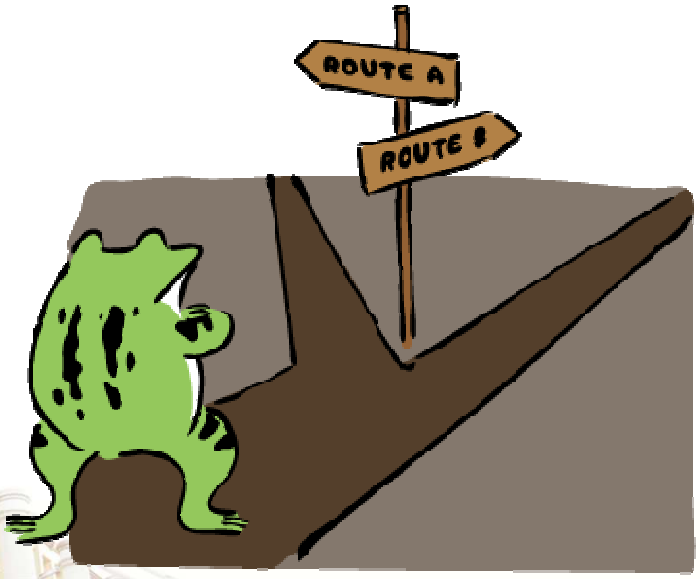
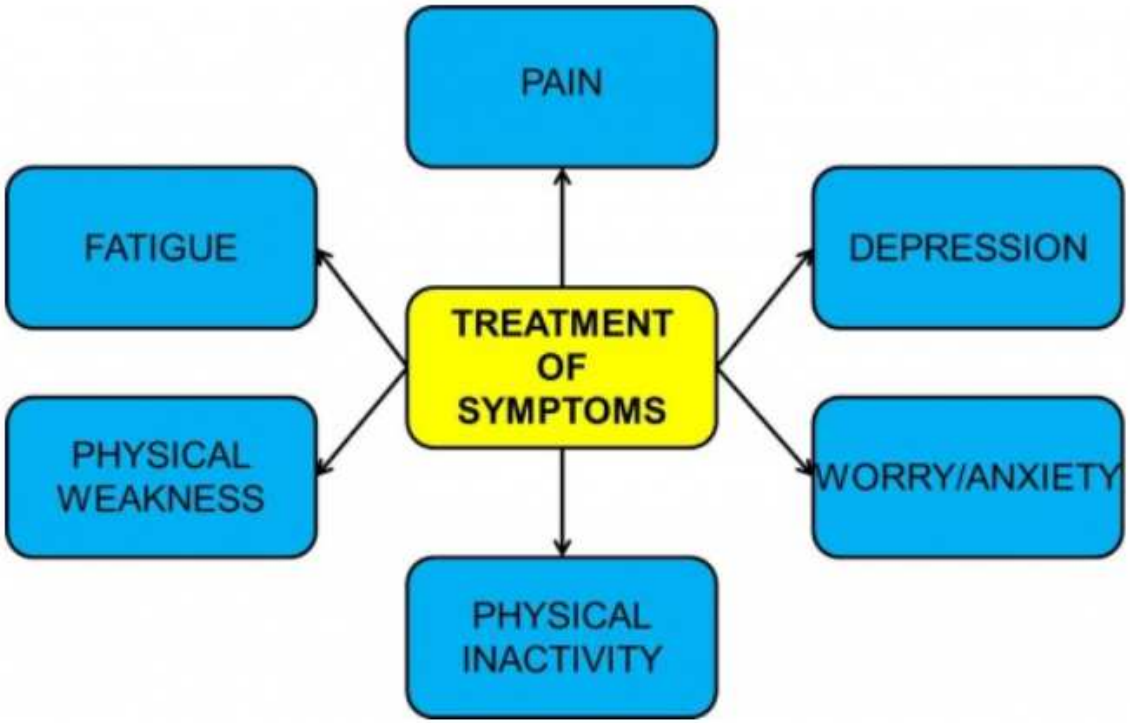
Overview of Cancer pain management



報告人：台中榮總麻醉部醫師 楊士杰

臺中榮民總醫院
Taichung Veterans General Hospital

Pain and symptom management are the cornerstone of palliative care



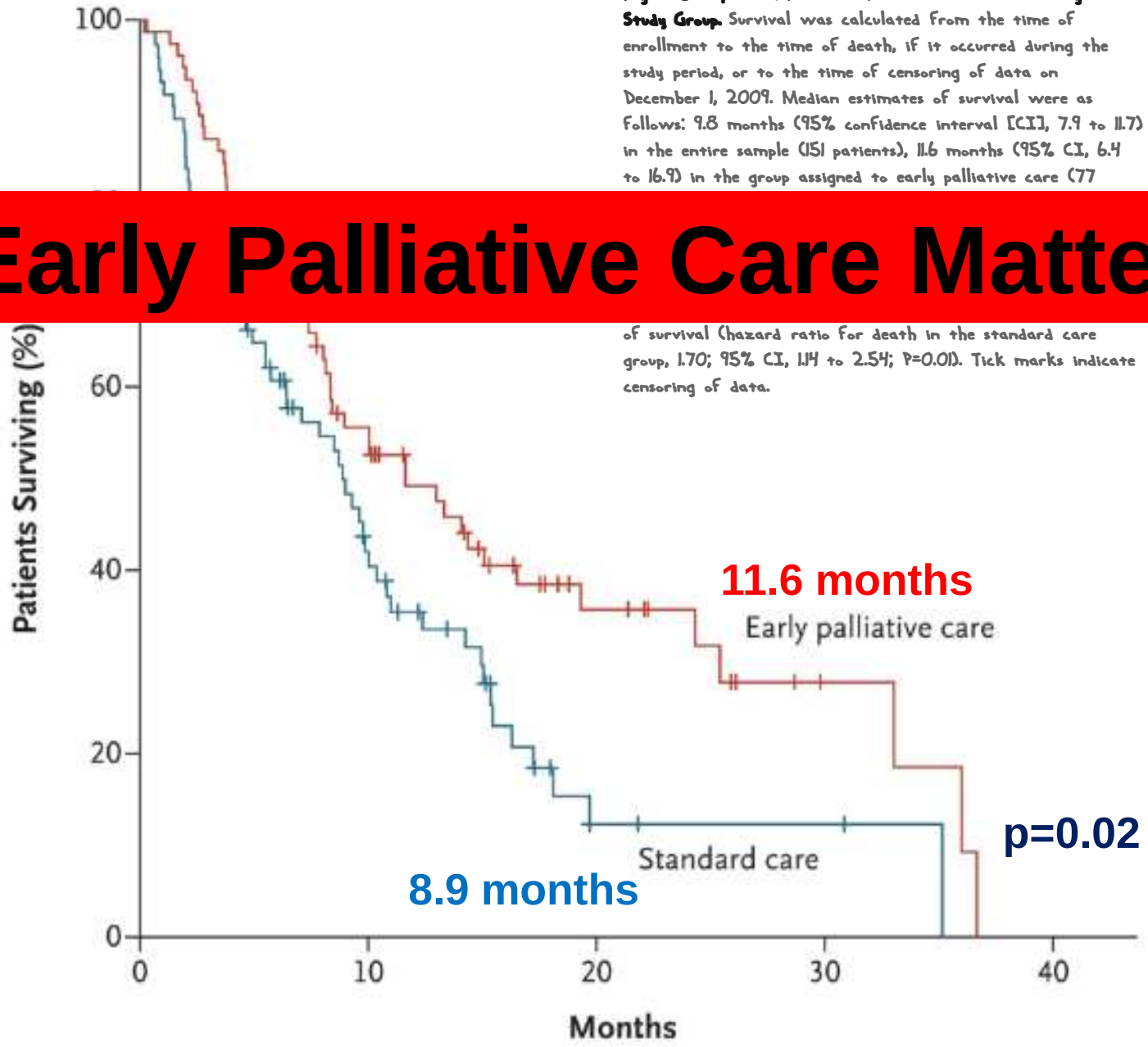
Common symptoms experienced by palliative care patients and physiotherapy treatment of these symptoms.

https://www.physio-pedia.com/Promoting_the_role_of_Physiotherapy_in_Palliative_care:_Information_for_allied_health_professionals

Early Palliative Care Matters

Figure 3. Kaplan–Meier Estimates of Survival According to Study Group. Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2009. Median estimates of survival were as follows: 9.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77

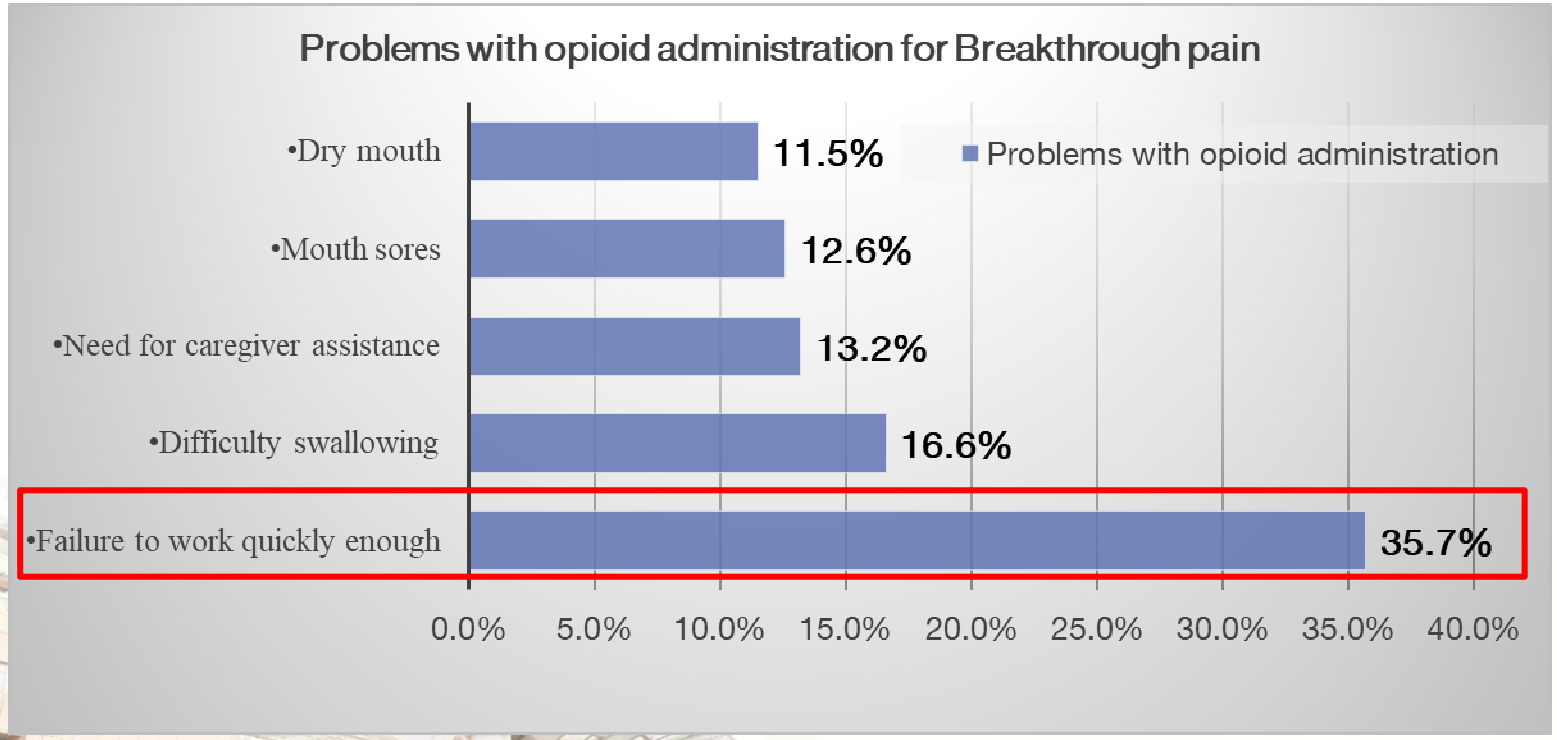
of survival (hazard ratio for death in the standard care group, 1.70; 95% CI, 1.14 to 2.54; P=0.01). Tick marks indicate censoring of data.



N Engl J Med 2010; 363:733-742

Canada Oncology nurses' perspectives on the management of BTcP

72.2%病患**不滿意**其現有之突發痛治療



A Canadian online survey of oncology nurses' perspectives on the management of breakthrough pain in cancer (BTPc) *Can Oncol Nurs J. 2013 Winter;23(1):28-43.*

- **Methods**
  - 686 patients from 2018/1/1 to 2018/12/31 in our hospital
    - Except ICU, neonatology, pediatric intensive care, emergency room, and psychiatry
  - Pain assessments
    - Questionnaires by additional assessors
    - Electronic records by nursing staff

疼痛易被低估

- **Results**
  - Underestimated (PEN < PEP)
    - 539 patients (78.6%)
  - Matched (PEN = PEP)
    - 126 patients (18.3%)
  - Overestimated (PEN > PES)
    - 21 patients (3.1%)
  - Risk factors
    - Surgical interventions, long-lasting pain over 24 hours
  - No significant differences
    - Gender, receiving anesthesia, type of anesthesia, patient-controlled analgesia

		PEN				
		No pain	Mild pain	Moderate pain	Severe pain	Total
PEP	No pain	26	20	0	0	46
	Mild pain	62	95	1	0	158
	Moderate pain	75	111	4	0	190
	Severe pain	64	222	5	1	292
Total		227	448	10	1	686

PEN (pain intensity evaluated by nurse), PEP (pain intensity evaluated by patient)

Outline

- Cancer and Cancer Pain
- Evaluation of cancer pain
- Management of cancer pain by WHO analgesic ladder and NCCN guideline

Sources of Cancer Pain

- Multi-factorial

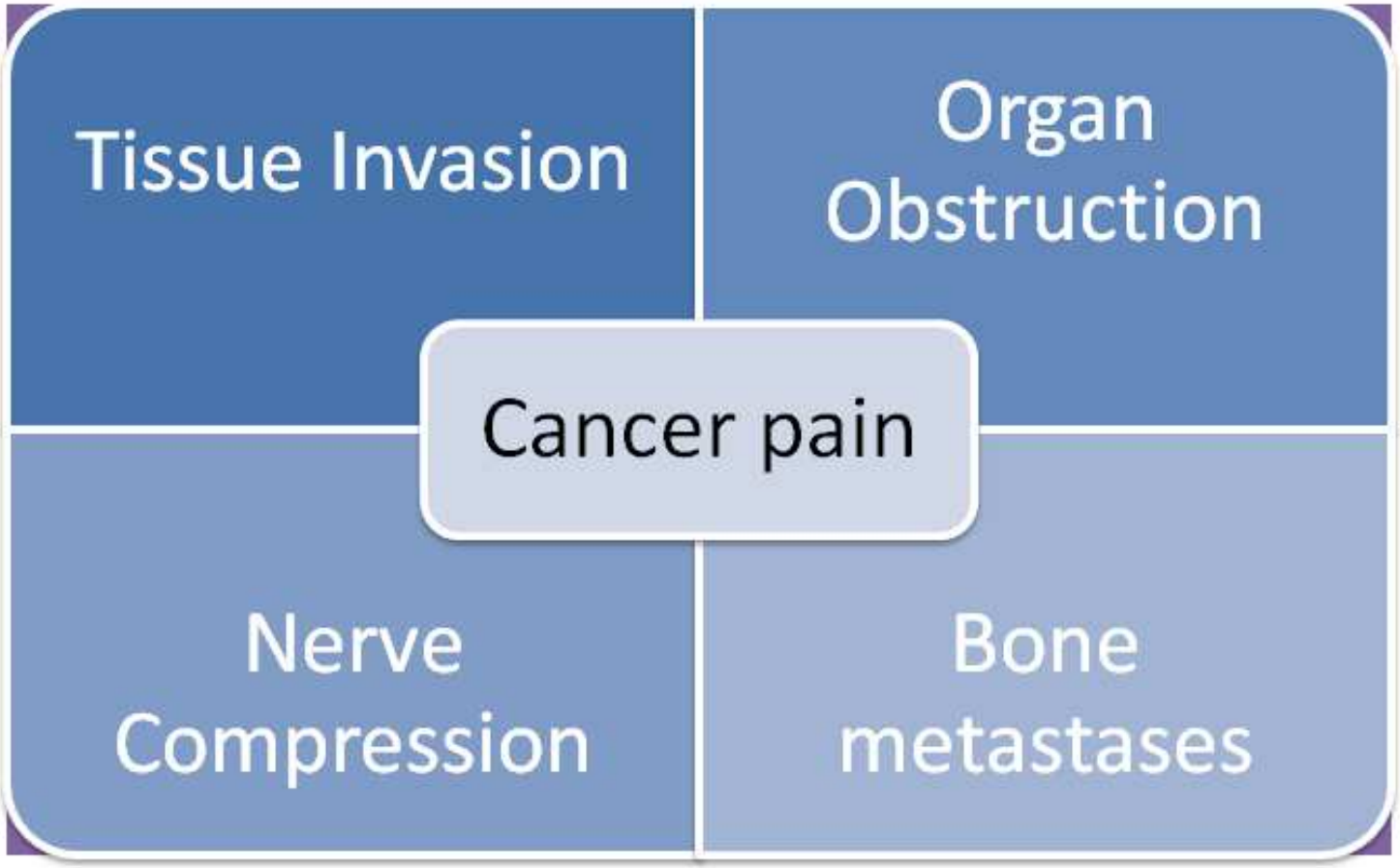


TABLE 5. Chronic Pain Syndromes Related to Cancer Treatment

Surgical pain syndromes	
• Postamputation phantom pain	• Postmastectomy pain
• Post-thoracotomy pain	
Radiation-related pain syndromes	
• Chest pain/tightness	• Osteoradionecrosis
• Cystitis	• Pelvic fractures
• Enteritis	• Peripheral nerve entrapment
• Fistula formation	• Plexopathies
• Myelopathy	• Proctitis
• Osteoporosis	• Secondary malignancies
Stem cell transplantation-mediated chronic graft-versus-host disease	
• Scleroderma-like skin changes	• Dyspareunia, vaginal pain
• Eye pain and dryness	• Paresthesias
• Oral pain and reduced jaw motion	• Arthralgias, myalgias
• Dysuria	
Chemotherapy-related pain syndromes	
• Chemotherapy-induced peripheral neuropathy	• Osteonecrosis from corticosteroids
Hormonal therapy-related pain syndromes	
• Osteoporotic compression fractures	• Arthralgias

TABLE 5. Chronic Pain Syndromes Related to Cancer Treatment

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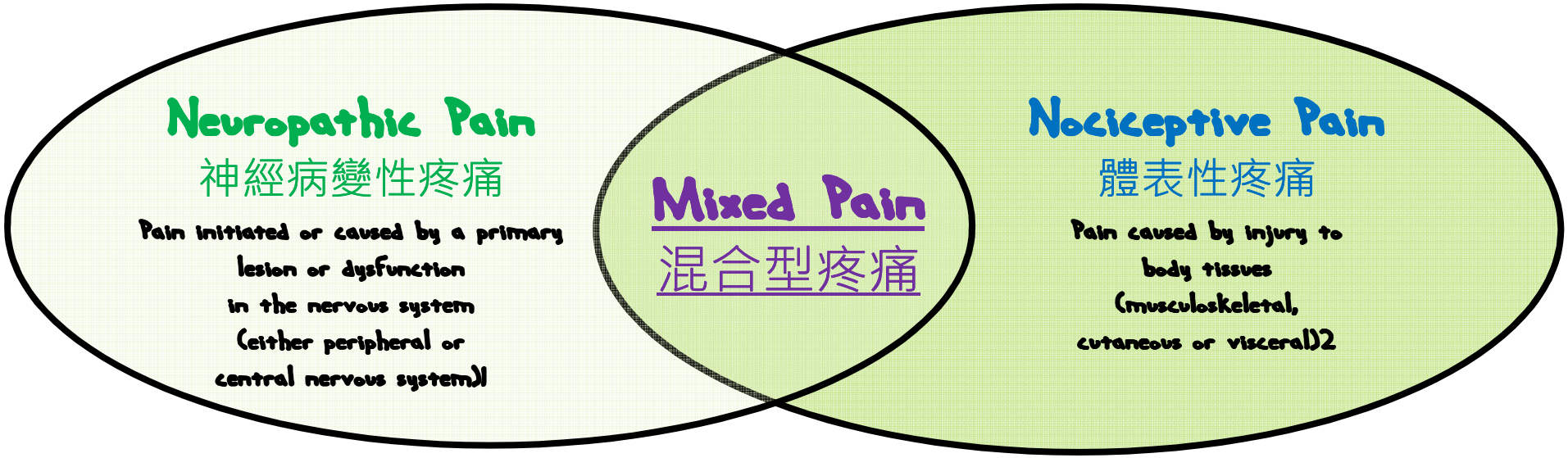
Hormonal therapy-related pain syndromes	
• Osteoporotic compression fractures	• Arthralgias

Cancer pain

不只來自 cancer

也來自 treatment



Examples

Peripheral

- Postherpetic neuralgia
- Trigeminal neuralgia
- Diabetic peripheral neuropathy
- Postsurgical neuropathy
- Posttraumatic neuropathy

Central

- Poststroke pain

Common descriptors[2]

- Burning
- Tingling
- Hypersensitivity to touch or cold

Examples

- Low back pain with radiculopathy
- Cervical radiculopathy
- **Cancer pain (~70%)**
- Carpal tunnel syndrome

Examples

- Pain due to inflammation
- Limb pain after a fracture
- Joint pain in osteoarthritis
- Postoperative visceral pain

Common descriptors[2]

- Aching
- Sharp
- Throbbing

1. International Association For the Study of Pain. IASP Pain Terminology.
2. Raja et al. in Wall PD, Melzack R (Eds). Textbook of pain. 4th Ed. 1999:11-57.

Outline

- Cancer and Cancer Pain
- **Evaluation of cancer pain**
- Management of cancer pain by WHO analgesic ladder and NCCN guideline

疼痛分類

感覺接受性疼痛

神經性疼痛

類型	體感性疼痛 (Somatic pain)	內臟性疼痛 (Visceral pain)	神經病變性疼痛 (Neuropathic pain)
原因	體表、骨骼、肌肉受損;骨轉移	臟器受損、阻塞;平滑肌痙攣	神經組織受損
疼痛性質	刀刺痛、銳痛、搏動性痛	悶痛、絞痛、不明體表疼痛	灼痛、刺痛、電擊痛
特點			
治療			

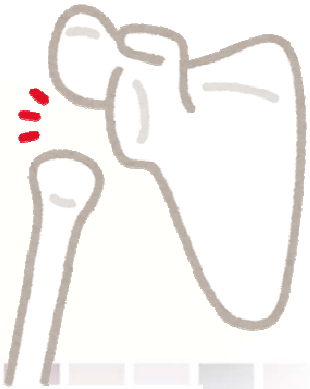
Somatic pain

感覺接受性疼痛 體表痛/體性痛/體腔痛

- 體表、肌肉和骨骼受損
  - 酸痛、抽痛、刺痛、銳痛、壓痛
  - 持續的疼痛
  - 固定疼痛部位

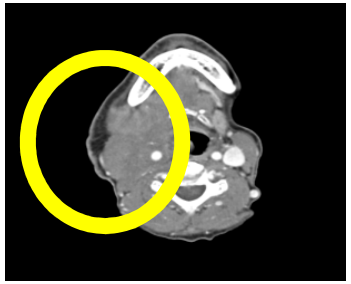
- 常見原因
  - 骨轉移，手術疼痛，關節痛…

- No refer pain, no radiation pain



體腔痛/體表疼痛

(2) 以腫瘤侵犯部位及其治療分類	
A. 體感性疼痛	
與腫瘤侵犯骨骼引起之疼痛症候群相關	骨骼疼痛：多處病灶或瀰漫性疼痛 (局部轉移或骨骼擴散) ・顱部轉移： ・眼眶症候群 (orbital syndrome) ・副蝶鞍症候群 (parasellar syndrome) ・顱內窩小孔症候群 (middle cranial fossa syndrome) ・頸靜脈孔症候群 (jugular foramen syndrome) ・枕骨髁症候群 (condyle syndrome) ・枕骨斜坡症候群 (clivus syndrome) ・蝶竇 (sphenoid sinus) 轉移 ・脊椎症候群： ・硬腦膜外或馬尾神經壓迫 (cauda equina compression)
與腫瘤侵犯骨骼引起之疼痛症候群相關	・寰椎或樞椎破壞與齒狀骨折 (atlanto-axial destruction and odontoid fracture) ・第 7 頸椎至第 1 胸椎症候群 ・第 12 胸椎至第 1 腰椎症候群 ・薦骨症候群 ・骨盆及髖關節症候群 ・長骨 (long bone) 轉移或腫瘤侵犯
與治療相關	骨壞死：放射線或皮質類固醇引起之骨骼壞死



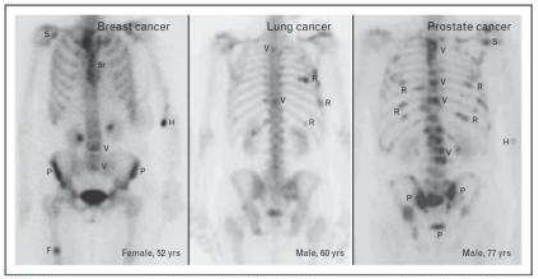


FIGURE 1. Common cancers metastasize to multiple skeletal sites during disease progression. Technetium-99 bone-scan of male and female patients with active breast, lung, and prostate cancer metastases to multiple skeletal sites. Bone metastasis sites include vertebrae (V), scapula (S), humerus (H), pelvis (P), femur (F), sternum (St), and ribs (R).

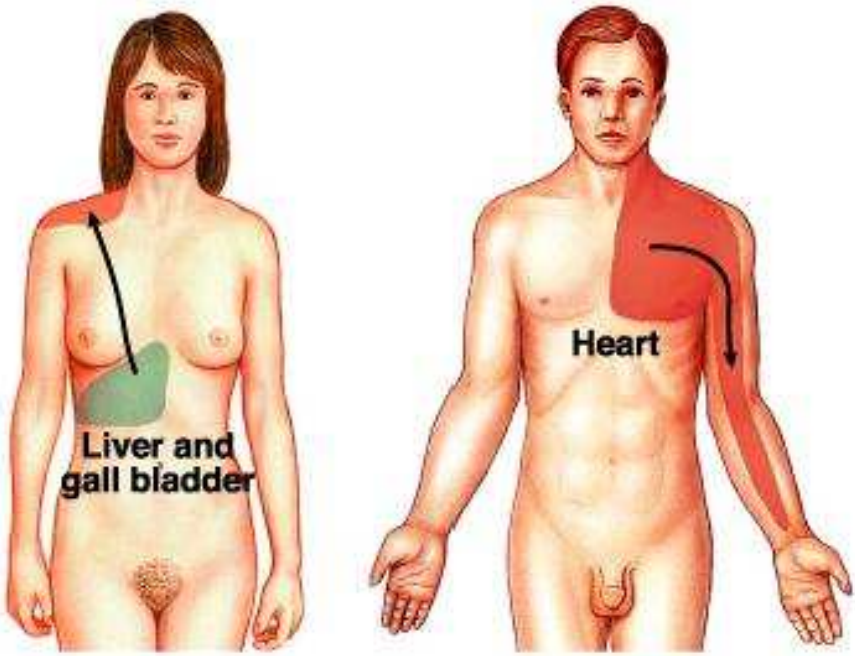
Mantyh PW. Curr Opin Support Palliat Care. 2014 ;8(2):83-90.

