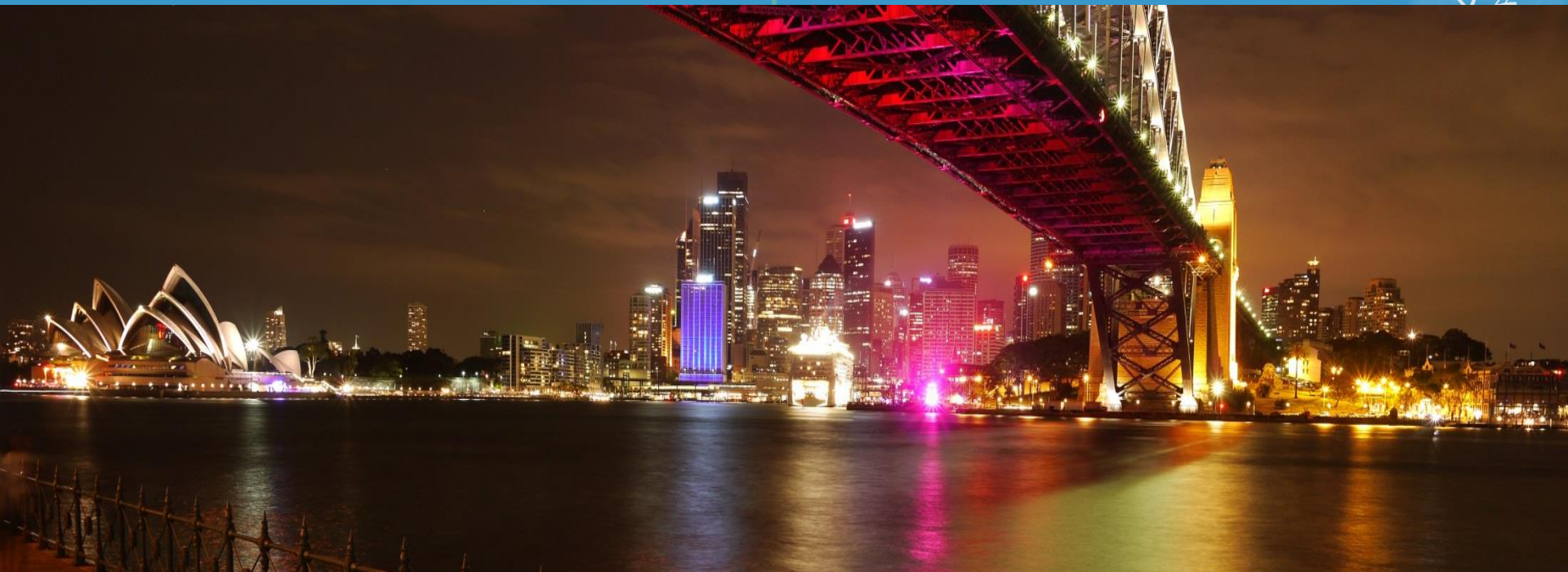


ORAL OXYCODONE FOR ACUTE PAIN SERVICE IN POSTOPERATIVE PAIN MANAGEMENT

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INTRODUCTION

- ❖ Pain is a likely outcome of any surgical procedure
- ❖ In several countries the use of oxycodone has surpassed morphine in post-operative pain management
- ❖ Oxycodone is a strong opioid
 - ❖ Acts at mu- and kappa-opioid receptors
 - ❖ Greater analgesic potency to morphine
- ❖ Prolonged-release form of oxycodone
 - ❖ Fast onset of analgesia
 - ❖ Control pain for 12 hours
- ❖ It has relevant points of difference from other opioids and as such may be a suitable alternative to morphine

