疼痛治療的現在與未來

宋俊松

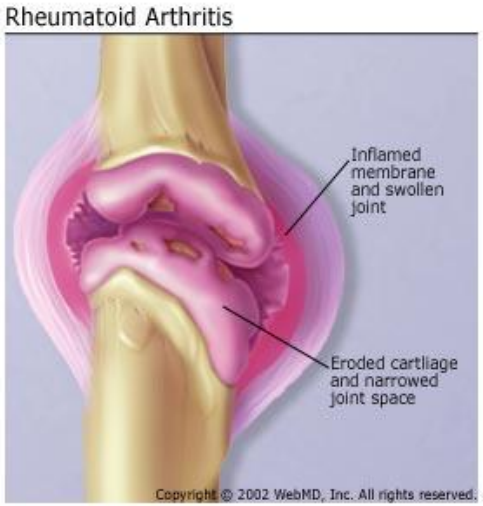
臺北榮總麻醉部疼痛控制科

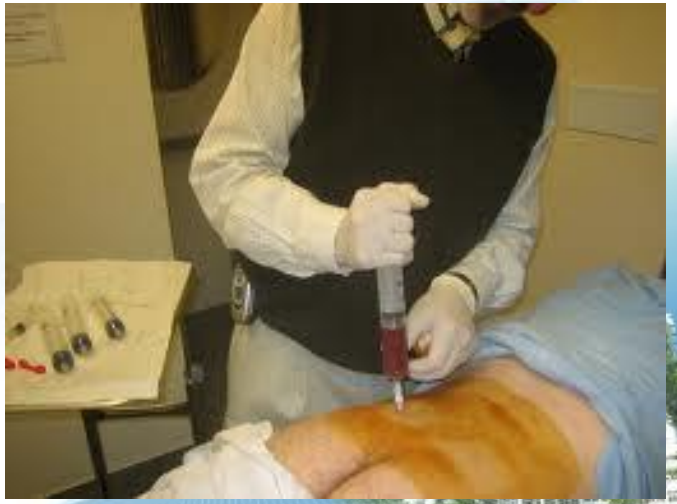
大 綱

1. 疼痛概論
2. 止痛藥物
3. 神經止痛注射、調控與破壞
4. 非藥物治療的其他止痛方式
5. 現在發展與未來的趨勢
6. 結論

疼痛

真實或潛在的**組織傷害**，造成生物體**感覺**與**情緒**上的**不愉快經驗**。(IASP)



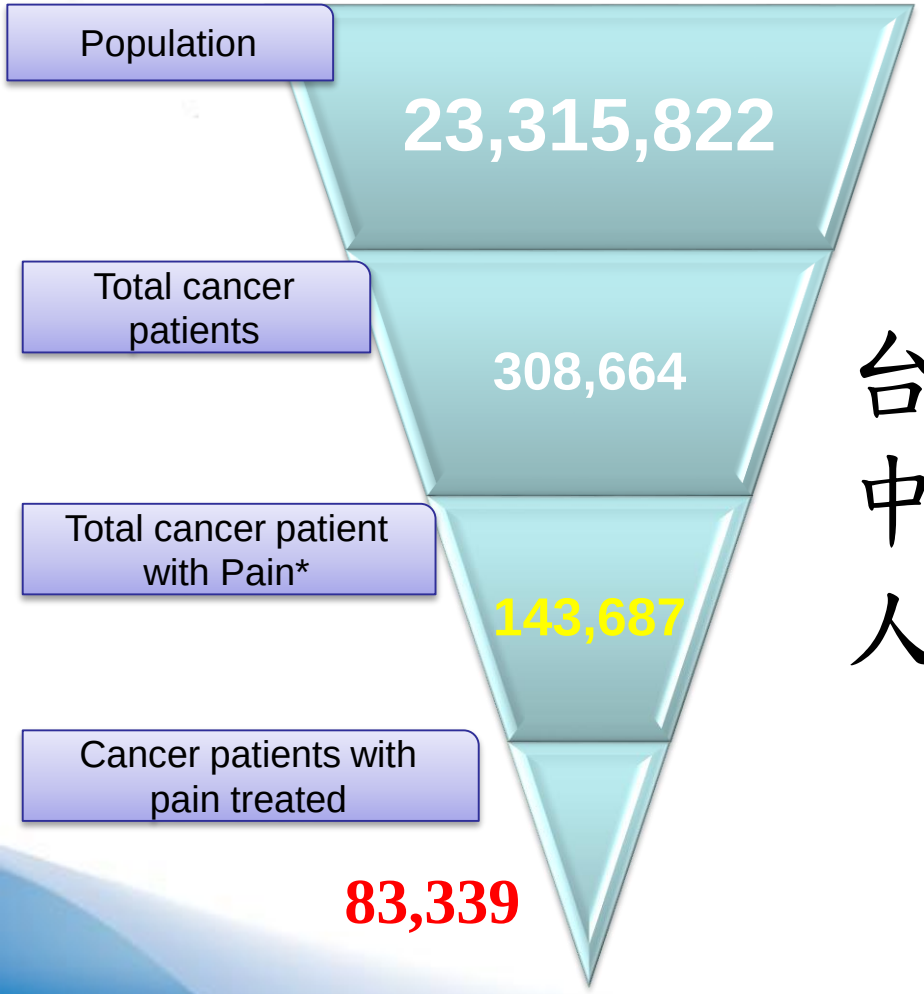


臨床上常見需要介入的疼痛

Survey	Pain prevalence
Marks and Sachar (1973)	73% (內科)
Donovan et al. (1987)	79%
Abbott et al. (1992)	50%-67%
Cleeland et al. (1994)	67% (門診癌症病人)
Costantini M (2000)	43%-56%
Trentin et al. (2001)	44%
Italian Towards a Pain-free Hospital Project (Dolore IT, 2001)	46%-91%
AGS Panel on Persistent Pain in Older Persons (2002)	45%-80% (安養中心、護理之家)
Apfelbaum et al. (2003)	80% (外科)
Maier et al. (2010)	87.6% (外科), 83.3% (非外科)

台灣癌症病人疼痛

IPSOS 市調 2013



台灣14萬名癌痛病人中，有6萬多名癌痛病人沒有接受止痛治療

手術後疼痛

- >80% 病人抱怨疼痛
- **～75%** 中度以上疼痛
- **>50%** 止痛不符病人需求
- 影響身體復原、情緒起伏與社會功能
- 產生慢性疼痛

該是愛護妻子的雙手，卻得親手送妻子上黃泉，悲劇就發生在這棟透天厝，悲傷的丈夫面對媒體，一句話都不說，轉身趕緊關上家門，他的妻子顳顎疼痛長達11年，不堪病魔折騰，不斷要求先生幫忙了結性命，妻子還特地寫了這封遺書，白紙上字體抖的很厲害但語氣卻很堅定，遺書一開始就寫著，我活著好痛苦，是我哀求我老公幾萬次，請不要爲難他，寫下這封遺書之後，妻子便要求丈夫幫她自殺，兩人還特地要就讀大學的兒子迴避，丈夫就這樣用雙手，親手勒斃妻子，事發之後淚流滿面的丈夫，跟著兒子一起上派出所自首，能就是，顳顎關節疼痛跟三叉神痛，劇發生。

疼痛會要人命的！！！

新聞最亮點，來關心這起家庭悲劇，高雄市，有一位婦人、吳秋燕，這11年來、她飽受身體病痛的折磨，因爲久病厭世、她不斷要求丈夫，幫她自殺，還特地寫了一封遺書、請外界不要責難丈夫。丈夫始終狠不下心，但昨天凌晨、他含著眼淚、用毛巾勒斃了最愛的人、也讓妻子，獲得解脫。

99年8月7日18:58

積極的緩和醫療能幫助癌症病人活得更好更久

緩和醫療：疼痛控制、精神支持與副作用緩解

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

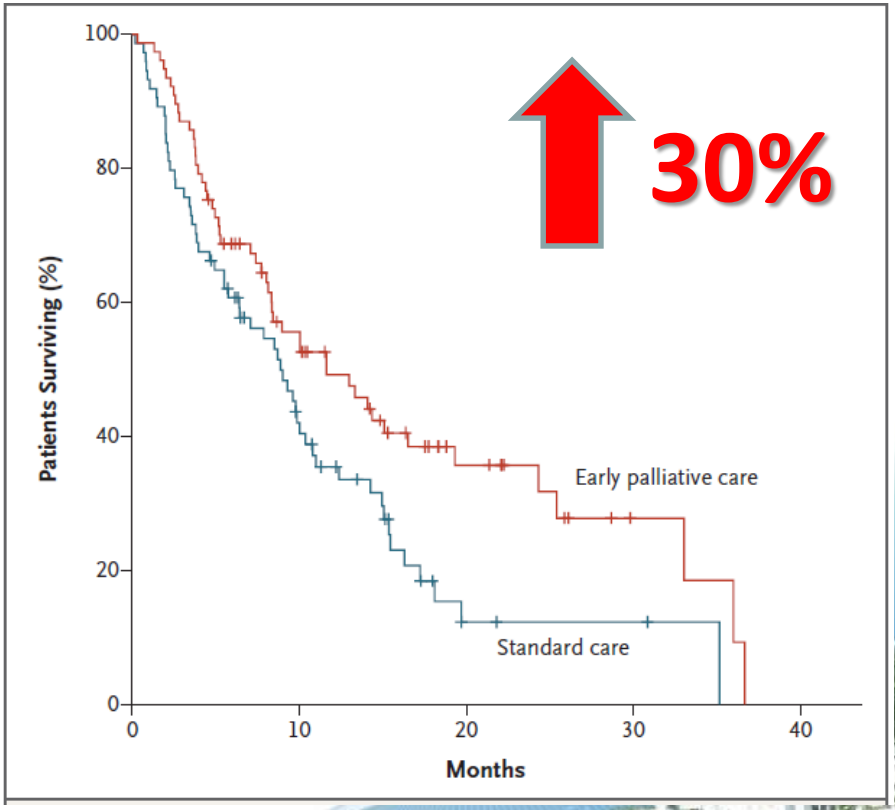
Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

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

	Early palliative care with oncologic care	Oncologic care	*P* value
P't No.	77	74	
Median survival	11.6 m	8.9 m	0.02

N Engl J Med 2010; 363:733-42.

A randomized study:
151 patients enrolled, newly diagnosed metastatic NSCLC

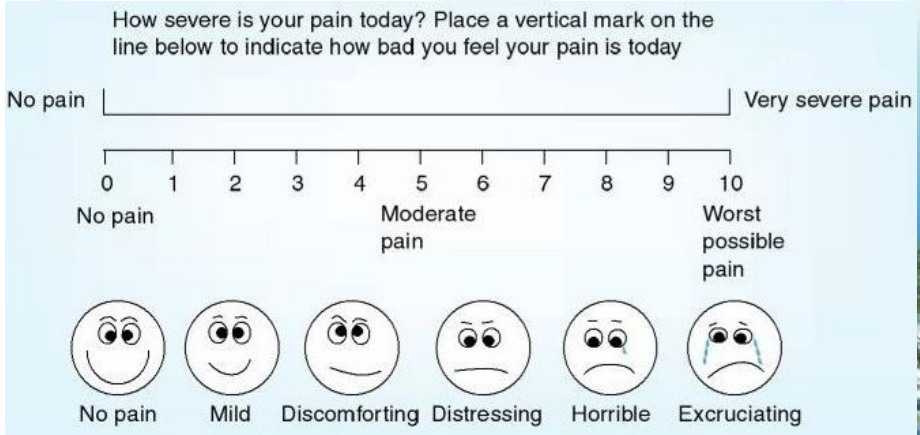



全球十六種語言發行
CHASING DAYLIGHT
How My Forthcoming Death Transformed My Life
尤金·歐凱利 Eugene O'Kelly —著 張琇雲—譯
一位跨國企業總裁的最後禮物
追逐日光
全球知名跨國企業KPMG總裁 尤金・歐凱利
在得知只剩下三個月的生命後，將此宣判視為一份禮物，
這一百天的人世應對與智慧沉澱，比三十年的商場縱橫更貼近生命本質，
讓他成為更完整的人和領導者！
宇宙光終身義工 孫越 | 台灣安侯建業會計事務所主席 張五益 | 遠雄企業團董事長 趙藤雄
王品集團董事長 戴勝益 | 知名作家 李家同 聯合推薦

疼痛評估與治療策略

疼痛是第五種生命徵象

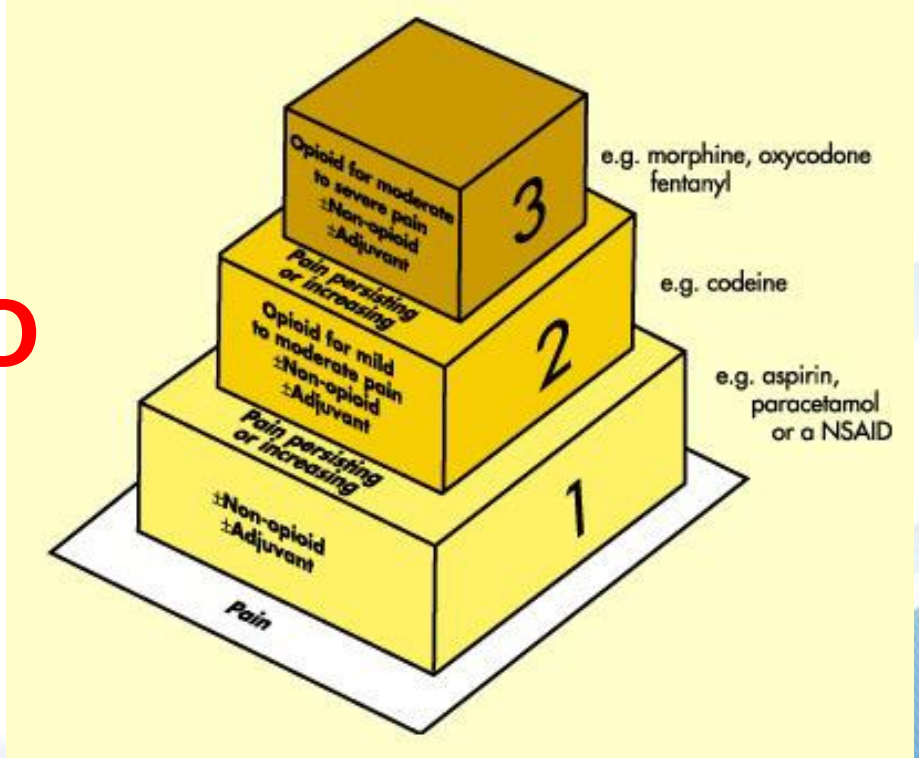
- 體溫
- 心跳
- 呼吸
- 血壓
- **疼痛**
- 特質
- 強度
- 功能影響
- 溝通



根據疼痛嚴重度給予適當止痛藥物

強度	分級	消炎止痛藥	類鴉片製劑	止痛佐劑
1—3	輕度	✓	偶爾	✓
4—6	中度	✓	經常	✓
7—10	嚴重	✓	經常	✓

1986 WHO



止痛治療的指引與共識

止痛指引與共識

- 術後快速復原學會 (ERAS)指南
- Guidelines on the management of postoperative pain 2016
- NeuPSIG recommendation 2015
- 1986 世界衛生組織(WHO)三階梯止痛指引
- 2013 歐洲安寧緩和醫學會(EAPC)止痛指引
- 2014 美國國家綜合癌症網絡(NCCN) 指南