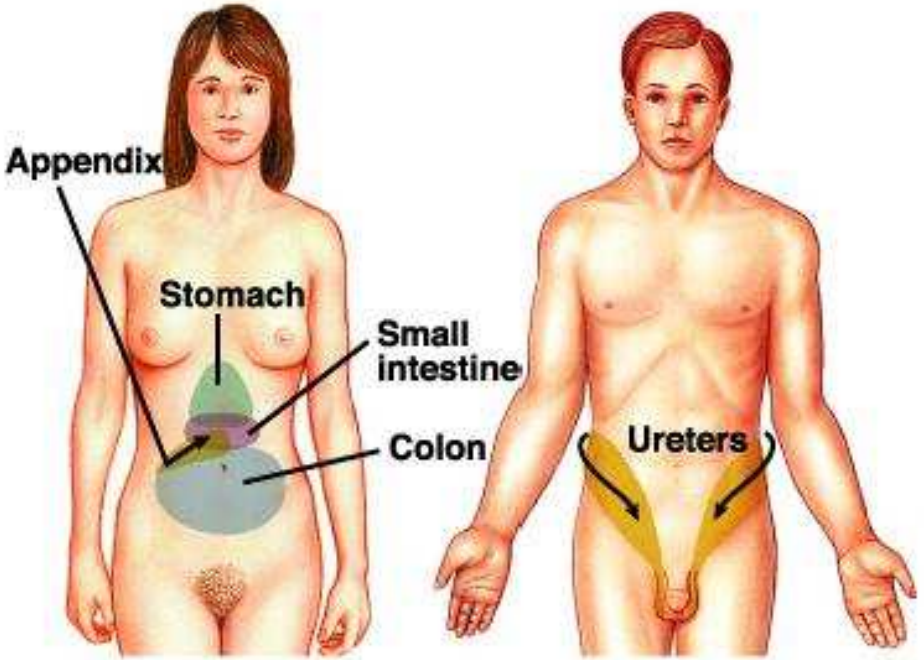
Visceral pain

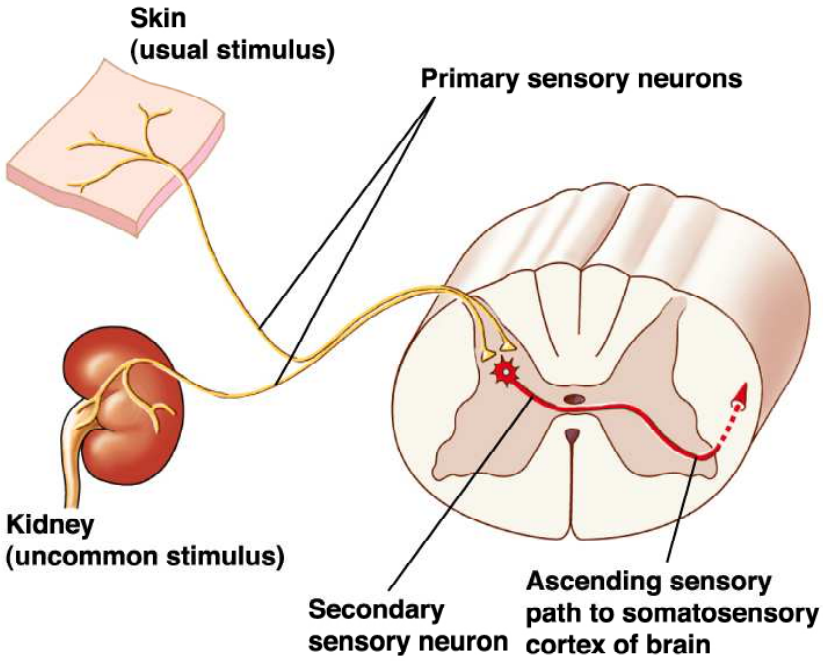
感覺接受性疼痛 臟器痛/內臟痛

- 臟器直接刺激輸入神經 afferent nerve
  - 悶痛、絞痛、脹痛和隱隱作痛
    - 來自中空的器官阻塞,表現為間歇性的鈍痛或絞痛
    - 來自實質器官的包膜或腸繫膜,表現為銳痛或脹痛

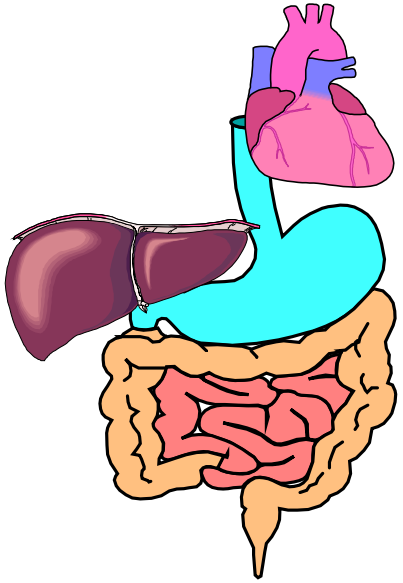
- 疼痛部位
  - 糢糊 (widespread, vague pain)
    - 常有轉移痛 (referred pain)







臟器痛/內臟痛



B. 內臟性疼痛	
與腫瘤相關	肝腫脹症候群 (hepatic distension syndrome) 上腹膜後腔症候群 (rostral retroperitoneal syndrome) 慢性腸阻塞及腹膜轉移 慢性輸尿管阻塞 惡性骨盆及會陰疼痛 其他實質器官受腫瘤直接侵犯
與治療相關	慢性腹部疼痛 ・因腹腔內化學療法　・因放射線治療 放射線治療引起之慢性骨盆腔疼痛

Neuropathic pain
神經病變性痛

- 神經受損或長期壓迫造成的劇烈疼痛
  - 尖銳痛、燒灼痛、刺痛、感覺異常(敏感、麻木)、電到的痛感
- 常見原因
  - 腫瘤浸潤或侵犯神經叢、帶狀庖疹感染、手術傷害神經、三叉神經痛、糖尿病病變神經痛…
- 對傳統止痛藥的反應不佳，部份抗憂鬱劑 (antidepressants) 或抗痙攣藥 (anticonvulsants)可能有用
-

C. 神經病變性疼痛	
與腫瘤直接侵犯或壓迫相關	腦神經病變 (cranial neuropathy) 脊神經根病變 (spinal neuropathy) 周邊神經病變 (peripheral neuropathy) 神經叢病變 ・頸部神經叢　・臂神經叢 ・腰薦神經叢　・薦部神經叢 硬腦膜外壓迫
與治療相關	手術後神經病變 ・乳房切除術後　・胸廓切開術後 ・頸部清除術後　・腎臟切除術後 ・截肢後幻肢痛或疼痛 放射線治療後 ・頸部、臂神經、或腰薦神經叢之放射線治療神經病變 ・放射線引起之脊髓病變 化學療法後 ・多發性神經病變

神經病變性疼痛

History + NOPQRST

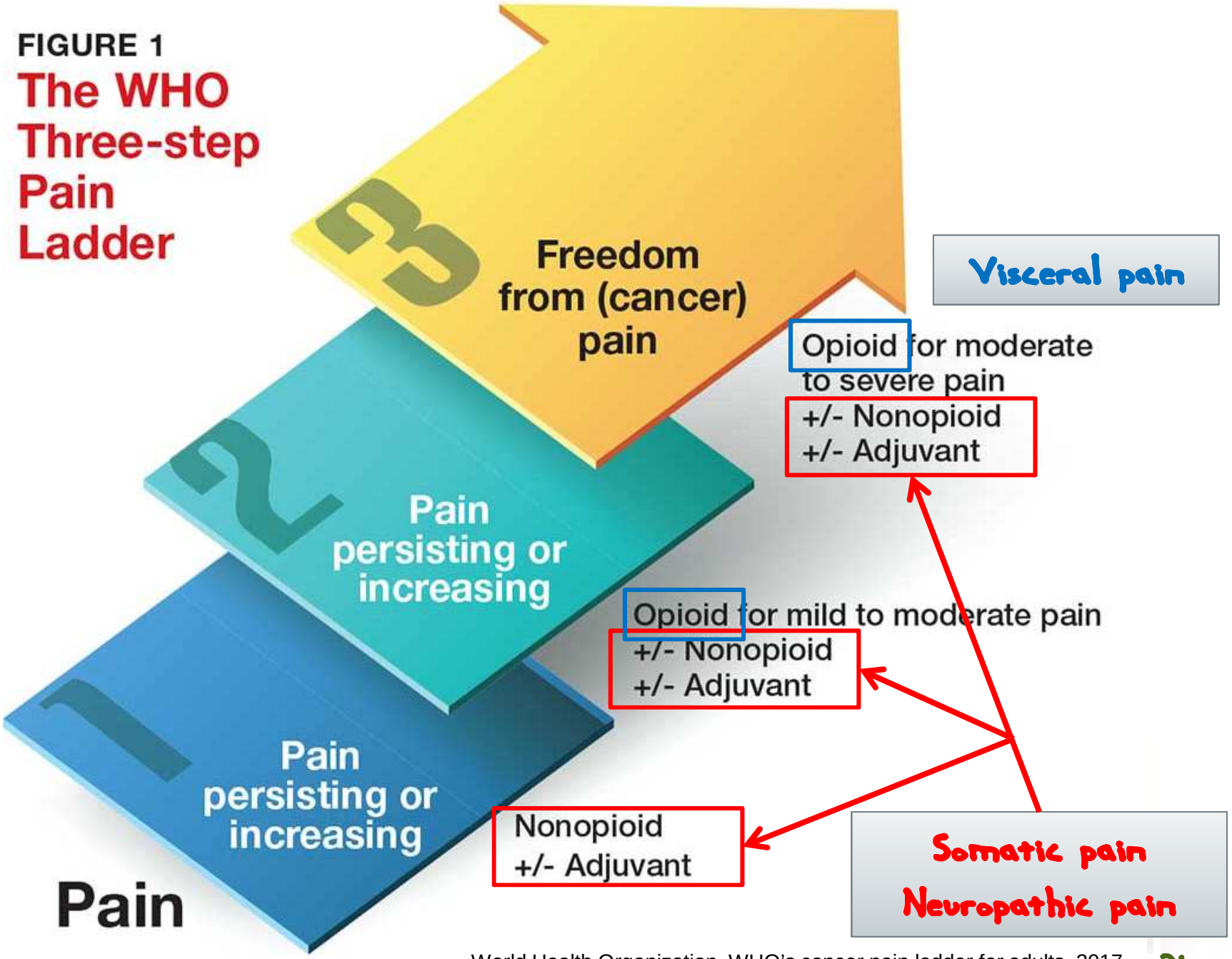
- Numbers 那幾個地方會痛
- Origins of the pain 可疑的根源
- Provocative or palliating factors 緩解/加劇疼痛的原因
- Quality of pain 什麼樣子的痛，怎麼痛
- Radiation or not 痛會跑來跑去或是侷限
- Severity of pain 疼痛有多嚴重
- Timing 疼痛的時間有多久、什麼時間比較會痛、多久會發作一次

Outline

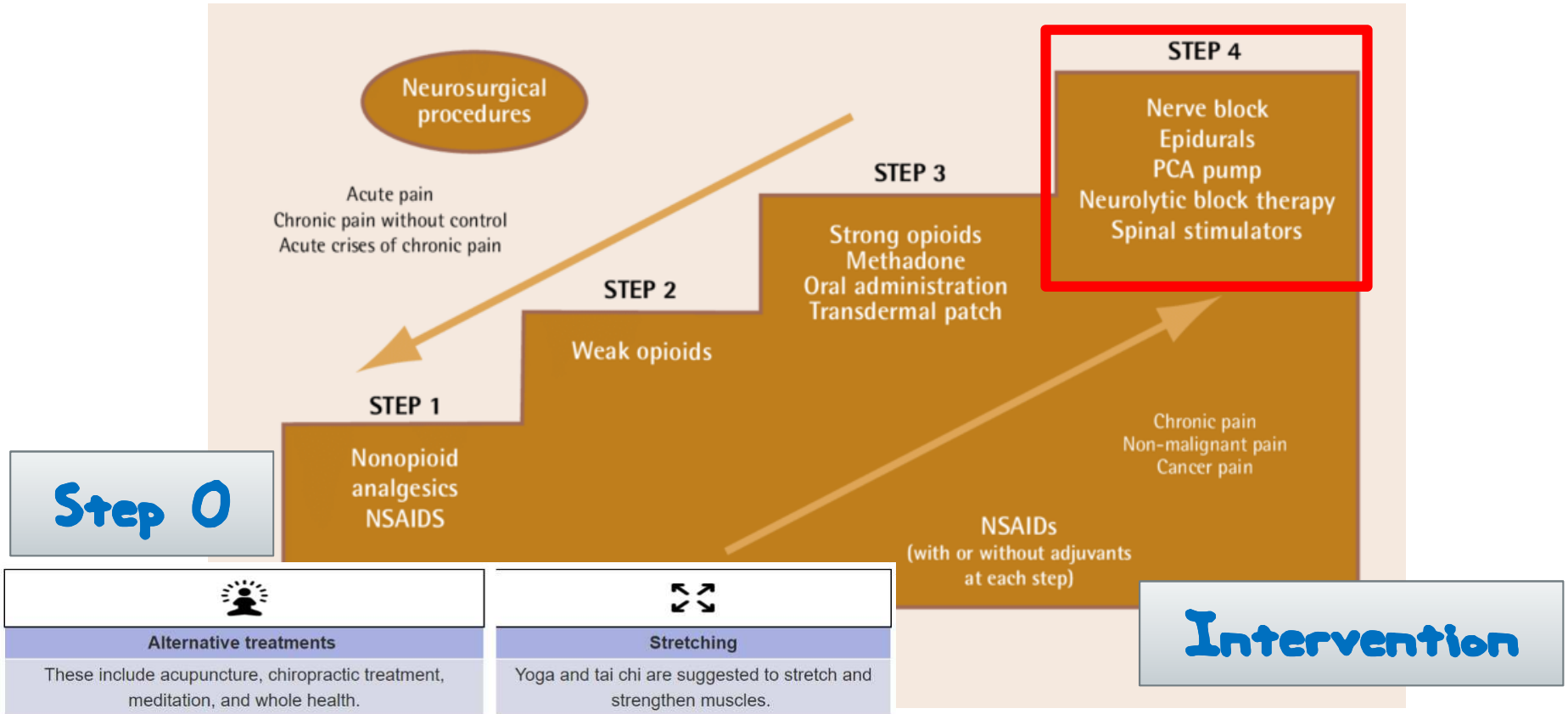
- Cancer and Cancer Pain
- Evaluation of cancer pain
- Management of cancer pain by WHO analgesic ladder and NCCN guideline

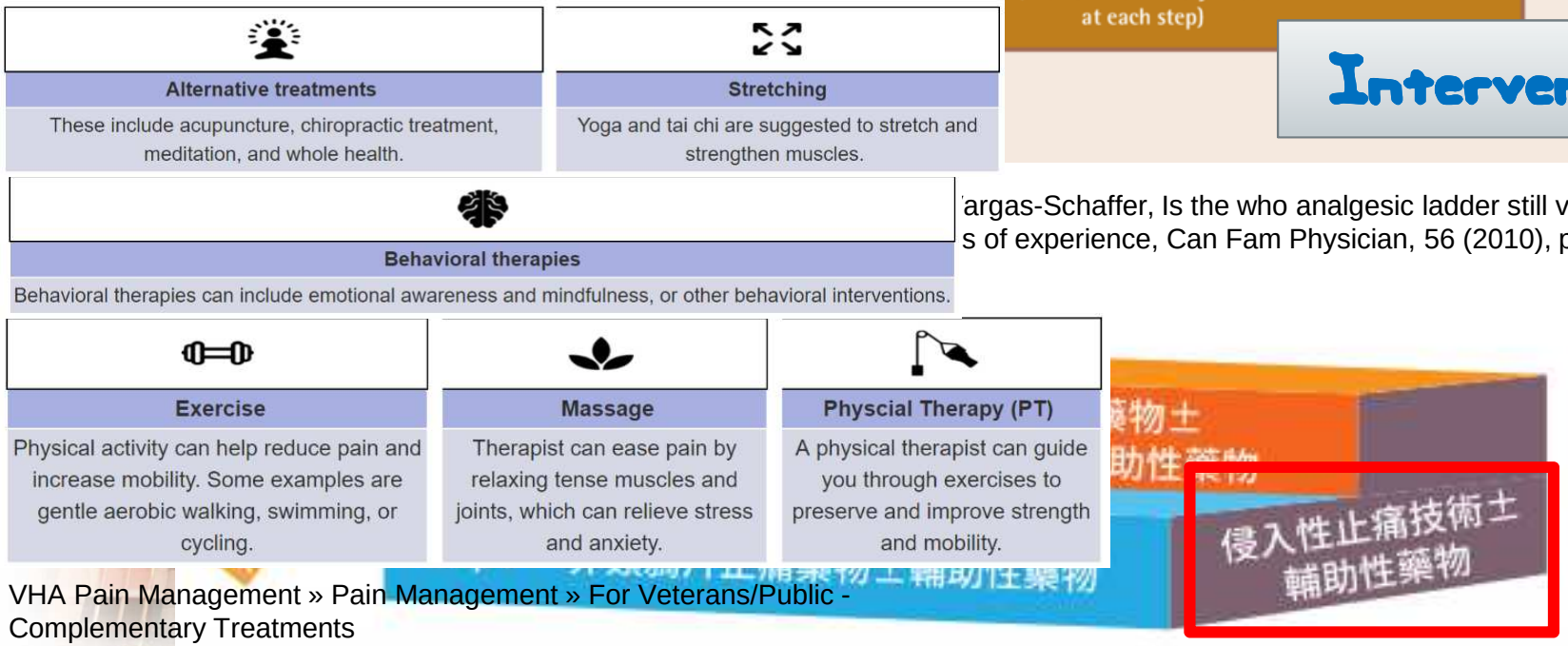
FIGURE 1

The WHO Three-step Pain Ladder



World Health Organization. WHO's cancer pain ladder for adults. 2017. www.who.int/cancer/palliative/painladder/en/. Accessed March 21, 2018.

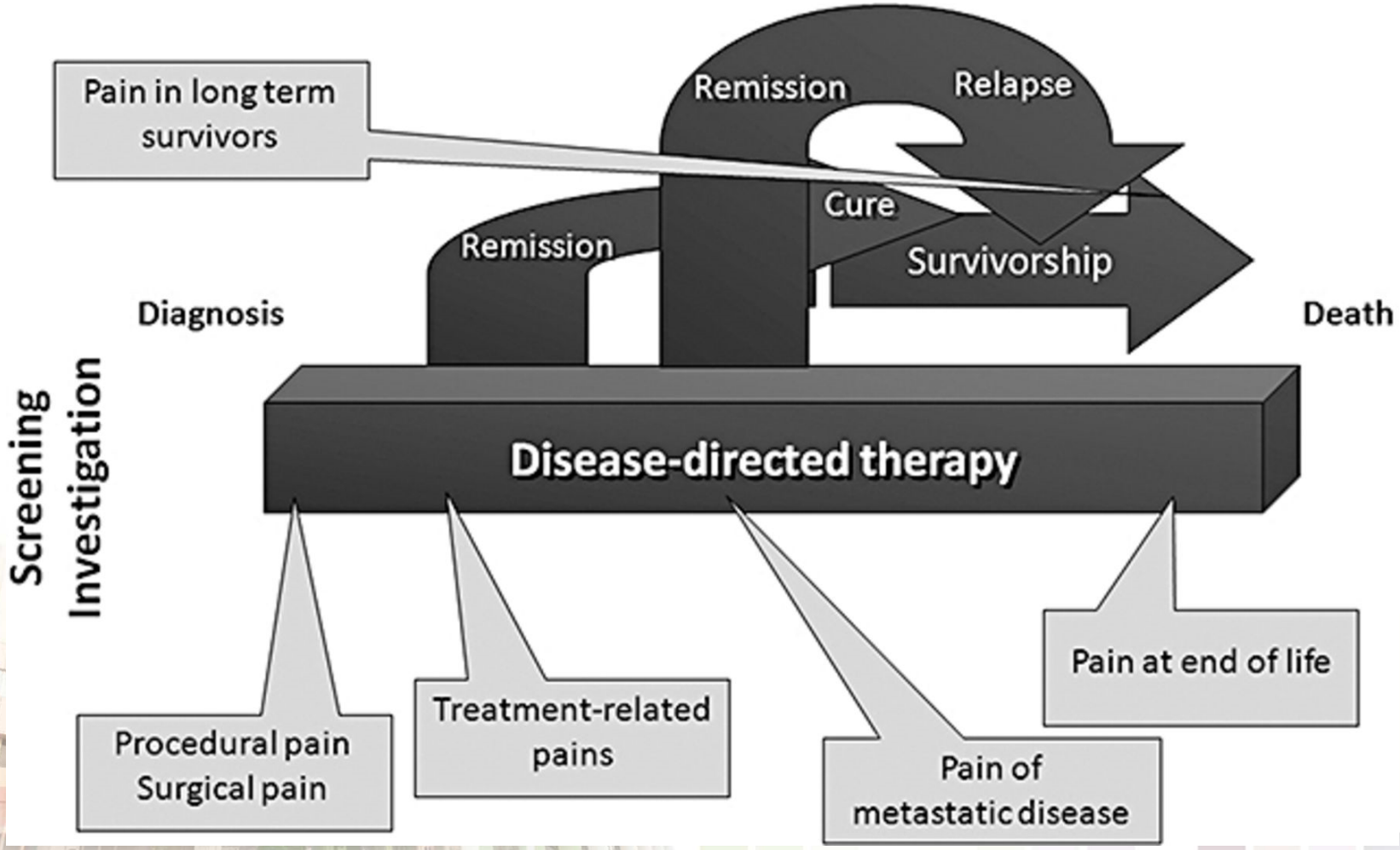




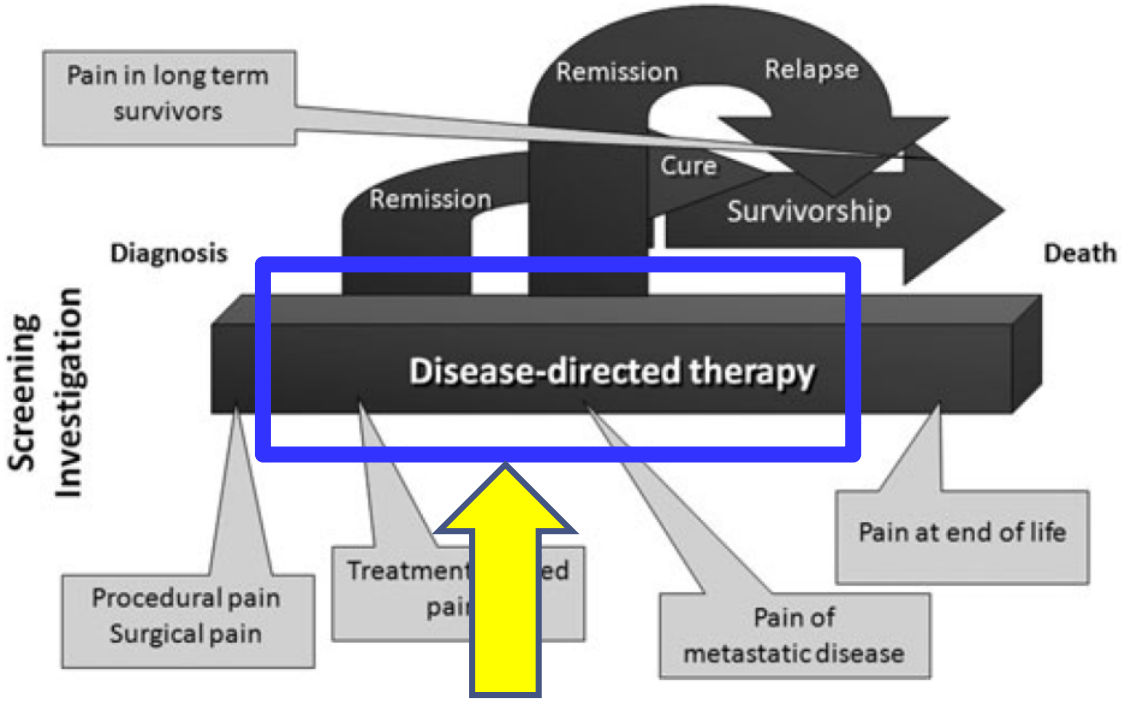
'argas-Schaffer, Is the who analgesic ladder still valid? Twenty-four s of experience, Can Fam Physician, 56 (2010), pp. 514-517

VHA Pain Management » Pain Management » For Veterans/Public - Complementary Treatments

Model of Cancer disease and Pains



Raphael J, Ahmedzai S, Hester J, et al. *Pain Medicine 2010; 11: 742–764*



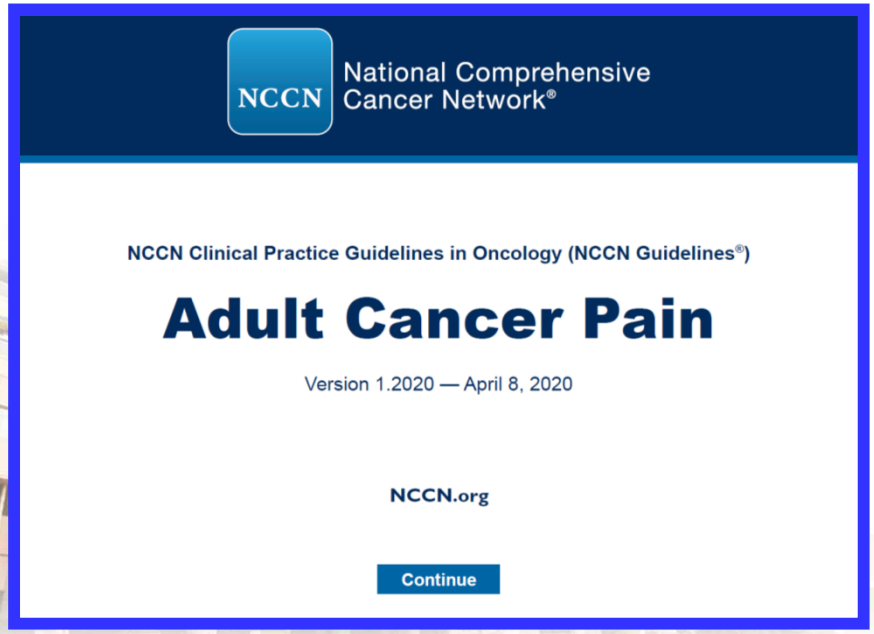
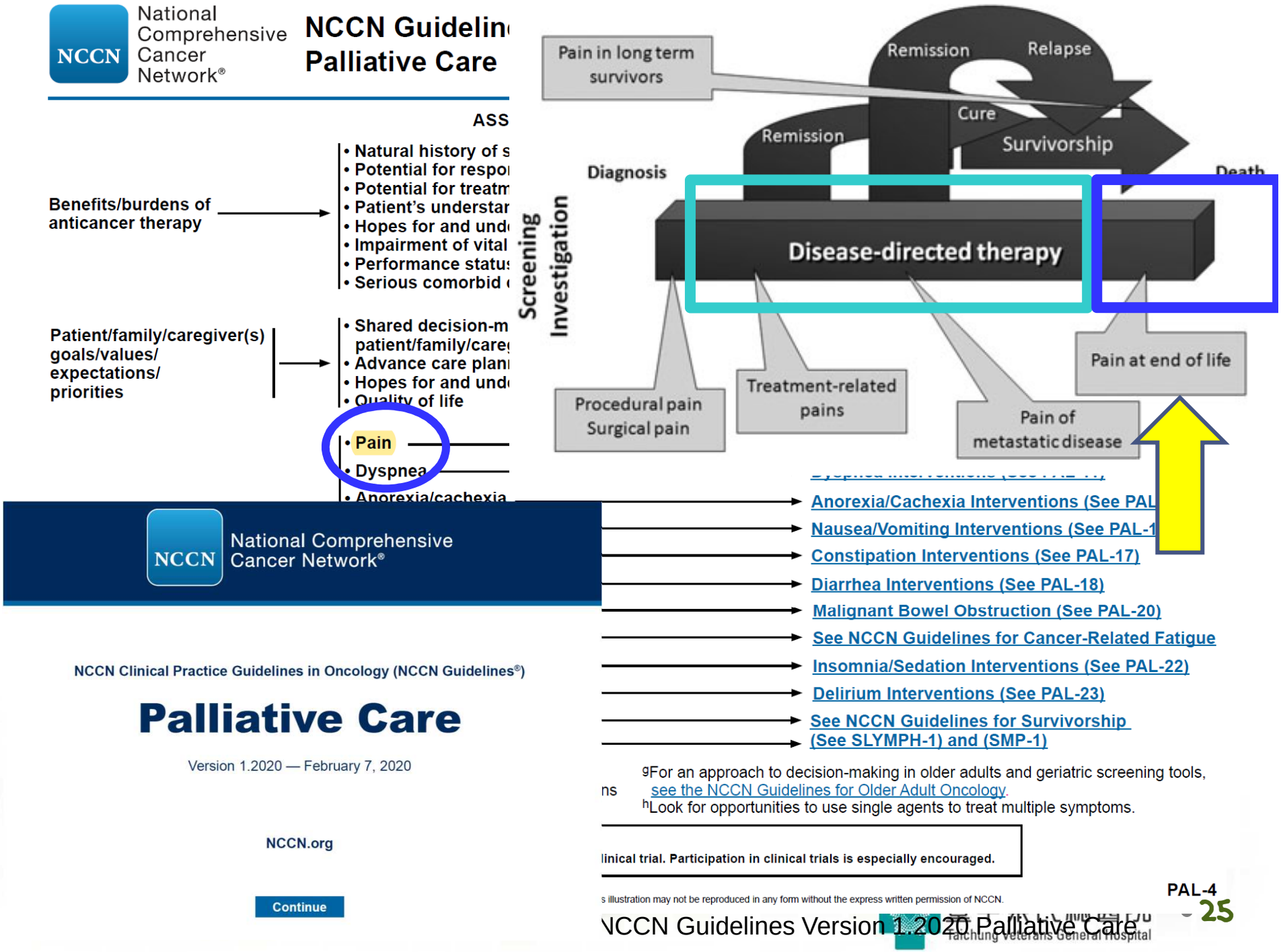


Figure 1 Model of cancer disease and pains.