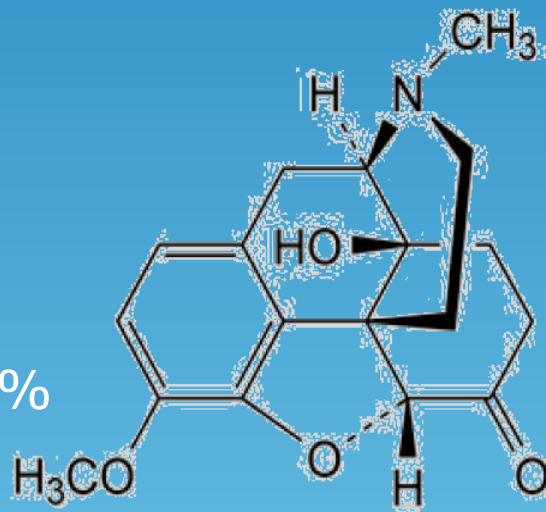
INTRODUCTION

- Visceral pain can be difficult to treat with classical μ -opioid agonists
 - Oxycodone has different effects compared to morphine
 - Clinical observations have shown that oxycodone may be superior to morphine
- In a study, 24 healthy subjects were randomised to treatment with either morphine (30 mg), oxycodone (15 mg) or placebo in a crossover study
 - The experimental pain model involved multi-modal (mechanical, thermal and electrical) pain tests in the skin, muscles and viscera
 - Morphine and oxycodone were equipotent in pain modulation of the skin and muscles
 - Oxycodone had superior analgesic effect to both morphine and placebo on the mechanical ($P < 0.001$) and thermal ($P < 0.001$) stimulations of the oesophagus **ie visceral pain**

OXYCODONE^{1,2}

- Semi-synthetic derivative of a morphine alkaloid, thebaine
- Full opioid receptor agonist activity on mu, kappa and delta receptors
- The clinical efficacy of oxycodone is similar to morphine, with a ratio of 1/1.5–2 for the treatment of cancer pain

- Up to **87% oral bioavailability**
- Plasma protein binding is 45%



OXYCODONE

- After oral administration of immediate release, analgesic effect may occur within 10-15 minutes and last 3-6 hours
 - Extended release commences after 1 hour and lasts 12 h
 - There is no differences between immediate and slow-release oxycodone, except half-life is 3-4 h, and 12 h, (1/2 of morphine)
- Stable plasma levels are reached within 24 h (2-7 days for morphine)
- Most of the drug is metabolised in the liver, while the rest is excreted by the kidney along with its metabolites
 - The two main metabolites are oxymorphone — which is also a very potent analgesic — and noroxycodone, a weak analgesic
- Oxycodone metabolism is more predictable than morphine, therefore titration is easier

OXYCODONE ANALGESIC EFFICACY



Citron 1998
Bruera 1998
Hagen 1997
Mucci-LoRusso 1998

Riley 2008
Heiskanen 1997
Biancofiore 2006



Roth 2000
Zautra 2005
McCroskery 2000
Markenson 2005

OA pain

Neuropathic pain

Gatti 2009



Watson 1998
Sindrup 1999

Post-herpetic neuralgia

Diabetic neuropathy

Hanna 2008
Watson 2003
Gimbel 2003



Post-operative pain

Curtis 1999
Sunshine 1996
Ginsberg 2003
Cheville 2001
De Beer 2005
Wirz 2005



OPIOIDS PLACE IN PAIN MANAGEMENT

- Patients with moderate-severe pain^{1,2}
- Other conservative methods of analgesia have been tried and failed¹
- Pain is having a significant impact on the patient's quality of life^{1,3}
- There is no psychological contraindication, drug-seeking behaviour or history of prescription medicine, illicit drug or alcohol misuse.¹

WHO ANALGESIC LADDER

○ Key concepts to effective pain management:

○ *By mouth:*

- If possible, the analgesic should be given by mouth

○ *By the clock:*

- Analgesics should be given at fixed time intervals and the dose should be titrated according to the patient's pain.
- The next dose should be given before the previous dose has fully worn off

