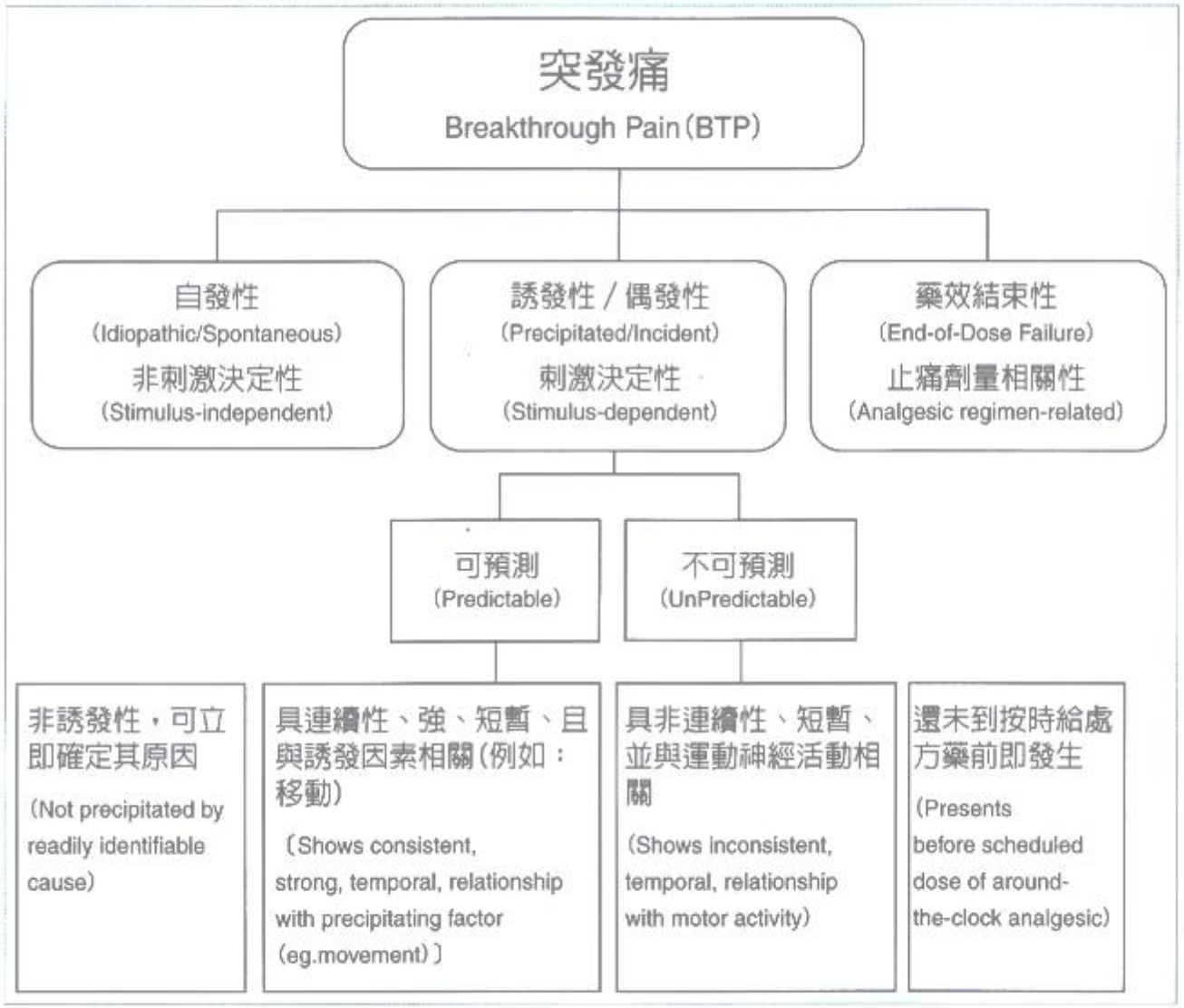


圖12-2 突發痛的分類與次型。

Incident Pain
偶發性/預期性疼痛

Pain occurring as a direct and immediate consequence of a movement or activity

疼痛直接與移動或活動有關

出現預期性疼痛Incident Pain常見狀況

- 骨轉移
- 神經性疼痛
- 腹腔內疾病: 與呼吸有關
  - » 呼吸動作
  - » 腹部器官發炎、肝出血
- 皮膚潰瘍 : 換藥/ 清瘡
- 處理硬便
- 放置導尿管

處理突發痛的理想藥物
breakthrough cancer pain (BTCP)

- It is effective (**a strong opioid**)
- It has pharmacokinetic properties that closely match the temporal characteristics of a BTCP episode, i.e. has **a rapid onset and relatively short duration 作用快但短效** of action
- It is patient-friendly, i.e. **non-invasive and simple 簡單非侵入性** to administer
- It has **minimal adverse** effects 副作用少
- It is cost-effective