Raphael J, Ahmedzai S, Hester J, et al. *Pain Medicine 2010; 11: 742–764*


National Comprehensive Cancer Network®
NCCN Guidelin
Palliative Care
ASS
Benefits/burdens of anticancer therapy
• Natural history of s
• Potential for respo
• Potential for treatm
• Patient's understar
• Hopes for and und
• Impairment of vital
• Performance status
• Serious comorbid
Patient/family/caregiver(s) goals/values/ expectations/ priorities
• Shared decision-m patient/family/care
• Advance care plan
• Hopes for and und
• Quality of life
• Pain
• Dyspnea
• Anorexia/cachexia
Pain in long term survivors
Remission
Relapse
Cure
Remission
Survivorship
Diagnosis
Death
Screening
Investigation
Disease-directed therapy
Procedural pain Surgical pain
Treatment-related pains
Pain of metastatic disease
Pain at end of life
Anorexia/Cachexia Interventions (See PAL
Nausea/Vomiting Interventions (See PAL-1
Constipation Interventions (See PAL-17)
Diarrhea Interventions (See PAL-18)
Malignant Bowel Obstruction (See PAL-20)
See NCCN Guidelines for Cancer-Related Fatigue
Insomnia/Sedation Interventions (See PAL-22)
Delirium Interventions (See PAL-23)
See NCCN Guidelines for Survivorship (See SLYMPH-1) and (SMP-1)
gFor an approach to decision-making in older adults and geriatric screening tools, see the NCCN Guidelines for Older Adult Oncology.
hLook for opportunities to use single agents to treat multiple symptoms.
linical trial. Participation in clinical trials is especially encouraged.
s illustration may not be reproduced in any form without the express written permission of NCCN.
PAL-4
National Comprehensive Cancer Network®
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Palliative Care
Version 1.2020 — February 7, 2020
NCCN.org
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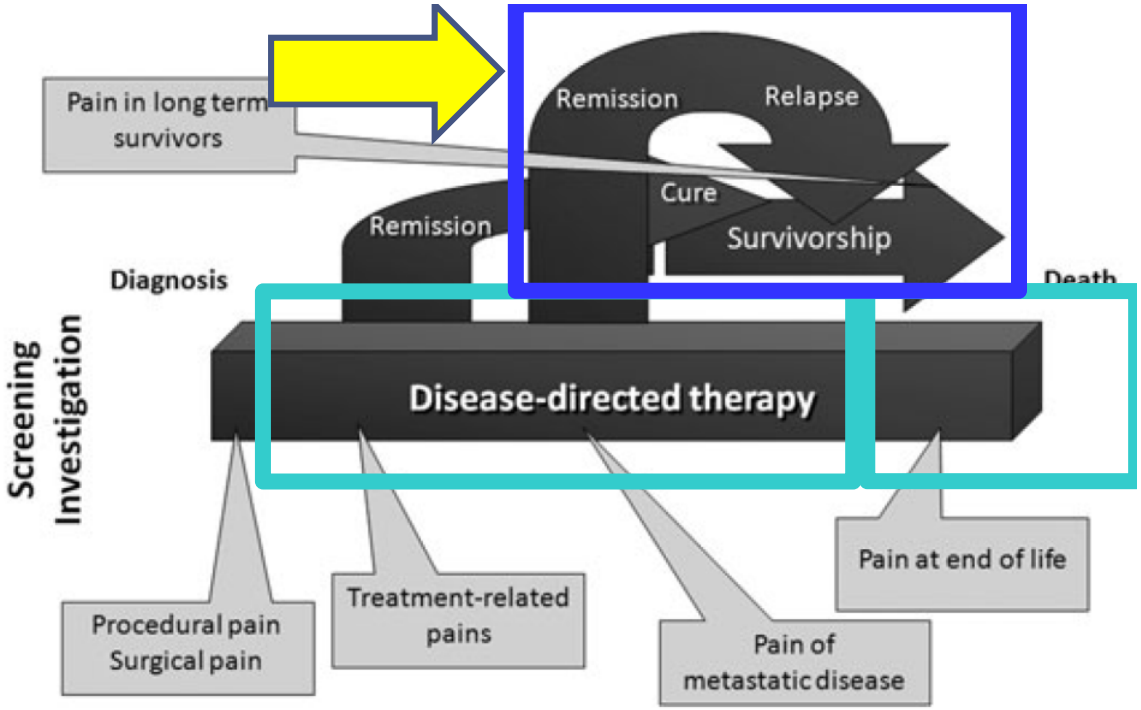
National Comprehensive Cancer Network®

NCCN Guideline
Survivorship

SURVIVO
Pleas

Survivorship Concerns	Survivorship Care Survey
Cardiac Toxicity	1. Do you have shortness of breath or chest pain 2. Do you have shortness of breath when lying fla
Anxiety, Depression, Trauma, and Distress	3. In the past two weeks, have you been bothered 4. In the past two weeks, have you been bothered 5. Has stress, worry, or being nervous, tense, or i
Cognitive Function	6. Do you have difficulties with multitasking or pay 7. Do you have difficulties with remembering thing 8. Does your thinking seem slow? Yes/No
Fatigue	9. Do you feel persistent fatigue despite a good nig 10. Does fatigue interfere with your usual activities 11. How would you rate your fatigue on a scale of
Lymphedema	12. Since your cancer treatment, have you had any Yes/No
Hormone-Related Symptom	13. Have you been bothered by hot flashes/night s 14. Have you been bothered by other hormone-related symptoms (ex, vaginal dryness, incontinence)? Yes/No
Pain	15. Are you having any pain? Yes/No 16. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Sexual Function	17. Do you have any concerns regarding your sexual function, sexual activity, sexual relationships, or sex life? Yes/No s? Yes/No
	staying asleep, or waking up too early? Yes/No ess (ie, sleepiness or falling asleep in inappropriate situations or sleeping more during a ently or that you stop breathing during sleep? Yes/No
	ty or exercise, such as brisk walking, jogging, weight/resistance training, bicycling, swimming, etc.? Yes/No
	least 2½ cups of fruits and/or vegetables each day? Yes/No t? Yes/No nts? Yes/No
	flu season? Yes/No s/No/Don't know



National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Survivorship

Version 1.2020 — March 17, 2020

NCCN.org

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d.
t with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

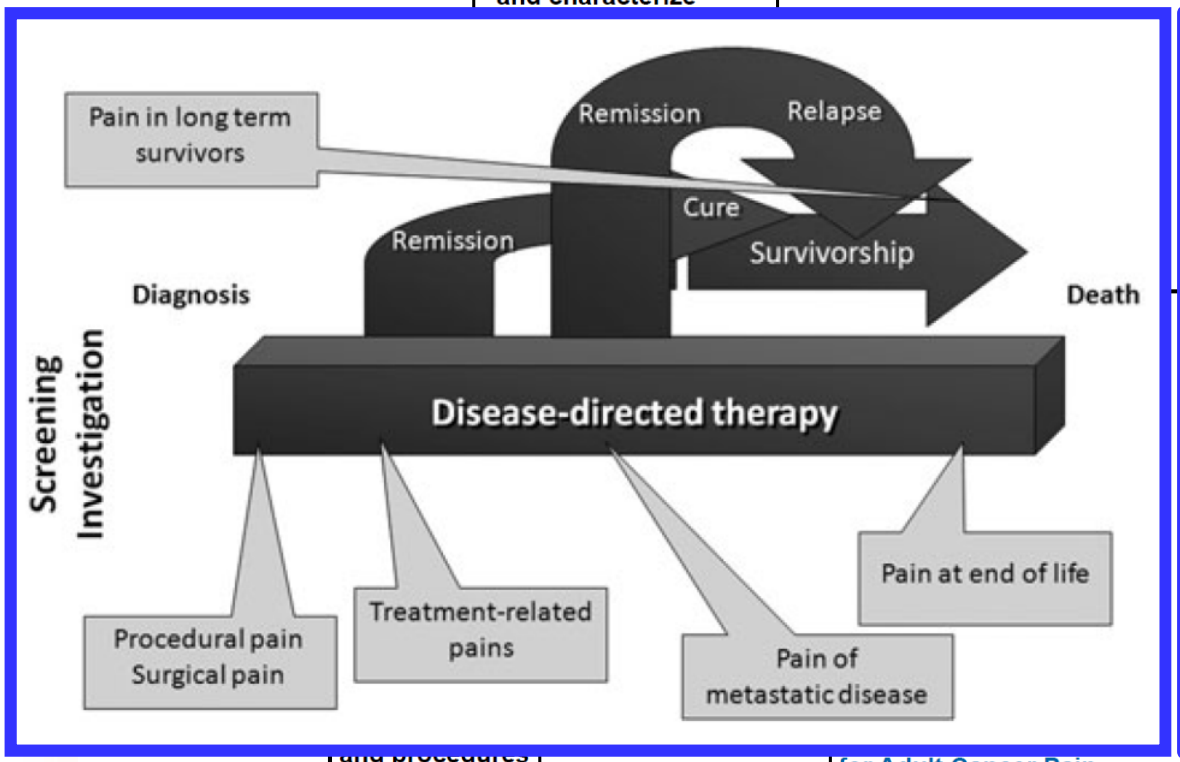
SURV-A
1 OF 2

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Survivorship: Pain

UNIVERSAL SCREENING | **ASSESSMENT** | **CANCER PAIN SYNDROMES** | **TREATMENT[b]**

• Quantify pain intensity and characterize



- Neuropathic pain → See (SPAIN-4)
- Chronic pain syndromes (amputation, neck dissection, mastectomy, thoracotomy) → See (SPAIN-5)
- Myalgias, arthralgias → See (SPAIN-6)
- Skeletal pain → See (SPAIN-7)
- Myofascial pain → See (SPAIN-8)
- Gastrointestinal/urinary/pelvic pain → See (SPAIN-9)
- Post-radiation pain → See (SPAIN-10)
- Lymphedema → See (SLYMPH-1)

for Adult Cancer Pain

[a]Referral to primary care physician for non-cancer treatment-related workup and pain management … of pain due to cancer recurrence.

[b]See General Principles of Pain Management (SPAIN-1).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participatio…

Non cancer related pain

How do we choose medications to control pain?

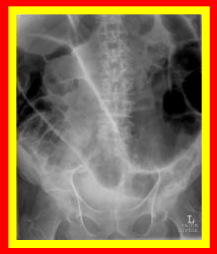
- Oncologic emergency
- Mild pain
- Moderate to severe pain

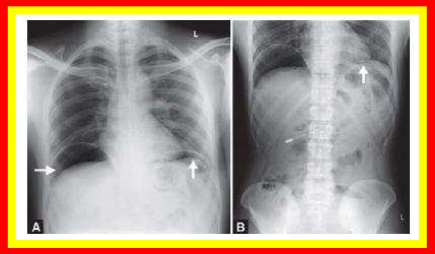
How do we choose medications to control pain?

- Oncologic emergency
- Mild pain
- Moderate to severe pain

A.去急

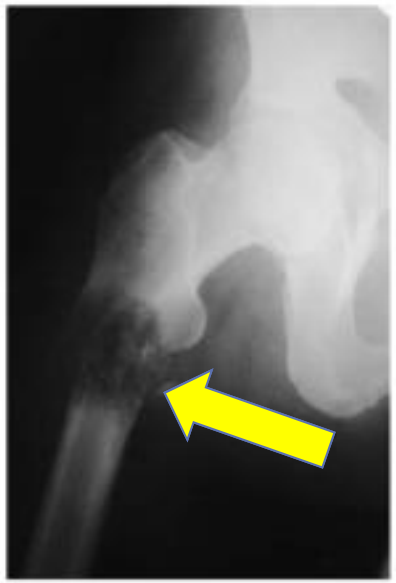
Surgical indications



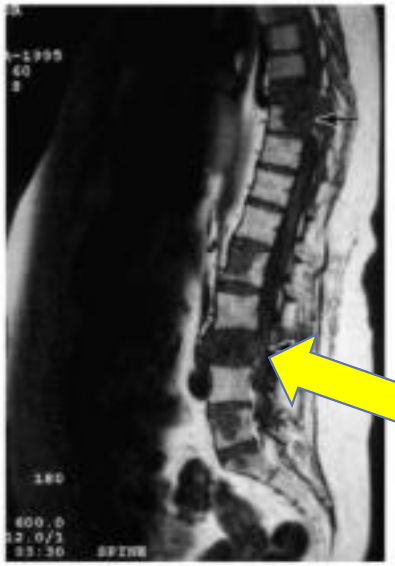


Oncologic Emergency

- **Bone fracture** or impending fracture of weight-bearing bone
- Obstructed or perforated viscus (**acute abdomen**)
- **Neuroaxial metastases** with threatened neural injury
- **Infection**



Radiograph showing pathological fracture of the femur

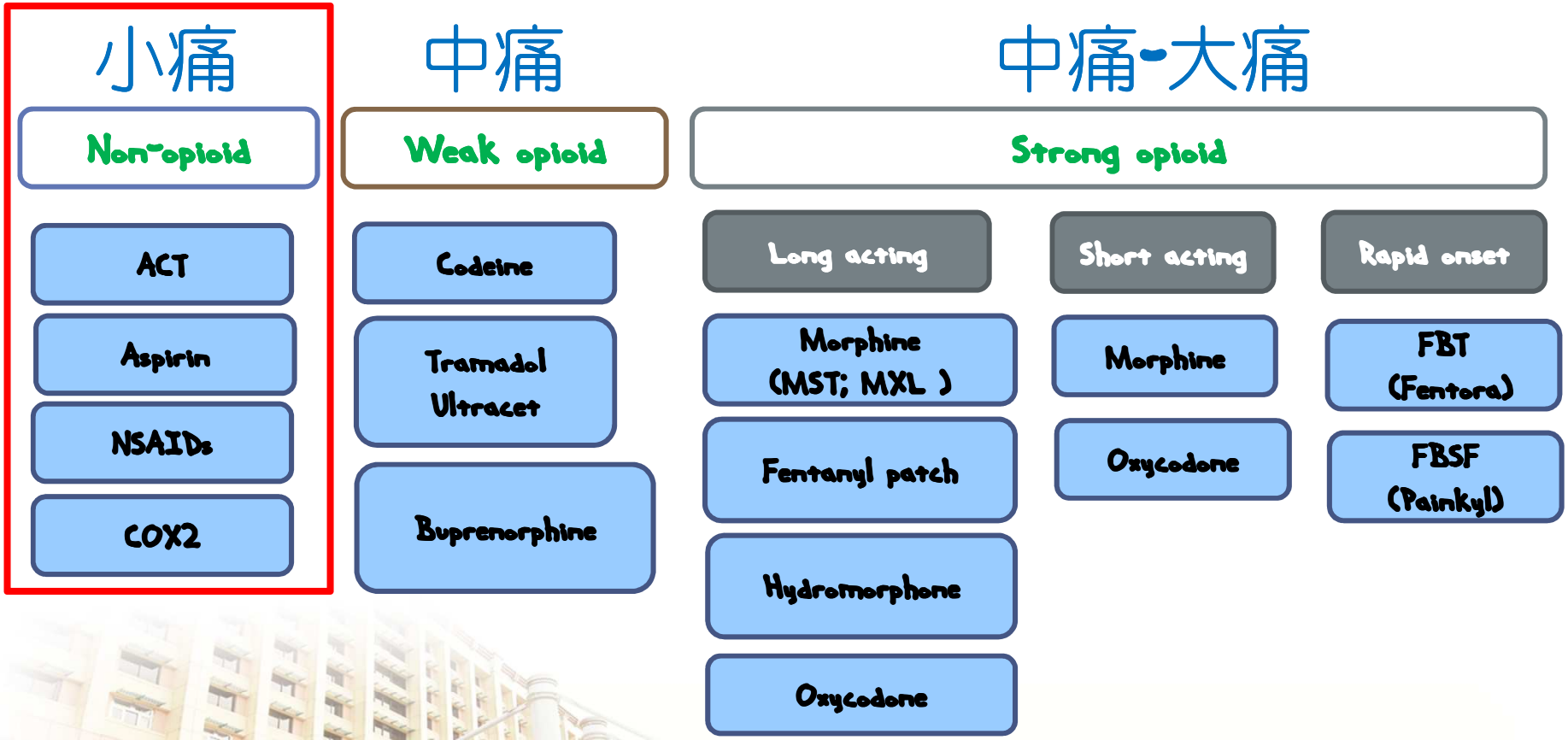


Magnetic resonance image showing patient with spinal cord compression at two different sites (arrows)

How do we choose medications to control pain?

- Oncologic emergency
- Mild pain
- Moderate to severe pain

治療癌症疼痛的藥物



Adjuvant analgesics

Antidepressants, Anticonvulsants, Corticostroids, Bisphosphonate, GABAergic adjuvant analgesics….

1. CNS Drugs 26(6): 509-535.
2. 2020 NCCN guideline Adult Cancer Pain

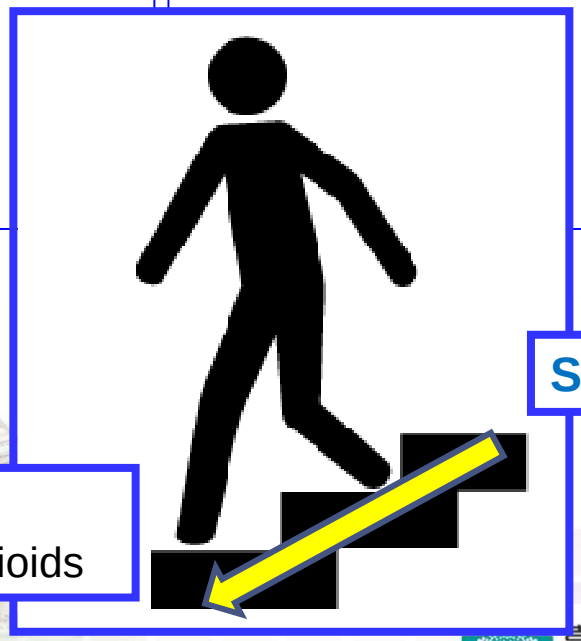
B. Mild Pain

Opioid-Naïve

- First consider non-opioids and adjuvant therapies
- Contraindication
  - Adverse effects, potential drug interactions, comorbid conditions

Opioid-Tolerant

- ↓ Opioids
- ↑ Non-opioids and adjuvant therapies



Strong opioids

Non-opioids
Reducing doses of opioids

Definition: Opioid tolerant

- Chronically receiving opioid analgesic **on a daily basis**
- The FDA identifies tolerance as receiving at least
  - **60 mg oral morphine daily**
  - An **equianalgesic dose** of another opioid
    - 25 mcg/h fentanyl patch
    - 30 mg of oral oxycodone daily
    - 8 mg of oral hydromorphone daily
- **≥ 1 wk**

Opioid Reduction

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Adult Cancer Pain

NCCN Guidelines Index
Table of Contents
Discussion

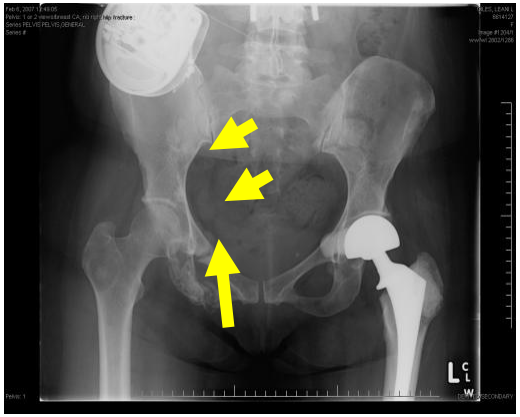
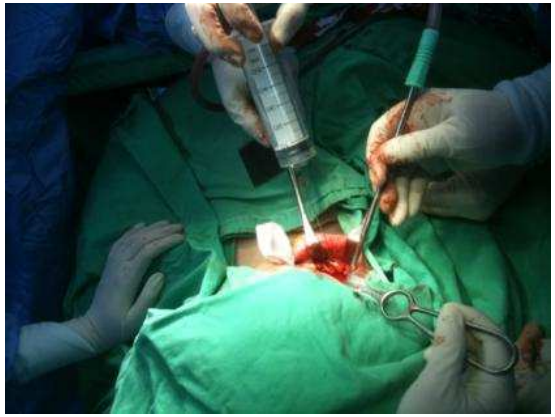
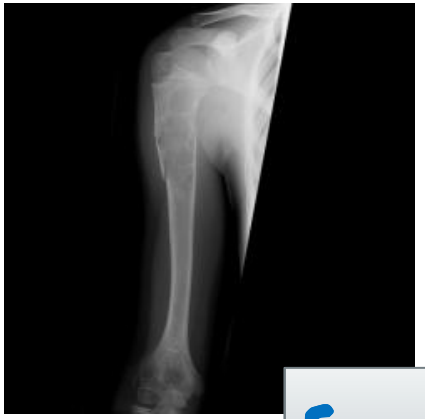
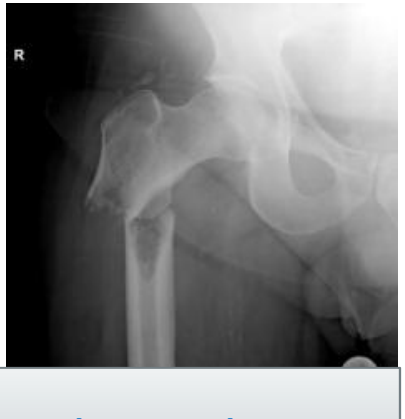
OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Principles of Opioid Dose Reduction

- Consider opioid dose reduction by 10% to 20% when possible; situations that may warrant dose reduction include:
  - Patient never or rarely needs breakthrough analgesic
  - Completion of acute pain event
  - Improvement of pain control through use of non-opioid pain management therapies
  - Well-controlled pain in the setting of stable disease
- If patient is experiencing unmanageable adverse effects and pain is ≤3 (mild), consider downward dose titration by approximately 10% to 25% and reevaluate. Close follow-up is required to make sure that the pain does not escalate, and that the patient does not develop symptoms of withdrawal.
  - If patient has significant safety issues (eg, marked sedation due to sepsis), opioid dose reduction by 50% to 75% may be necessary.
- If pain is worsened with increasing dose, consider opioid hyperalgesia; opioid dose reduction or rotation with attention to other pain therapies may be indicated.

- 病人不需要 PRN 止痛、已完成 acute pain 治療、疼痛可透過 non-opioid 進行改善、stable disease 且疼痛控制良好 → 減量10-20%
- 病人用 opioid 有副作用，疼痛 ≤ 三分 → 減量10-25%
- 病人用 opioid 有危及生命的副作用 → 減量50-75%

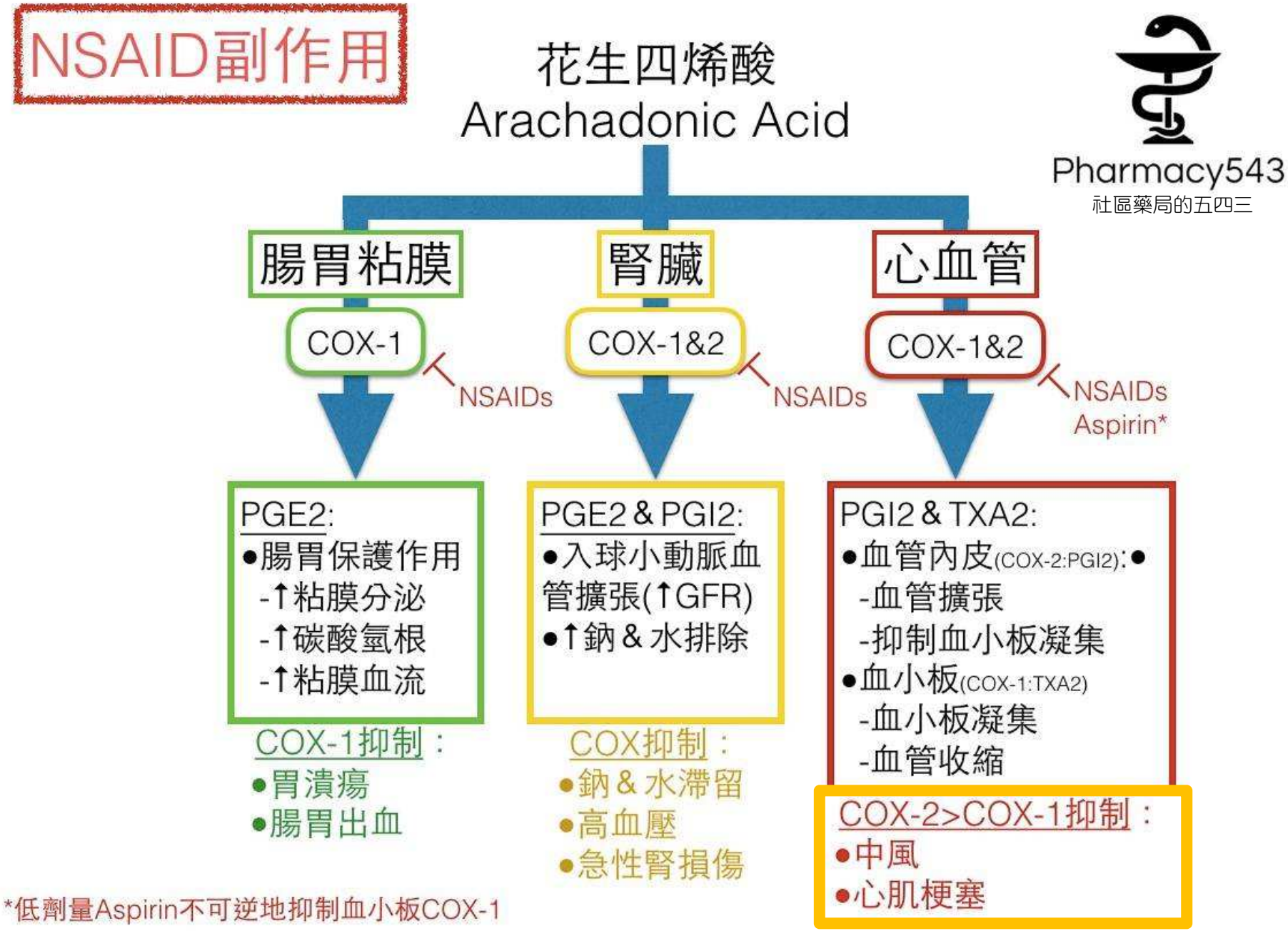
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Somatic pain

- 抗發炎效果，用於骨轉移和軟組織疼痛
- 解熱(退燒)、鎮痛、抗發炎
- 通常止痛效果越強者，副作用較多
- 以建議量之最小量開始使用，注意 ceiling effect

NSAID副作用


花生四烯酸
Arachadonic Acid
Pharmacy543
社區藥局的五四三
腸胃粘膜
腎臟
心血管
COX-1
COX-1&2
COX-1&2
NSAIDs
NSAIDs
NSAIDs
Aspirin*
PGE2:
●腸胃保護作用
-↑粘膜分泌
-↑碳酸氫根
-↑粘膜血流
PGE2 & PGI2:
●入球小動脈血管擴張(↑GFR)
●↑鈉 & 水排除
PGI2 & TXA2:
●血管內皮(COX-2:PGI2):●
-血管擴張
-抑制血小板凝集
●血小板(COX-1:TXA2)
-血小板凝集
-血管收縮
COX-1抑制：
●胃潰瘍
●腸胃出血
COX抑制：
●鈉 & 水滯留
●高血壓
●急性腎損傷
COX-2>COX-1抑制：
●中風
●心肌梗塞
*低劑量Aspirin不可逆地抑制血小板COX-1

Selective/preferential Cox-2抑制劑
仿單須加註心血管疾病警語

賴世珍

:

繼默沙東藥廠自願全球下市 Vioxx® (rofecoxib，偉克適) 後，相似作用機轉之選擇性抑制cyclooxygenase 2 (COX-2) 的非類固醇止痛藥 (NSAIDs) 之安全性引起醫療界及民眾的極大關注。由於此類 COX-2 抑制劑均有相似的心血管疾病潛藏危險，且根據今年2月美國藥物食品管理局 (FDA) 之關節炎藥物諮商委員會與藥物安全暨危機管理諮商委員會聯合會議討論的結果，不僅美國 FDA 對境內 NSAIDs 藥品的使用做出明確的聲明，在台灣，衛生署也要求廠商必須在今年3月15日前將selective/preferential COX-2 抑制劑之仿單加註心血管疾病副作用之警語，此包括Celebrex® (celecoxib，希樂葆)、Arcoxia® (etoricoxib，萬克適)、申請中之 Bextra® (valdecoxib)，及含有 meloxicam (例如 Mobic®, 骨敏捷)、nimesulide (例如 Mesulid®, 每舒寧)、nabumetone (例如Relifex®, 美伏疼)等成份之藥品共33個品項。

FDA 今年2月的聯合會議的討論重點主要是對所有的非選擇性 NSAIDs 及COX-2選擇性抑制劑做出心血管疾患危險性的已知文獻評估及提出臨床應用建議。聯合會中主要討論的C 2選擇性抑制劑有三種： celecoxib、valdecoxib 及 rofecoxib；根據現有文獻證據，所有 COX-2 選擇性抑制劑一致被認爲存在有心血管疾病危險性。就效益/風險性評估， Celecoxib 得到大多數的專家學者贊成繼續於臨床上使用，而 valdecoxib 及 rofecoxib 則因現有文獻證據的限制，反對及贊成的學者人數相當。依據會議結果， FDA 要求廠商在 celecoxib 藥品仿單中加上 NSAIDs 類止痛藥可能引起心血管及腸胃道危險性的警語及禁忌症，並且應在病人用藥指導單中告知病人可能潛藏的心血管及腸胃道危險性； valdecoxib 則因已有明確的心血管危險性，且較其他 COX-2 選擇性抑制劑更容易發生嚴重致命的皮膚副作用 (如Stevens-Johnson syndrome, toxic epidermal necrolysis 等)，因此FDA要求廠商能主動下市此藥品。至於 rofecoxib 是否可重獲允許再上市， FDA 表示會仔細審查廠商提請重新上市之計畫書後再定奪。

Table
Currently Available and Future Coxibs

Coxib	Administration	Half-life, h	Pain Indications*
Currently Available†			
Celecoxib 	Oral	8–11	Osteoarthritis, rheumatoid arthritis, acute pain, dysmenorrhea
Valdecoxib	Oral	8	Osteoarthritis, rheumatoid arthritis, dysmenorrhea
Future			
Etoricoxib 	Oral	24	Osteoarthritis, rheumatoid arthritis, back pain, pain, dysmennorrhea, gout, acute pain, spondyloarthropathy
Lumiracoxib	Oral	3–6	Osteoarthritis, rheumatoid arthritis, acute pain, dysmenorrhea
Parecoxib 	Intravenous or intramuscular	8	Acute pain, surgical pain

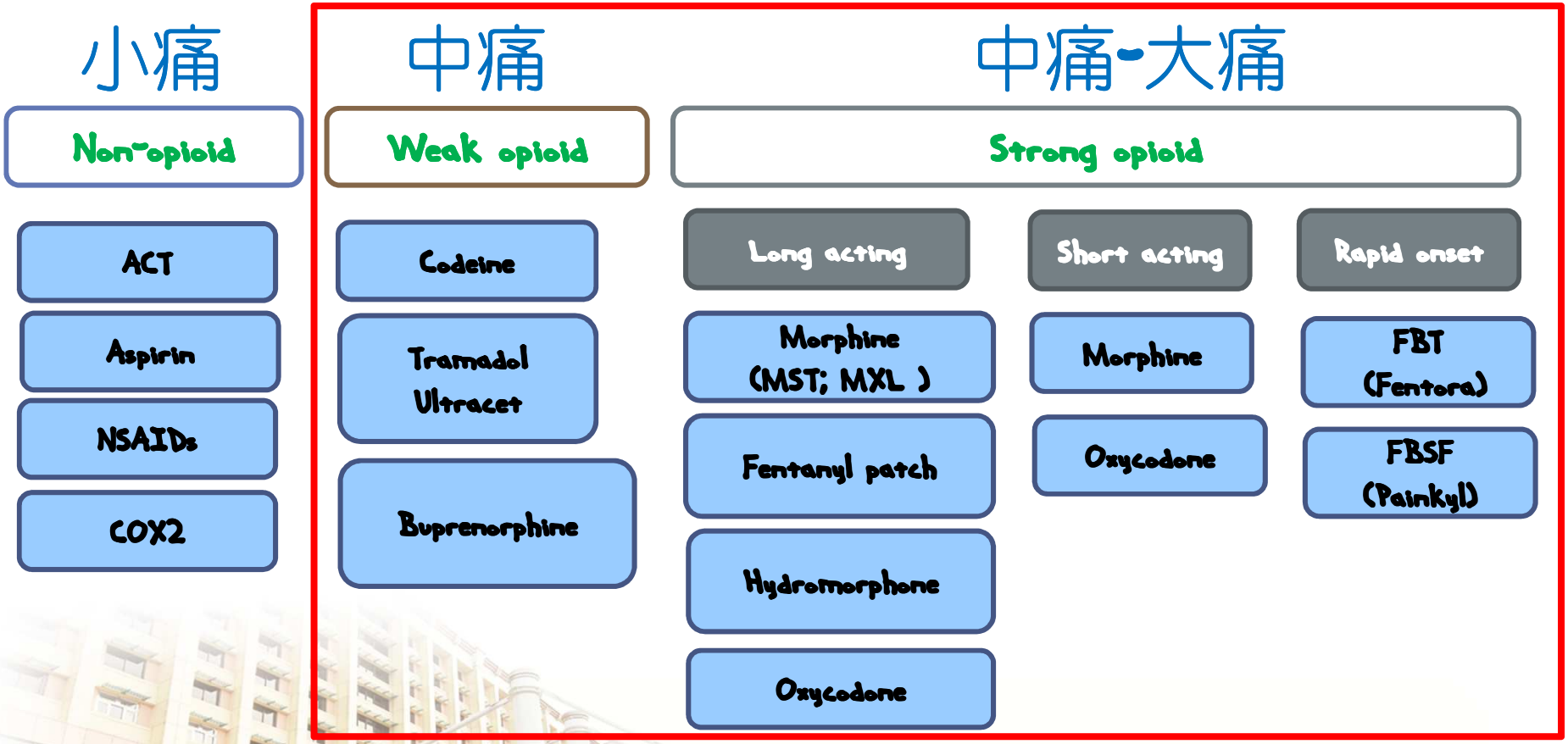
* Potential pain indications are listed for the coxibs likely to be available in the future.
† Available until just before this issue went to press, rofecoxib (Vioxx) was withdrawn from the market by the manufacturer (Merck & Co) because of the risk of cardiovascular events associated with long-term use. It had been indicated for the pain of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, acute pain, dysmenorrhea, and migraine.

