

# 慢性非癌症疼痛

## 病例用藥討論

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## Case Report-1

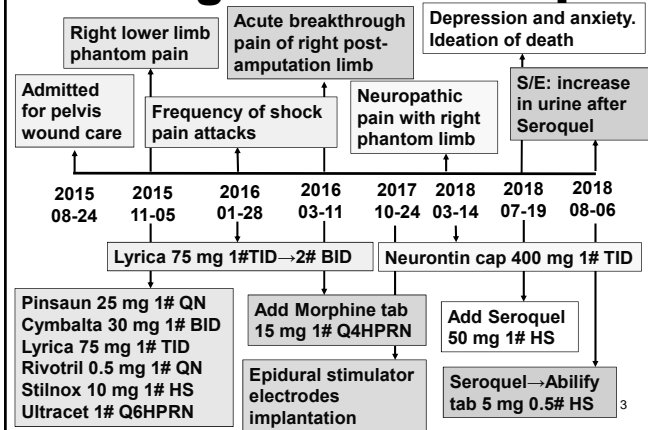
Ms. Kao 38 y/o 160 cm 53.3 kg OPD 2019/03/11

### Subjective:

- Trauma with right pelvic fracture s/p right hemipelvectomy on 2015/2/4, complicated with poor wound healing with phantom limb pain
- Right flank and sacral region wounds s/p debridement and wound closure on 2015/10/08
- Open wound over bilateral hips with iliac bone fracture
- Left SI joint osteoarthritis and screw loosening
- Multiple organ laceration and bone fracture

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## During OPD Follow-up



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## Case Report-2

### Objective:

日期	BUN	CREA	ALT	NA	K	WBC	Hgb	PLT	INR	SEG	LYM	EOS
2015-09-01	13	0.62	12	136	5.8	-	-	-	-	-	-	-
2015-09-24	9	0.61	-	142	3.3	-	-	-	-	-	-	-
2015-09-29	-	0.77	-	138	3.5	-	-	-	-	-	-	-
2015-10-08	13	0.57	-	140	3.8	-	-	-	-	-	-	-
2017-10-22	16	0.79	20	145	3.6	7400	14.2	297000	1.02	66.2	21.9	3.8
2017-12-10	12	0.73	19	142	4.1	6200	13.0	250000	1.05	50.9	35.9	4.9

### Assessment:

- Neuropathic pain with right phantom limb pain
- Major depression
- Insomnia

### Plan to do:

- Continue rehabilitation therapy and soft exercise
- Keep current drug therapy

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## Patient Drug Profile

藥名/含量/劑量/頻次	2015		2016		2017		2018		2019	
	10/19	11/05	01/28	03/11	10/24	03/14	07/19	08-06	10/11	03/11
Lyrica hard cap 75 mg (Pregabalin)	1#	TID	PO	2# BID						
Neurontin cap 400 mg (Gabapentin)	1#	TID	PO							
Ultracet tab (Acetaminophen 325 mg/ Tramadol 37.5 mg)	1#	Q6HPRN	PO				Q6HV			
Muaction tab 100 mg (Tramadol)	1#	BIDPRN	PO							
Morphine sulfate tab 15 mg	1#	Q4HPRN	PO				Q8HPRN			
OxyNorm IR cap 5 mg (Oxycodone HCl)	1#	Q6HPRN	PO				Q12H			
OxyContin CR tab 10 mg (Oxycodone HCl)	2#	Q12H	PO							
Durogesic D-Tran patch 12 ug/hr (Fentanyl) 1Tap	1#	Q3D	SK							
Pinsaun tab 25 mg (Amitriptyline)	1#	QN	PO							
Cymbalta cap 30 mg (Duloxetine)	1#	BID	PO							
Seroquel XR tab 50 mg (Quetiapine)	1#	HS	PO							
Abilify tab 5 mg (Aripiprazole)	0.5#	HS	PO							
Rivotril tab 0.5 mg (Clonazepam)	1#	QN	PO							
Stilnox tab 10 mg (Zolpidem)	1#	HS	PO							
Lexotan tab 1.5 mg (Bromazepam)	1#	Q8HPRN	PO							

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## Discussion

- Introduction of chronic non-cancer pain (CNCP)
- Choice of therapy by type of pain
  - Neuropathic pain
  - Nociceptive pain
- Treatment of chronic non-cancer pain
  - Non-opioid analgesic agents
  - Anticonvulsants
  - Antidepressants
  - Opioids

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## Introduction of CNCP

### • Epidemiology

- Prevalence of CNCP: 20% (in Taiwan), 5-33% (in U.S.), 8.2% (in Canada), 10-30% (in Europe), 19% (in Denmark), 46.5% (in UK)
- Costing a staggering \$560 billion to \$635 billion annually in U.S.