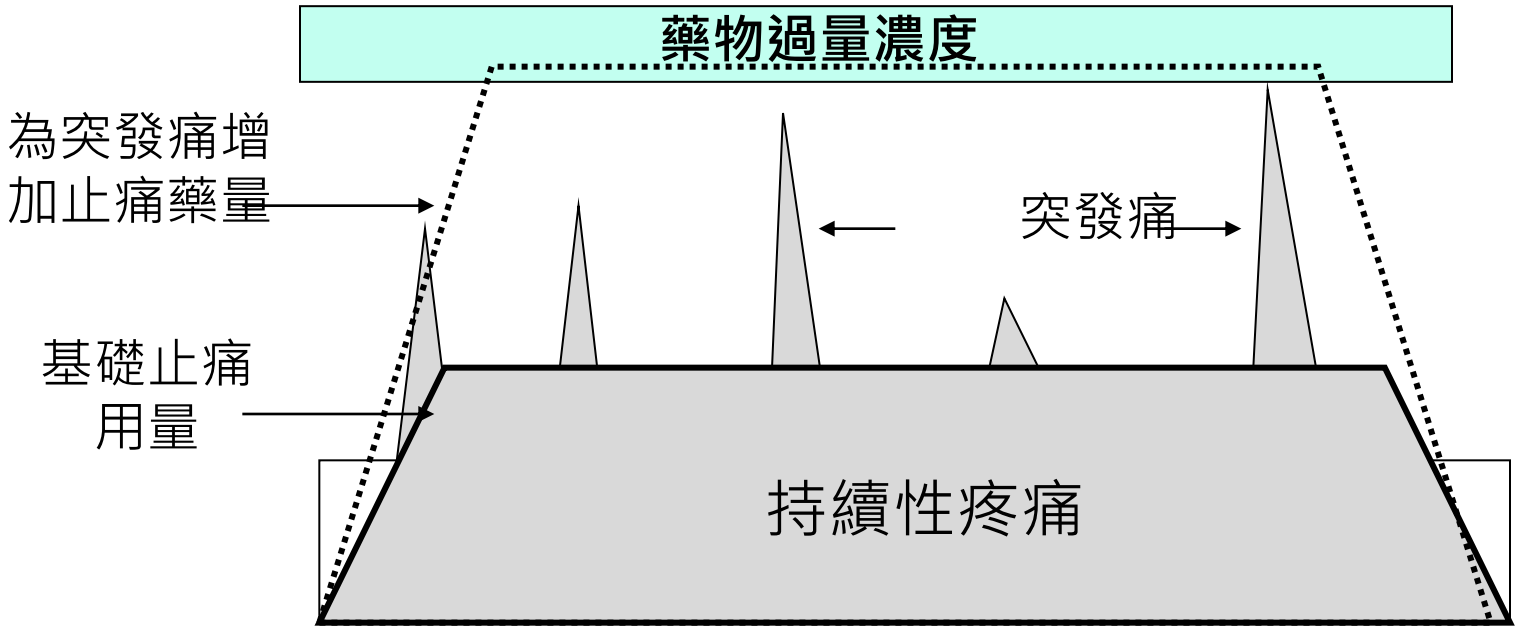
*European Oncology Nursing Society (2013a)

Breakthrough pain management

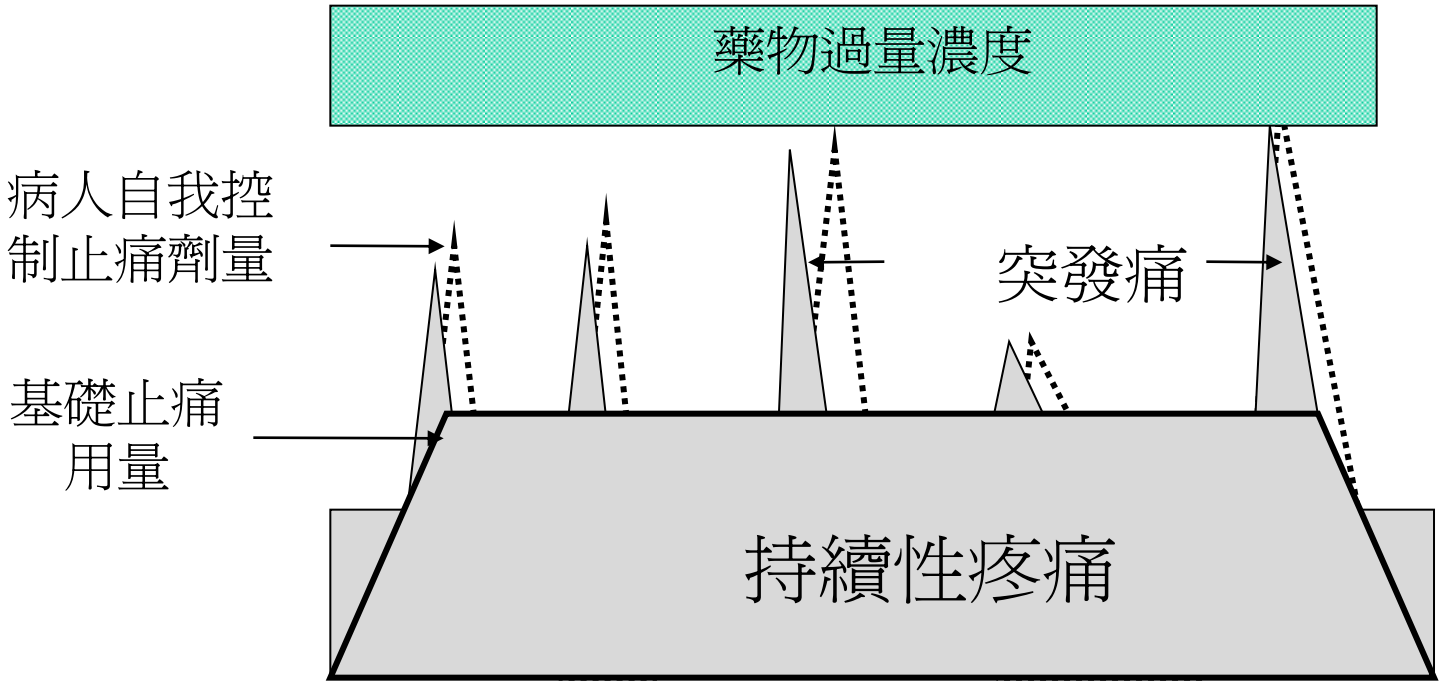
- Increase dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve pain at peak effect or at end of dose.
- Allow rescue doses of short-acting opioids of 10% to 20% of 24-h oral dose (mg) every1h as needed.
- Consider rapidly acting transmucosal fentanyl (various formulations and delivery systems are available) in opioid-tolerant patients for brief episodes of incident pain