JAOA 2004;104(1):S19-24.

How do we choose medications to control pain?

- Oncologic emergency
- Mild pain
- Moderate to severe pain

治療癌症疼痛的藥物



Adjuvant analgesics

Antidepressants, Anticonvulsants, Corticostroids, Bisphosphonate, GABAergic adjuvant analgesics….

1. CNS Drugs 26(6): 509-535.
2. 2020 NCCN guideline_Adult Cancer Pain

C. Moderate/Severe Pain-I

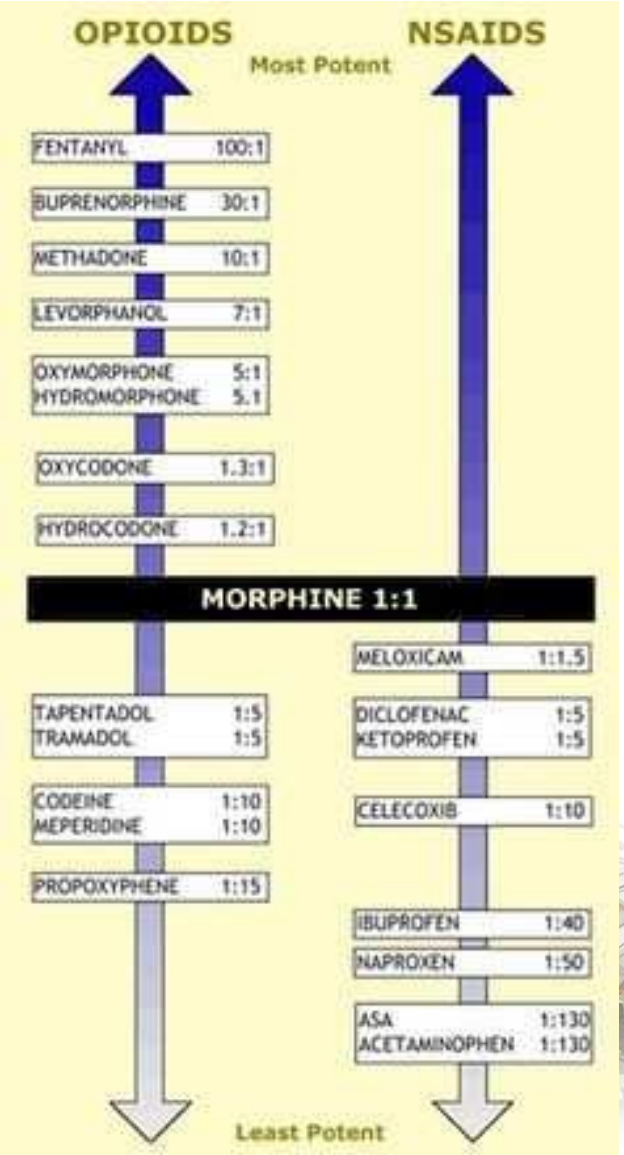
Opioid-Naïve

- Non-opioids + adjuvant
- Start and titrate short-acting opioid Q3-4HPRN
  - Oxycodone IR 2.5-5 mg
    - +/- acetaminophen 325 mg
  - Hydrocodone 5mg
    - +/- acetaminophen 325 mg
  - Hydromorphone 2mg
  - Morphine 5mg SC IV or IR 7.5 mg

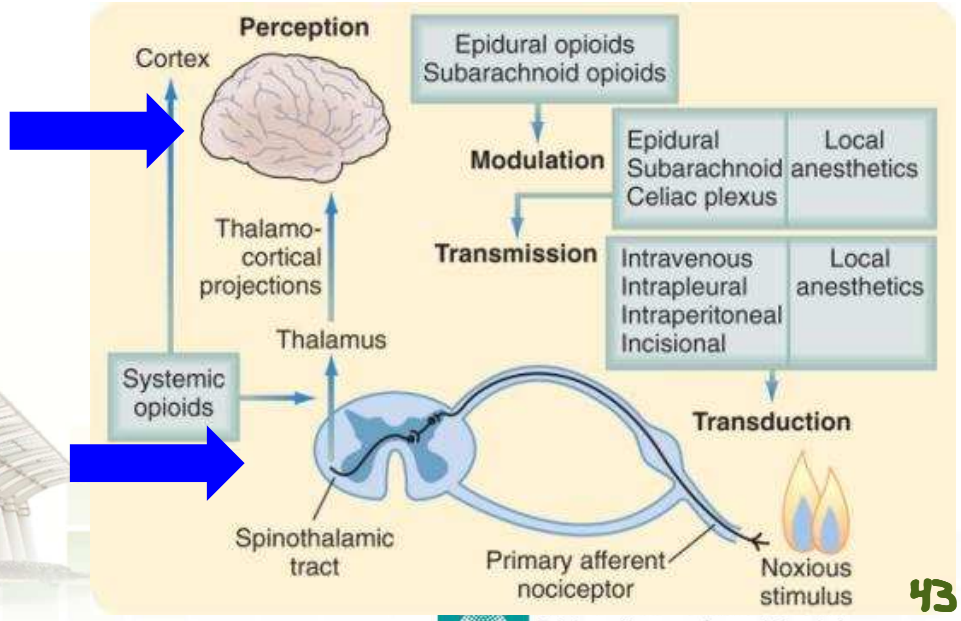
Opioid-Tolerant

- Non-opioids + adjuvant
- ↑ 30-50% Short-acting opioid
- ≥ 4 doses PRN
  - Add a long-acting opioid based on the total daily dose

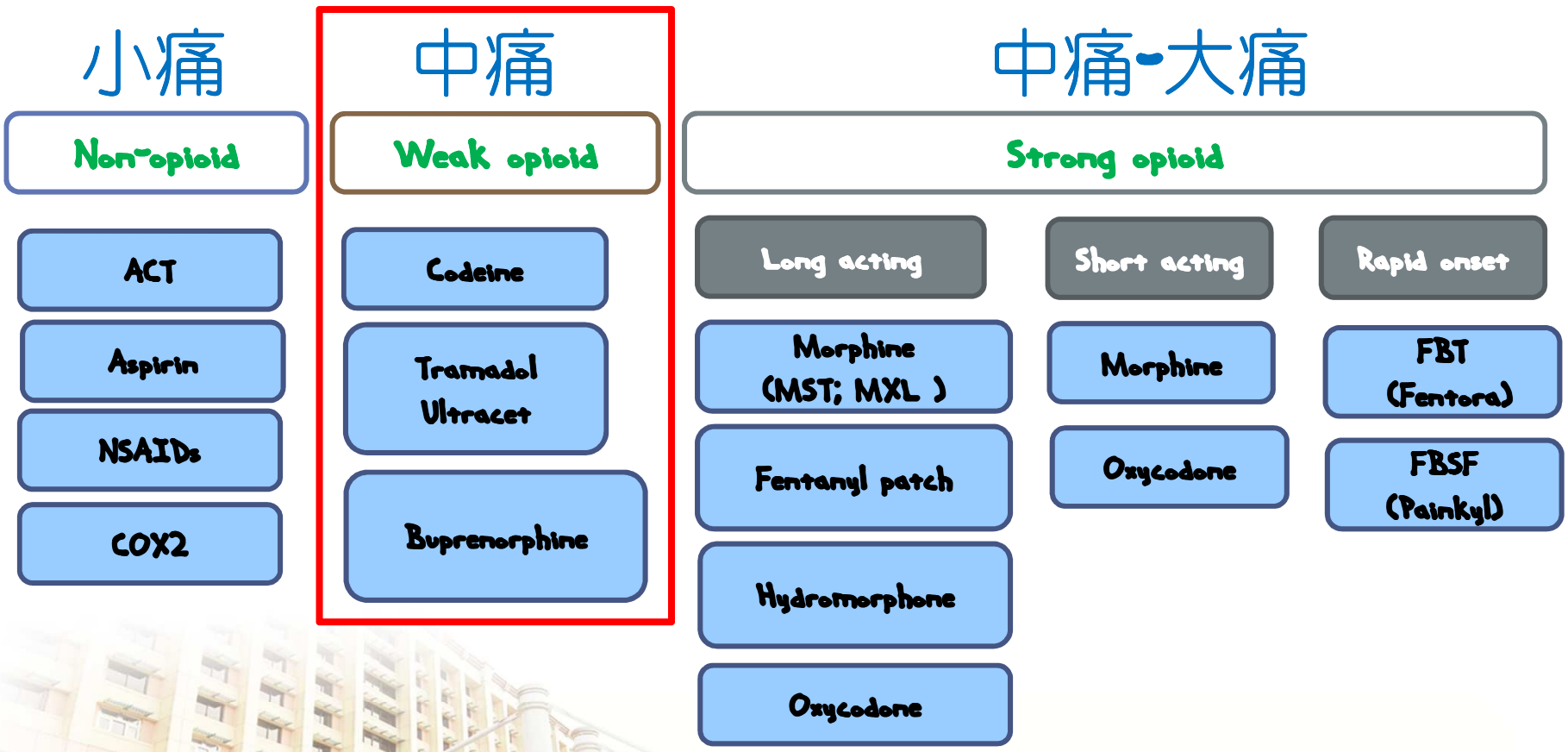
NCCN Clinical Practice Guidelines in Oncology Adult Cancer Pain Version 1.2020



- 止痛比一般消炎止痛藥強
- 多由肝臟代謝、腎臟排除
  - 肝腎功能異常將會提高藥物之生體可用率
- 一般並不會影響肝腎功能



治療癌症疼痛的藥物



Adjuvant analgesics

Antidepressants, Anticonvulsants, Corticostroids, Bisphosphonate, GABAergic adjuvant analgesics….

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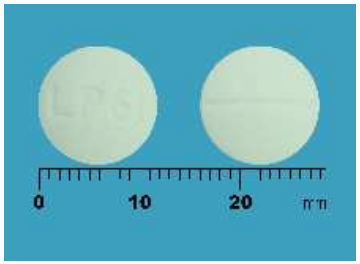
Tramadol

兩種效果

- Opioid receptors
- ↓ Norepinephrine, serotonin reuptake
  - < 400mg /day
    - Renal impairment: <200mg/day
    - Cirrhosis: 50mg Q12H

Tramadol 50mg



Tramadol SRT 100mg

- Side effects
  - Dizziness or vertigo (dose related), dry mouth, light-headedness, constipation, pruritus, rash, vasodilation, orthostatic hypotension, syncope, tachycardia
- Less constipation to typical opioids
-

Leppert W, Luczak J. The role of tramadol in cancer pain treatment--a review. Support Care Cancer 2005; 13(1):5-17. Epub 2004 Nov 18.

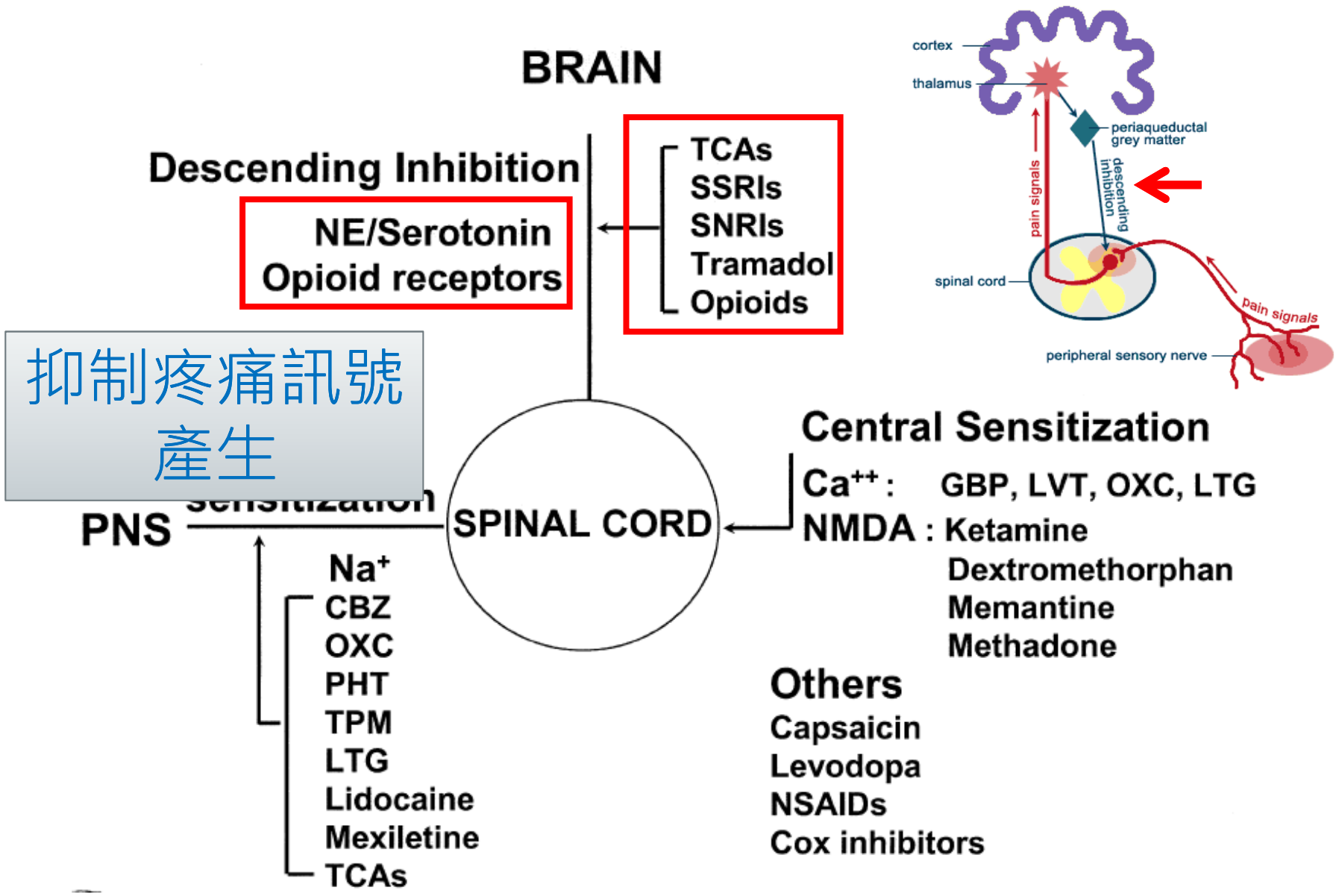


Fig. 4. Mechanistic stratification of antineuralgic agents. PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPA = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressant; NE = norepinephrine; SSRI = selective serotonin re-uptake inhibitor; SNRI = serotonin and norepinephrine re-uptake inhibitor; GBP = gabapentin; LVT = levetiracetam; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug.

Ultracet

- Tramadol 37.5mg + Acetaminophen 325mg
  - o ≤ 8#/day
  - o 不傷肝、腎、胃

Ultracet

Acetaminophen (Fast)

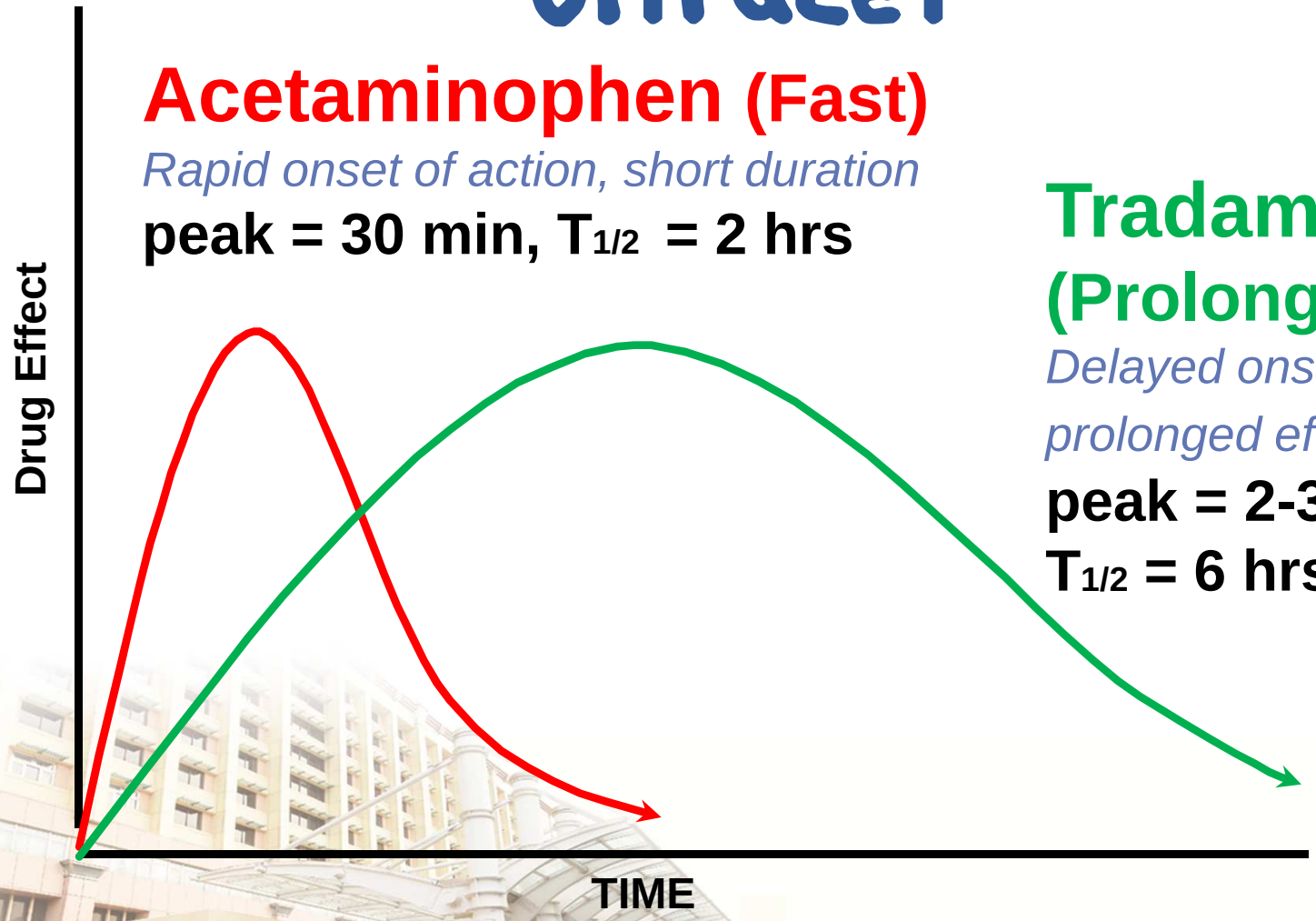
Rapid onset of action, short duration

peak = 30 min, $T_{1/2}$ = 2 hrs

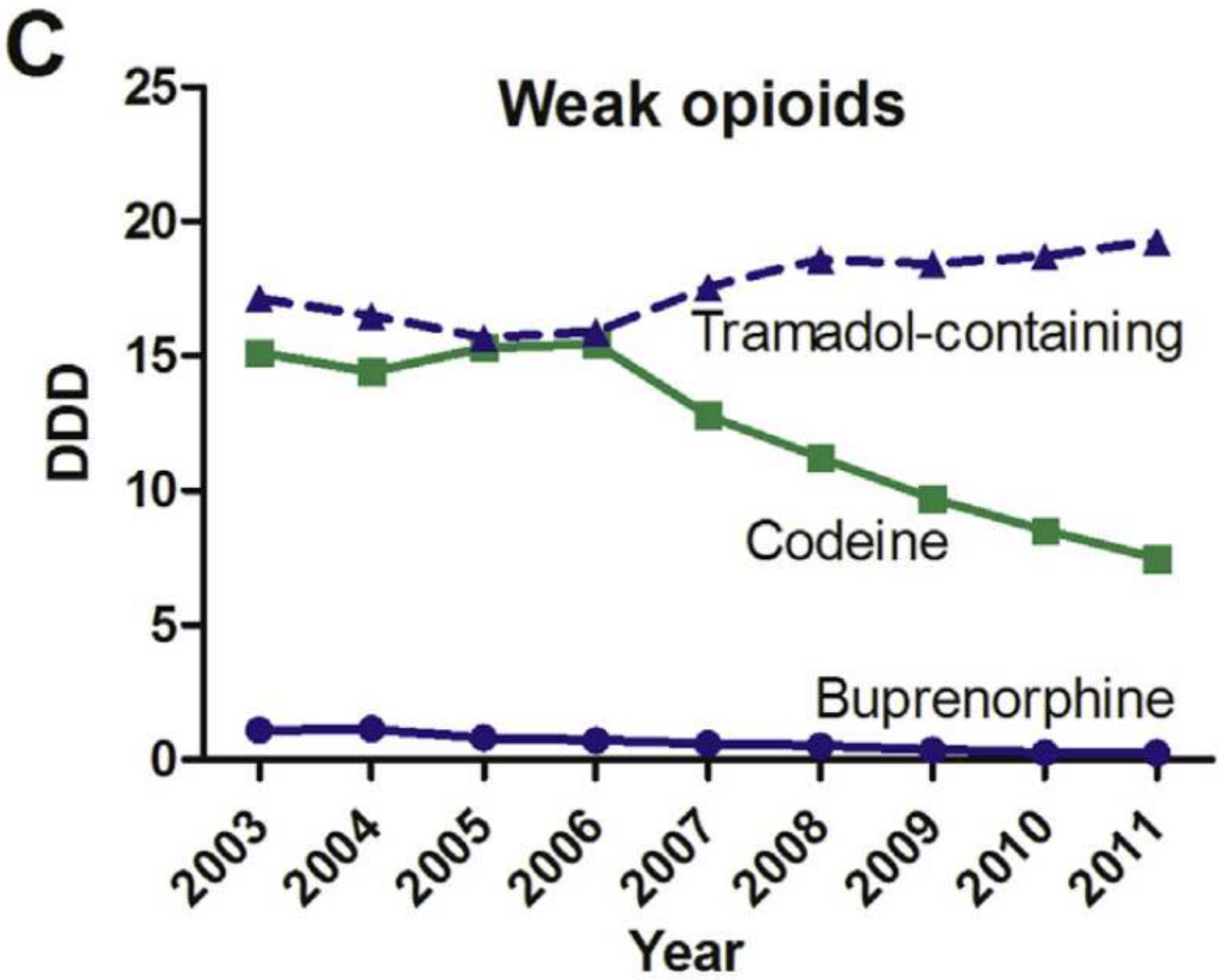
Tradamol (Prolonged)

Delayed onset but prolonged effect

peak = 2-3 hrs, $T_{1/2}$ = 6 hrs



The combination: Fast onset + Prolonged action



Lin CP, Hsu CH, Fu WM, et al. Acta Anaesthesiol Taiwan. 2016;54(2):51-6.