### • Definition

- Pain that persists beyond normal tissue healing time, which is assumed to be three months

Breivik H et al. Eur J Pain 2006; Elliott AM et al. Lancet 1999; 7  
International Association for the Study of Pain. 2010

## Physiological Mechanisms

### Nociceptive pain

**Cause:** normal processing by nociceptors in response to noxious stimuli (tissue damage, compression, inflammation, etc.).  
**Sensation:** based on subtype

### Neuropathic pain

**Cause:** abnormal processing by the peripheral or central nervous system.  
**Sensation:** Sharp, stabbing, burning, tingling, numb

**Visceral pain:**  
• From inflamed or obstructed visceral organs, such as GI tract and pancreas  
• Vague, diffuse cramping or throbbing, nausea

**Somatic pain:**  
• From bone, joint, muscle, skin, connective tissue  
• Localized stabbing, ache, throbbing

• Peripherally: diabetic neuropathy, trigeminal neuralgia

• Centrally generated pain: phantom limb pain, spinal cord injury

Carver et al. Holland-Frei Cancer Medicine, 6th edition <sup>8</sup>

## Therapy by Type of Pain

### • Nociceptive pain

- Acetaminophen as 1<sup>st</sup> line therapy
- Oral nonsteroidal anti-inflammatory drugs (NSAIDs)
- Opioids as alternative choice

### • Neuropathic pain

- Antidepressants: tricyclic antidepressants, dual reuptake inhibitors of serotonin and norepinephrine
- Anticonvulsants: calcium channel alpha 2-delta ligands
- Topical therapy: topical lidocaine
- Opioids: should be considered a 2<sup>nd</sup> option
- Combination therapy is often required UpToDate 2019 <sup>9</sup>

## Nonopioid Analgesics

Drug	Role	Dosage	Consideration
Acetaminophen	Osteoarthritis (hip or knee)	1000-4000 mg/day	Hepatotoxic at doses greater than 3-4 g/d
NSAIDs (Celecoxib, diclofenac, ibuprofen, meloxicam, naproxen)	Low back pain, osteoarthritis (mild to moderate pain)	<ul style="list-style-type: none"> <li>• Celecoxib: 100 mg BID or 200 mg QD</li> <li>• Diclofenac: 75-100 mg TID</li> <li>• Ibuprofen: 200-400 mg Q6H-Q8H</li> <li>• Meloxicam: 7.5-15 mg QD</li> <li>• Naproxen: 375 mg-500 mg BID</li> </ul>	<ul style="list-style-type: none"> <li>• Lower dose in the elderly</li> <li>• Synergistic effect with opioids</li> <li>• S/E: GI bleeding, peptic ulcer, fluid retention, CVD</li> <li>• Avoid in severe renal dysfunction (CrCl&lt;30 ml/min) and severe hepatic impairment, during pregnancy</li> </ul>

## Anticonvulsants

Drug	Role	Dosage	Consideration
Carbamazepine	Trigeminal neuralgia	ID: 100 mg-200 mg QD; MD: 200 mg-800 mg per day	<ul style="list-style-type: none"> <li>• S/E: liver toxicity, blood dyscrasias</li> <li>• DC or reduce dose every 3 month</li> <li>• Reduce dose by 20% each week</li> </ul>
Gabapentin	Neuropathic pain	ID: 300 mg HS; MD: 400 mg-1800 mg TID	<ul style="list-style-type: none"> <li>• S/E: dizziness, drowsiness</li> <li>• Titrated dose at least over 1 week</li> </ul>
Pregabalin	Neuropathic pain	ID: 75 mg BID; MD: 150 mg BID	<ul style="list-style-type: none"> <li>• S/E: sedation, dizziness</li> <li>• Doses titrated up to at least 300 mg/d</li> </ul>
Ms.Kao: pregabalin 75 mg TID → 150 mg BID → 75 mg TID → gabapentin 400 mg TID ID: initial dose; MD: maintenance dose; DC: discontinue <sup>11</sup>			