調整固定止痛劑量以處理突發痛

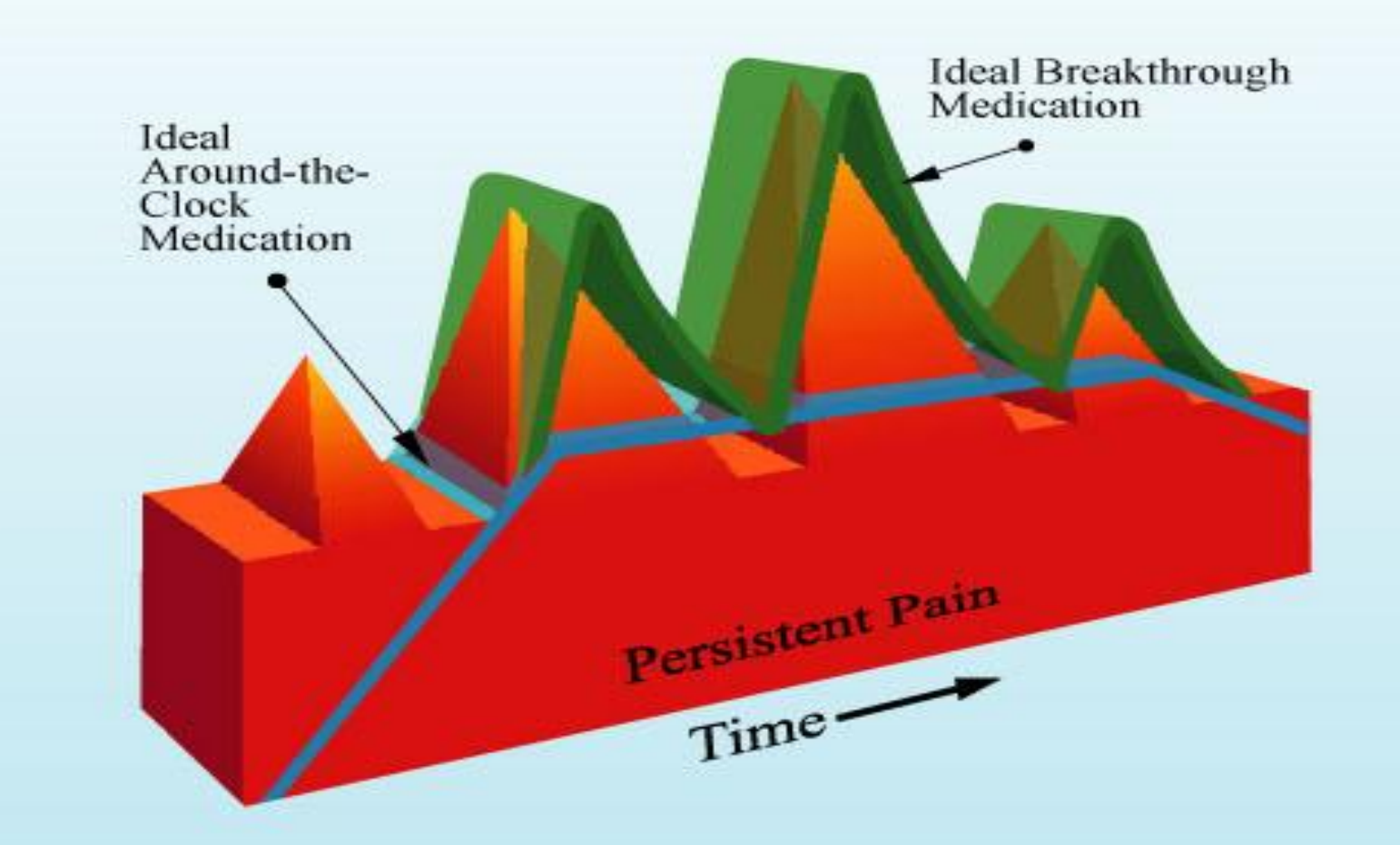
- 增加藥物過量機會-



PCA 基本概念

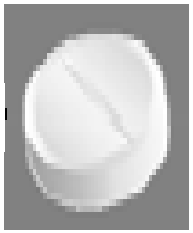


Good Pain Management Model



BTcP Therapies: Delivery Systems

1998	2006/2008	2009	2008	2009	2009
Oral trans -mucosal fentanyl citrate OTFC	FENTORA® (US)/ EFFENTORA™(EU)	ONSOLIS™ (US) FBSF	Rapinyl™/ Abstral (EU) SLF	Instanyl™ (EU) INFS	Nasalfent ® (EU) FPNS



Oral Transmucosal Lozenge	Effervescent Buccal Tablet	Fentanyl Buccal Soluble Film	Sublingual Fentanyl	Intranasal Fentanyl Spra	entayl Pectin Nasal Spray

Table I. Characteristics of opioids used for breakthrough pain

Opioid	Analgesic onset (min)	Availability (%)	Dwell time (min)
Oral morphine	30–45	30	NA
Oral oxycodone	30–45	40–50	NA
OTFC	15	50	15
FBT	15	65	15
SLF	15	70	2
INFS	5–10	70–90	NA
FPNS	5–10	70–90	NA

FBT = fentanyl buccal tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **NA** = not applicable; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl.

嗎啡類藥物的轉換

鴉片類藥物轉換
Opioid Switching

- Opioid switching is done more often when pain is not well controlled and side-effects limit dose escalation than when pain is not controlled but the side-effects are tolerable.