2020 in Taiwan

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衛生福利部
Ministry of Health and Welfare
促進全民健康與福祉

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本部簡介 最新消息 便民服務 法令規章 衛教視窗 本部各單位及所屬機關

最新消息

- 焦點新聞
- 真相說明
- 公告訊息
- 活動訊息
- 招標資訊
- 就業資訊

首頁 / 最新消息 / 焦點新聞

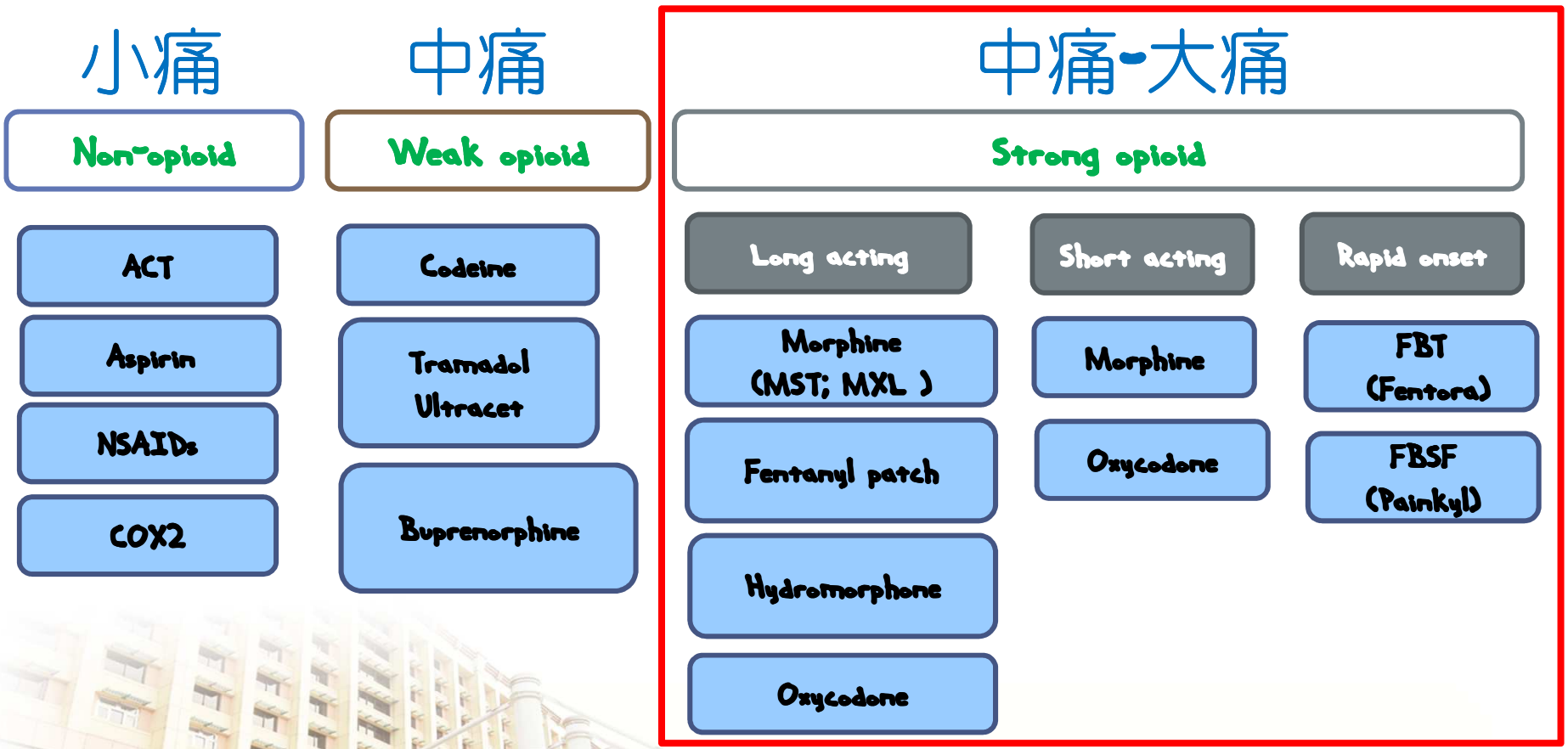
公告含tramadol成分藥品之臨床效益與風險再評估結果相關事宜

• 資料來源：食品藥物管理署 • 建檔日期：109-08-10 • 更新時間：109-08-10

含tramadol成分藥品具有導致呼吸緩慢、呼吸困難之嚴重風險，衛生福利部食品藥物管理署(以下簡稱食藥署)雖於106年9月12日公告要求含該成分藥品應於仿單「警語及注意事項」加註呼吸風險相關警語。惟考量我國全國不良反應通報系統近年曾接獲疑似使用該成分藥品導致呼吸相關之嚴重不良反應通報案件，為確保民眾用藥安全，食藥署重新評估該成分藥品之臨床效益及風險，並提藥品安全評估諮議小組討論，決議修訂含該成分藥品之使用原則，自109年8月10日起公告含tramadol成分藥品禁止使用於發生顯著呼吸抑制的病人。

食藥署提醒醫師應依據109年8月10日公告使用原則處方含tramadol成分藥品。另提醒民眾該成分藥品屬於醫師處方及第4級管制藥品，應遵循醫囑服用，同時應注意用藥後情形，若於服藥後出現呼吸緩慢或微弱、呼吸困難等症狀，請立即回診尋求醫師協助。

治療癌症疼痛的藥物



Adjuvant analgesics

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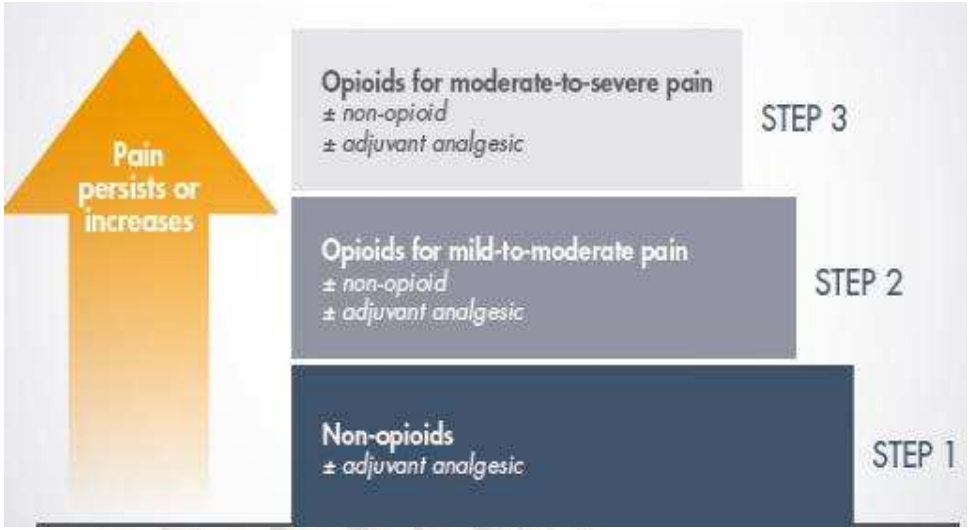
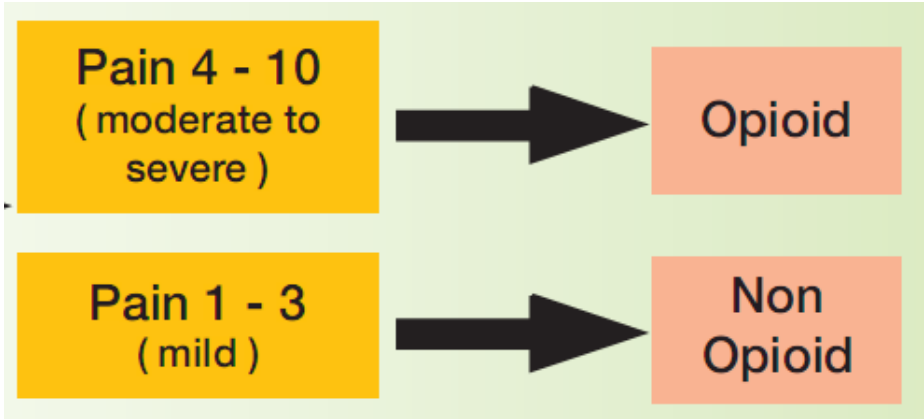
NSAIDs | **Opioids- strong** | Adjuvants | Others | Intervention

WHO[1]



ESMO/EAPC/NCCN[2]



ESMO European Society of Medical Oncology

EAPC European association of palliative care

NCCN National Comprehensive Cancer Network

1. WHO. Cancer pain relief: with a guide to opioid availability. 2nd ed. Geneva:The Organization;1996. Sin
2. National Comprehensive Cancer Network (NCCN) GuidelinesTM Ver. 2010-1.2020: Adult Cancer

治療：定期止痛藥物(長效) + 突發性疼痛控制(短效)

Breakthrough pain(突發性疼痛)突然發生的短暫劇烈疼痛，即使已經使用止痛劑也可能發生。

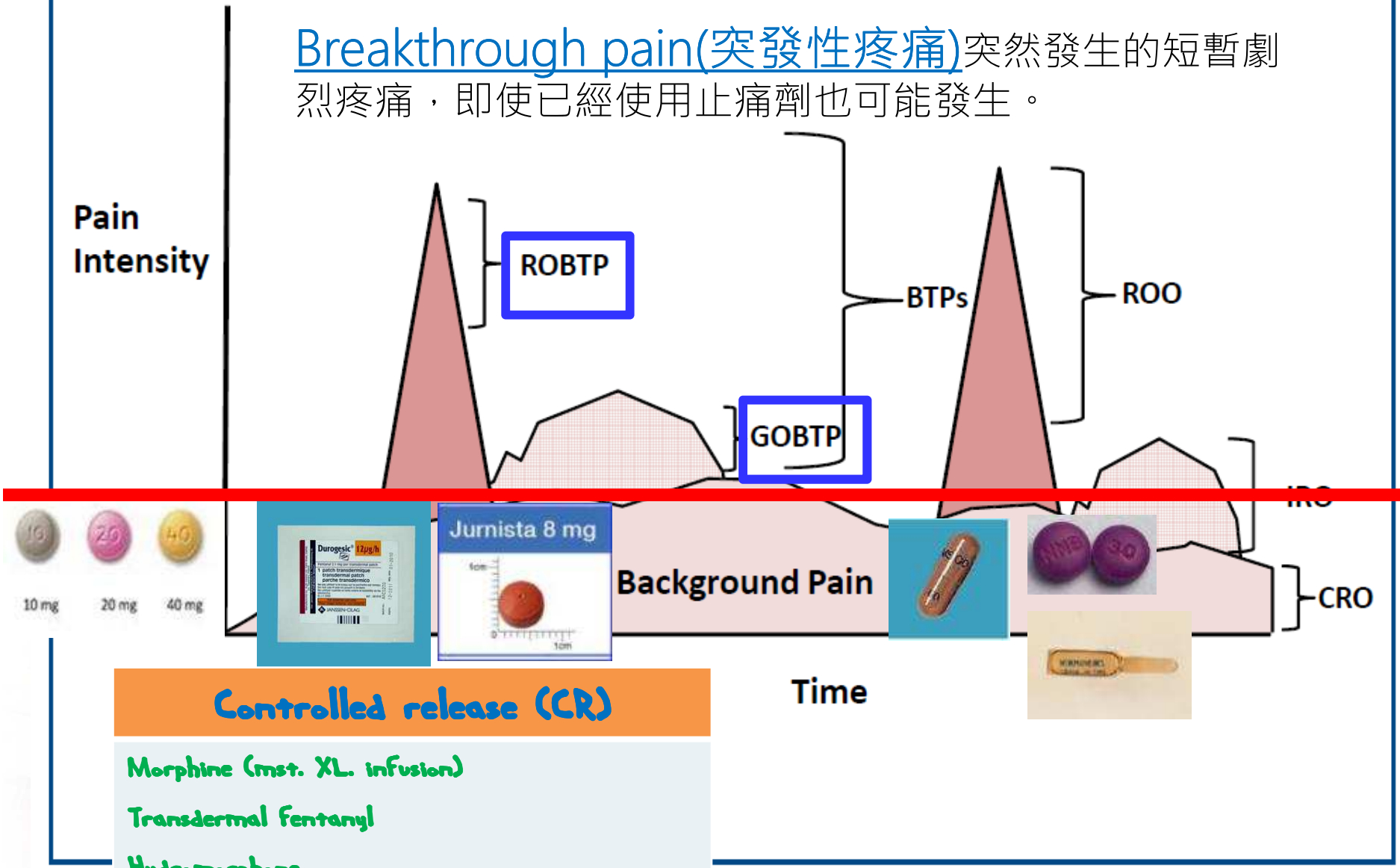


Figure "matching" opioid treatment.

Smith HS. Ann Palliat Med 2012;1(1):45-52.

治療：定期止痛藥物(長效) + 突發性疼痛控制(短效)

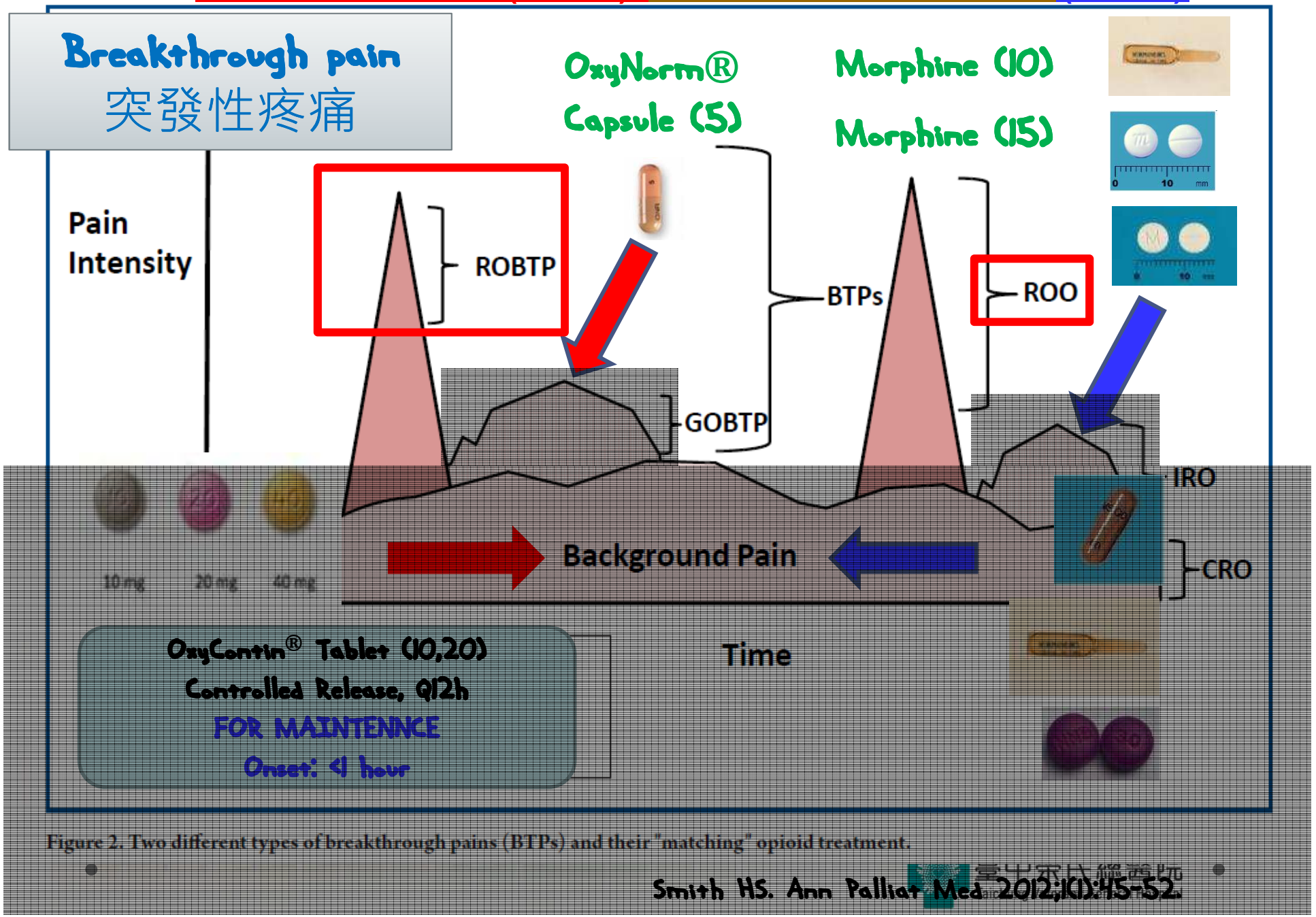


Figure 2. Two different types of breakthrough pains (BTPs) and their "matching" opioid treatment.

Smith HS. Ann Palliat Med 2012;1(1):45-52.

ROO (Rapid onset opioid)

Onset夠快

Rapid onset

Incident <5min

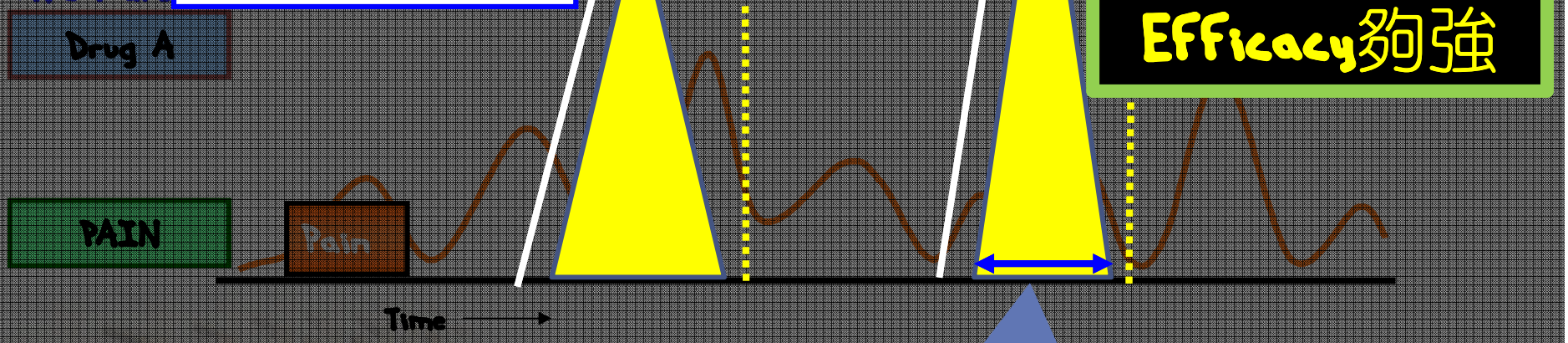
Spontaneous <10min to peak

Averages 3-6 episodes per day

Accessible

Moderate-to-severe pain

Efficacy夠強



Duration夠就好

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

*maximal pain intensity:3-15 mins or even within secs**

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

Potency

IV : PO = 1:3

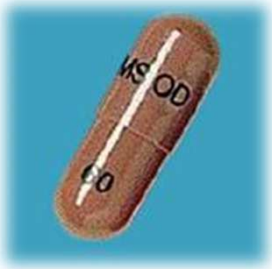
Mu receptors

Duration

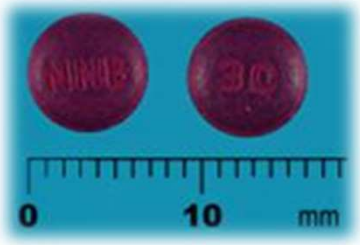
MXL : 24 hours

MST : 8-12 hours

Morphine tab:4 hours



MXL CAPSULES 60MG
(MORPHINE SULFATE CAP 60MG/默痛舒持續性膠囊)

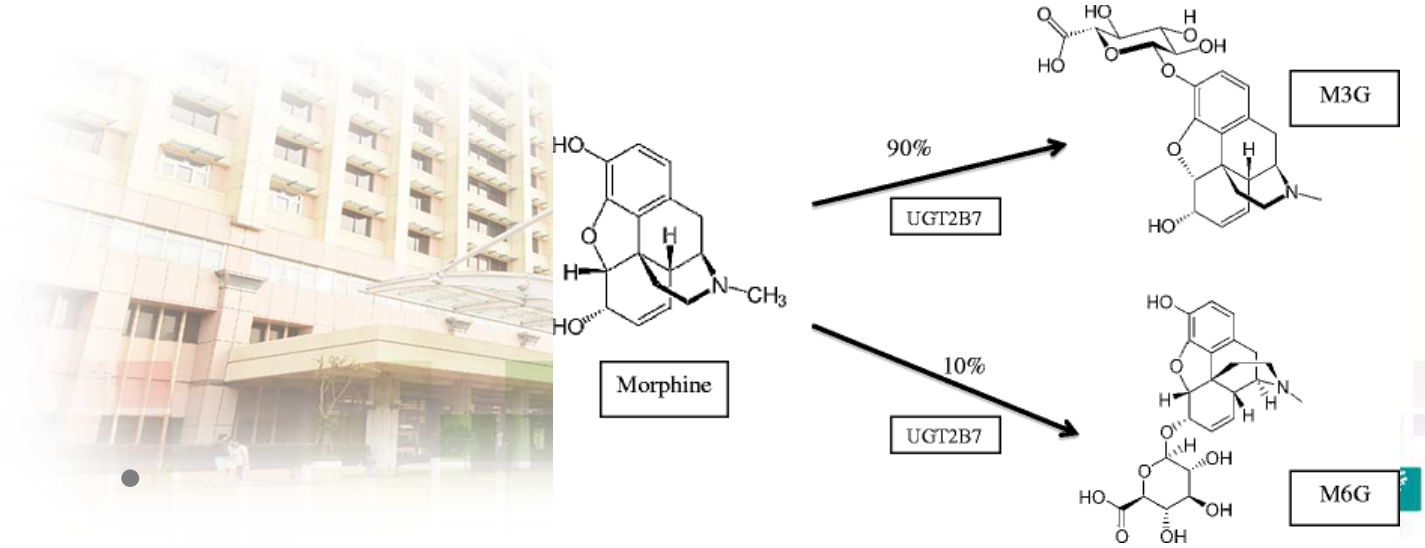


MORPHINE CONT. MST TAB 30MG
(MORPHINE SULFATE)

MORPHINE TAB 15MG
(MORPHINE SULFATE)

Morphine

- 肝代謝、腎排除
  - Morphine-3-glucuronide (M3G, 75-85%)
  - Morphine-6-glucuronide (M6G, 5-10%)
    - Active metabolite
    - Patients with renal failure can develop very high levels of M6G and life-threatening respiratory depression



Potency

Over oral morphine

5* - 7.5*

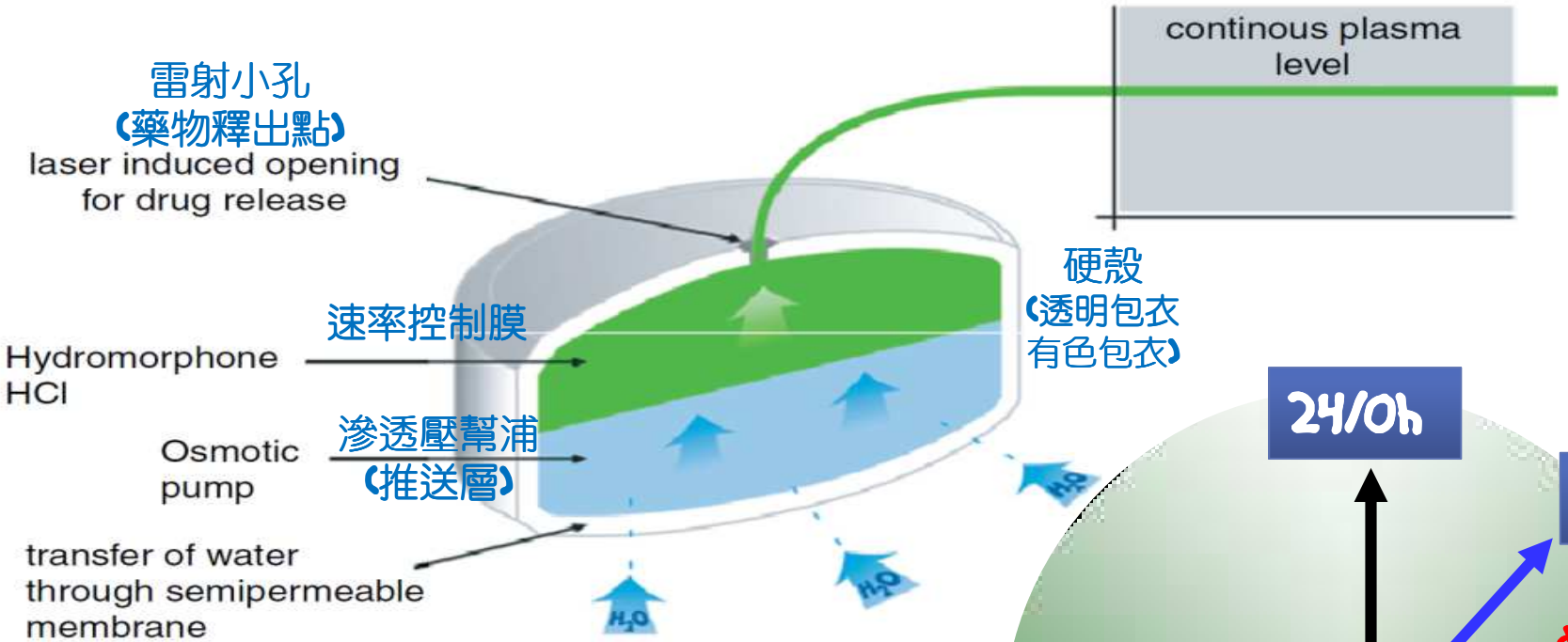
Mu receptors

Duration

24 hours

Hydromorphone /Jurnista

(8mg/tab)



Jurnista® OROS® Hydromorphone Prolonged-Release Tablets (8mg)
釋通 緩釋錠®

Potency

Over oral morphine

1.5* - 2.0*

Mu receptors

Kappa receptor

Duration

Oxynorm: 6 hours

Oxycontin:12 hours

OxyContin® Tablet

Controlled Release, Q12h

MAINTENNCE

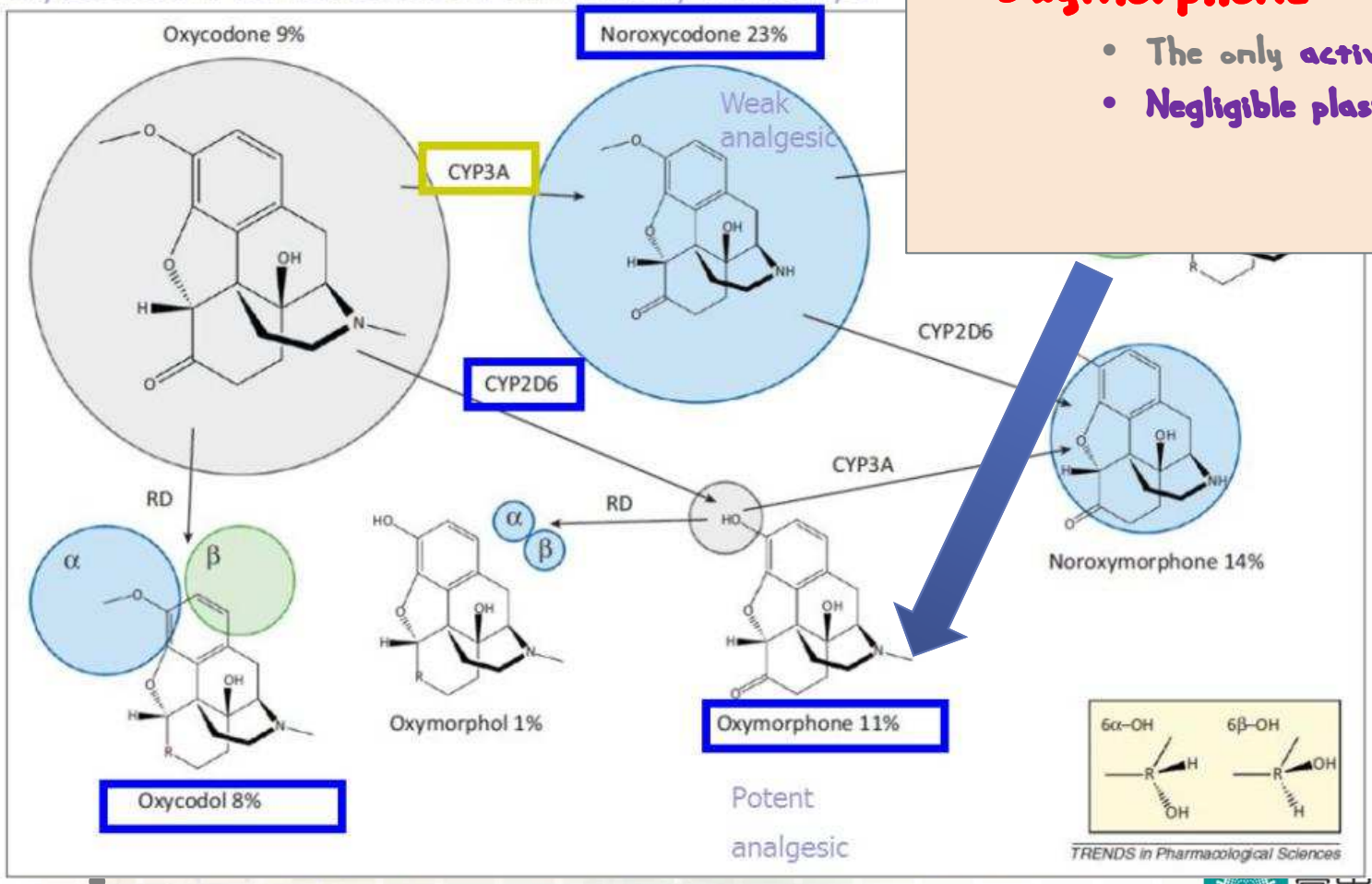
OxyNorm® Capsule

Immediate Release, Q6h

BREAKTHROUGH PAIN

Metabolism

- CYP 450
- Oxymorphone
  - The only active metabolite
  - Negligible plasma levels



Olkkola KT, Kontinen VK, Saari TI, et al. Trends Pharmacol Sci. 2013;34(4):206-14.

Table 3 Number of patients complaining of adverse effects and acceptance to the study drugs

	Combined phase	Morphine-alone phase
Nausea*	1	8
Vomiting*	0	7
Dry mouth	3	2
Hallucination	0	0
Somnolence	7	11
Pruritus	1	1
Constipation	4	5
Sensation of empty head	1	0
Anorexia	14	13
Dyspnoea	0	0
Acceptance to the study drugs	22	21
Patient satisfaction	22	18

OxyContin® Tablet

Controlled Release, Q12h

MAINTENNCE

OxyNorm® Capsule

Immediate Release, Q6h

BREAKTHROUGH PAIN

Advantages

- **Less adverse effects** than morphine
- The same long and short form "10mg"
- **Abuse-deterrent (?)**

British journal of cancer 2003, 89, 2027-2030

普渡製藥遭索賠780億　申請破產

更新時間 (HKT): 2019.09.17 02:20

A A A

製造鴉片類止痛藥「奧施康定」（OxyContin、圖）的美國藥廠普渡製藥（Purdue Pharma）被指是當地鴉片類藥物濫用問題肆虐的元凶之一。這家受2,600多宗訴訟纏繞的藥廠，為應付要賠償100億美元（780億港元）的和解協議，前晚申請破產保護令。

Potency

PO morphine 100x

Mu receptors

Duration

48-72 hours

強效型鴉片類藥物 Fentanyl

- 一般需3天更換一次（少數患者2天）
  - 止痛效果與morphine相似
  - 便秘問題明顯低於morphine

第一片12小時內輔以短效型鴉片類藥物

- 謹慎增加或降低劑量，以免引發戒斷症候群
- 不適用於急性疼痛的緩解或疼痛起伏不穩的患者
- 不是撒隆巴斯，不是貼痛處，不是貼在腫瘤處

Table 2. Recommended Dose Conversion from Morphine to Transdermal Fentanyl[15]

Transdermal Fentanyl	Morphine	
	IV/SubQ *	Oral
12 mcg/h	10 mg/d	30 mg/d
25 mcg/h	20 mg/d	60 mg/d
50 mcg/h	40 mg/d	120 mg/d
75 mcg/h	60 mg/d	180 mg/d
100 mcg/h	80 mg/d	240 mg/d

Version. NCCN	Ver 2.2014	Ver 2.2015	Ver 1.2016
Oral morphine (mg/d)	Table oriented	Oral 2mg/d → Pacth 1ug/hr	Oral 200mg/d → Pacth 100ug/hr
30mg	12 ug/hr	15 ug/hr	15 ug/hr
120mg	50 ug/hr	60→50 ug/hr	60→50 ug/hr

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY (8 of 11)

CONVERT OR ROTATE FROM ANOTHER OPIOID TO TRANSDERMAL FENTANYL

1. Determine the 24-h analgesic requirement of morphine.
2. For conversion from oral morphine to transdermal fentanyl, consider ratio of 2 mg/d oral morphine: 1 mcg/h of transdermal fentanyl patch.[16]
3. Conversion ratio is not to be used for converting from fentanyl patch to oral morphine.

are approximate and clinical judgment must be used to titrate to the

Table 2. Recommended Dose Conversion ine to Transdermal Fentanyl[15]

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100 mcg/h	80 mg/d	240 mg/d

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Convert or Rotate From Another Opioid to Transdermal Fentanyl

1. Determine the 24-h analgesic requirement of morphine.
2. For conversion from oral morphine to transdermal fentanyl, consider ratio of 200 mg/day oral morphine = 100 mcg/h fentanyl patch.
   See Table 2 PAIN-E, 7 of 13 for converting other opioids to morphine equivalent with subsequent conversion to transdermal fentanyl.[20]
3. Clinical data are unavailable to recommend specific ratio to convert from fentanyl patch to oral morphine. (Common clinical practice is to use a similar conversion ratio as when switching from oral morphine to transdermal fentanyl. Titrate with caution.)