多模式跨領域止痛

藥物

- NSAIDs & acetaminophen
- Opioids
- Co-analgesics
  - Antidepressant
  - Anticonvulsant
  - Local anesthetics
  - NMDA antagonist
  - Sympatholytics
  - Muscle relaxant
  - Steroid
  - Analgesic balm

非藥物

- 復健物理治療
- 精神科職能治療
- 心理
- 正念觀想、調整行為模式
- 教育
- 針灸推拿、TENS
- 介入性神經調控
- 破壞性止痛治療
- 關懷與支持
- 信仰

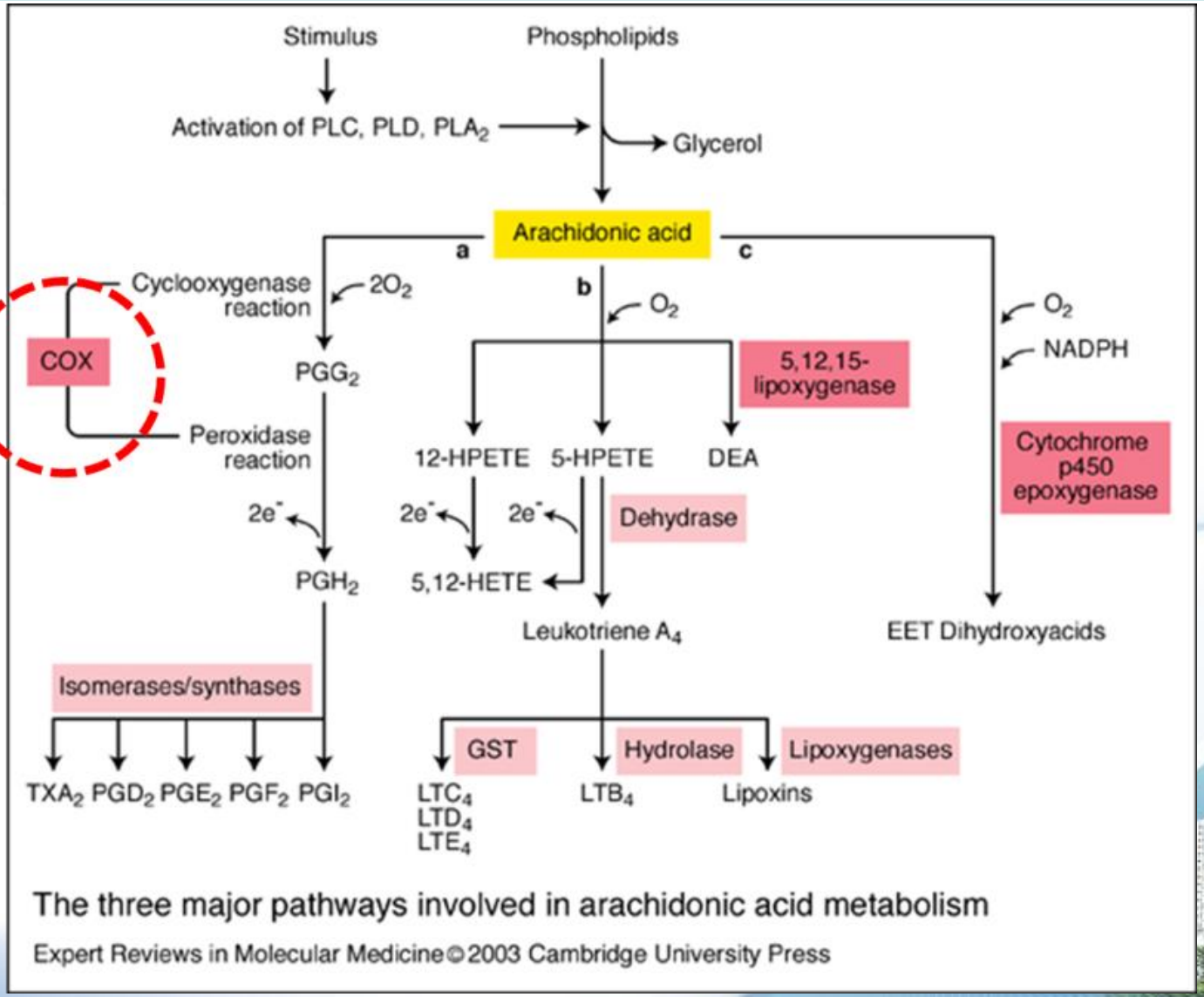
疼痛藥物治療

藥物治療理念

- 客製化
- 經口
- 定時常規給藥
- 中度以上疼痛就給額外止痛藥
- 考慮病人需求與差異性
- 對止痛藥與止痛方式的想法
- 教育與溝通

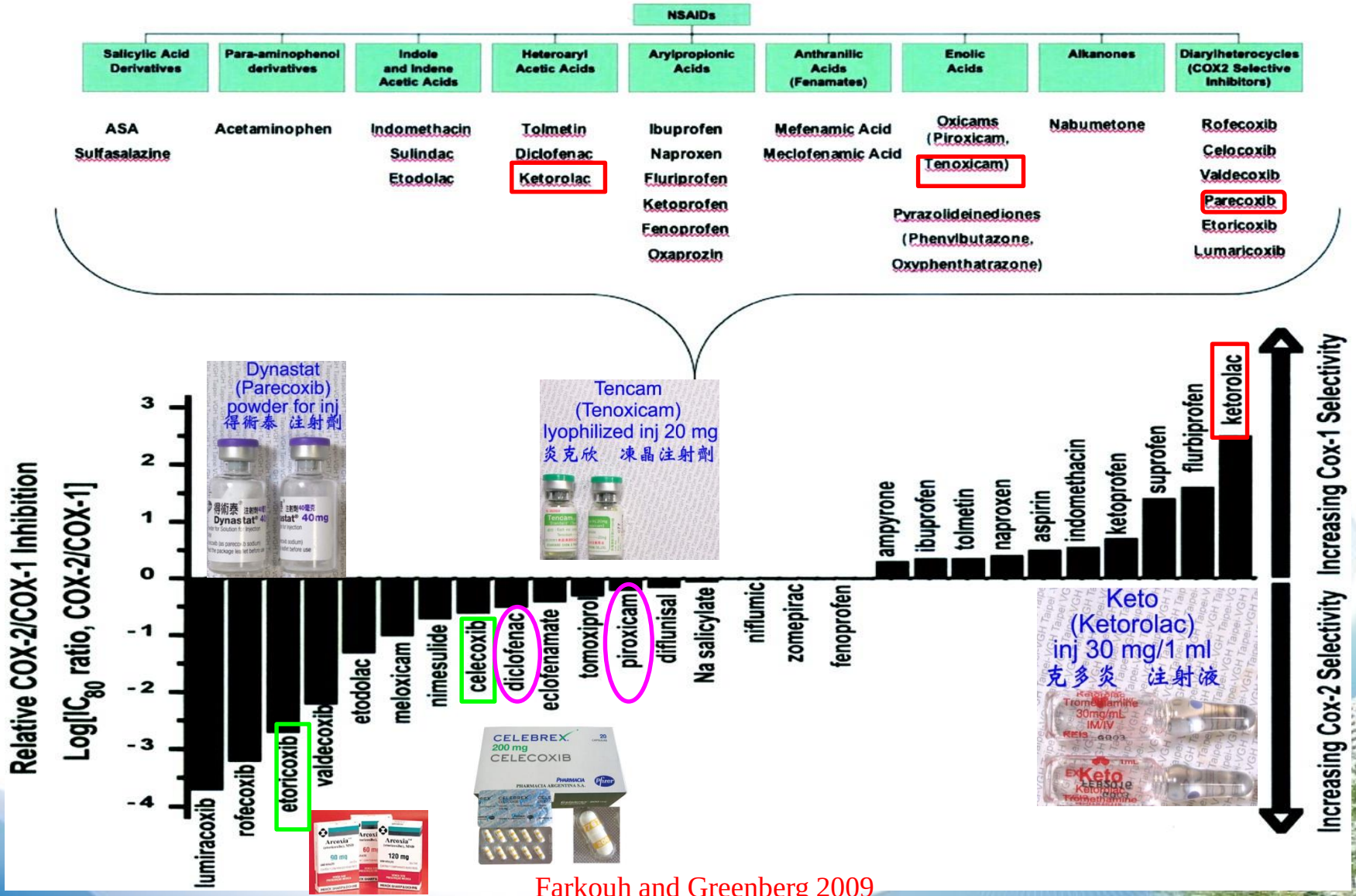
Non-steroidal anti-inflammatory drugs (NSAIDs) & acetaminophen

作用標的：COX enzymes



The three major pathways involved in arachidonic acid metabolism

COX selectivity of NSAIDs



Farkouh and Greenberg 2009

NSAIDs & acetaminophen

- 目的
- 效益：因人而異、個體差異性大
- **Ceiling effect**
- 副作用
- **不建議長期使用**

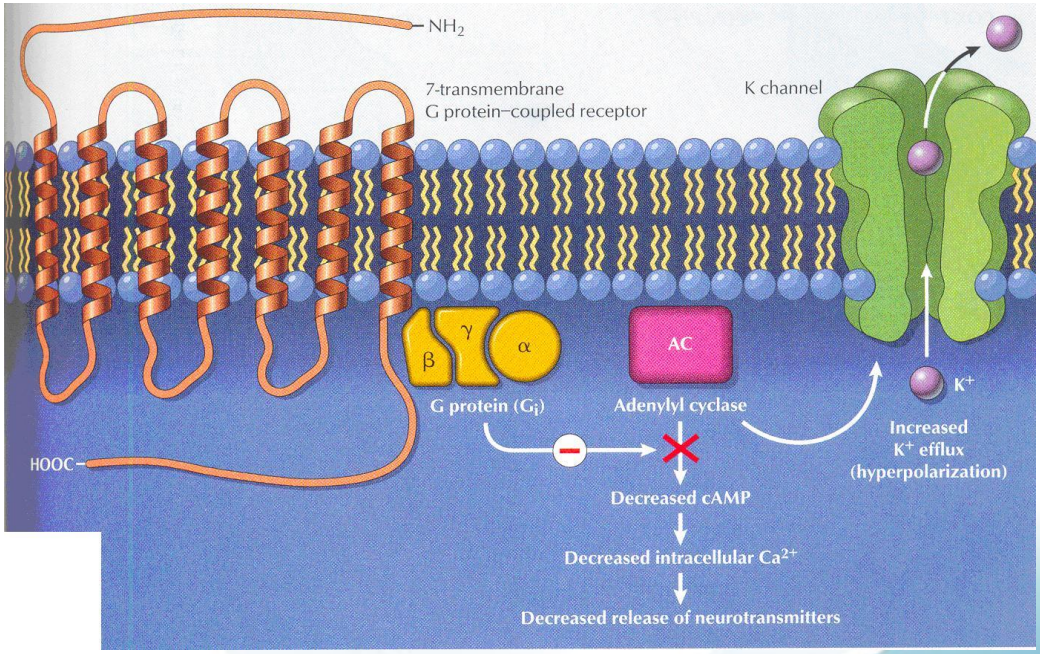
Opioids 鴉片類止痛劑

Opioid categories

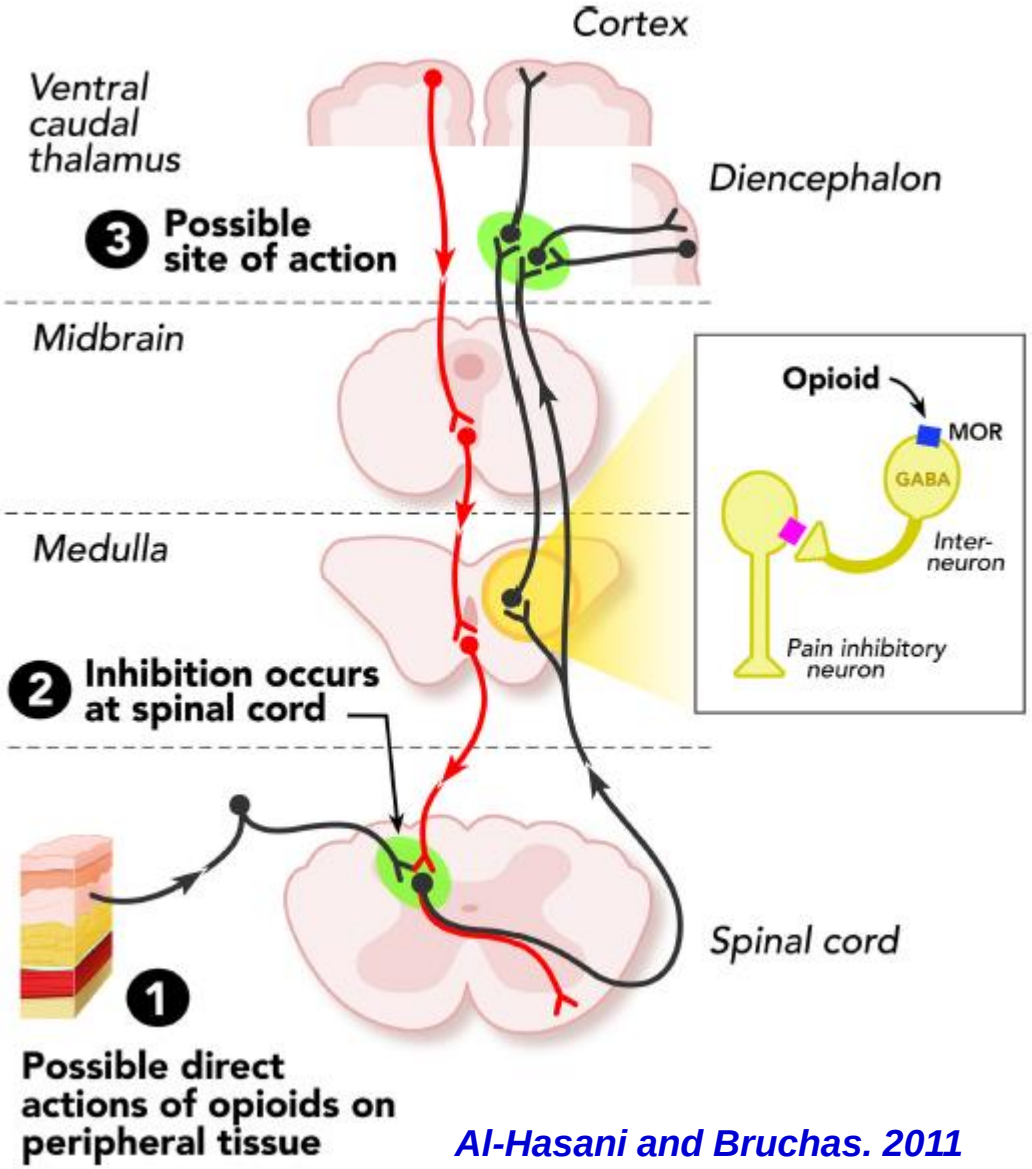
Rapid-onset opioids	Short-acting opioids	Long-acting opioids
Oral transmucosal fentanyl citrate (OTFC)	Codeine	Fentanyl TD patch
Fentanyl buccal tablet (Fentora)	Buprenorphine	Buprenorphine patch (Butrans)
Fentanyl buccal film (Painkyl)	Morphine hydrochloride or sulfate	Morphine ER (MXL, MS Contin)
Sublingual fentanyl	Oxymorphone	Oxymorphone ER (Opana ER)
Intranasal fentanyl	Oxycodone IR (OxyNorm)	Oxycodone ER (OxyContin)
	Tapentadol (Nucynta)	Levorphanol (Levo-dromoran)
	Hydromorphone (Hydrostat IR)	Methadone
	Hydrocodone (Vicodin)	Hydromorphone ER (Jurnista)