- Success rates of switching ranges from 40% to 80%
- Most frequent switch is from morphine, hydromorphone, or fentanyl to methadone

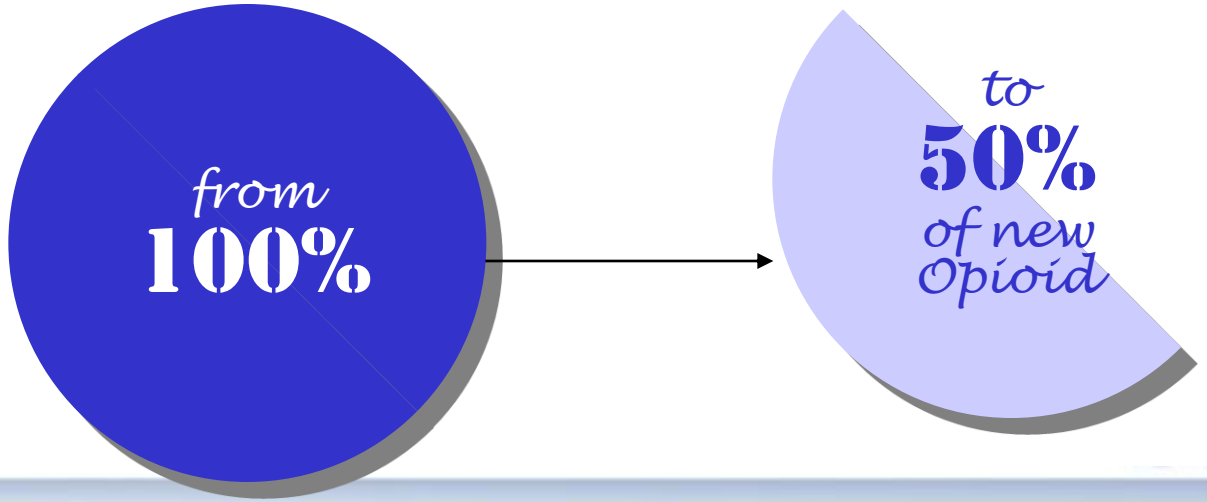
Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC Lancet Oncol2012; 13: e58–68

Guidelines for opioid substitution

- Calculate the equianalgesic dose of the new drug
  - **Decrease the dose by 25-50% to accommodate cross-tolerance**
- Adjust according to prior pain control
  - Reduce less if patient in sever pain
- Adjust according to the patient's general condition
  - Reduce more if elderly, frail, or significant organ dysfunction
- Give 50-100% of the 4 hourly dose for breakthrough pain
  - Reassess and titrate new opioid against pain and side effects

Incomplete cross-tolerance

- If a switch is being made from one opioid to another it is recommended to **start the new opioid at ~50%** of the equianalgesic dose.
- This is because the ***tolerance*** a patient has towards one opioid, may not completely transfer ("incomplete cross-tolerance") to the new opioid.