Clinical data are unavailable to recommend specific ratio to convert from fentanyl patch to oral morphine.

- Common clinical practice is to use a similar conversion ratio as when switching from oral morphine to transdermal fentanyl
- Titrate with caution

[20] Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology (Williston Park) 2000;14:695-702.
[21] Kornick CA, Santiago-Palma J, Khojainova N, et al. A safe and effective method for converting patients from intravenous to transdermal fentanyl. Cancer 2001;92:3056-3061.

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當一個病人明明已經
規則使用足夠長效
OPIOIDS...

PAIN

PRN藥品有沒有效?

Oxynorm (5)

Morphine (15)

有

平均一天吃幾次PRN?

四次以上

四次以內

上調ATC劑量

持續觀察

PRN止痛效果

判斷是否換PRN的關鍵

短效藥(救急的止痛藥)有沒有效?

吃了之後多久才能止痛？

疼痛次數

判斷是ATC不足還是PRN不足的關鍵

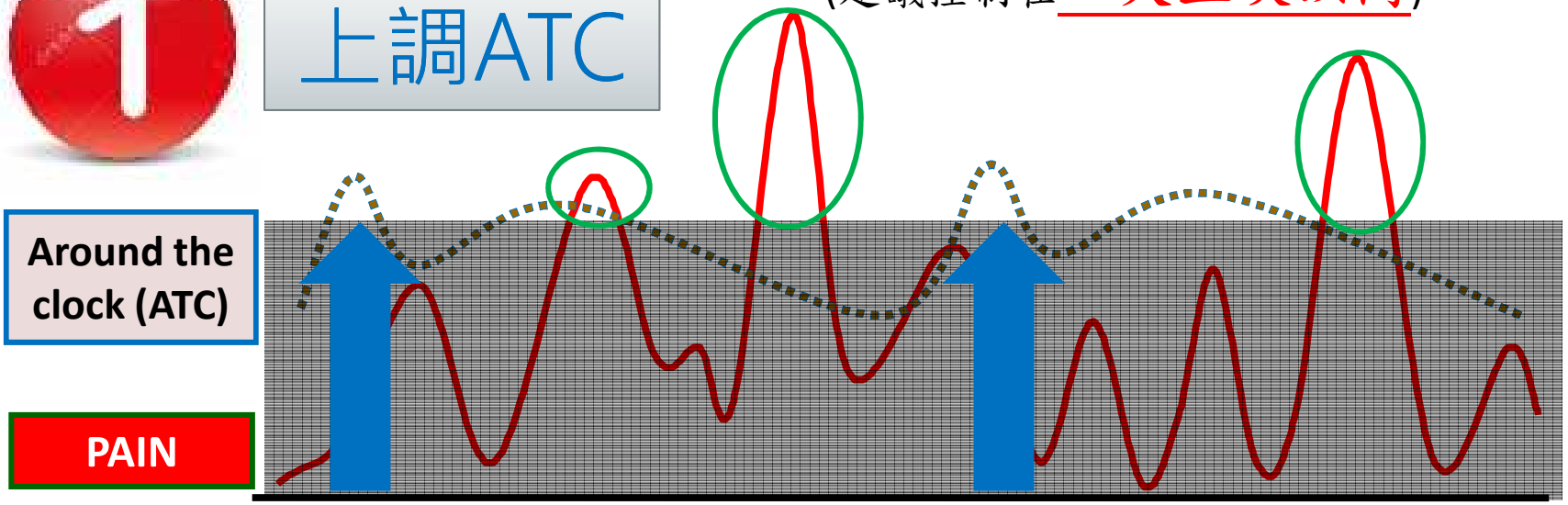
現在一天大概痛幾次？(短效藥吃幾次)

Breakthrough pain
(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)
- **Frequent in nature** 頻繁發生

(建議控制在一天三次以內)

1 上調ATC



Oxycodone (Oxycontin)

Hydromorphone (Jurnista)

Buprenorphine (Transtec)

Fentanyl Patch

MXL, morphine cont

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

OPIOID PR

NANCE OPIO
s appropriate
r long-acting
pioids.
rting to long-

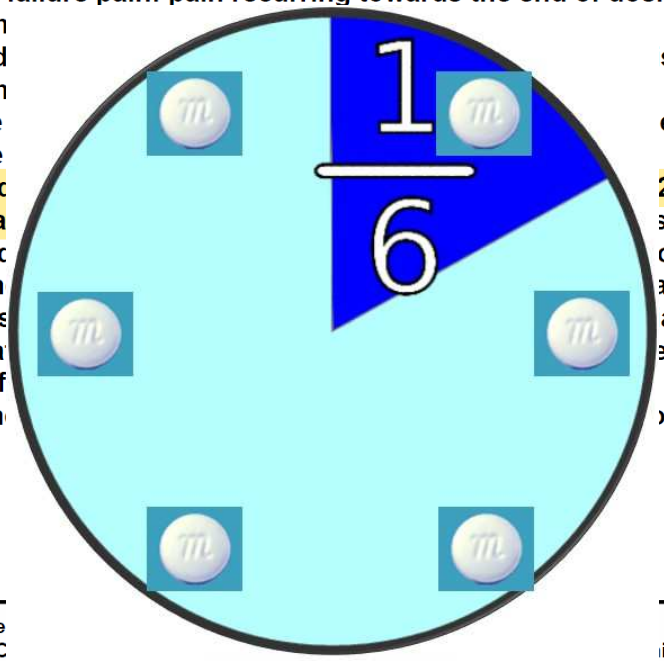
Allow rescue doses of short-acting opioids of 10-20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every 1 hour as needed.

(1) ---- > Rapid onset opioids (rapidly acting transmucosal fentanyl) not included

選擇短效
PRN

ioid
ort-a
s to
ved
gori
with

- End-of-dose failure pain: pain recurring towards the end of dosing interval for regularly scheduled opioid, potentially managed by increasing th
- Uncontrolled sting regularly scheduled opioid, potentially managed by adjusting dose of regularly sch



- Increase dose eeds doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve
- Allow rescue d 24-hour total of long-acting or regularly scheduled oral opioid dose up to every 1 hour a s may indicate a need for adjustment of regularly scheduled opioid dose.
- Consider rapic ons and delivery systems are available) in opioid-tolerant patients for brief episodes of in around-the-clock opioid.
  - Data do not s analgesic to other opioids or between different transmucosal formulations. Always initia en formulation and titrate to effect. (See specific transmucosal prescribing information f
- Continue to m oid use that may suggest misuse or abuse. (See Pain E 3 of 11)

Continued on next page

Note: All recomme
Clinical Trials: NCC ical trial. Participation in clinical trials is especially encouraged.

Adult Cancer Pain

Guidelines Index
Adult Cancer Pain TOC
Discussion, References

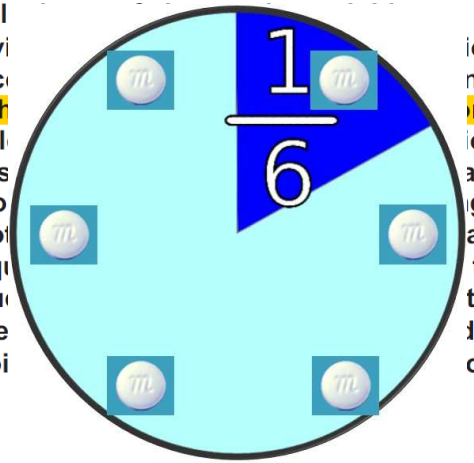
GENERAL PRINCIPLES

- The appropriate dose is the d … g unmanageable side effects.
- Generally, oral route is most … sal, buccal) can be considered as indicated to ma…
- Calculate dosage increase ba… the previous 24 h.
- Increase both around the cloc… severity of the symptoms. See Management of Pain in O…
- According to FDA guidelines, … pirin or acetaminophen) to pure opioid preparation if … opioid component of combination. (See PAIN-K)
- Steady state is achieved in ab…
- If patient is experiencing unm… oximately 25% and reevaluate. Patient would require close follow-up to make sure pain did not escalate.
- Consider opioid rotation if pain inadequately controlled or persistent side effects from current therapy.

PRINCIPLES OF MAINTENANCE OPIOID TH…

- For continuous pain, it is appropriate to gi…
- Add extended release or long-acting formu… stabl…
- Provi… exac…
  - Wh… r short-acting and extended release forms.
  - All… res… oids of 10% to 20% of 24-h oral dose (mg) every 1 h as needed. Ongoing need for repeated adjustment of regularly-scheduled opioid dose.
  - Co… not… eq… bu… ge, tablets, film) only in opioid tolerant patients for brief episodes of acute exacerbation of pain around the clock opioid. Data do not support a specific transmucosal fentanyl dose transmucosal fentanyl with lowest dose (200 mcg lozenge or 100 mcg buccal tablet or 200 mcg t. (See specific transmucosal prescribing information for appropriate dosing intervals.)
- Incre… opioi… l if patient persistently needs doses of as needed opioids or when dose of around the clock or at end of dose.

When possible, use the same opioid for short-acting and extended-release forms.



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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

“儘量長短效同成分搭配” 的建議從2019年第三版便被移除

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Adult Cancer Pain

NCCN Guidelines Index
Table of Contents
Discussion

OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, AND SAFETY

Principles of Maintenace Opioid Therapy

- For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain.
- Add extended-release or long-acting formulation to provide background analgesia 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% to 100% of the daily requirement, depending on expected pain natural history.
- When using methadone as a long-acting opioid, consider supplementing with doses of short-acting opioid.
- 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.

PAIN-E 4 of 13

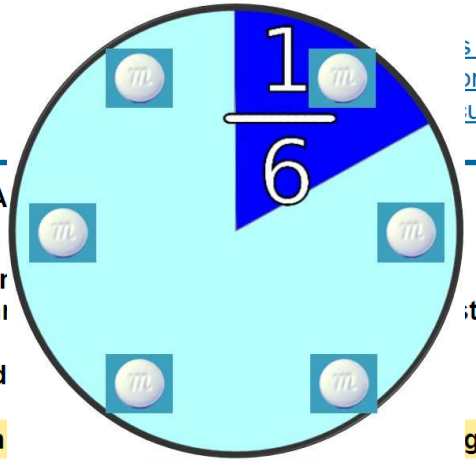
- Bullet 3 was revised: "~~When possible, use the same opioid for short-acting and extended-release forms.~~ When using methadone as a long-acting opioid, consider..."

episodes of incident pain not relieved by traditional immediate-release opioids and not attributed to inadequate dosing of around-the-clock opioid.

  - Data do not support a specific transmucosal fentanyl dose equianalgesic to other opioids or between different transmucosal formulations. Always initiate transmucosal fentanyl with lowest dose in chosen formulation and titrate to effect. (See specific transmucosal prescribing information for appropriate dosing intervals.)
- Continue to monitor patients/family for abnormal patterns of opioid use that may suggest misuse or abuse. (See PAIN-E 6 of 13)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

- 2019 NCCN guideline_Adult Cancer Pain v3
- 2020 NCCN guideline_Adult Cancer Pain v1

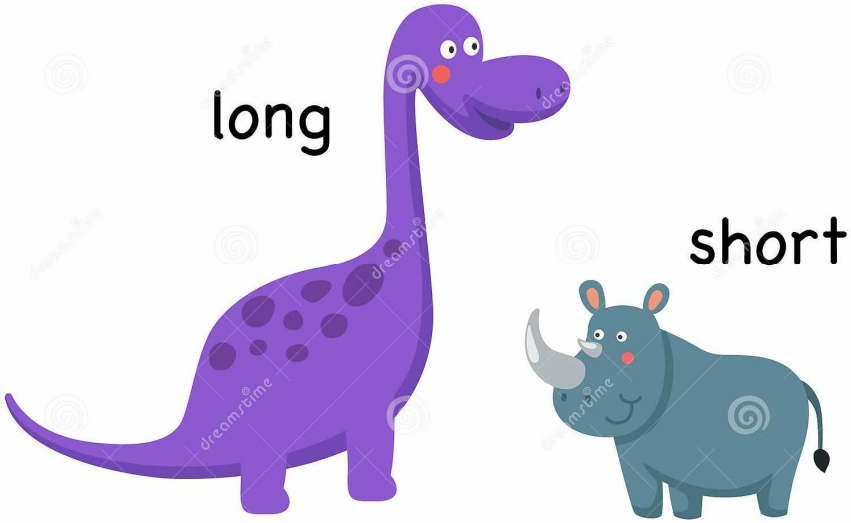


OPIOID PRINCIPLES, PRESCRIBING, TITRATION, MAINTENANCE, A

Principles of Maintenance Opioid Therapy

- For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemer
- Add extended-release or long-acting formulation to provide background analgesia for control of chi stable doses of short-acting opioids.
  - Initial range for converting to long-acting opioid would be 50% to 100% of the daily requirement, d history.
  - If using different forms of long-acting and short-acting opioids, particular care must be taken with g.
- When using methadone as a long-acting opioid, a short-acting opioid should also be provided for breakthrough pain.
- Increase dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid
- al her
- dose of
- Allow rescue doses of short-acti y scheduled oral opioid dose up to every 1 hour as needed (if hourl vention is recommended).
  - For regular use, short-acting o
  - For end-of-life care with severe ded) may be considered.
- Consider rapidly acting transmu e) in opioid-tolerant patients for brief episodes of incident pain not rel dequate dosing of around-the-clock opioid.
  - Data do not support a specific different transmucosal formulations. Always initiate transmucosal fe e specific transmucosal prescribing information for appropriate dos
- Continue to monitor patients/fan g use and/or diversion. (See PAIN-E, 6 of 13)
- Consider potential drug interact

If using **different forms** of long-acting and short-acting opioids, particular care must be taken with **conversions and appropriate dosing**.



Note: All recommendations are category 2A u
Clinical Trials: NCCN believes that the best n lly encouraged.

當一個病人明明已經
規則使用足夠長效
OPIOIDS...

PAIN

PRN止痛效果

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Oxynorm (5)

Morphine (15)

有

平均一天吃幾次PRN?

四次以上

四次以內

上調ATC劑量

持續觀察

當一個病人明明已經規則使用足夠長效OPIOIDS...

PAIN

PRN藥品有沒有效?

Oxynorm (5)

Morphine (15)

無

有

哪裡痛?怎樣痛?

評估轉移/神經痛可能

無

有

考慮換PRN

考慮加上輔助藥品

疼痛部位/性質

(判斷是否有復發/轉移/其他的痛: 例如肌肉痛,神經痛的關鍵)

這次痛的地方跟上次一不一樣?

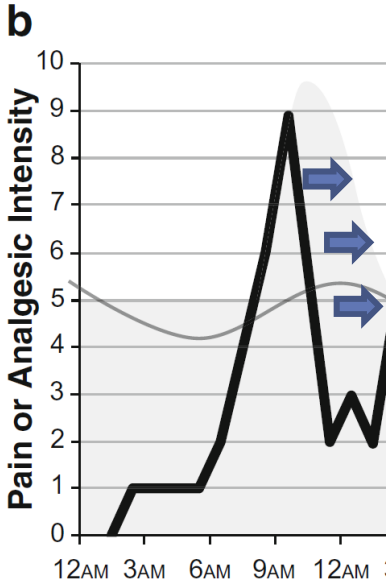
這次痛的樣子跟上次一不一樣?

門診再評估

PRN藥品有沒有效?

無

哪裡痛?怎樣痛?



評估轉移/神經痛可能

無

ROO

- 藥品作用慢無法馬上緩解疼痛?
- 病人沒有痛那麼久?
- Home care遇到不可預期突發痛?
- PRN藥物不是完全沒效只是太慢發作

臺中榮民總醫院
Taichung Veterans General Hospital

NSAIDs | Opioids | Adjuvants | Others | Intervention

Cancer Pain Medication Control

Effective Pain Control

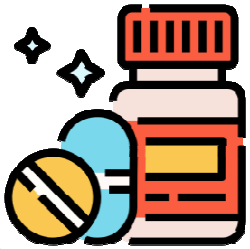
80~95%

Cancers 2019, 11, 443

Br J Anaesth 2008; 101: 95–100

Cancer Pain Medication Control

“Refractory Pain” **5~20%**



Effective Pain Control **80~95%**

Cancers 2019, 11, 443

Br J Anaesth 2008; 101: 95–100

Cancer Pain Medication Control

"Warning from WHO"

Refractory Pain

- Fail to achieve acceptable pain state
- Intolerable side effect

***May benefit from a Interventions !**

Cancers 2019, 11, 443
Br J Anaesth 2008; 101: 95 – 100
NCCN Practice Guideline 2020
WHO guideline for cancer pain 2018

ONGOING CARE

- If applicable, convert from parenteral to oral/transdermal opioids (if feasible) including extended-release or long-acting agent with rescue doses (Conversion
  - Simplify an
- Have regular
  - Assess pai or more fre
    - Patient's
    - Institutio
    - Regulato
- Monitor for th factors for or
- Provide writt (See PAIN-I)
- Ensure conti
  - Collaborate
  - Clarify whic
- Address syst
  - Analgesic c
  - Availability
  - Local laws/
- Instruct the p
  - Following c
  - Scheduling
  - Contacting controlled, of analgesi
  - Safe handli
- Reevaluate p available the
- Maintain com and relevant NCCN Guide

Routinely reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety

GOALS OF TREATMENT

(See PAIN-E 5 of 13)

- See Universal Screening and Assessment (PAIN-2)
- Consider pain management specialty consultation (PAIN-L)
- Consider interventional strategies (PAIN-M) or other treatments
- Consider palliative care consultation (See NCCN Guidelines for Palliative Care)
- Evaluate for other sources of distress (eg, psychological, social, spiritual), which may contribute to poorly controlled physical pain. (See NCCN Guidelines for Distress Management)

Not achieved →

ollow-up
for opioids
ropriate
3)

eening and
-2)
nagement
ation (PAIN-L)
tional
M) or other

e care
NCCN
liative Care)
sources of
hological,
which may
rly controlled
e NCCN
stress

Note: All recomm
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Cancer Pain Interventions

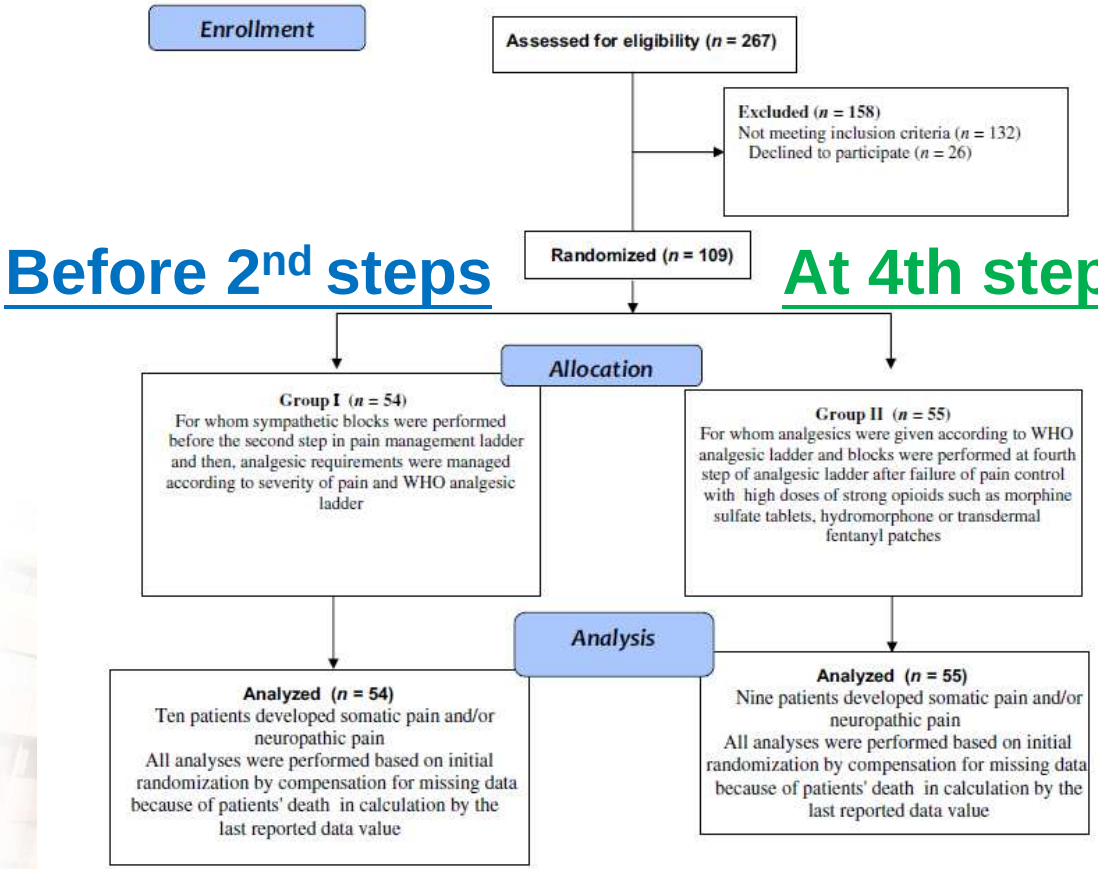
When ?

Block Before Severe ?

Block After Failure ?

Cancer Pain Interventions

When ?



Before 2nd steps

At 4th steps

Fig. 1. Flow diagram of patient progress through the phases of the randomized trial.

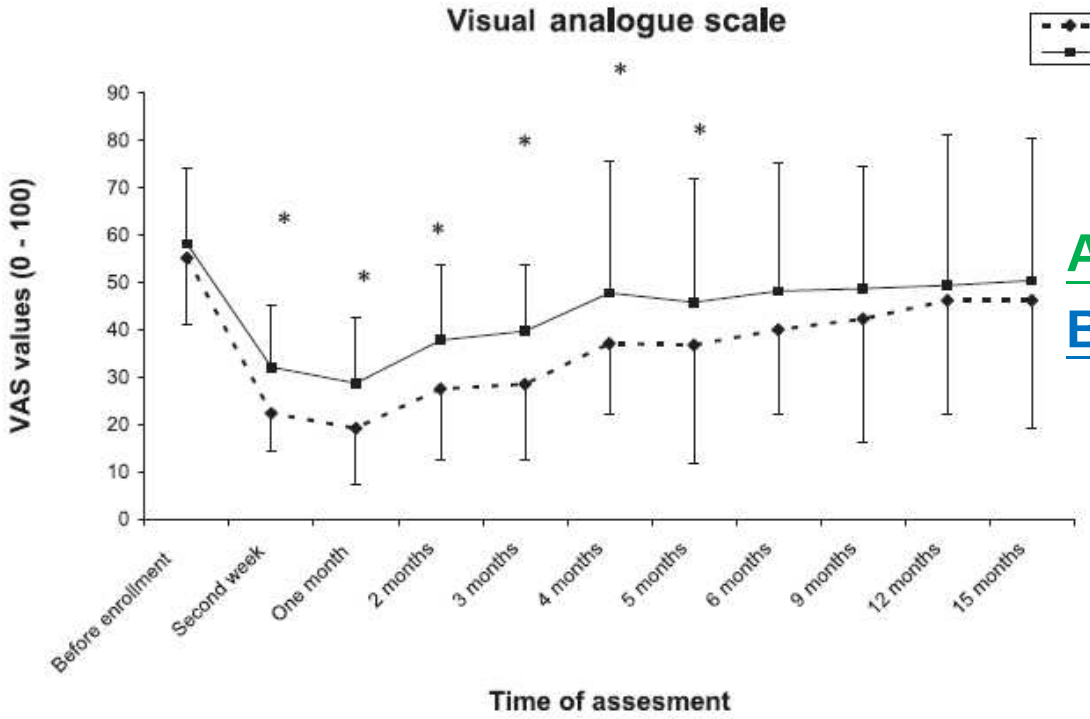
- A Prospective, Randomized Multicenter Study
- 109 patients
- Sympathetic blocks for abdominal and pelvic cancer

J Pain Symptom Manage. 2014 Nov;48(5):944-56.e2.

Cancer Pain Interventions

When ?

VAS



At 4th steps

Before 2nd steps

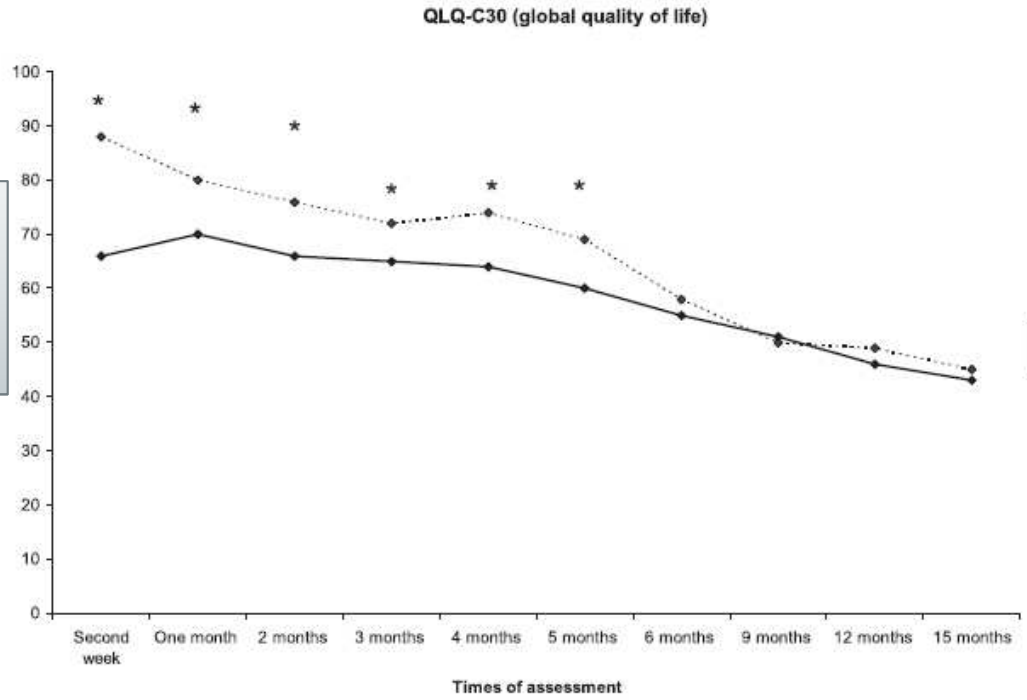
Fig. 9. Pain scores during follow-up period for both groups expressed as mean ± SD. "*" Significant difference in Group II vs. Group I. Missing data in calculation of mean because of patient deaths are compensated for by using the last reported data value. Therefore, 54 and 55 patients were used at all times of assessment in each group, respectively.

J Pain Symptom Manage. 2014 Nov;48(5):944-56.e2.

Cancer Pain Interventions

When ?

QOL



Before 2nd steps

GroupI
Group II

At 4th steps

Fig. 10. QLQ-C30 subscales of global quality of life; data were expressed as mean in each group. "*" Significant difference in Group II vs. Group I. Missing data in calculation of mean because of patient death are compensated for by using the last reported data value. Therefore, 54 and 55 patients were used at all times of assessment in each group, respectively.

J Pain Symptom Manage. 2014 Nov;48(5):944-56.e2.

Cancer Pain Interventions

When ?

Table 2

Opioid Consumption (Represented in Equivalent Doses of Oral Morpine Sulfate [mg/d]) During Follow-Up Period for Both Groups

Tim	Before 2nd steps	At 4th steps	
Second week	65.5 ± 15.4	98.4 ± 16.5	<0.0001[a]
1 Month	60.8 ± 14.5	95.2 ± 13.5	
2 Months	84.4 ± 29.5	120.5 ± 27.3	
3 Months	107.5 ± 35.5	142.5 ± 31.6	
4 Months	115.6 ± 14.5	160.0 ± 29.5	
5 Months	110. 7 ± 27.5	172.5 ± 39.5	
6 Months	119.28 ± 28.5	176.87 ± 38.5	
9 Months	125.3 ± 28.5	153.3 ± 35.7	
12 Months	165.5 ± 20.5	198.0 ± 45.5	
15 Months	188.5 ± 25.5	208.0 ± 45.5	0.007[a]

Data expressed as mean ± SD.

[a]Significant difference in Group II vs. Group I. Missing data in calculation of mean ± SD because of patient death are compensated for by using the last reported data value. Therefore, 54 and 55 patients were used at all times of assessment in each group, respectively.

Opioid Comsuption

J Pain Symptom Manage. 2014 Nov;48(5):944-56.e2.

Cancer Pain Interventions

Complications

When ?

Table 3

Incidence of Opioid Side Effects During the Follow-Up Period

Side Effects	Before 2nd steps	At 4th steps	
Nausea	12	23	0.03[a]
Constipation	12	26	0.006[a]
Pruritus	4	16	0.005[a]
Insomnia	10	8	0.14
Urine retention	3	5	0.09
Loss of appetite	18	21	0.06

[a]Significant difference in Group II vs. Group I, $P < 0.05$.

J Pain Symptom Manage. 2014 Nov;48(5):944-56.e2.