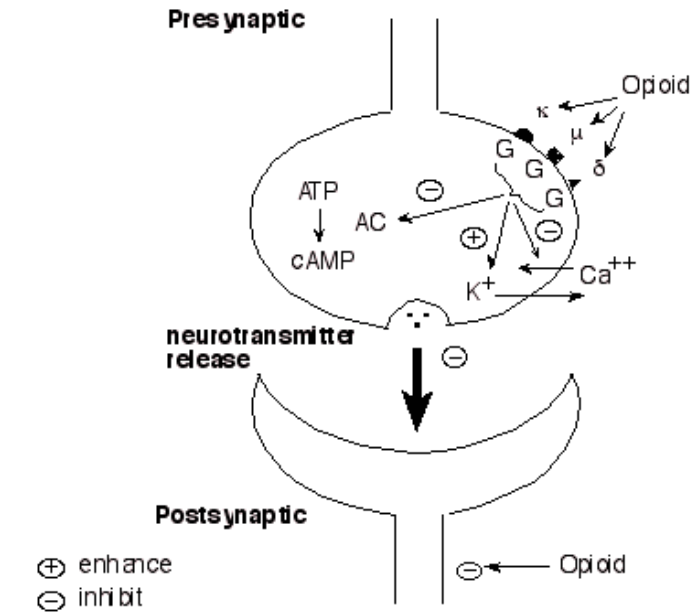
Opioids and opioid receptors

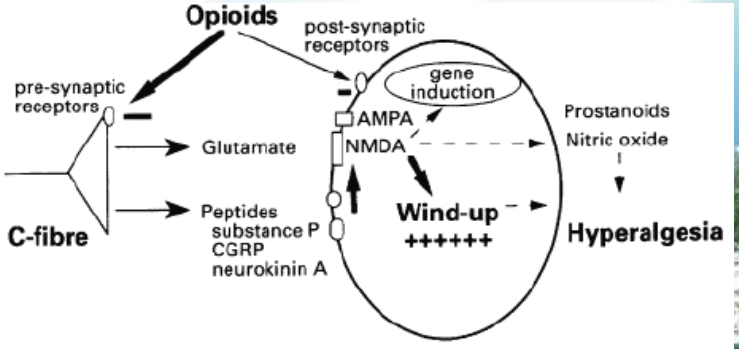
- μ-, κ-, and δ-opioid receptor
- **No ceiling effect**
- Codeine
- Tramadol
- Demerol
- Morphine
- Fentanyl, alfentanil, remifentanil
- Hydromorphone; Oxycodone



Analgesic mechanism

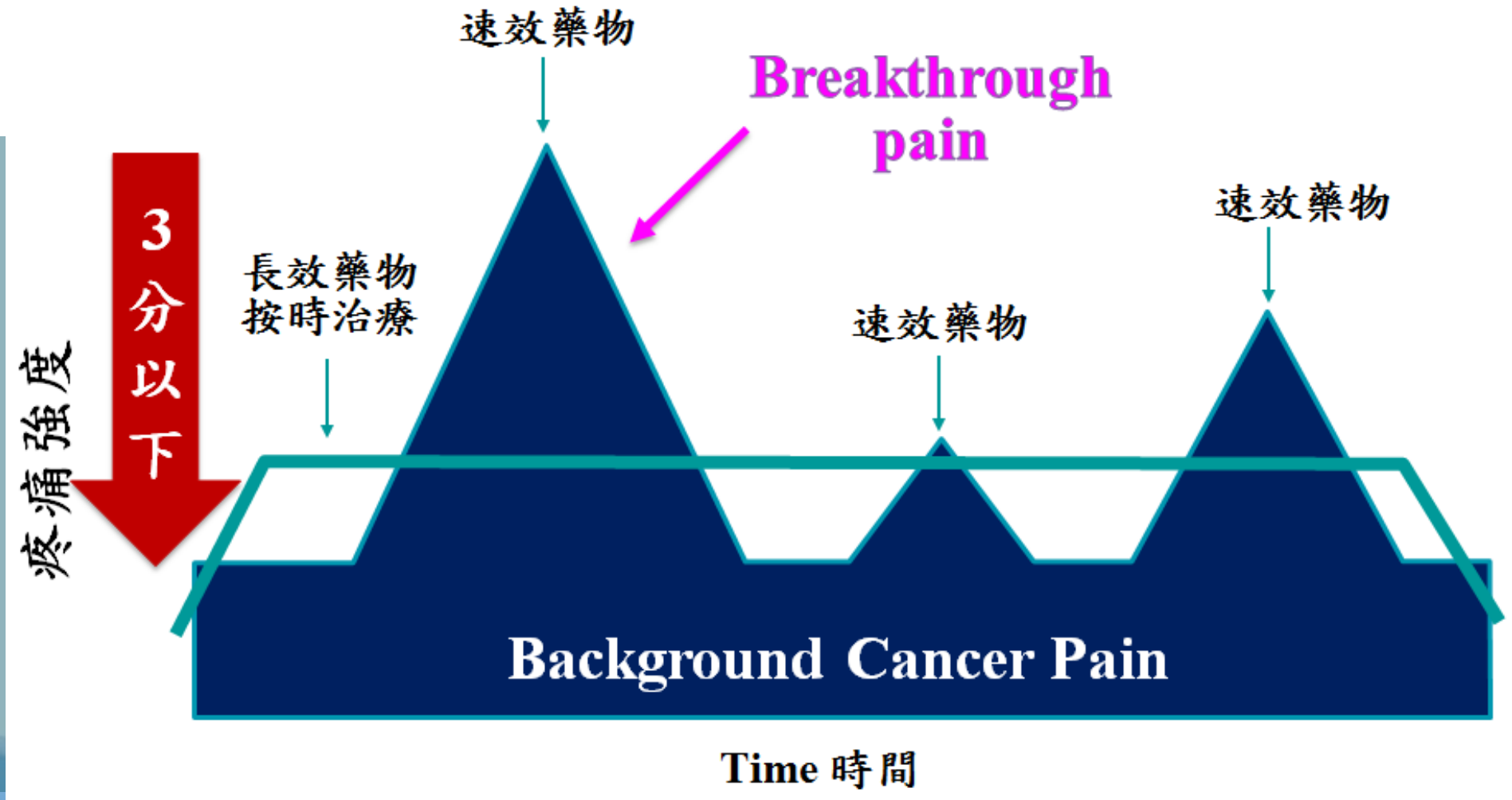






Al-Hasani and Bruchas. 2011

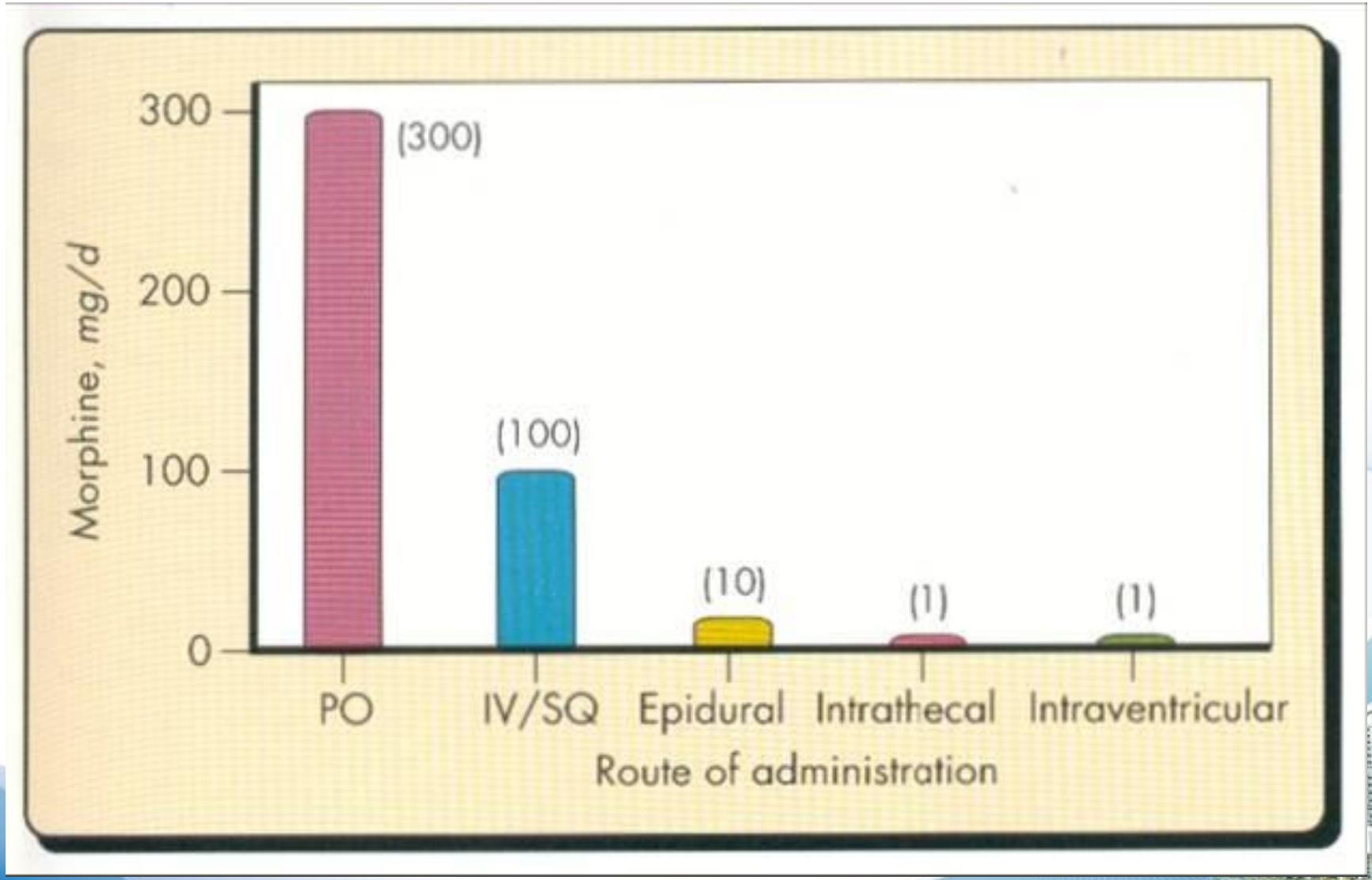
癌痛（Cancer pain）



劑量轉換（1）

Analgesic	Strength (relative)	Equivalent dose (10 mg)	Bioavailability
Aspirin	1/360	impractical	100%
Ketorolac (IM)	1/5-2/5 (mean 1/3)	18-36 mg (mean 30 mg)	
Codeine	1/10	100 mg	≈ 90%
Tramadol	1/10	100 mg	68-72%
Pethidine	1/3	28 mg	50-60%
Oxycodone	2	5 mg	60-87%
Morphine (oral)	1	10 mg	≈ 25%
Morphine (IV/IM)	3	3.33 mg	100%
Fentanyl	50-100 (chronic); 33 (acute)	0.1-0.2 mg; 0.33 mg	33% (PO); 92% (TD)
Hydromorphone	5	2 mg	20-26%

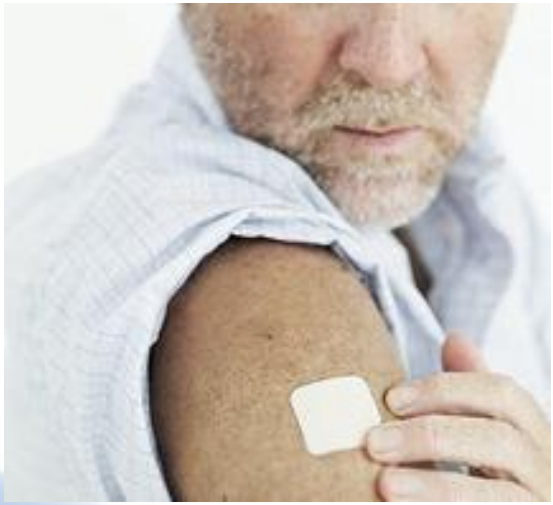
劑量轉換（2）

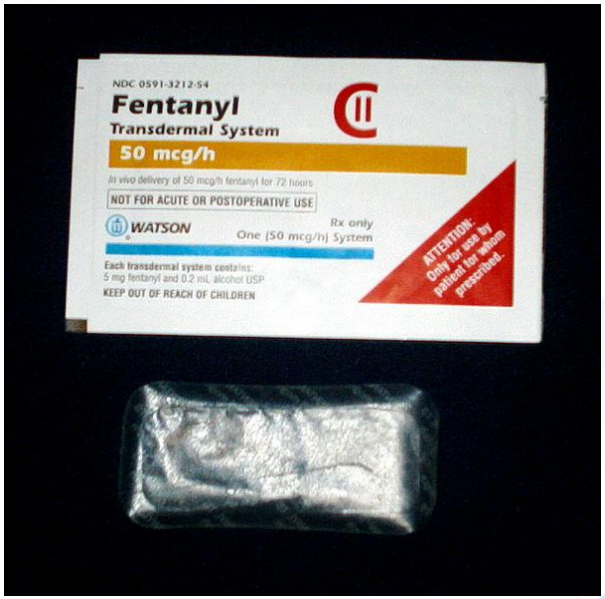

300
200
100
0
Morphine, mg/d
(300)
(100)
(10)
(1)
(1)
PO
IV/SQ
Epidural
Intrathecal
Intraventricular
Route of administration

Adverse effect of opioids

- Nausea/sedation, respiratory depression, **constipation**
- Sex hormone hypofunction
- GI effects: decreased intestinal peristalsis, constipation, sphincter of Oddi spasm
- Neuropsychiatric adverse effects

Fentanyl transdermal patch – not suitable for acute pain management





Painkyl®(fentanyl buccal film)

癌症病患
18歲以上

正在使用ATC opioid，並符合嗎啡類耐受條件

突發性疼痛

Opioid tolerant:

- 60 mg oral morphine/day
- 25 μg transdermal fentanyl/hour
- 8 mg oral hydromorphone/day
- 30 mg oral oxycodone/day
- 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for **one week or longer**

Crisis of opioid therapy

- Prescription opioid misuse, dependence, abuse, and addiction
- Pain under-treatment and over-treatment
- Mitigation strategy
  - Screening tools to identify and monitor, urine drug screening, etc.
  - Alternative tx (non-opioid analgesics, interventional and neural modulation therapies, non-pharmacologic tx, etc)
  - Adhere to guidelines
  - Change route of opioid administration

Co-analgesics

Antidepressants, Anticonvulsants, Local anesthetics, Skeletal muscle relaxants, NMDA receptor antagonist, α2-adrenergic agonist