## Antidepressants

Drug	Role	Dosage	Consideration
TCAs (Amitriptyline, nortriptyline, imipramine)	Neuropathic pain; Fibromyalgia	<ul style="list-style-type: none"> <li>• Amitriptyline ID: 10 mg-25 mg QD; MD: 25 mg-125 mg/day</li> <li>• Imipramine: 25-75 mg/day</li> </ul>	<ul style="list-style-type: none"> <li>• S/E: constipation, sedation, dry mouth, urinary retention, confusion, weight gain, prolonged QT interval</li> <li>• Caution in elderly</li> </ul>
Duloxetine	Neuropathic pain due to diabetes; Fibromyalgia; Osteoarthritis	60 mg/day	<ul style="list-style-type: none"> <li>• S/E: headache, GI upset, insomnia, drowsiness</li> <li>• Contraindicated in hepatic or severe renal impairment</li> </ul>
Fluoxetine	Fibromyalgia	20 mg/day (up to 80 mg/day)	<ul style="list-style-type: none"> <li>• S/E: headache, nausea, anxiety, leation</li> </ul>
Ms.Kao: Amitriptyline 25 mg QN + Duloxetine 30 mg BID <sup>12</sup> TCA: Tricyclic antidepressants			

## Suicidal Ideation ↔ GABA Analogue

- 10% of patients started on pregabalin: developed depression or suicidal ideation

Diagnosis	# at Risk	# Attempts		Rate per 1,000		ERR <sup>2</sup>	95% CIs for ERR		P-value
		Before	1,000	After	1,000		ERR	P-value	
Bipolar Disorder	3,783	181	47.85	119	31.46	0.62	0.41-0.94	0.026	
Major Depressive Disorder	25,203	436	17.30	319	12.66	0.65	0.52-0.82	< 0.001	
Schizophrenia	598	38	63.55	28	46.82	0.74	0.41-1.35	0.326	
Other Psychiatric Disorder	31,847	409	12.84	323	10.14	0.69	0.55-0.88	0.002	
Epilepsy	1,411	12	8.50	10	7.09	0.83	0.34-2.04	0.683	
Pain Disorder	107,816	345	3.20	370	3.43	0.99	0.78-1.26	0.944	
All	131,178	456	3.48	453	3.45	0.93	0.76-1.14	0.487	
Gabapentin Monotherapy <sup>d</sup>	57,085	17	0.30	9	0.16	0.53	0.16-1.73	0.294	

No significant difference in suicide attempt rates before (3.20/1000 patient years--PY) versus after (3.43/1000 PY) gabapentin prescription.

Mayor S, et al., *BMJ* 2018; Gibbons RD, et al., *Pharmacoepidemiol Drug Saf* 2010

## Opioid Selection and Dosing

- Starting opioid therapy
  - Short-acting are recommended (shorter T<sub>1/2</sub>)
  - Lessen the danger of overdose
  - Easier to titrate to an effective dose
- Consider a transition to long-acting opioids
  - Pain is not adequately relieved by short-acting opioids
  - Patient has withdrawal symptoms
  - Pain is moderate to severe and constant

CDC Guideline for Prescribing Opioids for Chronic Pain, 2016<sup>14</sup>

## Short-Acting Opioids

Drug	Dosage	Consideration
Codeine (μ)	15-60 mg q3h-q6h	<ul style="list-style-type: none"> <li>• Codeine alone is a weak analgesic (usually combined with APAP)</li> <li>• More nausea and constipation than other</li> <li>• Caution in elderly, hepatic or renal dysfunction</li> </ul>
Fentanyl buccal (μ)	Not recommended in chronic non-cancer pain (including those with only as needed)	
Oxycodone IR (μ)	5-10 mg q4h-q6h	<ul style="list-style-type: none"> <li>• Reduce dose in elderly, caution in hepatic or renal dysfunction</li> </ul>
Morphine IR (μ)	10-30 mg q4h	<ul style="list-style-type: none"> <li>• Extreme caution in elderly</li> <li>• Reduce dose in hepatic or renal dysfunction</li> </ul>
Tramadol (serotonin, NE, μ)	25-50 mg q6h	<ul style="list-style-type: none"> <li>• Renal impairment: q12h (not exceed 200 mg/d)</li> <li>• Increase seizure risk (esp. concurrent use with SSRIs, TCAs, MAOIs)</li> </ul>