Fentanyl與Morphine 轉換量

每四小時口服嗎啡量（mg）	24小時口服嗎啡總量（mg）	Fentanyl 貼片劑量（μg/h）
5-20	30-130	25
25-35	140-220	50
40-50	230-310	75
55-65	320-400	100

轉換因子：Conversion factor ： **3.6**

24小時口服嗎啡總量(mg) / **3.6** = Fentanyl 貼片劑量(μg/h)

Relative opioid analgesic potencies

- clinical experience suggests that the second opioid should be started at a dose lower than that calculated from published equipotency ratios.

	Relative analgesic ratio	Strength of the recommendation for use
Oral morphine to oral oxycodone	1:1·5	Strong
Oral oxycodone to oral hydromorphone	1:4	Strong
Oral morphine to oral hydromorphone	1:5	Weak
Oral morphine to TD buprenorphine*	75:1	Weak
Oral morphine to TD fentanyl†	100:1	Strong

TD=transdermal. *Example: 60 mg oral morphine to 35 µg/h TD buprenorphine (equivalent to 0·8 mg per 24 h). †Example: 60 mg oral morphine to 25 µg/h TD fentanyl (equivalent to 0·6 mg per 24 h).

Table 2: **Relative analgesic ratios for opioid switching**

嗎啡的神經性副作用/併發症

Three Complications of Chronic High Dose Opioid Therapy

- Neurotoxicity
- Tolerance
- Opioid Induced Hyperalgesia

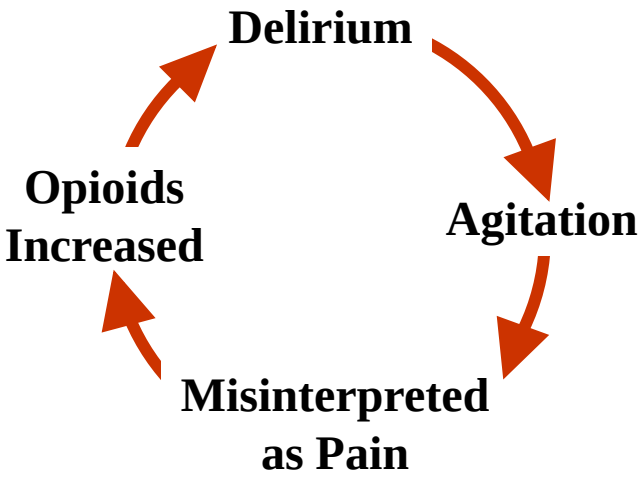
Spectrum of Opioid-Induced Neurotoxicity

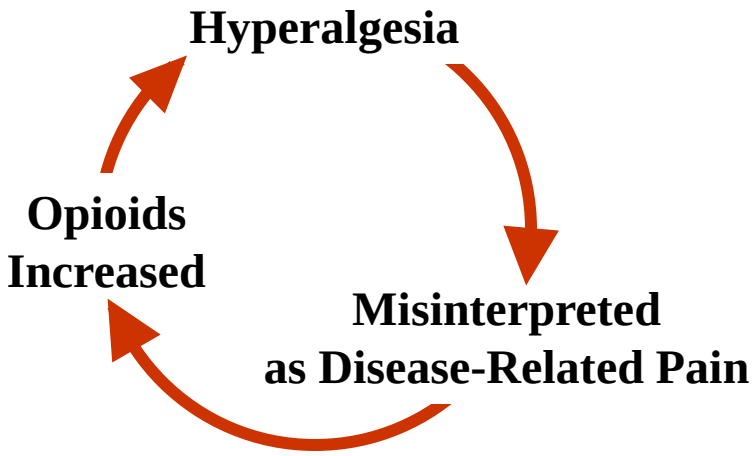
Opioid tolerance

Mild myoclonus (eg. with sleeping)

Severe myoclonus

Seizures, Death





Opioid-induced Neurotoxicity

- Dehydration, infection, or adding drugs that depress the central nervous system can tip a frail older adult into opioid toxicity.
- A patient who has been receiving a stable dose of an opioid for more than 2 weeks is unlikely to develop OIN unless precipitated by dehydration, infection, or a drug interaction.
- OIN is managed by opiod rotation, dose or frequency reduction and rehydration.
- Opioids should not be discontinued if they are needed for pain or dyspnea.

OIN: Treatment

- Switch opioid (rotation) or reduce opioid dose; usually much lower than expected doses of alternate opioid required… often use *prn* initially
- Hydration
- Benzodiazepines for neuromuscular excitation

鴉片引發的過度疼痛
Opioid induced hyperalgesia

- 長期使用鴉片類藥物增加對疼痛的敏感性 .
- 臨床上會較廣泛的疼痛 而性質不那麼明確
- 處理上為減低相關鴉片劑量或換成其他的鴉片類藥物

不建議使用的嗎啡類藥物

- Meperidine (demeral)
  - Short (2-3 hour) duration of analgesia
  - Repeated administration may lead to CNS toxicity (tremor, confusion, or seizures)
- Agonist-antagonists: pentazocine, nalbuphine
  - Risk of precipitating withdrawal in opioid-dependent patients
  - Analgesic ceiling
  - Possible production of unpleasant psychotomimetic effects (e.g., dysphoria, delusions, hallucinations)
- Partial agonist: buprenorphine
  - Analgesic ceiling
  - Precipitate withdrawal

http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional

Pain Relief

- **NSAIDs** **(1st ladder)**
  - Aspirin(300) 1# q.i.d (bone pain)
- **Codeine(30)** **(2nd ladder)**
  - 1#--3# q4h , (+50%)qhs,skip sleeping hrs
- **Morphine(10)** **(3rd ladder)**
  - 1#--__# q4h
  - (25-50%)q1h p.r.n for breakthrough pain
  - (50-100%)qhs,skip sleeping hrs
- MST Continuous(30mg),(60mg) __#--__# q8-12h