Antidepressants

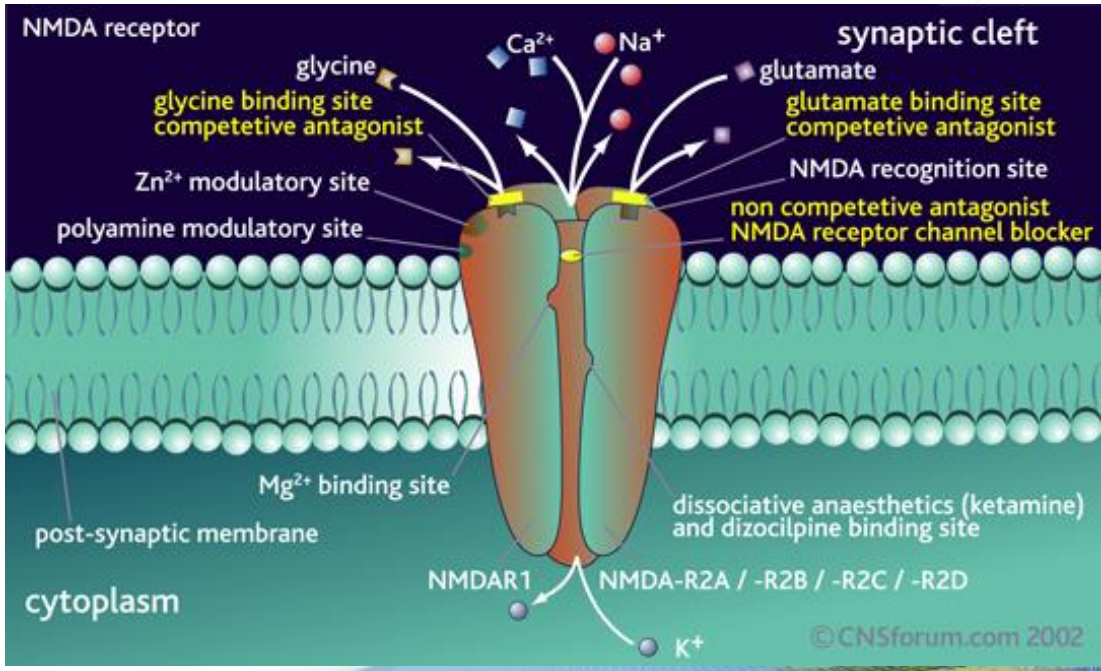
- Classifications:
  - Monoamine oxidase inhibitors (MAOI)
  - Tricyclic antidepressants (TCA)
  - Selective serotonin and norepinephrine reuptake inhibitors (SNRI)
  - Selective serotonin reuptake inhibitors (SSRI)
- Mechanism:
  - Pain modulation
  - Improvement of sleep and mood

Anticonvulsants

- Gabapentin and pregabalin
  - First-line anticonvulsant agent recommended for neuropathic pain treatment
  - α2-δ subunit of voltage-dependent Ca^{2+} channel blocker
- Carbamazepine and oxcarbamazepine
  - Na^{+}-channel blocker
  - Trigeminal neuralgia
- Divalproex: migraine prophylaxis

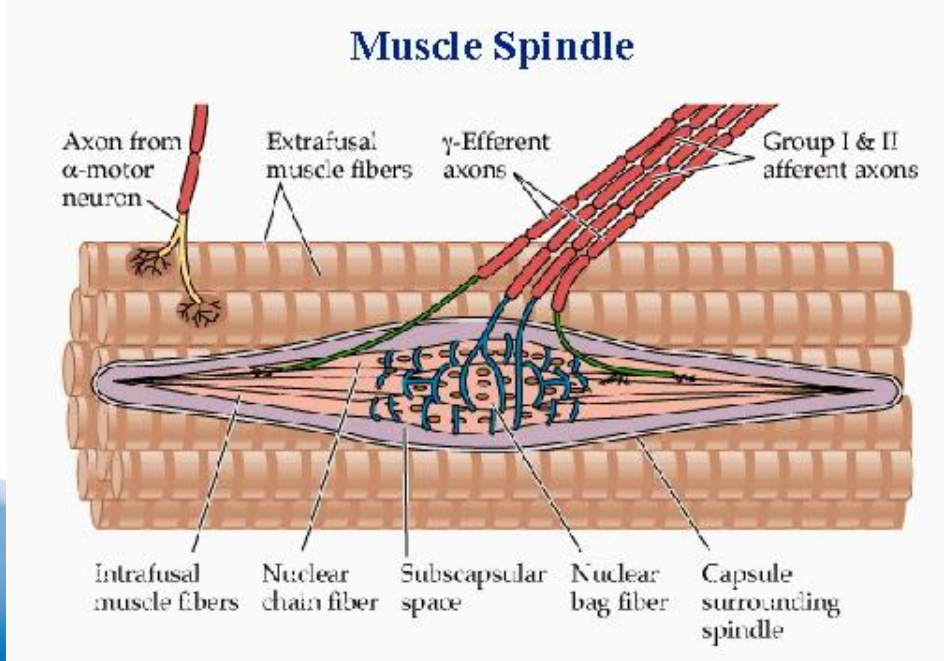
NMDA receptor antagonist

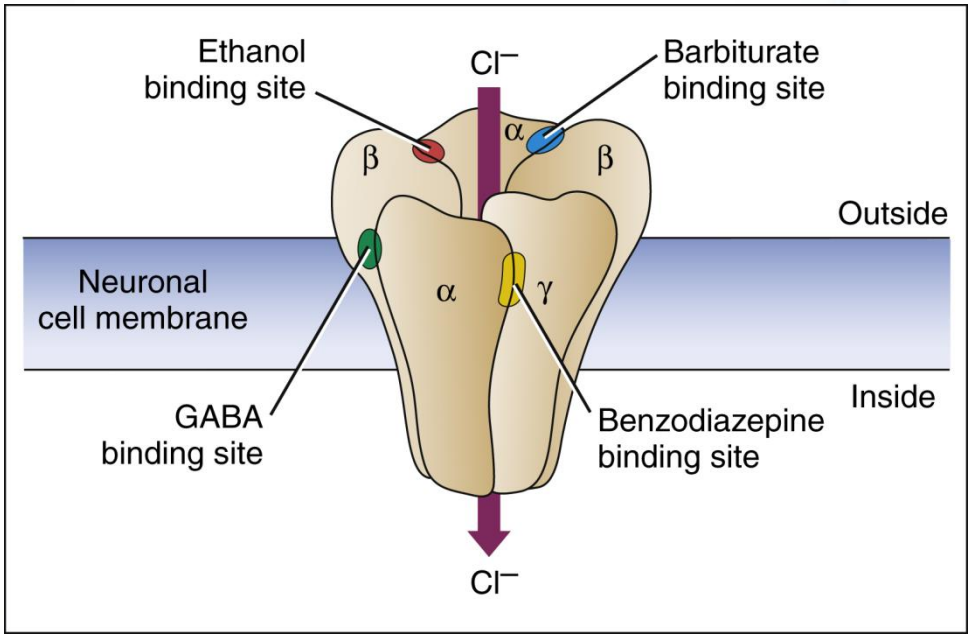
- Dextromethorphan (Regrow®, Medicon, Robitussin): painful diabetic neuropathy
- **Ketamine**: postoperative pain, multiple forms of neuropathic pain



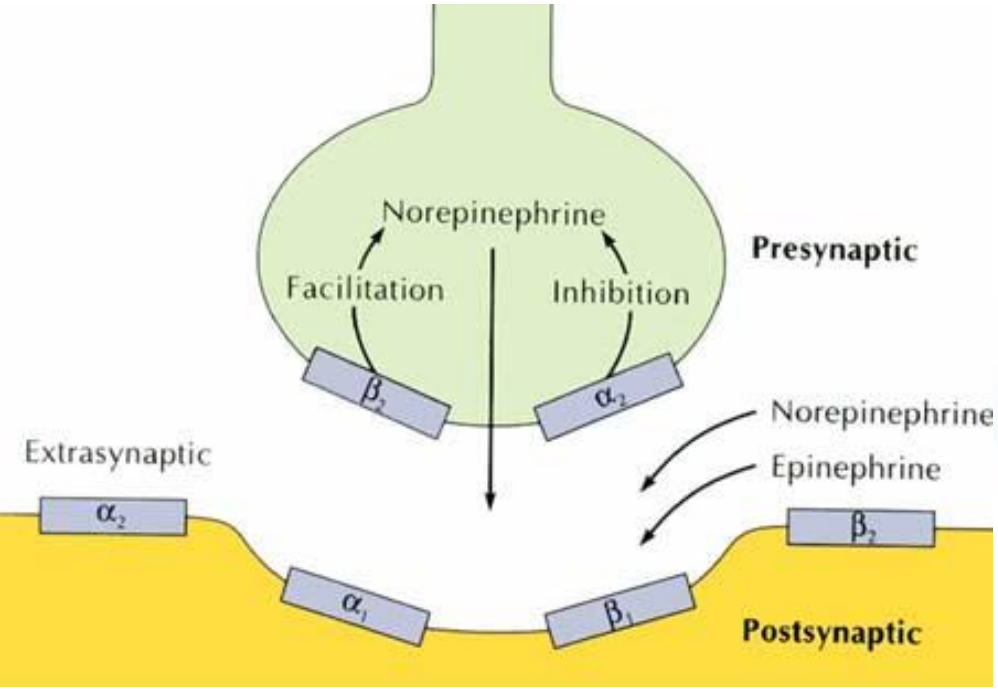
Skeletal muscle relaxant

- Reduce muscle spasticity
- Baclofen: $GABA_B$ receptor agonist
- Diazepam: $GABA_A$ receptor agonist
- Chlorzoxazone: a centrally acting (spinal cord and subcortical areas of the brain) muscle relaxant





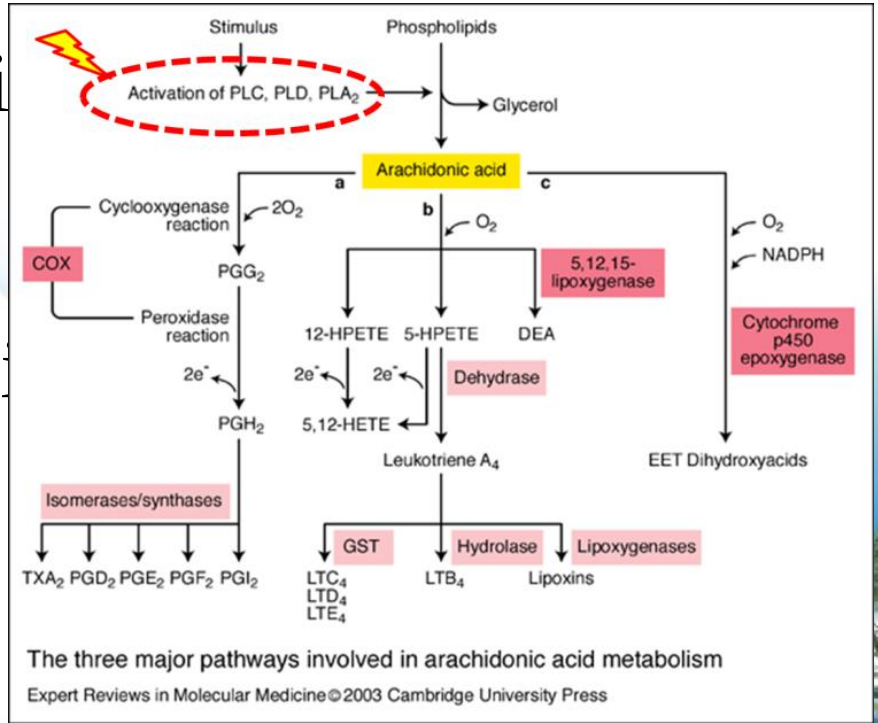
α2-adrenergic agonist (Clonidine, dexmedetomidine)



- Presynaptic and postsynaptic α2-AR
- Mechanism
  - open K^+- channel
  - ↓Ca^{2+} conductance
  - inhibition of cAMP
  - ↓ sympathetic outflow

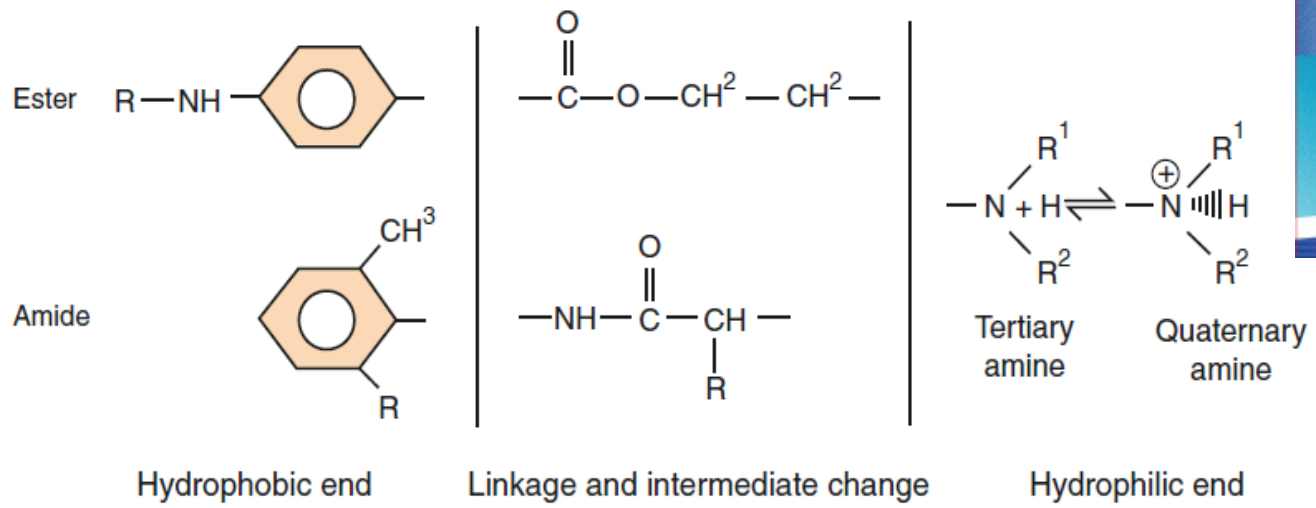
Steroids

- **Anti-inflammatory effects**: inhibits PLA_2
- Diminished spontaneous ectopic neural activity
- **Decrease perineural edema**
- Cell membrane stabilizati
- Restoration of balance of
- ↓ inhibition of glycinergi



The three major pathways involved in arachidonic acid metabolism

Local anesthetics



Hydrophobic end | Linkage and intermediate change | Hydrophilic end

- 2 classes: amino-esters and amino-amides
- Aminoester LA: plasma pseudocholinesterase
- Aminoamide LA: liver CYP450 enzymes
- Target: **voltage-gated Na^+-channels**

Analgesic balm

- Ingredients
- Menthol: activates κ-opioid receptors, inhibits voltage-gated Na^+ channel
- Capsaicin: initially activates but later desensitizes TRPV1 ligand-gated channels

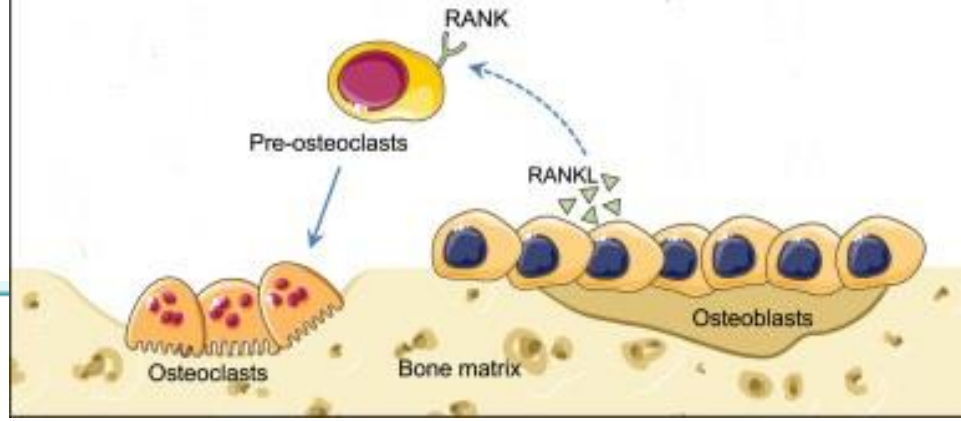
Osteoporosis and metastatic bone pain

Pharmacologic tx

Prevalence and pharmacotherapy

- ~2/3 patients with bone metastasis
- < 1/3 osteoporotic fracture patients
- Pharmacologic therapy: WHO 3-ladder analgesics + bone-modifying agents +/- corticosteroids
- **Bone-modifying agents**: bisphosphonates, denosumab, etc.