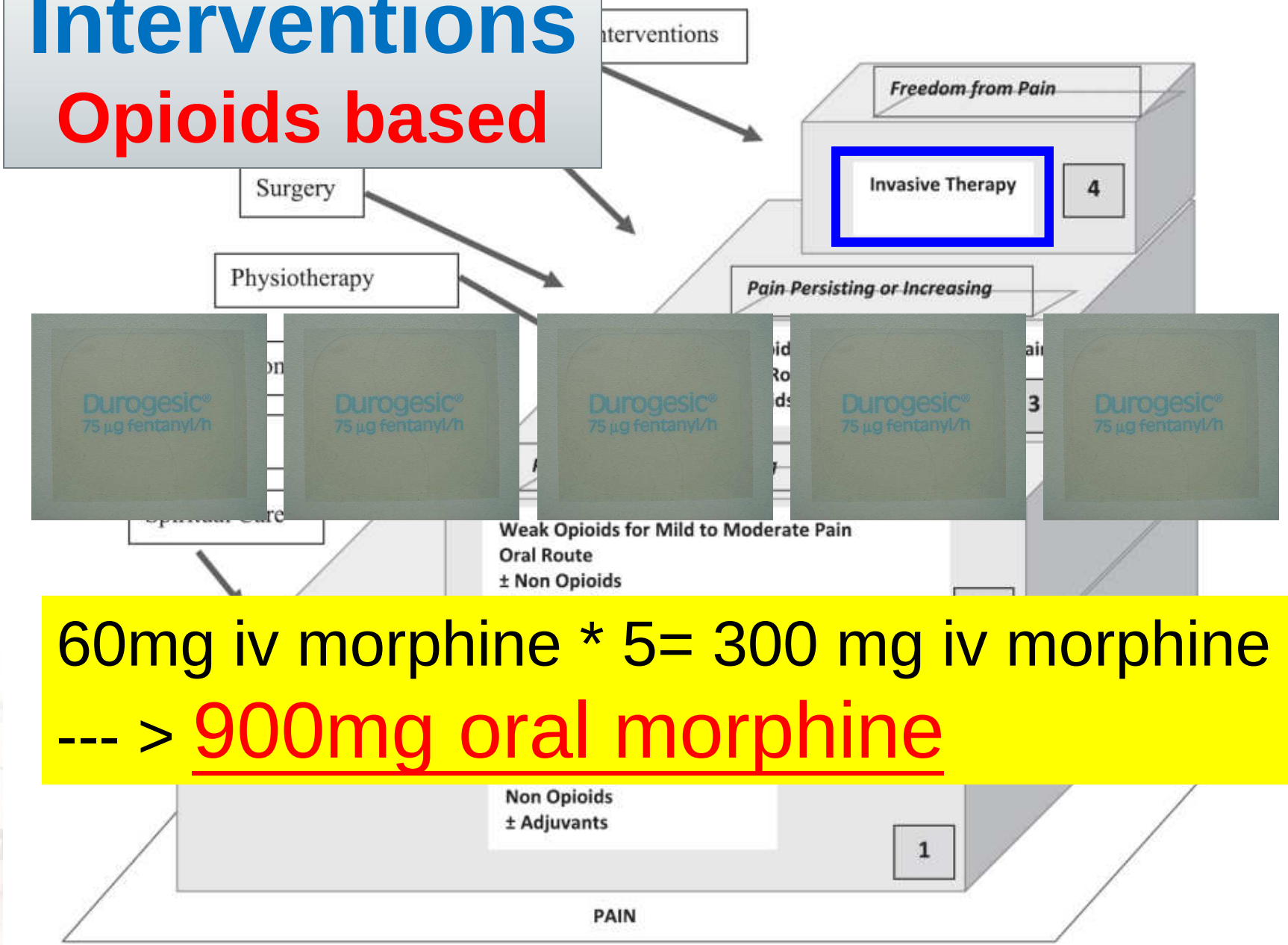
Cancer Pain Interventions

When ?

Block Before Severe

Block After Failure

Interventions
Opioids based



60mg iv morphine * 5= 300 mg iv morphine

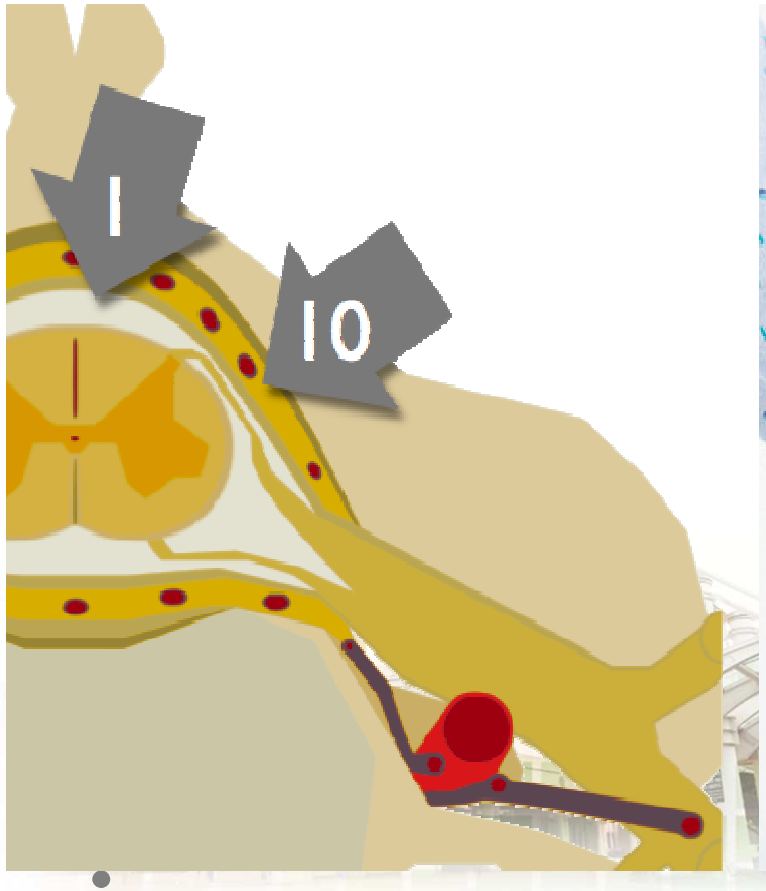
--- > 900mg oral morphine

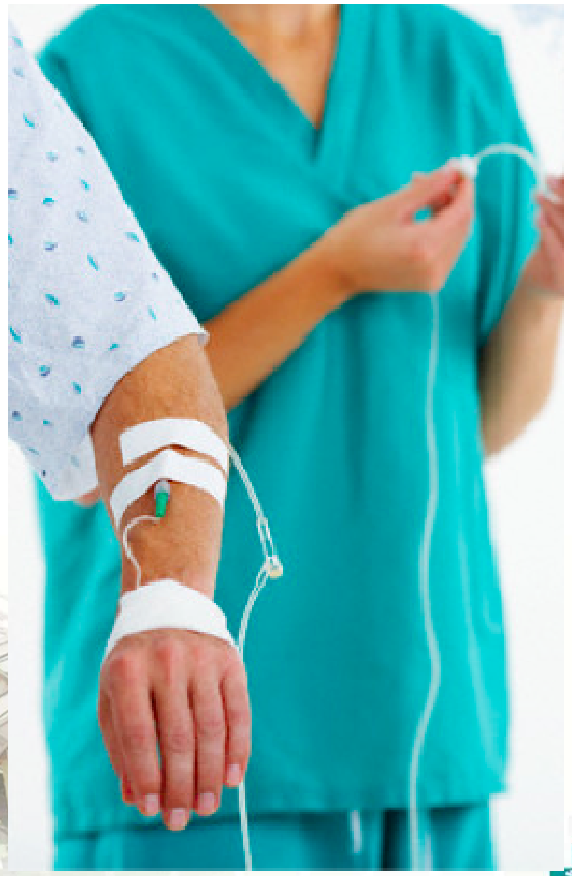
Vadalouca A, Raptis E, Moka E, et al. Pain Pract. 2012;12(3):219-51.

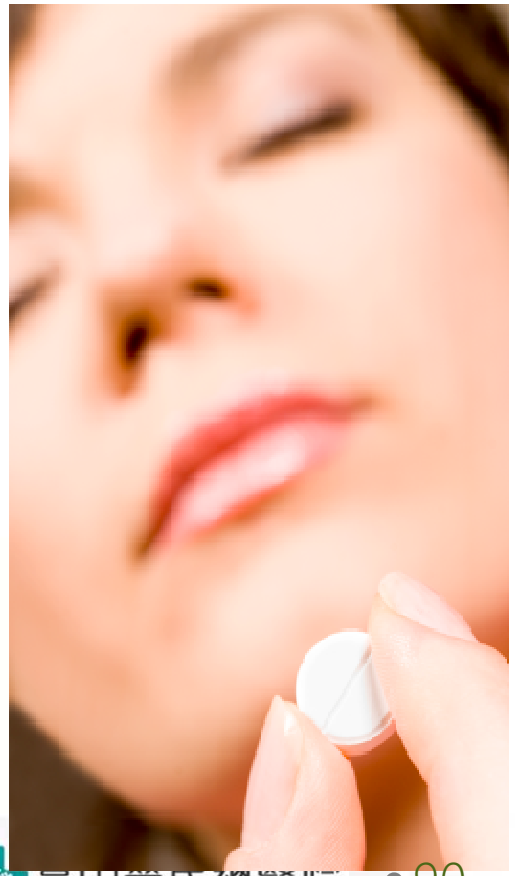
Morphine Conversion Ratio

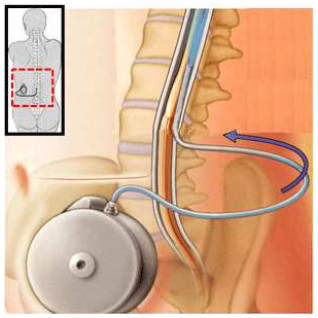
:100 **:300**

Intravenous ***Oral***





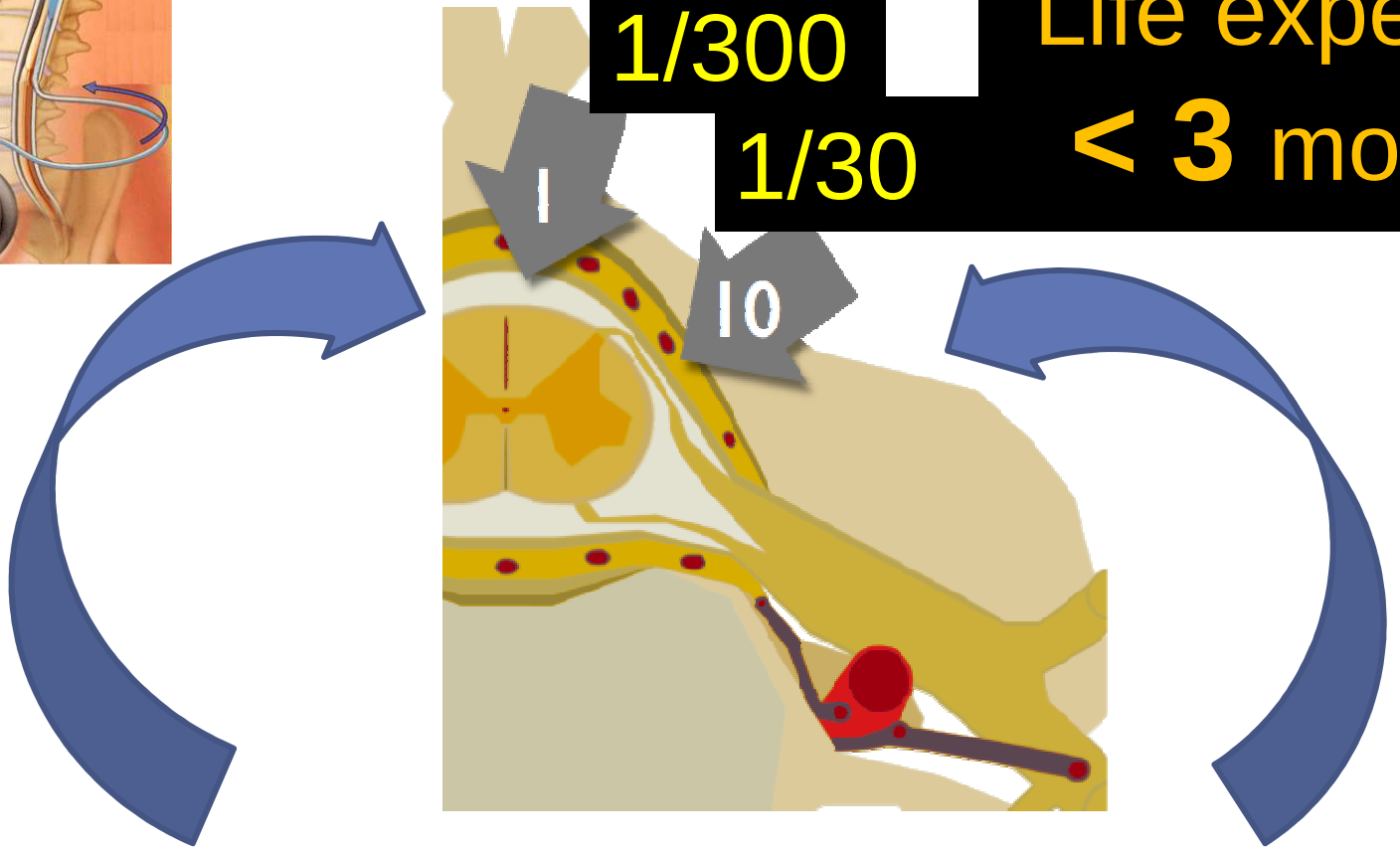




1/300

1/30

Life expectancy
< 3 months ?



Intrathecal catheter

Diffuse pain, Epidural space obliterated by tumor or surgery

Epidural catheter

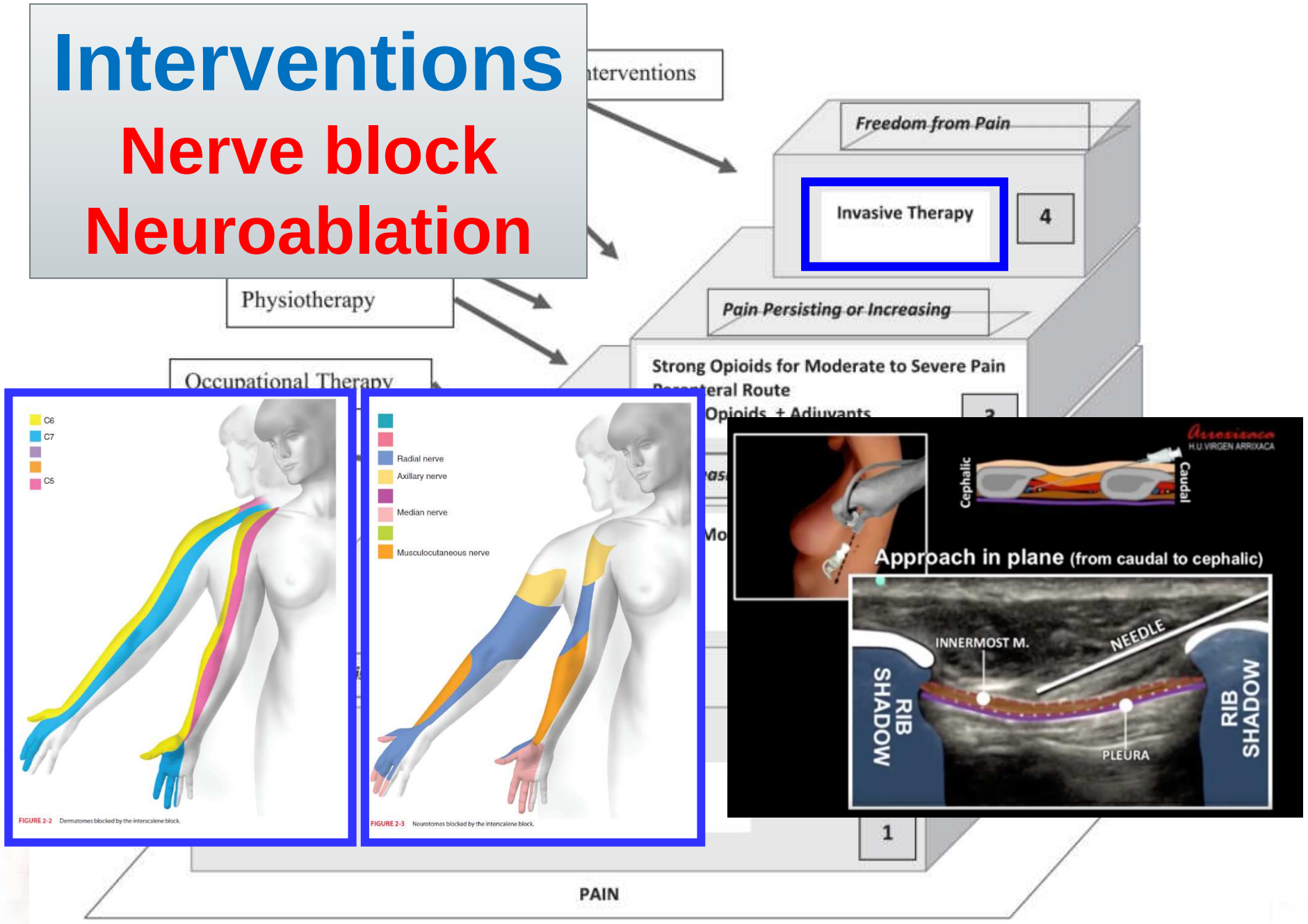
Need for focal local anesthetics

NTUH Protocol

Ann Oncol. 2012;23 Suppl 7:vii139-54.

Interventions

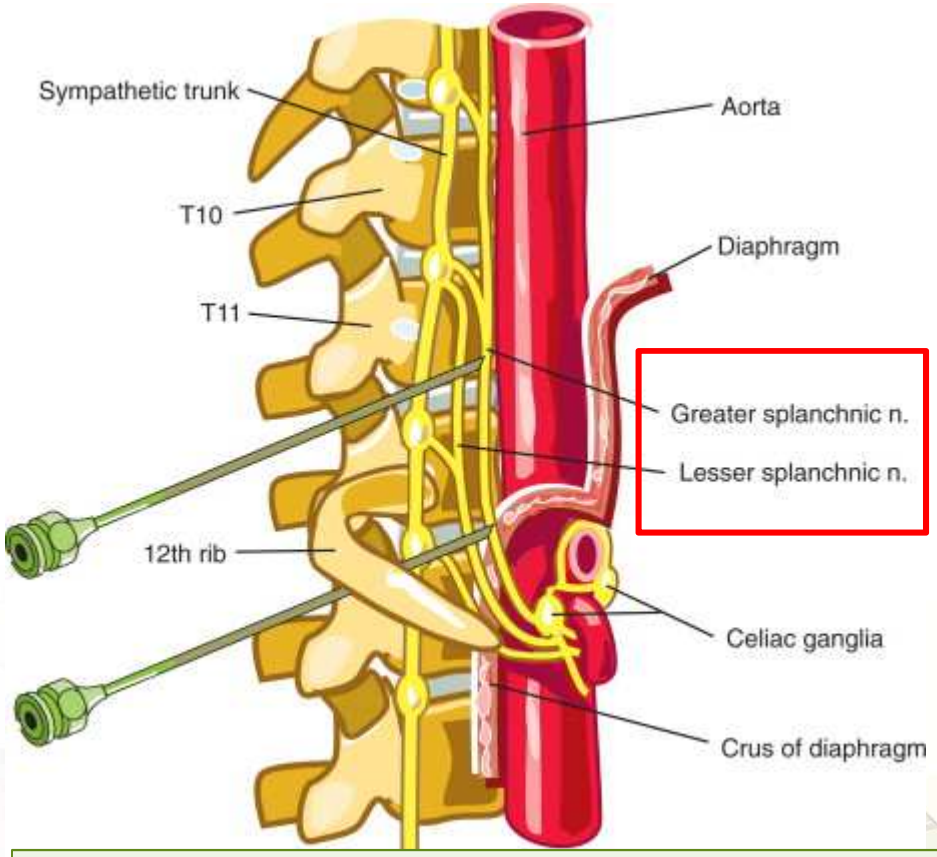
Nerve block
Neuroablation



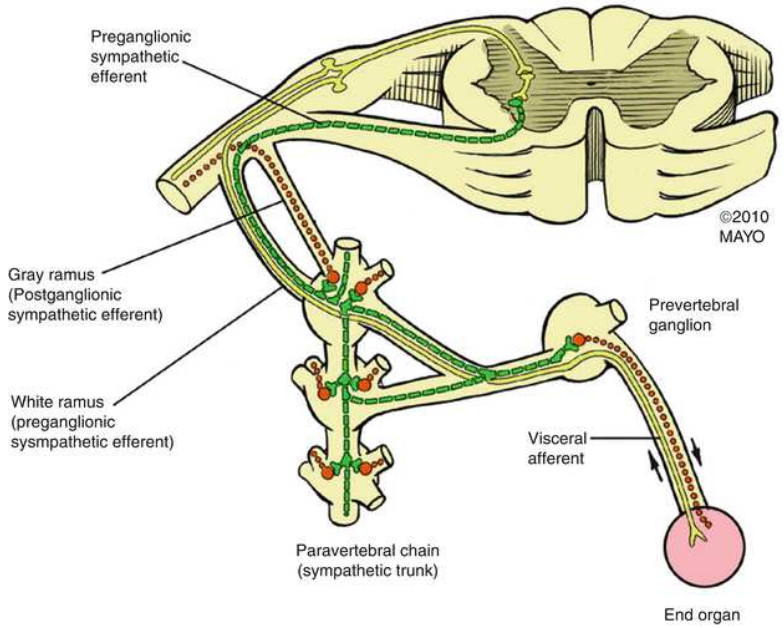
Vadalouca A, Raptis E, Moka E, et al. Pain Pract. 2012;12(3):219-51.

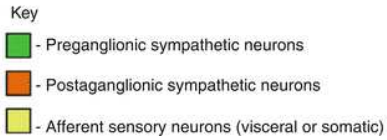
Interventions

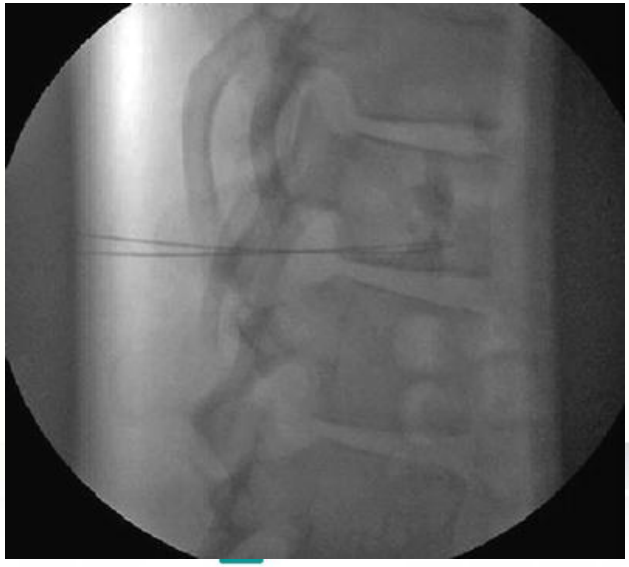
Sympathetic Blockade

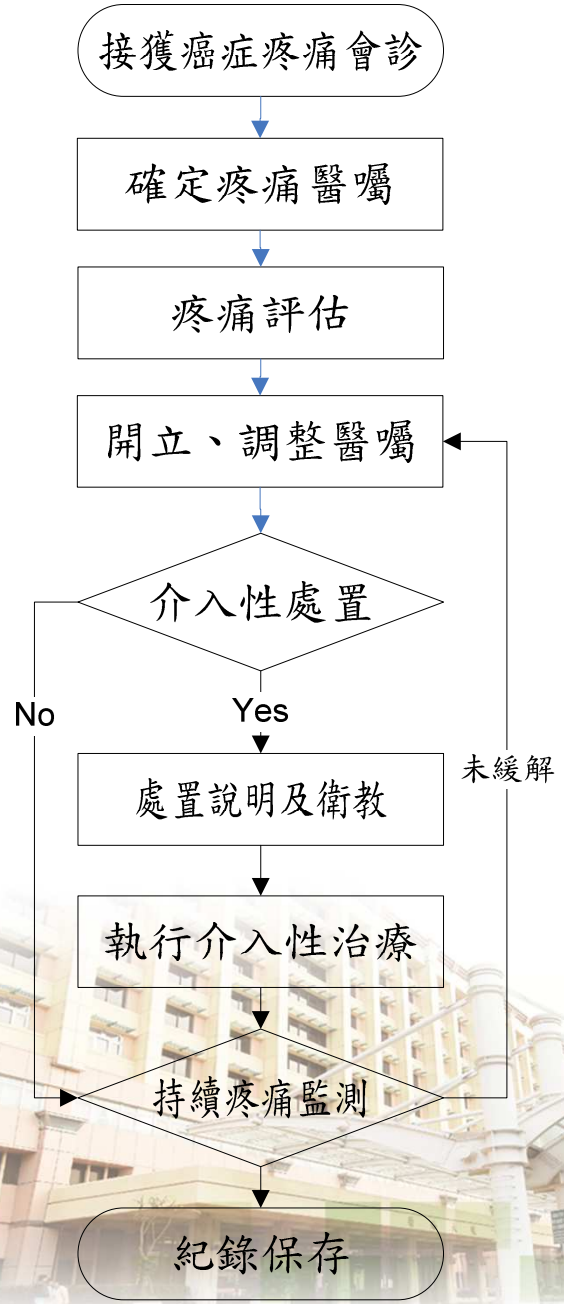


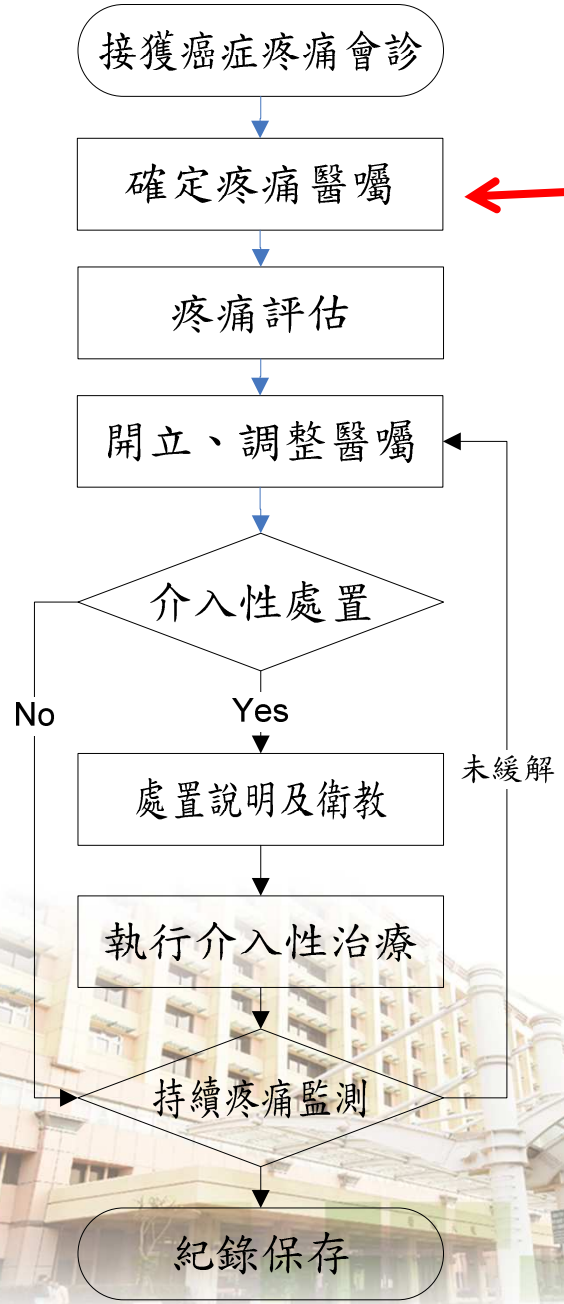
Splanchnic Nerve Block





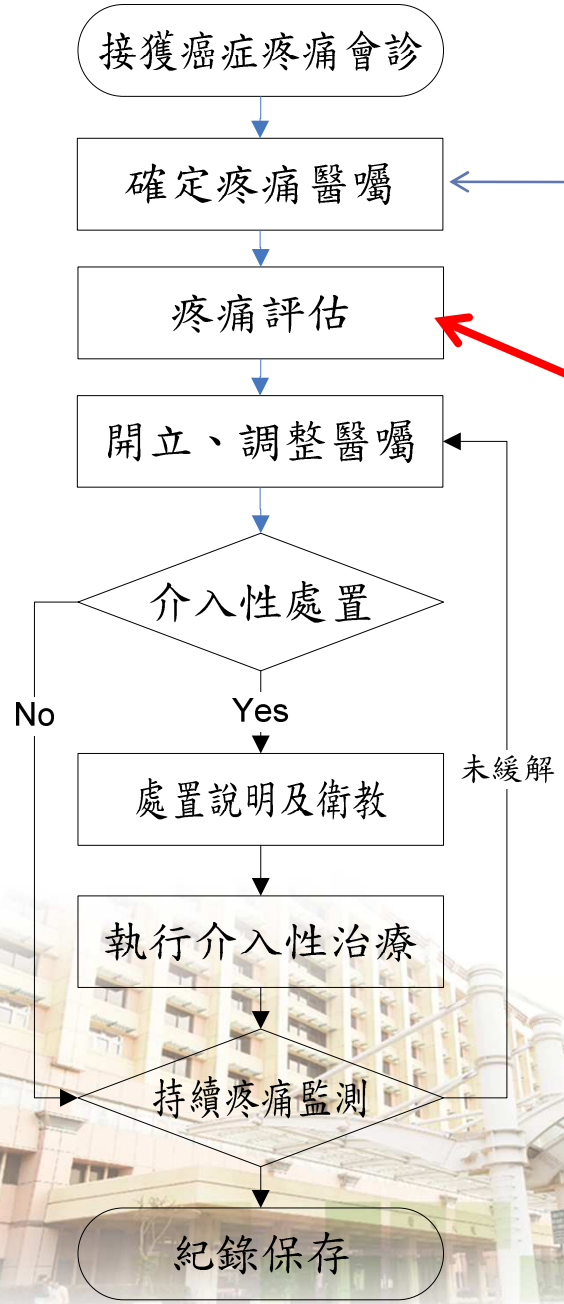



接獲癌症疼痛會診
確定疼痛醫囑
疼痛評估
開立、調整醫囑
介入性處置
No
Yes
處置說明及衛教
未緩解
執行介入性治療
持續疼痛監測
紀錄保存



主動追蹤院內疼痛控制不佳的患者

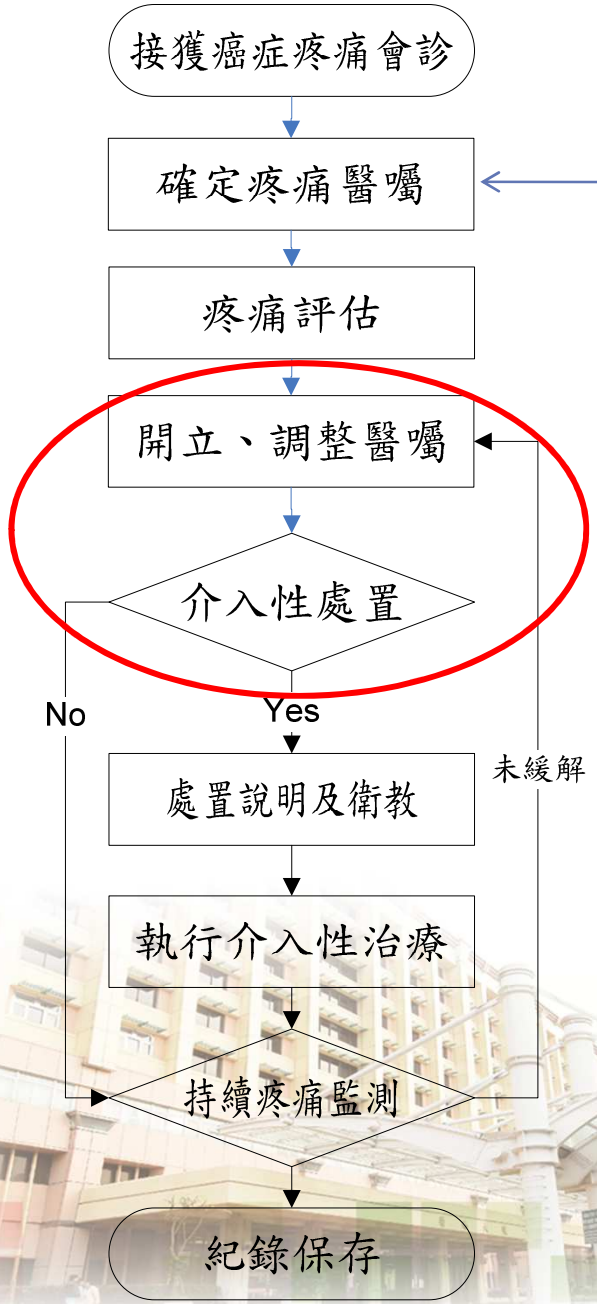
- 3324儀表板管理系統
  - “24小時” 期間
  - 次數” 3次以上”
  - 疼痛分數” 大於3分”