Neuropathic Pain

Damage or Alteration

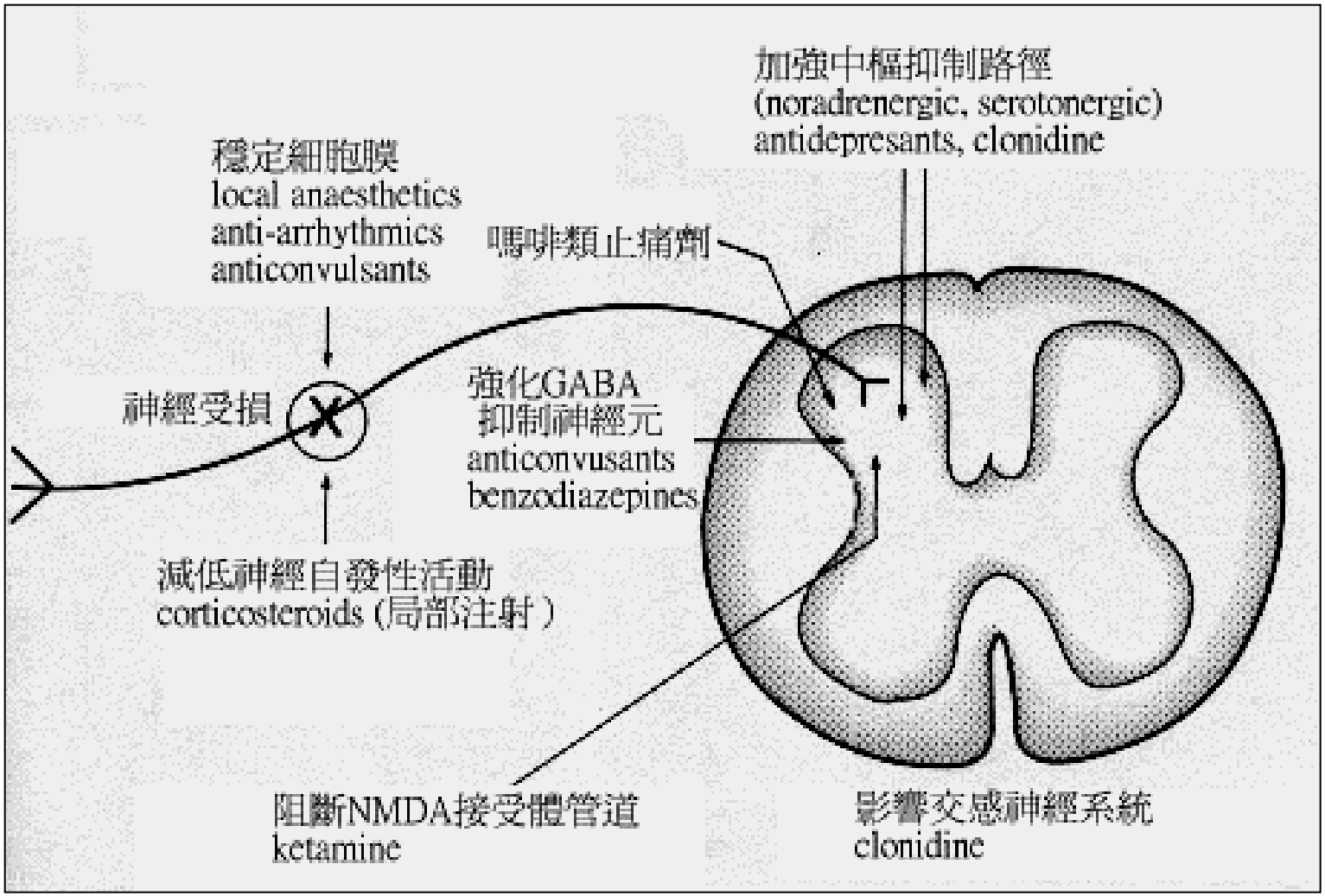
Nerve Tissue

- **Peripheral Nerve**
- **Nerve Root**
- **Spinal Cord**
- **Brain**

Neuropathic pain

- Unrelieved, persistent noxious stimuli

輔助止痛劑之作用機轉


加強中樞抑制路徑
(noradrenergic, serotonergic)
antidepresants, clonidine
穩定細胞膜
local anaesthetics
anti-arrhythmics
anticonvulsants
嗎啡類止痛劑
神經受損
強化GABA
抑制神經元
anticonvusants
benzodiazepines
減低神經自發性活動
corticosteroids (局部注射)
阻斷NMDA接受體管道
ketamine
影響交感神經系統
clonidine