Osteoporosis Tx



- Osteoporosis
  - Drugs
    - Antiresorptive drugs
      - Bisphosphonates
        - Alendronate (Fosamax)
        - Risedronate (Actonel)
        - Etidronate (Didronel)
        - Ibandronate (BONIVA)
      - Selective estrogen receptor modulators(SERMS)
        - Evista (Raloxifene)
        - Tamoxifen (Nolvadex)
      - Hormonal replacement therapy(HRT)
      - Tibolone
      - Calcitonin
    - Bone forming drugs
      - Parathyroid hormone
        - Teriparatide (Forteo)
    - Drugs with complex mechanism of action
      - Strontium ranelate
      - Vitamin D
      - Denosumab

病人自控式止痛

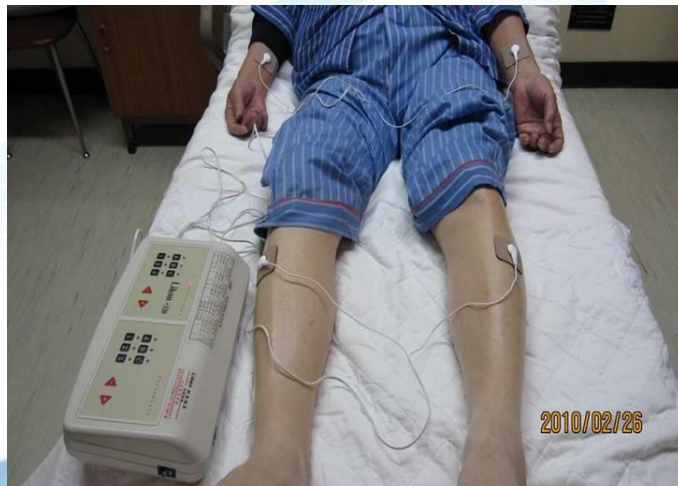
(Patient-controlled analgesia; PCA)

病人自控式止痛 (PCA)

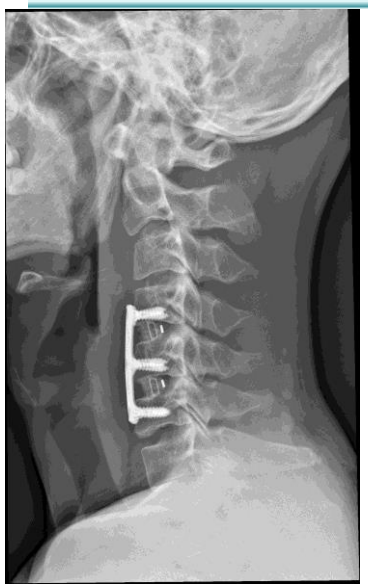
疼痛之非藥物治療

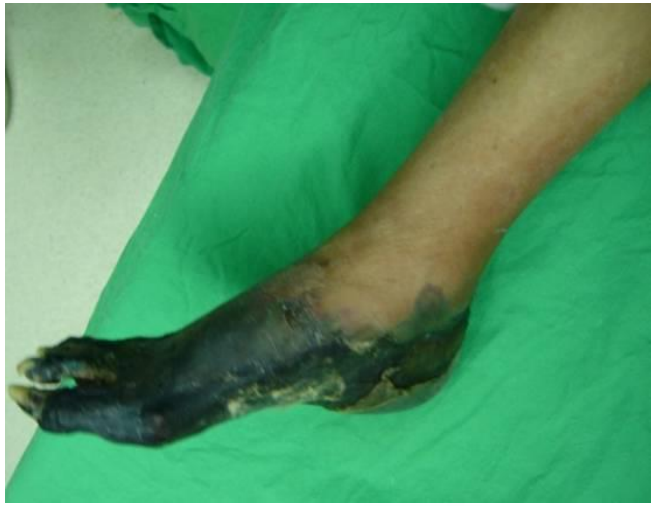
疼痛之非藥物治療

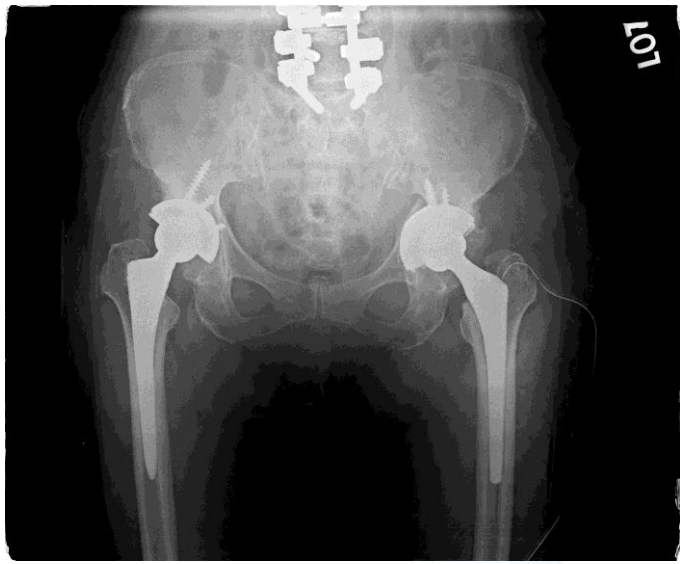
- 外科：手術矯正或治療
- 復健科：物理治療
- 精神科：認知行為職能治療與心理諮商
- 正念訓練、冥想、放鬆
- 針灸
- 經皮神經電刺激 (TENS)