主動追蹤院內疼痛控制不佳的患者

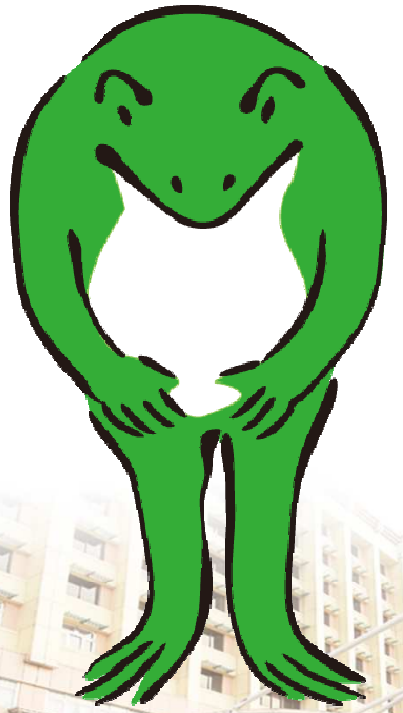
- 疼痛類型
  - Nociceptive, Neuropathic
  - Visceral, Somatic, Bone, Nerve
- 疼痛位置
  - Dermatome, Myotome, Sclerotome

類型	體感性疼痛 (somatic pain)	內臟性疼痛 (visceral pain)	神經病變性疼痛 (neuropathic pain)
原因	體表、骨骼、肌肉受損;骨轉移	臟器受損、阻塞;平滑肌痙攣	神經組織受損
疼痛性質	刀刺痛、銳痛、搏動性痛	悶痛、絞痛、不明體表疼痛	灼痛、刺痛、電擊痛
特點	可明確指出痛處	定位困難 廣泛，轉移痛	疼痛常沿神經分佈 敏感
治療	對一般藥物反應佳	需鴉片類藥物	多需合併輔助劑 Antidepressant Anticonvulsant



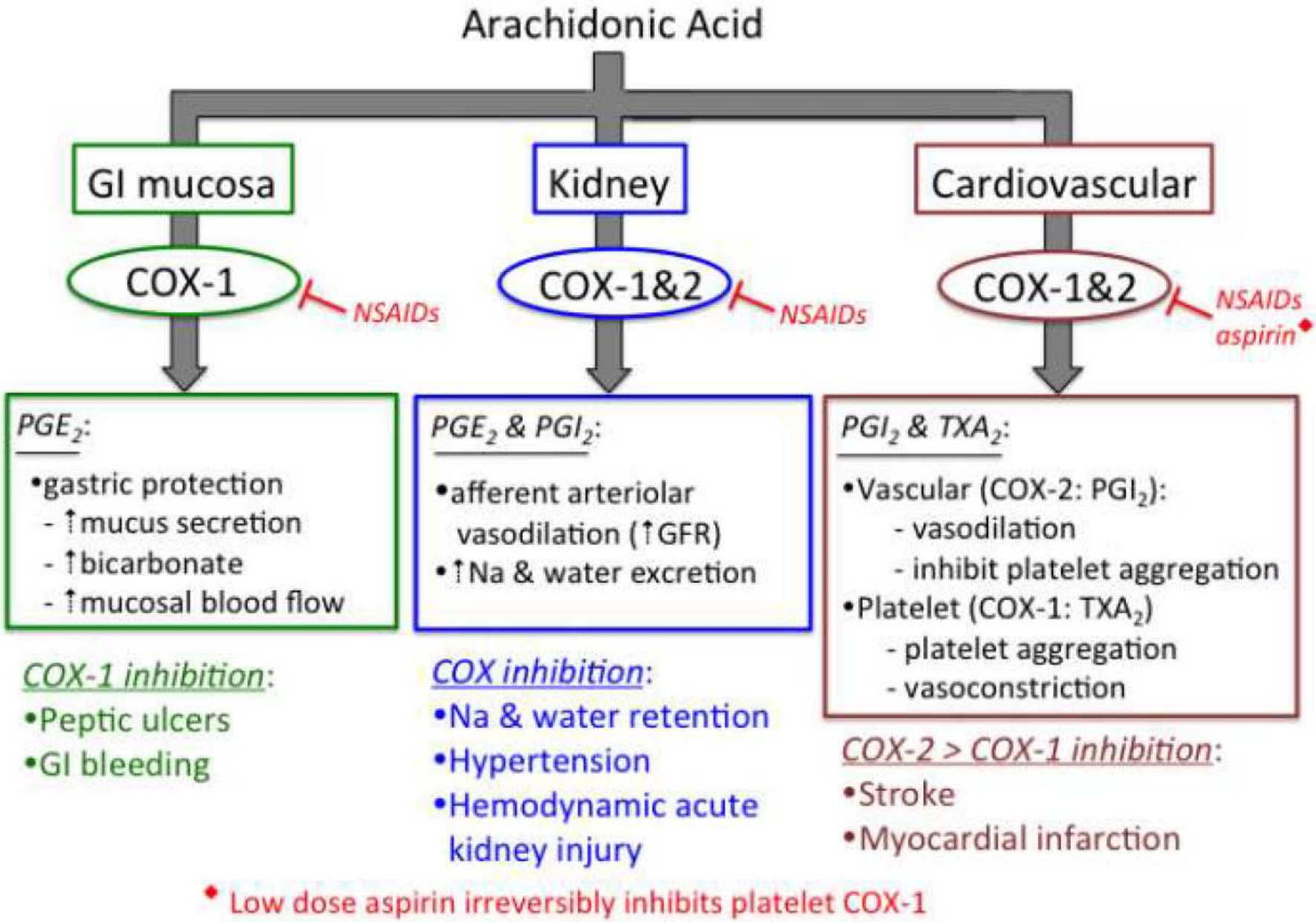
主動追蹤院內疼痛控制不佳的患者

- 同步評估藥物的使用與介入性治療的可行性



感謝聆聽

類型	體感性疼痛 (somatic pain)	內臟性疼痛 (visceral pain)	神經病變性疼痛 (neuropathic pain)
原因	體表、骨骼、肌肉受損;骨轉移	臟器受損、阻塞;平滑肌痙攣	神經組織受損
疼痛性質	刀刺痛、銳痛、搏動性痛	悶痛、絞痛、不明體表疼痛	灼痛、刺痛、電擊痛
特點	可明確指出痛處	定位困難 廣泛，轉移痛	疼痛常沿神經分佈 敏感
治療	對一般藥物反應佳	需鴉片類藥物	多需合併輔助劑 Antidepressant Anticonvulsant


Arachidonic Acid
GI mucosa
Kidney
Cardiovascular
COX-1
COX-1&2
COX-1&2
NSAIDs
NSAIDs
NSAIDs
aspirin
PGE2:
•gastric protection
- ↑mucus secretion
- ↑bicarbonate
- ↑mucosal blood flow
PGE2 & PGI2:
•afferent arteriolar vasodilation (↑GFR)
•↑Na & water excretion
PGI2 & TXA2:
•Vascular (COX-2: PGI2):
- vasodilation
- inhibit platelet aggregation
•Platelet (COX-1: TXA2)
- platelet aggregation
- vasoconstriction
COX-1 inhibition:
•Peptic ulcers
•GI bleeding
COX inhibition:
•Na & water retention
•Hypertension
•Hemodynamic acute kidney injury
COX-2 > COX-1 inhibition:
•Stroke
•Myocardial infarction
• Low dose aspirin irreversibly inhibits platelet COX-1

Potency

Ratio: oral morphine to TD-F 75-100:1

Mu receptors

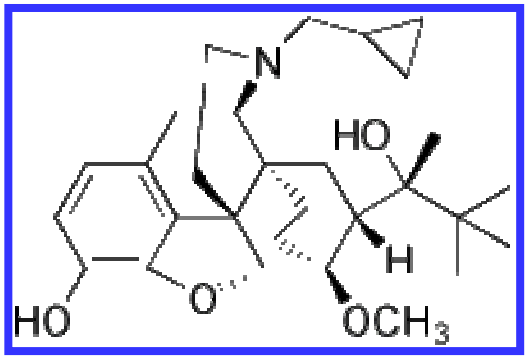
Duration

72-96 hours

35 ug/h (*)
52.5 ug/hr (*)

70 ug/hr

IMPLICATIONS OF BUPRENORPHINE
INTERACTIONS WITH OPIOID RECEPTORS



Chemical structure, buprenorphine

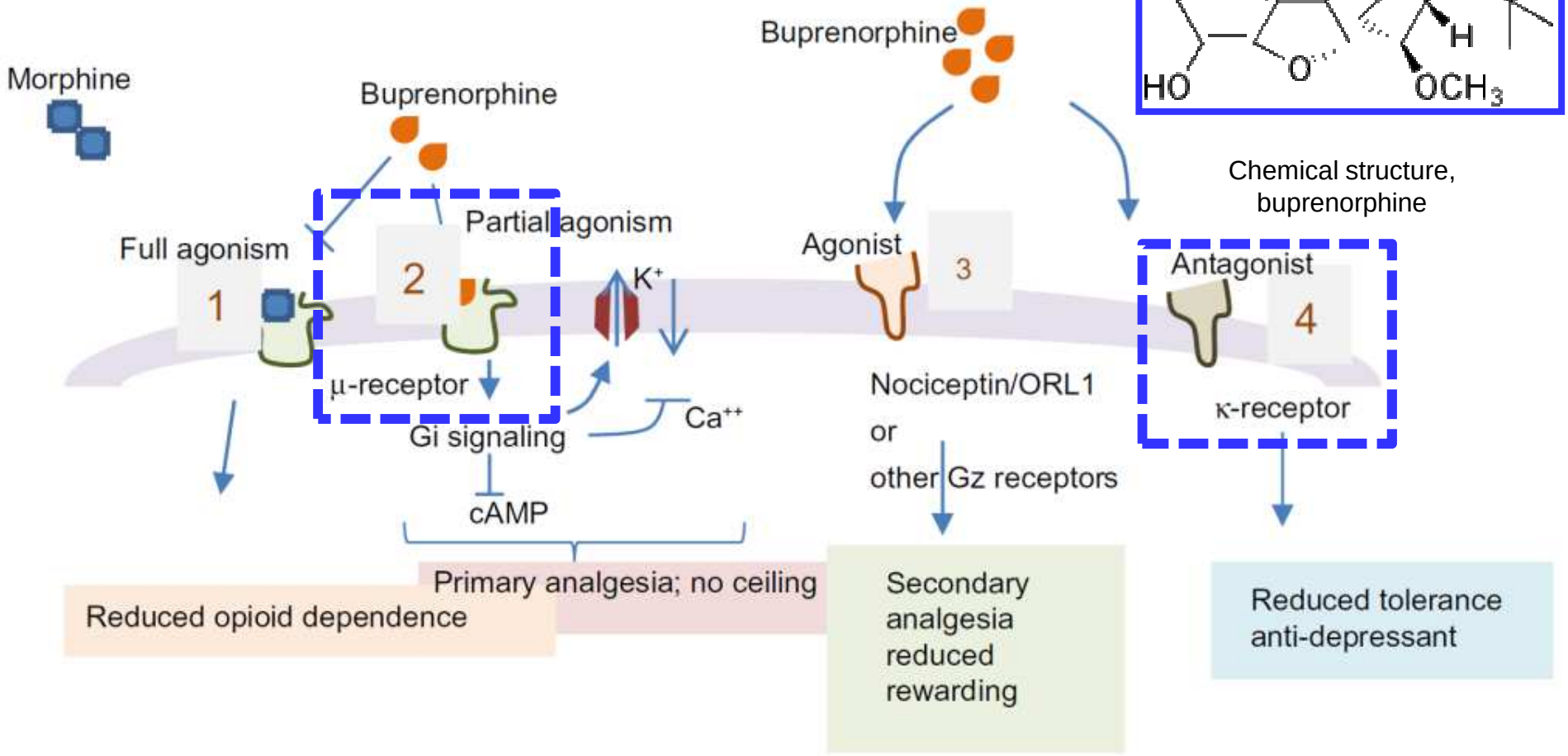
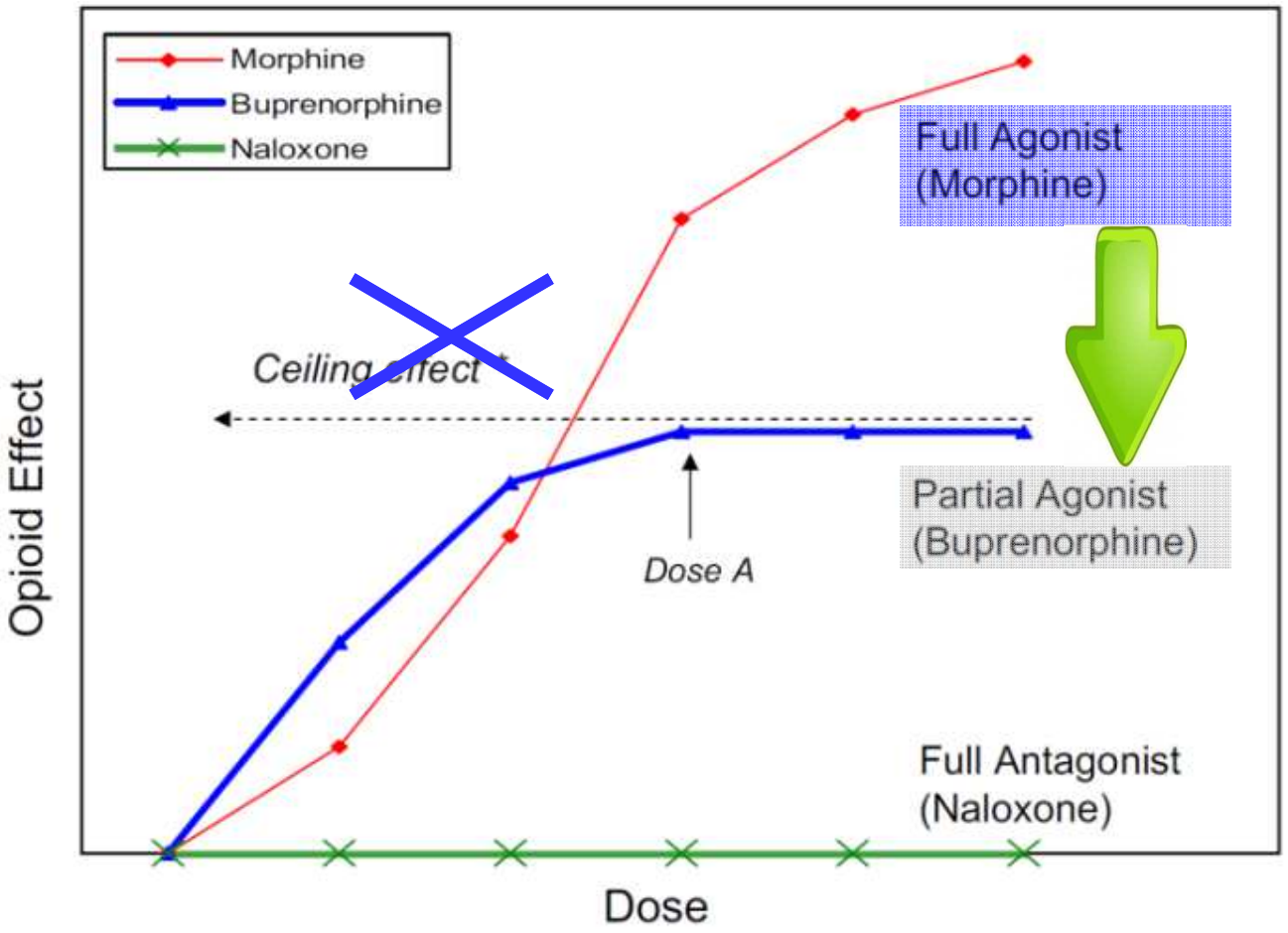
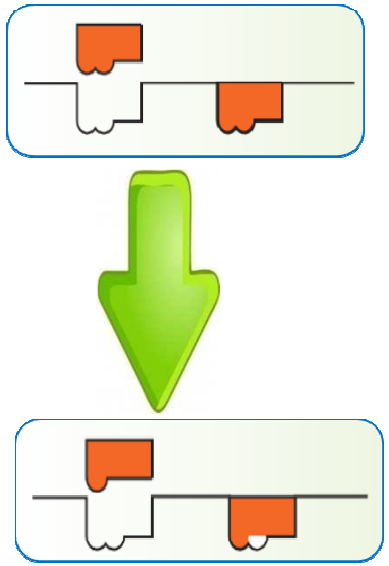


Figure 2 Implications of buprenorphine interactions with opioid receptors. Buprenorphine is a partial and potent agonist of μ-opioid receptor.
Notes: (**1**) It can displace or block morphine binding to μ-receptor thus contributes to reduced opioid dependence. (**2**) Buprenorphine agonist activity on μ receptor is the primary contributing factor to its analgesic signaling events. (**3**) Buprenorphine interacts with nociceptin/ORL1 with much lower affinity and thus is unlikely to contribute to analgesic effects at therapeutic doses. It is conceivable that buprenorphine interactions with other similar receptors could contribute secondary analgesia. (**4**) Buprenorphine is a potent antagonist of κ-opioid receptor and this interaction could contribute to reduced tolerance and antidepressant like activity.
Abbreviation: ORL1, opioid receptor-like 1.

Khanna IK, Pillarisetti S. J Pain Res. 2015 ;8:859-70.

Morphine, fentanyl , hydromorphone, oxycodone.





buprenorphine

*The effects of morphine (analgesia, respiratory depression) increase with increasing doses. The effects of buprenorphine increase until "Dose A" is reached. No further effect is seen with an increase in dose beyond "Dose A."

Journal of PeriAnesthesia Nursing, 25(6), 413-415, 2010.

Transtec (transdermal buprenorphine)

適應症: (3-4 days)

- 需長期全天性使用類鴉片鎮痛劑之中度至重度癌症疼痛
- 對非類鴉片鎮痛劑無效之重度疼痛。
- 說明:僅限使用於曾經使用過類鴉片藥物的患者

管制: 三級

Table I. Equipotent doses of transdermal (TD) fentanyl and buprenorphine based on the current conversion ratios of 1:100 and 1:75, respectively (approximate values).

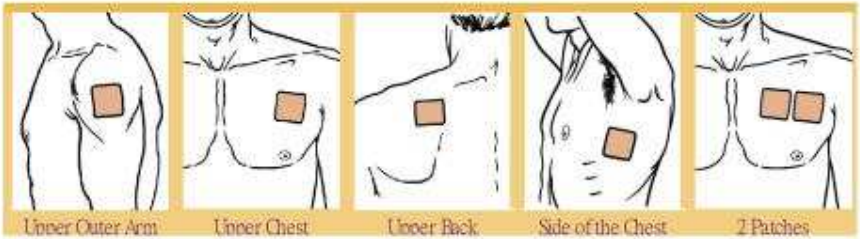
Fentanyl TD Dose		Equipotent Oral Morphine Dose,	Buprenorphine TD Dose	
µg/h	mg/d	mg	µg/h	mg/d
25	0.6	60	35	0.84
–	–	90	52.5	1.26
50	1.2	120	70	1.68
75	1.8	180	105	2.52
100	2.4	240	2 × 70	3.36

*70 + 35 µg/h.

Clin Ther. 2005 Feb;27(2):225-37.

Sovenor® 建議使用方法及貼片位置

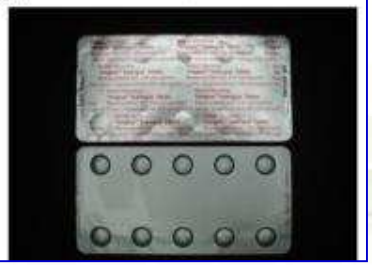
- 起始選用最低劑量：5mg（5µg/h）
  - 根據需要加用短效止痛藥(p.r.n) 以達到充分鎮痛效果
- 若需貼第二片時, 至少等72小時，直至達到完全鎮痛效果後再增加貼片。增加劑量時，可在不同的部位聯合使用。
- 建議慢性疼痛治療貼片一次不超過2片
- 台灣建議慢性疼痛使用Sovenor® 最高劑量為20mcg/hour



丁基原啡因舌下錠 0.2 公絲
TEMGESIC SUBLINGUAL TABLETS 0.2 MG
衛署藥輸字第 021625 號

成　分：
丁基原啡因舌下錠係白色，雙凸錠，每錠含Buprenorphine HCl 0.2 公絲(200 微公克)。
本劑同時含有Lactose, Mannitol, Maize Starch, Povidone, Citrate Buffer Solids及Magnesium Stearate。
主 成 份：每錠含Buprenorphine Hydrochloride....0.216mg (Equivalent to Buprenorphine Base....0.2mg)
適 應 症：中、重度疼痛。
用法用量：本藥須由醫師處方使用。應置於舌下溶解，不可咀嚼和吞服。
成人及 12 歲以上兒童：
本劑每次 1 - 2 錠 (0.2 - 0.4公絲)置於舌下並溶化之，以後每隔 6 - 8 小時或於必要時再給予之。
臨床上標準中度至重度之開始推薦劑量為每 8 小時舌下服用本劑 1 - 2 錠 (0.2 - 0.4 公絲)。
年 長 者：臨床上並無報告顯示對年長者之使用劑量需作任何調整。
12歲以下兒童：丁基原啡因舌下錠0.2公絲依下列劑量適用於12歲以下之兒童：
16.0- 25.0公斤體重：0.1 公絲 (1/2 錠)
25.0 - 37.5公斤體重：0.1 - 0.2 公絲 (1/2 錠至 1 錠)
37.5- 50.0公斤體重：0.2 - 0.3 公絲 (1 錠至 1-1/2 錠)
推薦之劑量應於每隔 6 - 8 小時再服用。
本劑不推薦使用於6歲以下之兒童。

舌下錠 0.2mg / tab



舒倍生®　2 毫克 Buprenorphine 及 0.5 毫克 Naloxone
Suboxone®　8 毫克 Buprenorphine 及 2 毫克 Naloxone
速百騰®　2 毫克 Buprenorphine
Subutex®　8 毫克 Buprenorphine

「調劑本藥應依管制藥品專用處方箋為之」本品應為醫事人員監督下服用
經衛署核准之替代療法執行機構，始得處方使用本製劑。

適應症：
鴉片類物質成癮之替代療法
說明：經精神科專科醫師診斷服和心理疾病診斷統計手冊第四版(DSM-IV)鴉片類成癮(opioid dependence)，且無不適合使用；或對丁基原啡因鹽酸鹽(buprenorphine)有使用禁忌者。

臺中榮民總醫院
Taichung Veterans General Hospital

強效性與弱效性鴉片類藥物劑量轉換表

Codeine	Tramadol	Morphine			Hydromorphone OROS®	Oxycodone	Fentanyl	Buprenorphine	
(mg/day)	(mg/day)	(mg/day)			(mg/day)	(mg/day)	(μg/hr)	(μg/hr)	
口服	口服	SC	IV	口服	口服	口服	穿皮貼片	穿皮貼片	
200	150	10	10	30		15-20	12.5		
	200			40	8				
	300	20	20	60	8-16	30-40	25	35*	
		30	30	90	16-24	40-60	37.5		52.5*
		40	40	120	24	60-80	50		
		60	60	180	36	90-120	75		
		80	80	240	48	120-160	100		

Buprenorphine patch (transtec)

癌症疼痛之藥物治療指引 第七版編

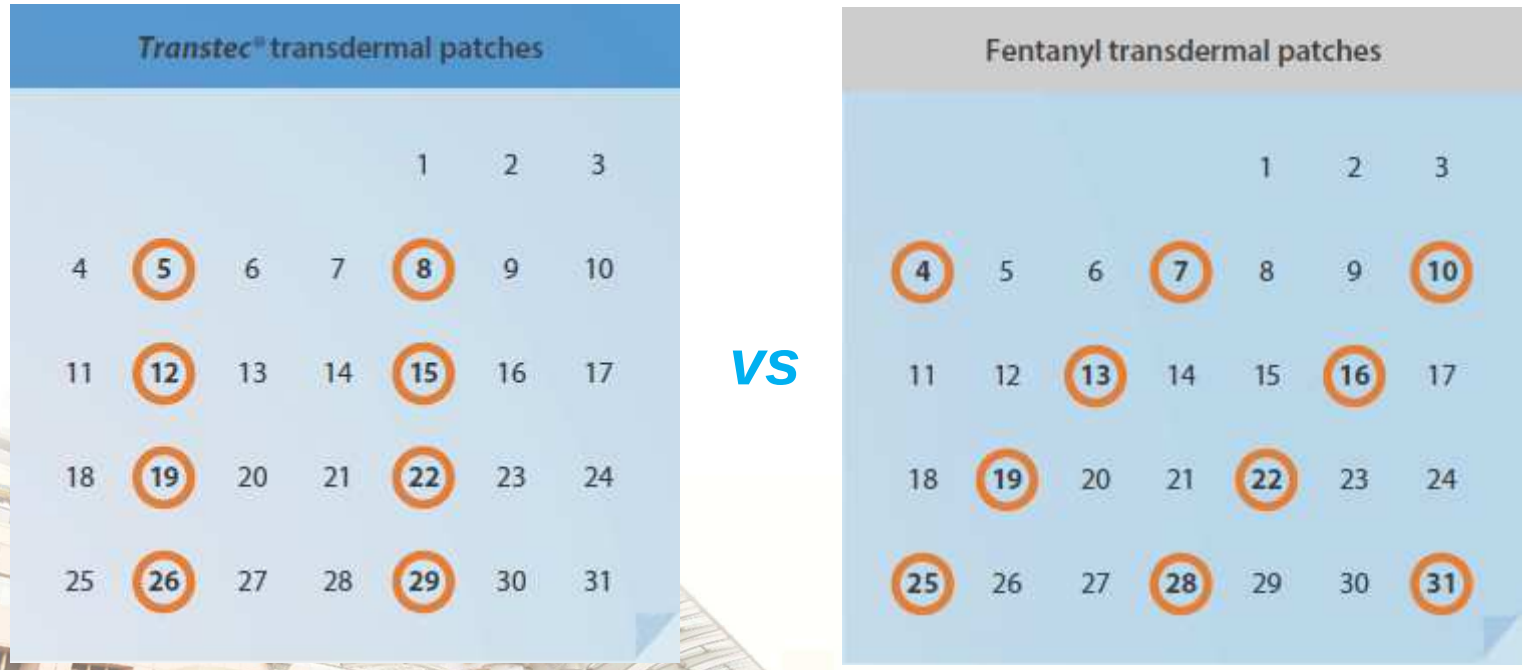
35 μg/hr 劑量相當於口服 morphine 60-90 mg/day；Fen 25ug/hr

52.5 μg/hr 劑量則相當於口服 morphine 90-145 mg/day; Fen 25+12 ug/hr

An easier dosing regimen

Transdermal Buprenorphine patches **TRANSTEC®** are now licensed to be worn **for up to 4-day wear**[1]

- In practice, this means that patients can **change** their **patches on the same 2 days every week**[1]



(1) TRANSTEC® 35, 52.5 and 70 micrograms transdermal patch. UK SmPC. Last Updated on eMC 24-Apr-2015. [https://www.medicines.org.uk/emc/medicine/8864] Accessed on 14/12/2015

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