MAOI: Monoamine oxidase inhibitor; TCA: Tricyclic antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors  
 APAP: N-acetyl-para-aminophenol (Acetaminophen)  
 UpToDate 2019;<sup>15</sup> Package insert

## Long-Acting Opioids

Drug	Dosage	Consideration
Morphine SR, MXL	10-30 mg q12h	<ul style="list-style-type: none"> <li>• Hepatic impairment: 1.5-2 times dose interval</li> <li>• Caution in elderly or renal dysfunction</li> </ul>
Oxycodone CR	10 mg q12h	<ul style="list-style-type: none"> <li>• Reduce dose by 50% in elderly</li> <li>• Increase dose by 25-50% of current dose every 1-2 days</li> <li>• Recommended for patients with intolerant to morphine and fentanyl</li> </ul>
Hydromorphone ER	8-64 mg q24h	<ul style="list-style-type: none"> <li>• For opioid-tolerant patients only (after DC all extended-release opioids)</li> <li>• Titrate dose every 3-4 days as needed</li> </ul>
Fentanyl transdermal	12-25 μg/h q3d	<ul style="list-style-type: none"> <li>• Use only in opioid-tolerant patients (taking &gt; 60 mg/day morphine for at least 1 week)</li> <li>• Recommended for patients with GI absorption problems or intestinal resection</li> </ul>

Ms. Kao: Oxynorm IR 5 mg q6hprn + oxycontin 20 mg q12h → oxynorm IR 5 mg q6hprn + fentanyl 12 μg/hr 1T q3d  
 Date 2019;<sup>16</sup> Package insert

## Safety of Chronic Opioid Use

- Inclusion: opioids use more than 2 week for CNCP

Figure 2. Analysis 1.1: Opioids versus placebo, any adverse event. CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel method of meta-analysis; P: probability; Z: Z score (standard score)

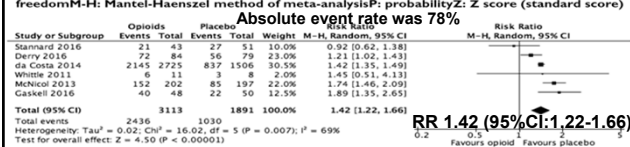
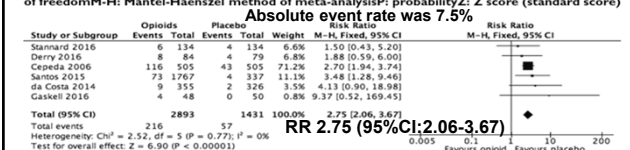


Figure 3. Analysis 1.2: Opioids versus placebo, any serious adverse event. CI: confidence interval; df: degrees of freedom; M-H: Mantel-Haenszel method of meta-analysis; P: probability; Z: Z score (standard score)



Els C et al. *Cochrane Database Syst Rev*. 2017

## Preventing and Managing S/E

Side effect	Prevention/Management
Respiratory depression	Screen for sleep apnea and avoid opioids if it is present. Avoid sedatives, benzodiazepenes, barbiturates, and alcohol.
Constipation	Educate patients to increase fiber and fluids; start osmotic agent or stool softener
Nausea or vomiting	Consider prophylactic antiemetic therapy. Ondansetron is recommended because it does not interact with opioids.
Itching	Reduce dose and increase frequency, change opioid, and/or consider antihistamines
Cognitive effects	Reduce dose and/or change opioid; avoid sedatives.
Perceptual effects (e.g., hallucinations, depression)	Rule out other causes, and eliminate all nonessential CNS-acting medications (e.g., steroids). Reduce opioid dose or switch opioid.

O'Mahony S, et al. *Oncology* 2001; Ford AC, et al. *Am J Gastroenterol* 2013

## **Take Home Message**

- **Treatment of CNCP**
  - Non-opioid analgesic agents (APAP, NSAIDs)
  - Anticonvulsants (TCAs, SNRIs)
  - Antidepressants (gabapentin, pregabalin)
  - Opioids (1<sup>st</sup> line for severe nociceptive pain, 2<sup>nd</sup> line for neuropathic pain)
- **Strategy of opioid therapy**
  - Start with low doses of short-acting agents
  - Adverse effects are common such as constipation, nausea, vomiting, sedation.
  - Reassessment at least every three months

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*Thanks for  
Your Attention*



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