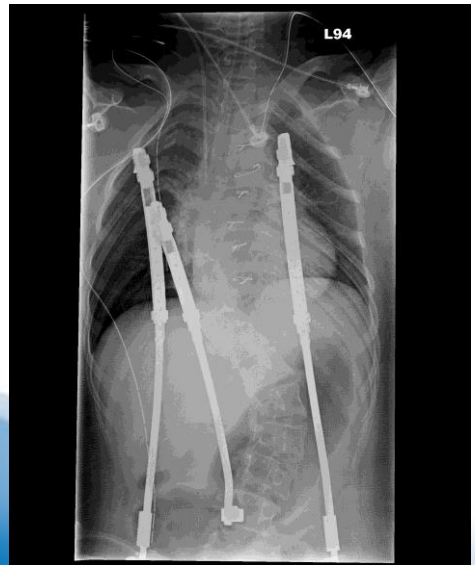


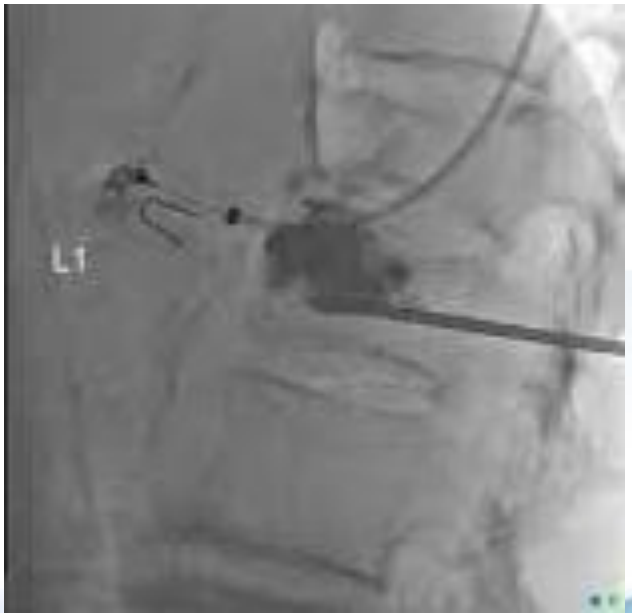
Surgical correction

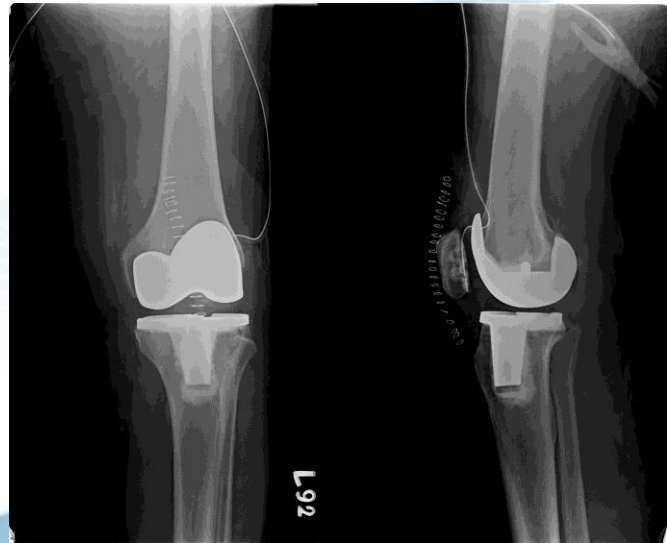










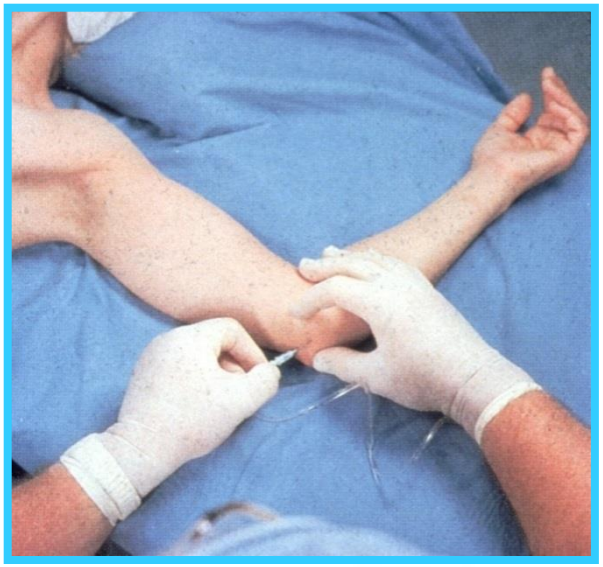


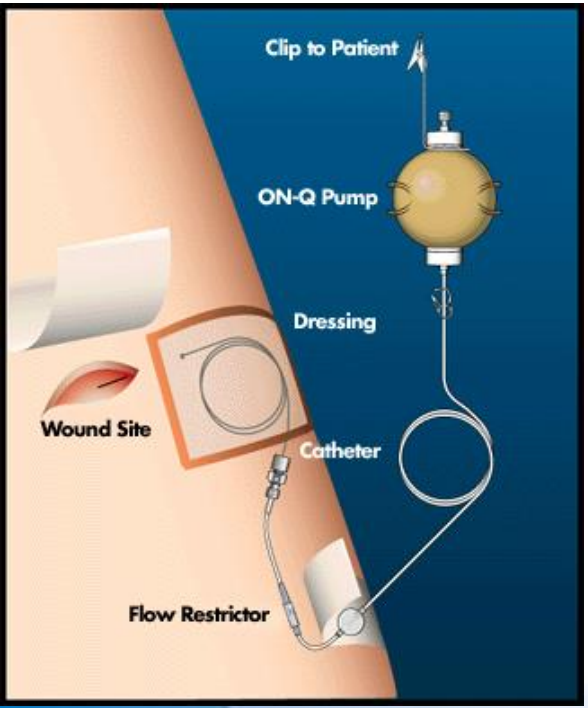
介入性疼痛治療

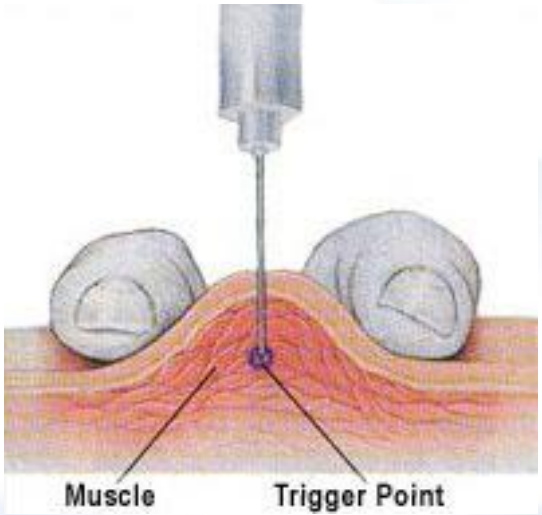
Interventional pain therapy

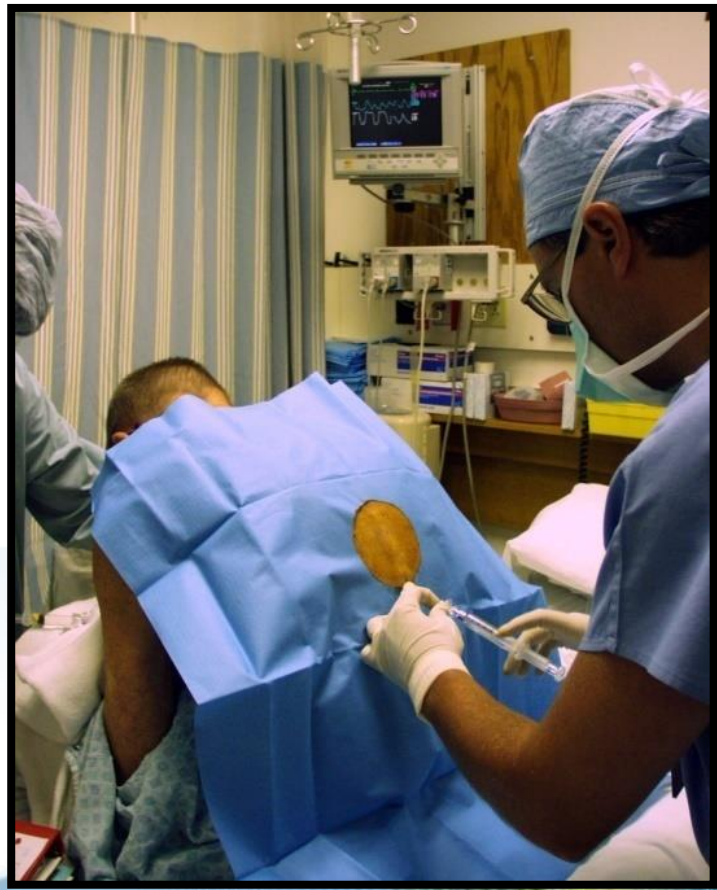
Neuromodulation, neuroablation

Intervention therapy

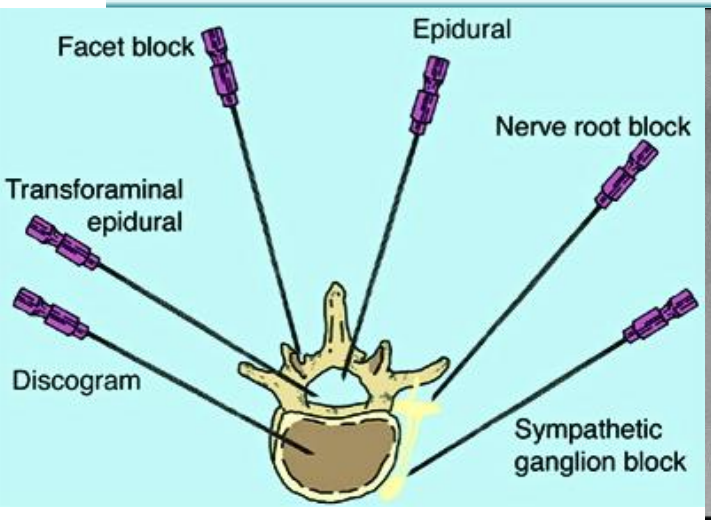


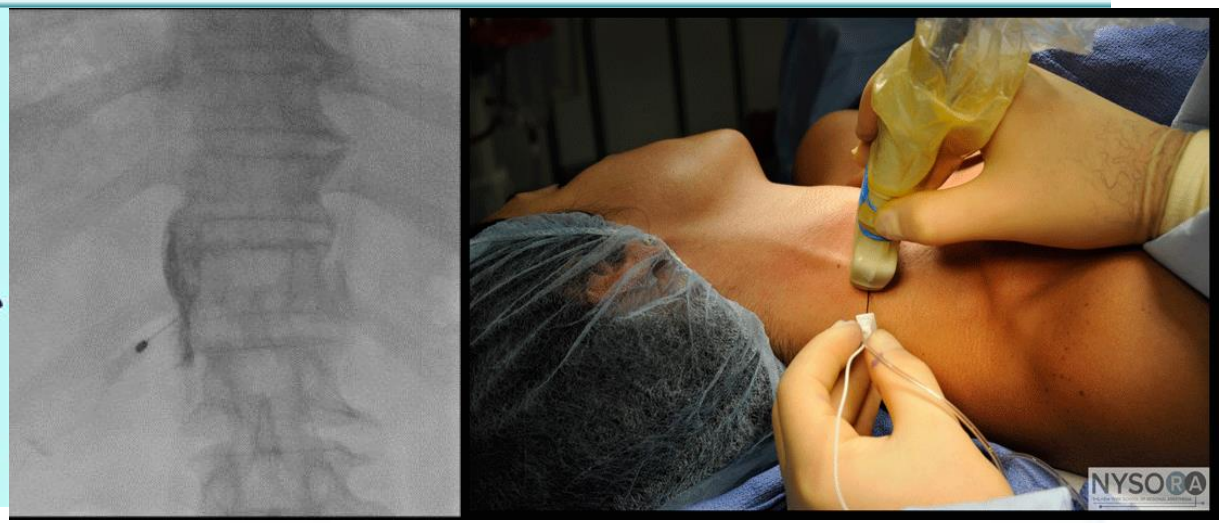


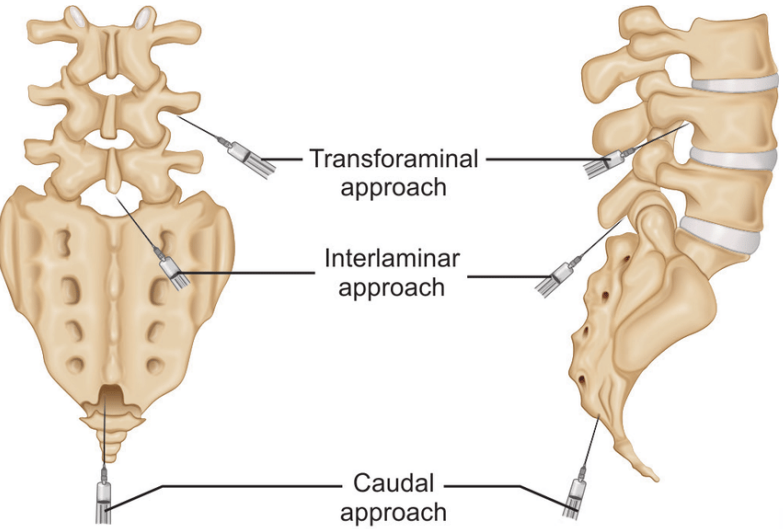


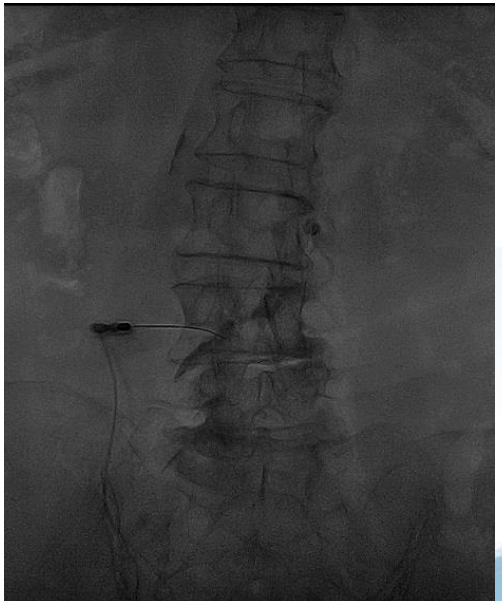


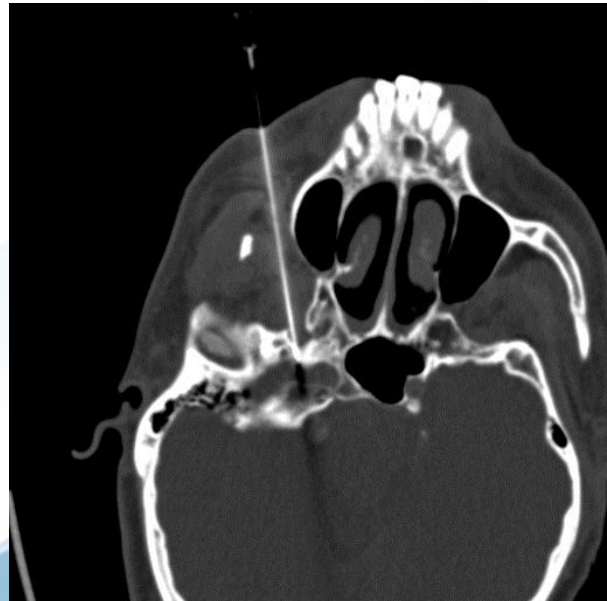
Interventional therapy



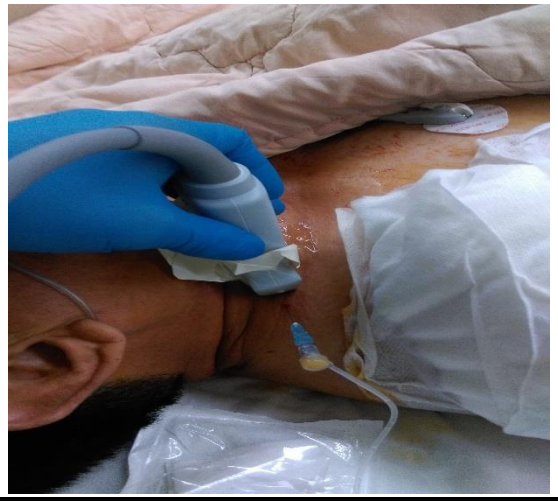


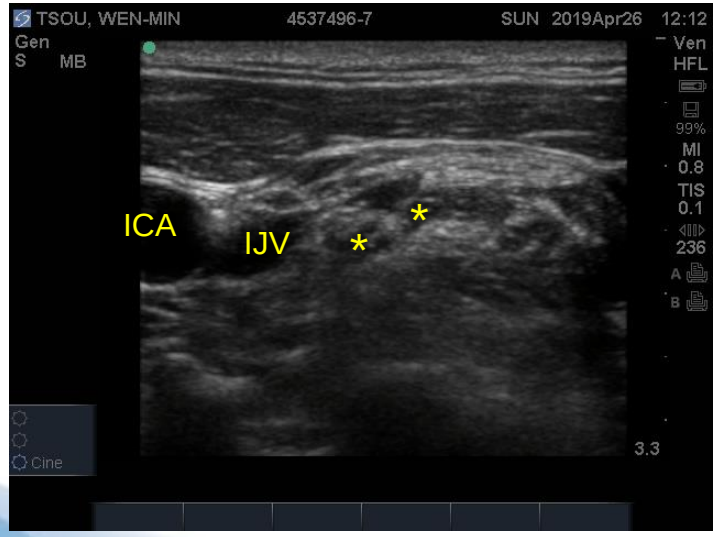


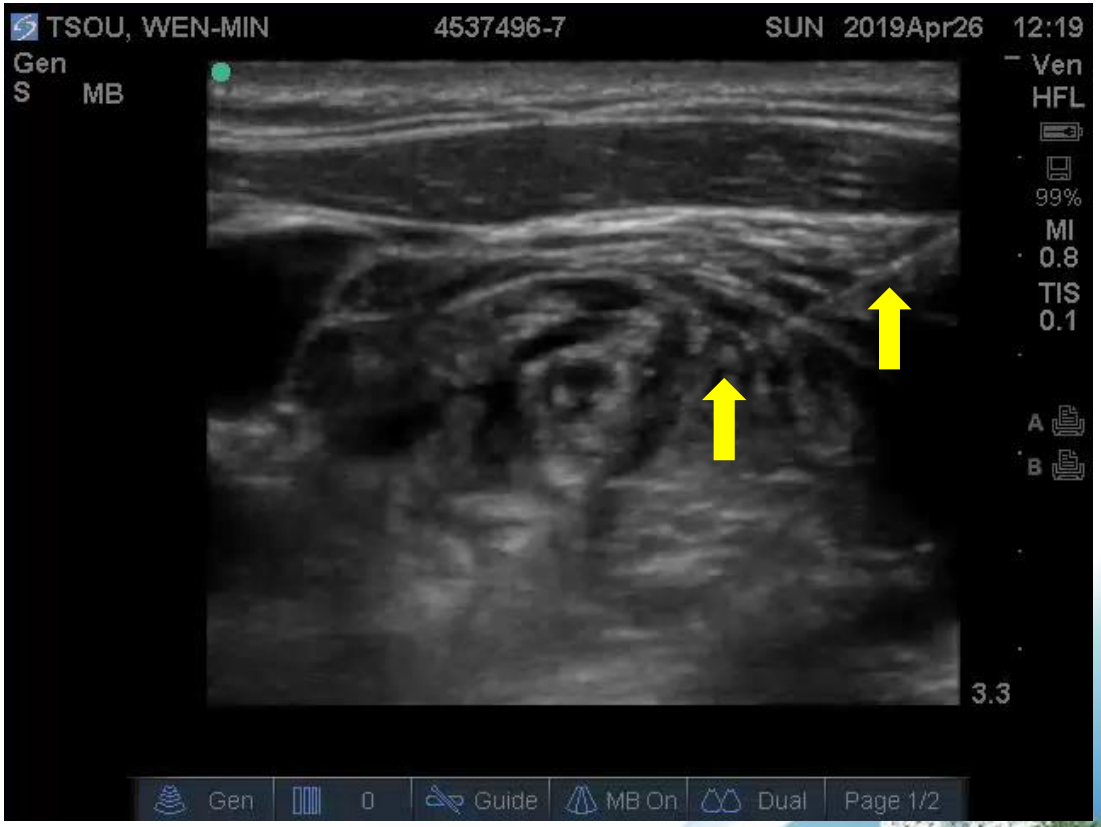




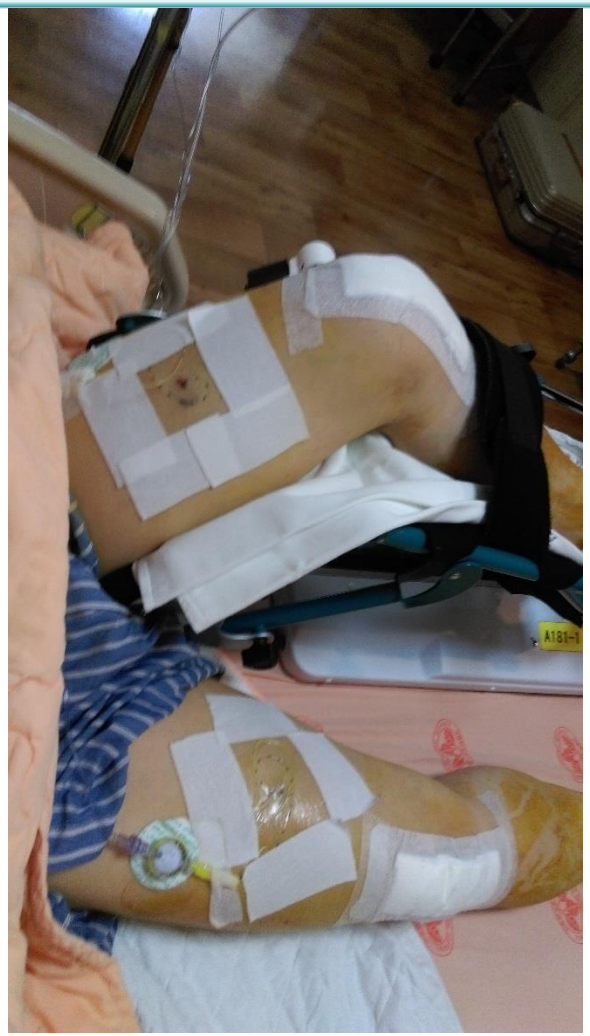
超音波導引頸部臂神經叢止痛注射