癌症疼痛輔助治療

神經受損疼痛

持續性異常不適

第一線
- Tricyclic antidepressants(TCA)
- Non-tricyclic antidepressents
- Oral local anaesthetics

不易控制個案
- α 2 adrenergic agonists
- Anticonvulsants
- Topical agents
- Neuroleptics
- NMDA receptor antagonists
- Calcitonin
- Baclofen

突發性神經痛，刺痛

第一線
- Anticonvulsants
- Baclofen

不易控制個案
- Local aneaesthestics
- Tricyclic Antidepressants(TCA)
- Non-tricyclic Antidepressents
- Neuroleptics
- α 2 adrenergic agonists
- Topical agents
- NMDA receptor antagonists
- Calcitonin

癌症骨頭疼痛

- Corticosteroids
- Calcitonin
- Bisphosphonated
  - Clodronate
  - Pamidronate
- Radionuclides
  - Strontium-89
- Gallium nitrate

Guidelines on Pharmacological Treatment of Neuropathic Pain

First Line for various conditions

- TCAs (25 to 150 mg/day)
- Gabapentin (1200 to 3600 mg/day)
- Pregabalin (150 to 600 mg/day)

First Line for restricted conditions

- Lidocaine plaster (up to three plasters/day): PHN
- Duloxetine (60 to 120 mg/day): PDN
- Venlafaxine (150 to 225 mg/day): PD
- Capsaicin 8% patch: PHN, HIV neuropathies
- Cannabinoids: MS
- Pregabalin SCI

First Line for neuropathic cancer pain

- Gabapentin
- Tramadol, TCAs level B of evidence

Combination therapy

- Gabapentin & TCAs
- Gabapentin & opioids

Second Line

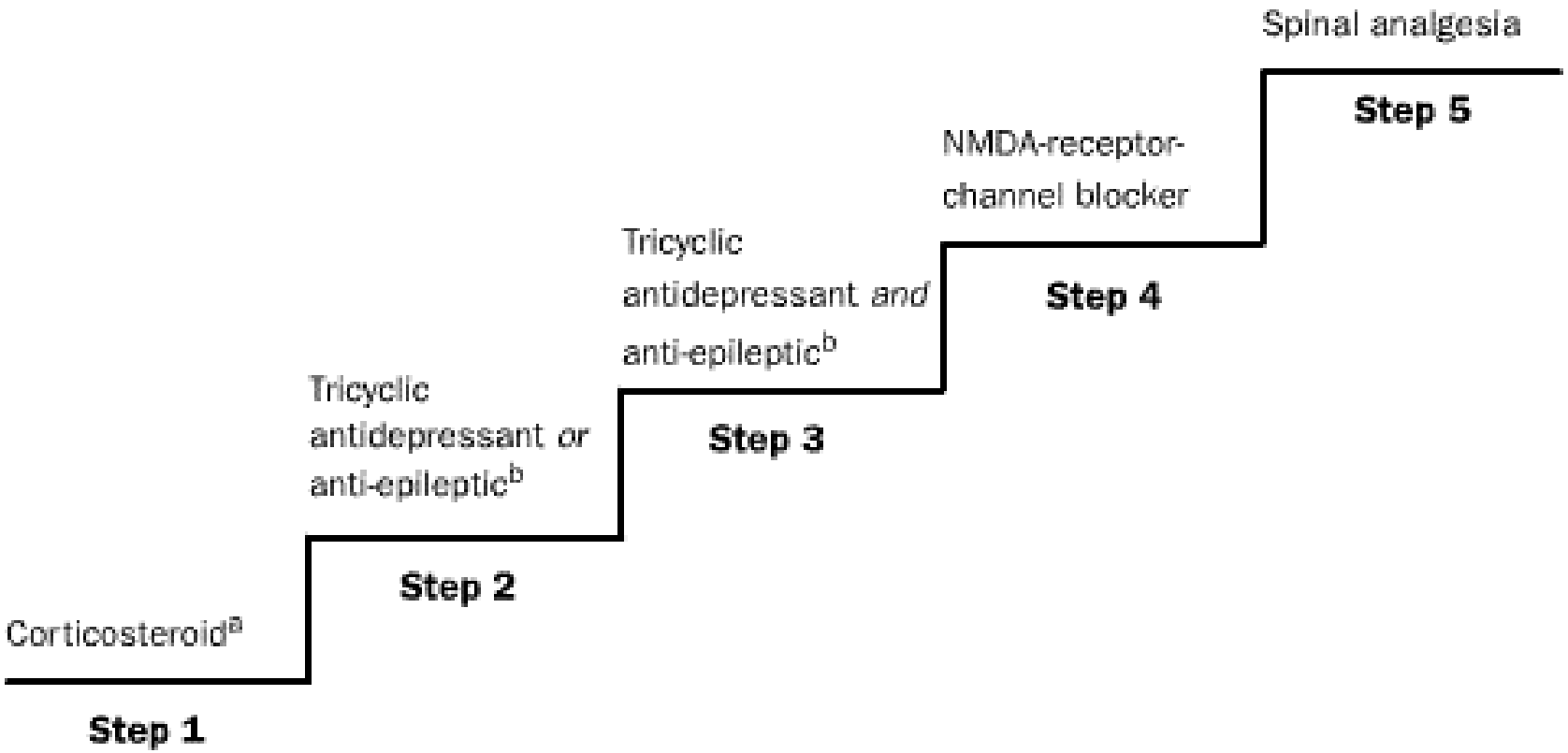
- Tramadol (200 to 400 mg/day)