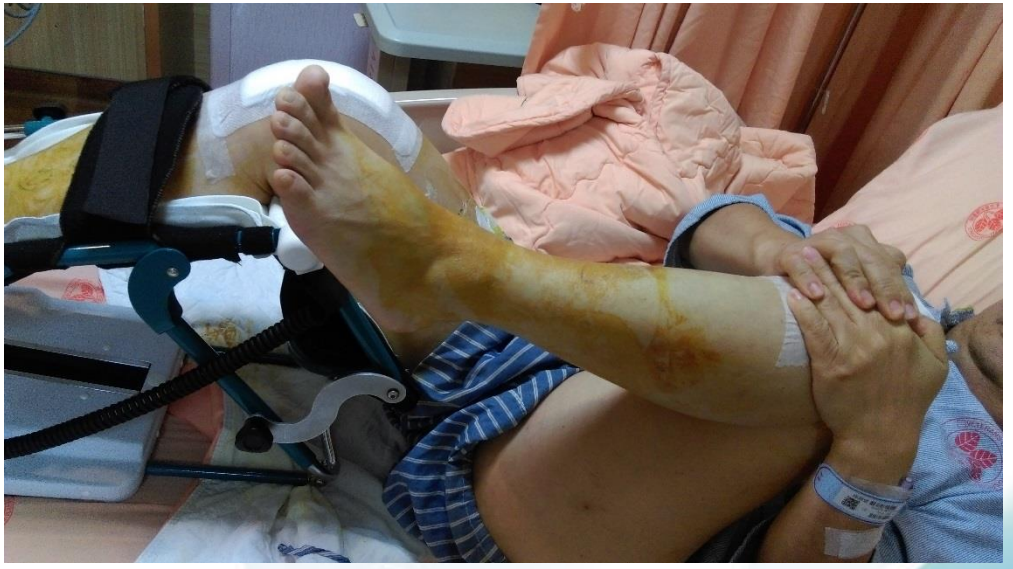




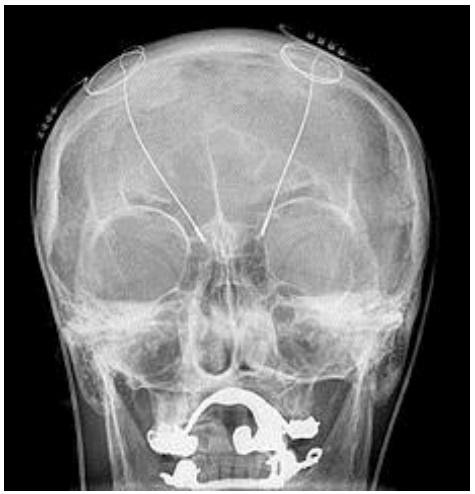


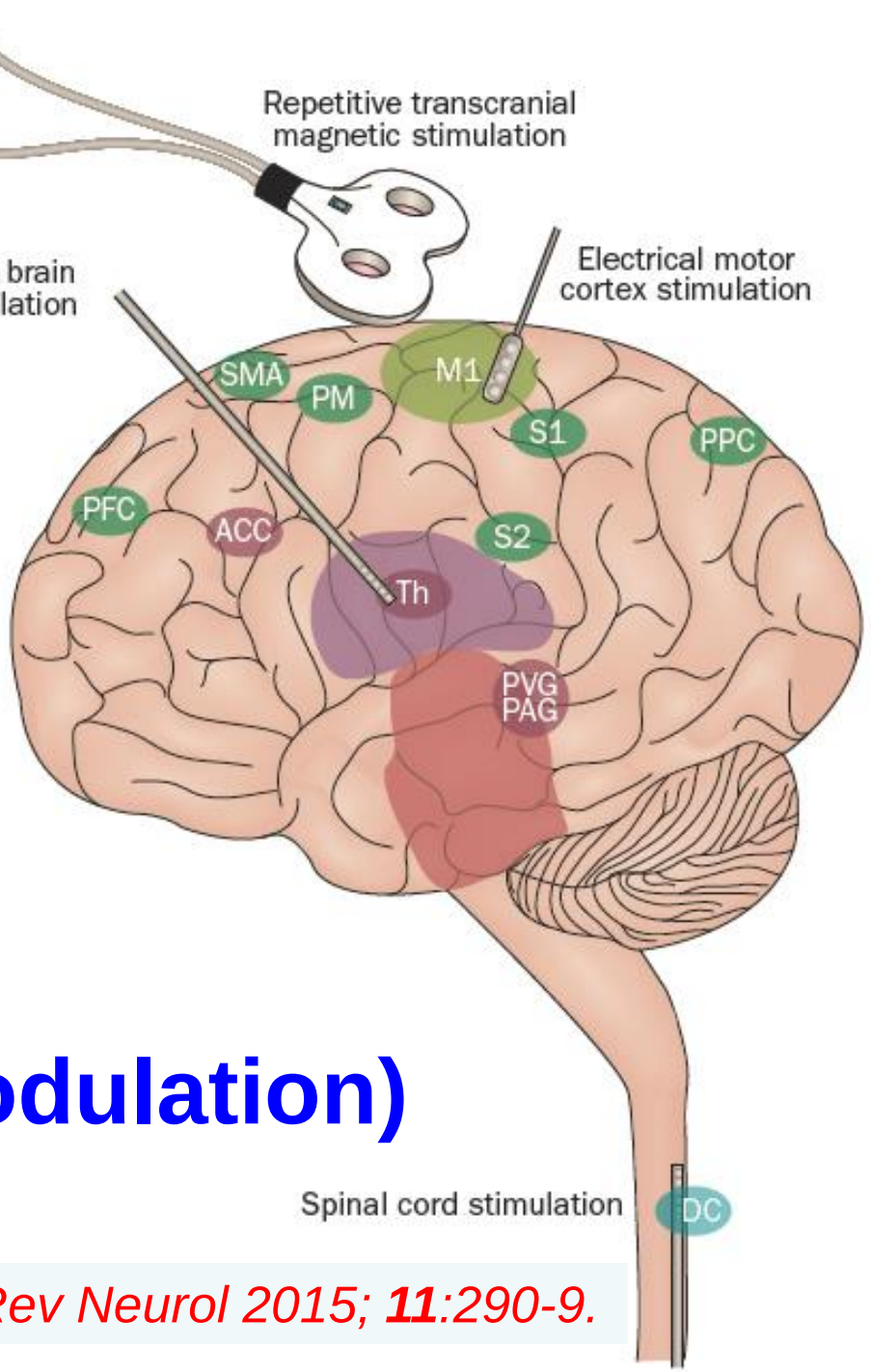
Continuous peripheral nerve block

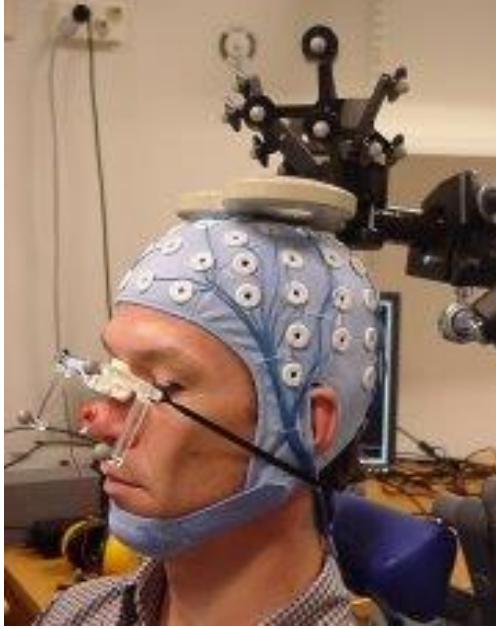




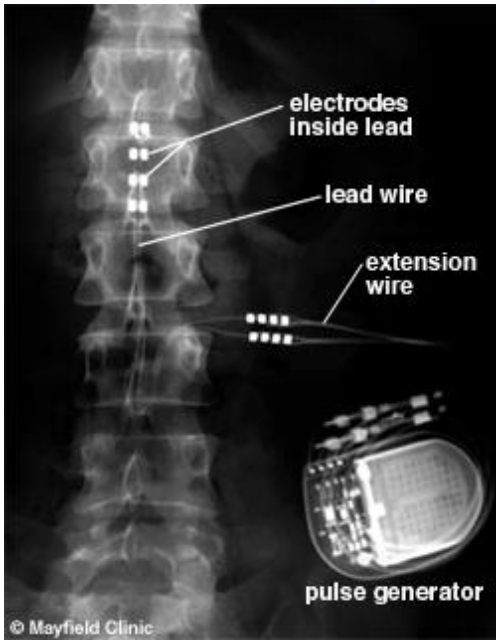
Post-op 19h







神經調控 (Neuromodulation)

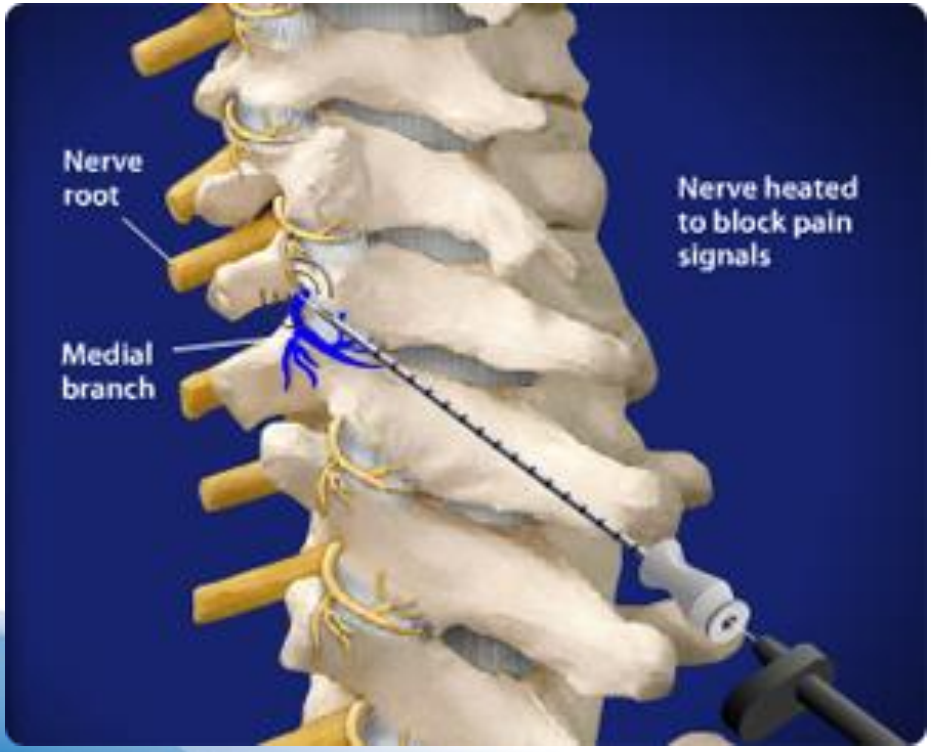


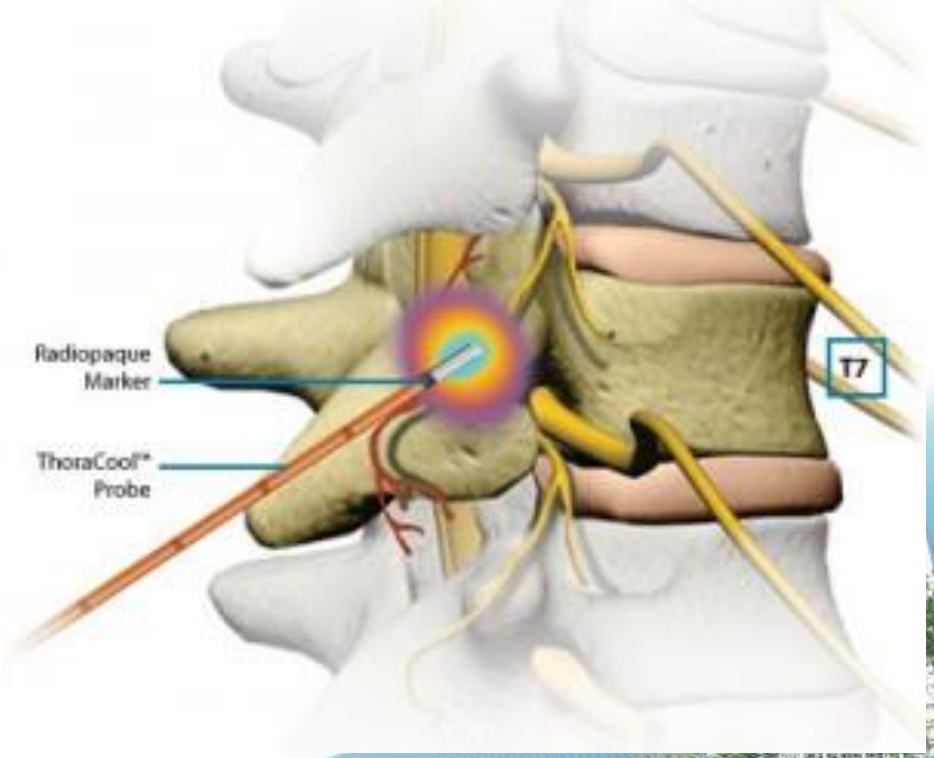
*Hosomi et al., Nat Rev Neurol 2015; **11**:290-9.*

射頻療法 (Radiofrequency)

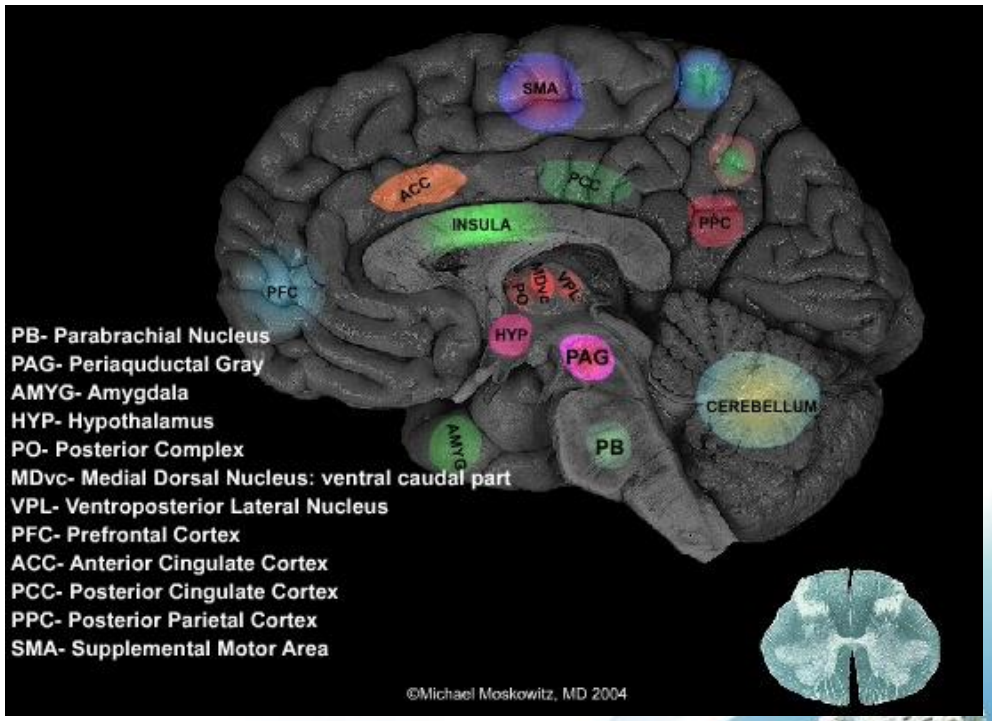
神經調控 (Neuromodulation)：Pulsed RF

神經破壞 (neuroablation)：RF ablation





神經破壞 (neuroablation)



宗 教 信 仰

因信而生力量

Recommendations or guidelines for pain management

2016 術後疼痛治療準則

American Pain Society

RESEARCH
EDUCATION
TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 2 (February), 2016: pp 131-157
Available online at www.jpain.org and www.sciencedirect.com

Guidelines on the Management of Postoperative Pain

Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council

重大胸腔與腹部手術，特別是心臟與肺併發症高風險或是腸阻塞病人，推薦使用硬脊膜外腔式止痛

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 17, No 2 (February), 2016: pp 131-157
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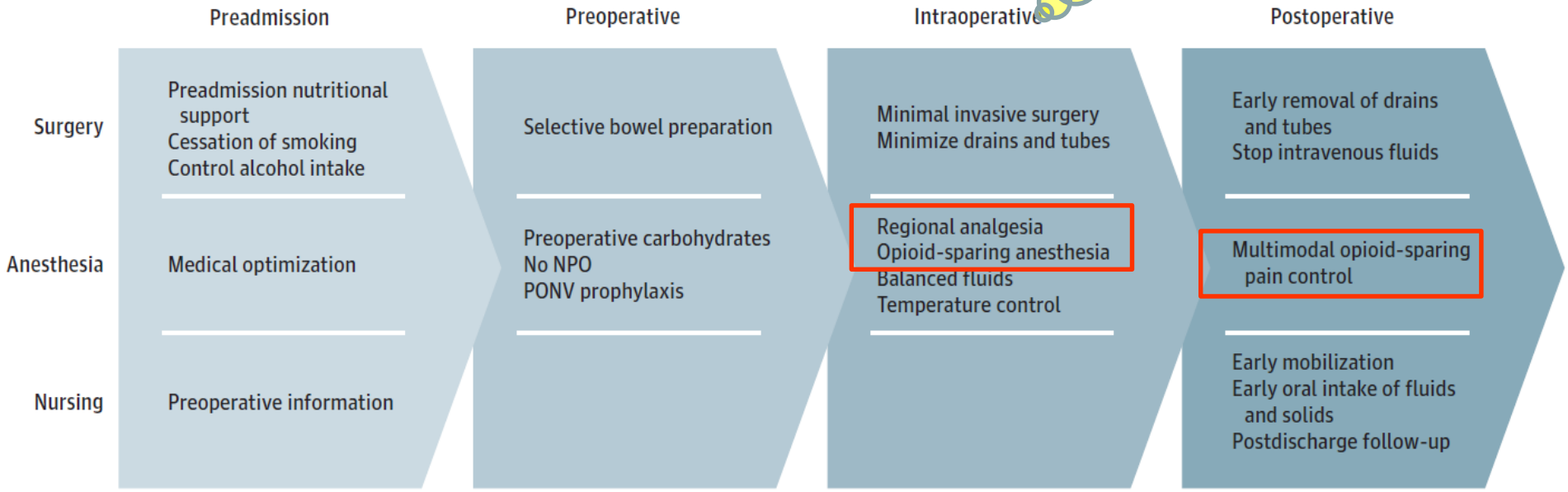
System-based holistic, polypharmacy, multimodal, and multidisciplinary approach

ERAS® Society

- 基於實證醫學論證
- **術後快速復原流程**
- 手術前、中、後的照護
- 多模式、多專科合作照護

鼓勵Regional analgesia
鼓勵多模式多藥物的止痛
減少嗎啡止痛的比重



神經性疼痛藥物治療

NeuPSIG recommendations 2015

NeuPSIG recommendation 2015

- First line recommendation: TCAs, SNRIs, pregabalin, gabapentin and gabapentin ER/enacarbil
- Second line recommendation: lidocaine patches, capsaicin patches and tramadol
- Third line recommendation: strong opioids (particularly oxycodone and morphine) and BTX-A

癌痛治療

WHO 3-ladder guideline 1986

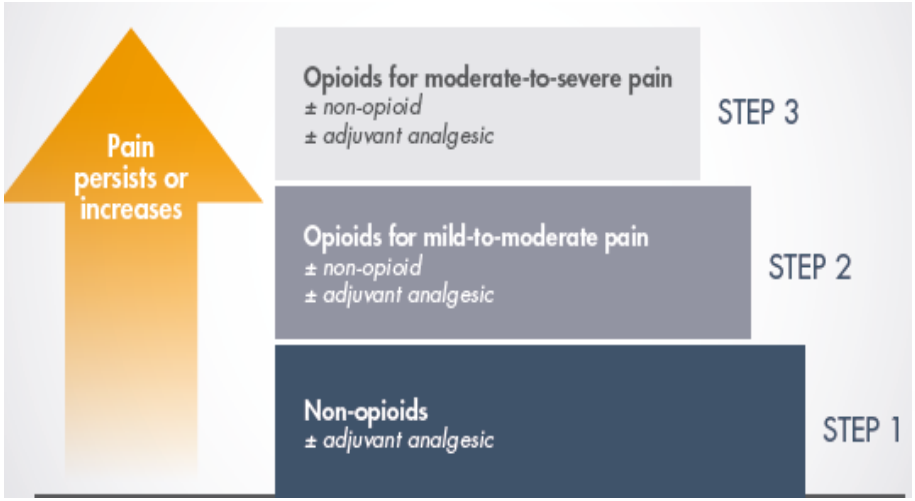
ESMO guideline 2012

EAPC guideline 2013

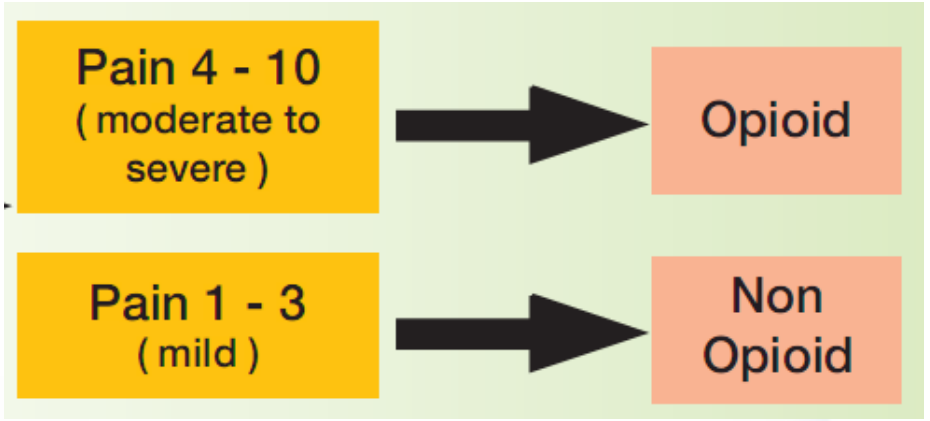
NCCN recommendation 2014

WHO三階梯止痛原則

WHO guideline 1986



NCCN guideline 2014



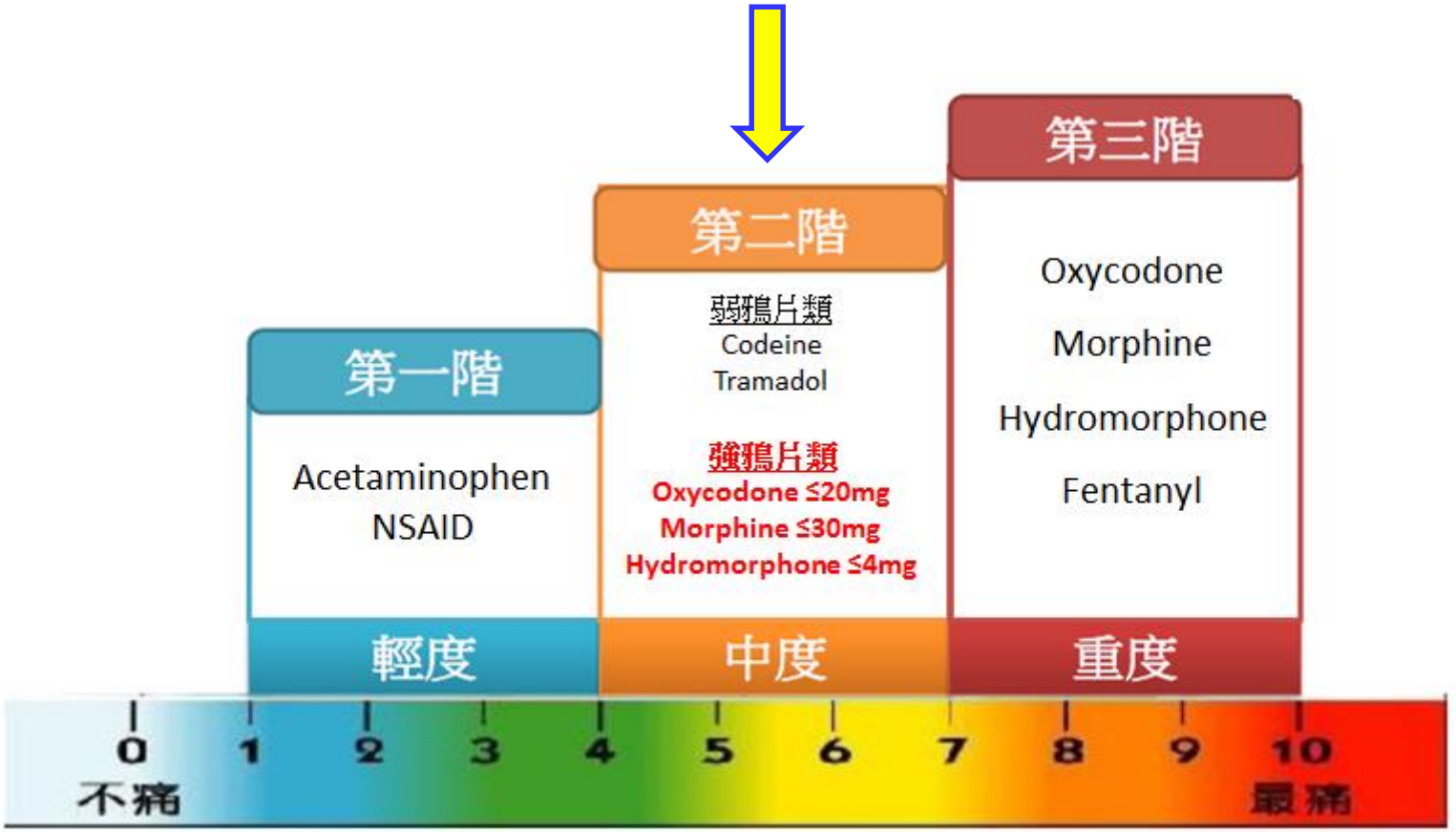
經口、按時、依階梯 、個制化、常規與救急藥物

ESMO Guidelines 2012

- 原則
- **Analgesic drugs** and an integrated approach to cancer pain management should be adopted; this **should incorporate**:
  - primary anti-tumor treatments
  - **interventional analgesic therapy**
  - **non-invasive techniques**

EAPC 2013癌痛指引：新二階梯建議

適當使用低劑量強鴉片類藥物緩解中度疼痛

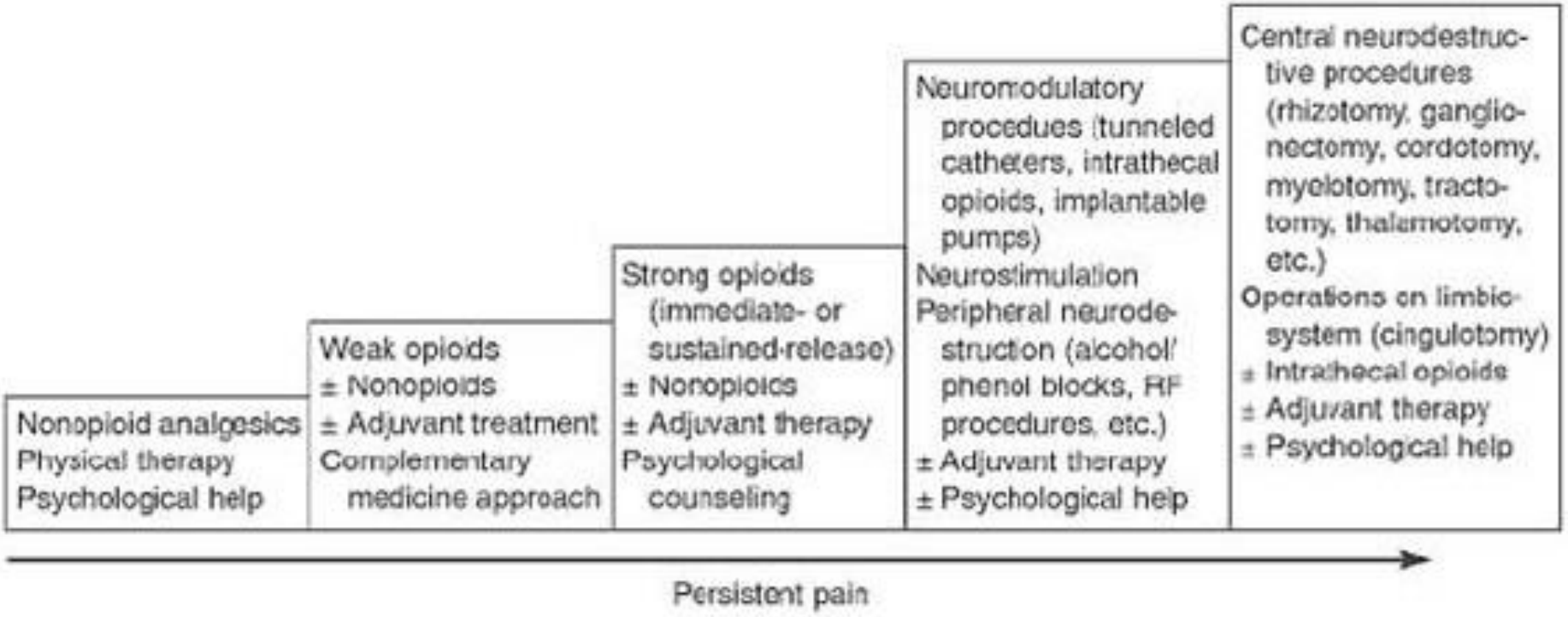


Lancet Oncol 2012; 13:e58–68

2014 NCCN guidelines

- 所有癌痛都必須:
  - 持續性止痛: **常規給藥 + rescue dose**
  - 治療副作用、心理支持、家屬/照顧者的衛教
- 癌痛以opioid治療為原則，加上其他藥物輔助
- 短效和長效盡量使用**同一種**鴉片類藥物
- **口服**為chronic therapy首選給藥方式

5階梯止痛原則


Nonopioid analgesics
Physical therapy
Psychological help
Weak opioids
± Nonopioids
± Adjuvant treatment
Complementary medicine approach
Strong opioids (immediate- or sustained-release)
± Nonopioics
± Adjuvant therapy
Psychological counseling
Neuromodulatory procedues (tunneled catheters, intrathecal opioids, implantable pumps)
Neurostimulation
Peripheral neurodestruction (alcohol/phenol blocks, RF procedures, etc.)
± Adjuvant therapy
± Psychological help
Central neurodestructive procedures (rhizotomy, ganglionectomy, cordotomy, myelotomy, tractotomy, thalamotomy, etc.)
Operations on limbic system (cingulotomy)
± Intrathecal opioids
± Adjuvant therapy
± Psychological help
Persistent pain

On-going and future development

Opioid-sparing and opioid-free

Opioids：現在的焦慮與管制

- Adverse effects
- Abuse, addiction, and overdose death
- Opioid crisis: law regulations and litigation
- Opioid-sparing strategy
- Development of opioid-free analgesia??

Opioid-free anesthesia/analgesia?

CURRENT OPINION

Opioid-free anesthesia: a different regard to anesthesia practice

Curr Opin Anesthesiol 2018; 31:556-561.

Patricia Lavand'homme[a] and Jean-Pierre Estebe[b]

Opioid-free Analgesia for Posterior Spinal Fusion Surgery Using Erector Spinae Plane (ESP) Blocks in a Multimodal Anesthetic Regimen

Spine 2019; 44:E379-E383.

Ki Jinn Chin, MBBS (Hons), MMed, FRCPC* and and Stephen Lewis, FRCSC†

Opioid-free anesthesia/analgesia

- Multimodal anesthesia/analgesia
  - Anesthesia: inhaled anesthesia or TIVA
  - Non-opioids
    - Intermittent use
    - Continuous infusion of ketamine, dexmedetomidine, and/or lidocaine
  - Regional analgesia

結論

- 首要：治療疼痛的源頭
- 藥物治療是止痛最常使用的模式
- 鴉片類藥物並非所有種類疼痛的首選藥物
- 考慮：疼痛的類型、病人的需要與...
- 多模式與多藥物模式的跨領域團隊止痛醫療
- 藥物與非藥物方式
- 身體、心理層面與教育
- 趨勢：Opioid-sparing and/or opioid-free?


福 慧 平 安