Second or Third Line

- Opioids

Pain Practice, Volume 12, Issue 3, 2012 219–251

Figure 5.5 Adjuvant analgesics for neuropathic pain. If caused by cancer, use only if the pain does not respond to the combined use of a NSAID and a strong opioid



a. important when neuropathic pain is associated with limb weakness

b. some centres use mexiletine, a local anaesthetic congener and cardiac anti-arrhythmic drug which blocks sodium channels, as an alternative to an anti-epileptic.[13,14]

Ketamine

作用:

- 最強NMDA –receptor-channel blocker
- 同時亦作用於 calcium / sodium channels, cholinergic transmission, noradrenergic /serotoninergic reuptake inhibition, mu,delta and kappa 類嗎啡效果
- 於憂鬱病人有抗憂鬱的效果

Ketamine 適應狀況

- 無法解除的癌症疼痛
  - 雖經轉換其他嗎啡morphine rotation 作最大的滴定titration
  - 嗎啡的副作用無法忍受
  - 無法口服其他治療神經性疼痛的藥物
  - 出現嗎啡引發過度疼痛 opioid-related hyperalgesia
  - 產生嗎啡的耐受性
- 缺血性疼痛ischemic 、炎性疼痛inflammatory
- 嚴重神經性疼痛對一般治療無效
- 換藥時疼痛對一般治療無效

口服及注射局部麻醉劑

- Xylocaine皮下或靜脈注射，(Mexiletine 口服 ?)
- 壓抑脊髓後角神經元之活性有關，減低神經活性以降低痛的傳遞
- 低劑量時會出現頭暈、咀巴週圍發麻、抖動等症狀
- 高劑量時會造成腦病變 ，心臟傳導障礙及心肌壓抑，心臟衰竭
- Mexiletine 常有噁心嘔吐、抖動、頭暈及痲木，藥物可與食物共同服用，以減輕噁心嘔吐副作用。口服劑量為 150 mg qd-tid
- 對急性神經痛而嗎啡類藥物無效時，2% Xylocaine 200mg IV infusion >60 min (2-5 mg/kg)，其效果可延續數日至數週

局部止痛劑

- 可用於週邊神經及皮膚引發之神經痛
- 常見產品包括capsaicin, 非類固醇消炎類藥物(NSAID)，局部麻醉劑。
- Capsaicin 可減少周邊輸入神經元之substance P濃度，使用時會有局部燒灼感，濃度為0.025% 及0.075%，每日塗抹3-4次，最少連續四週。
- 局部麻醉劑如EMLA(prilocaine / lignocaine 1:1混合)，可試用於慢性神經性疼痛。
- NSAID藥膏製劑用於慢性神經痛效果並未確定。

局部使用嗎啡

- 直接作用於疼痛部位，同時可減輕血中的嗎啡濃度，以減少不必要的副作用。
- 在受傷的組織，痛感透過各種介質(histamine，bradykinin，prostaglandins)，經由週邊神經末端(free nerve ending)傳送到脊髓神經到中樞，嗎啡接受體存在於各種週邊神經末端，平時並不明顯，但在受傷或發炎時則會增加

The Marie Curie
Palliative Care Institute
LIVERPOOL

Liverpool Care Pathway for the Dying Patient (LCP)

National LCP Renal Steering Group

Guidelines for LCP Drug Prescribing in Advanced Chronic Kidney Disease *(estimated glomerular filtration rate < 30 ml/min)*

June 2008

ENDORSED BY:

DH Department of Health

The Renal Association
founded 1950

BRITISH RENAL SOCIETY
MULTI-PROFESSIONAL TEAM

慢性腎衰竭
疼痛

病人是否已使
用嗎啡?

是

否

原劑量代換成
Fentanyl s/c

Fentanyl 25
ug s/c prn

超過 3 次 prn /24 hr

Fentanyl 100-250 ug/24hr
syringe driver
Prn dose: 1/8 24hr 總量

Hydromorphone 的代謝

- 不經CYP450酵素代謝
- 蛋白質結合率低(<30%)
- 代謝物中不會產生具活性的6-glucuronide，不會在腎臟堆積，減少呼吸抑制風險

神給我們的天賦

接受我們不能改變的事實、

有勇氣去改變我們能改變的事情、

有智慧去分辨這兩者的差異。

God grant me the serenity

To accept the things I cannot change,

The courage to change the things I can,

And the wisdom to know the difference.

Reinhold Niebuhr