○ *For the individual:*

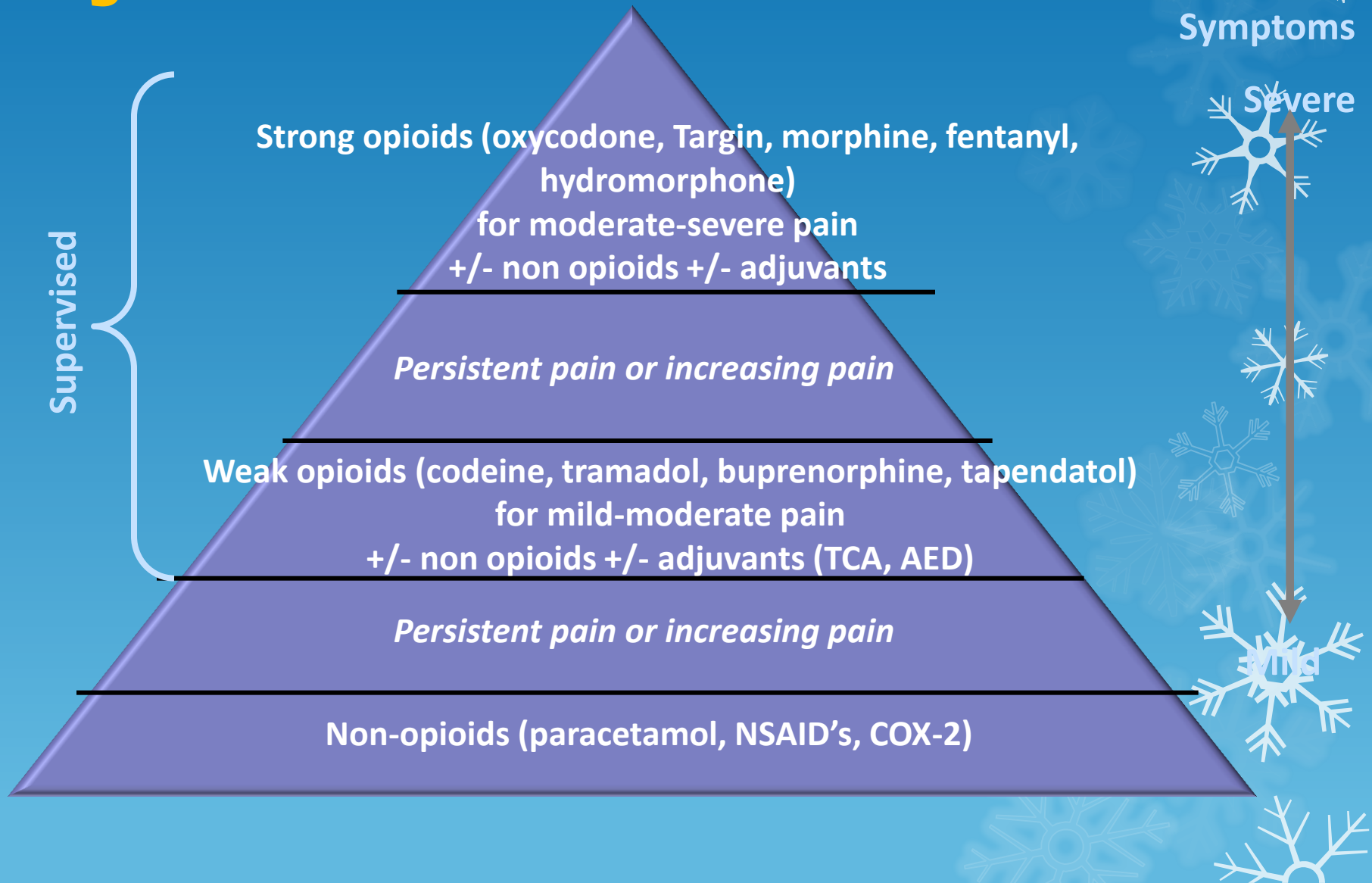
- The choice and dosage of the analgesics should be tailored to the patient

○ *By the ladder:*

- Stepped approach to the use of analgesics

WHO ANALGESIC LADDER

May 2013 (GENERALLY FOR NOCICEPTIVE PAIN)



OPIOID-RELATED SIDE EFFECTS

- Common^{1,2}
 - Constipation, nausea, anorexia
 - Sedation, dizziness, cognitive impairment
 - Postural hypotension
 - Pruritus, dry mouth, miosis
- Less common^{1,2}
 - Hormonal effects – reduced testosterone / oestrogen
 - Immunosuppression
 - Opioid-induced hyperalgesia
 - Respiratory depression

OPIOID-INDUCED CONSTIPATION (OIC)

- OIC is common and experienced by 40–95% of opioid-treated patients and typically continues for the duration of opioid therapy^{1–3}



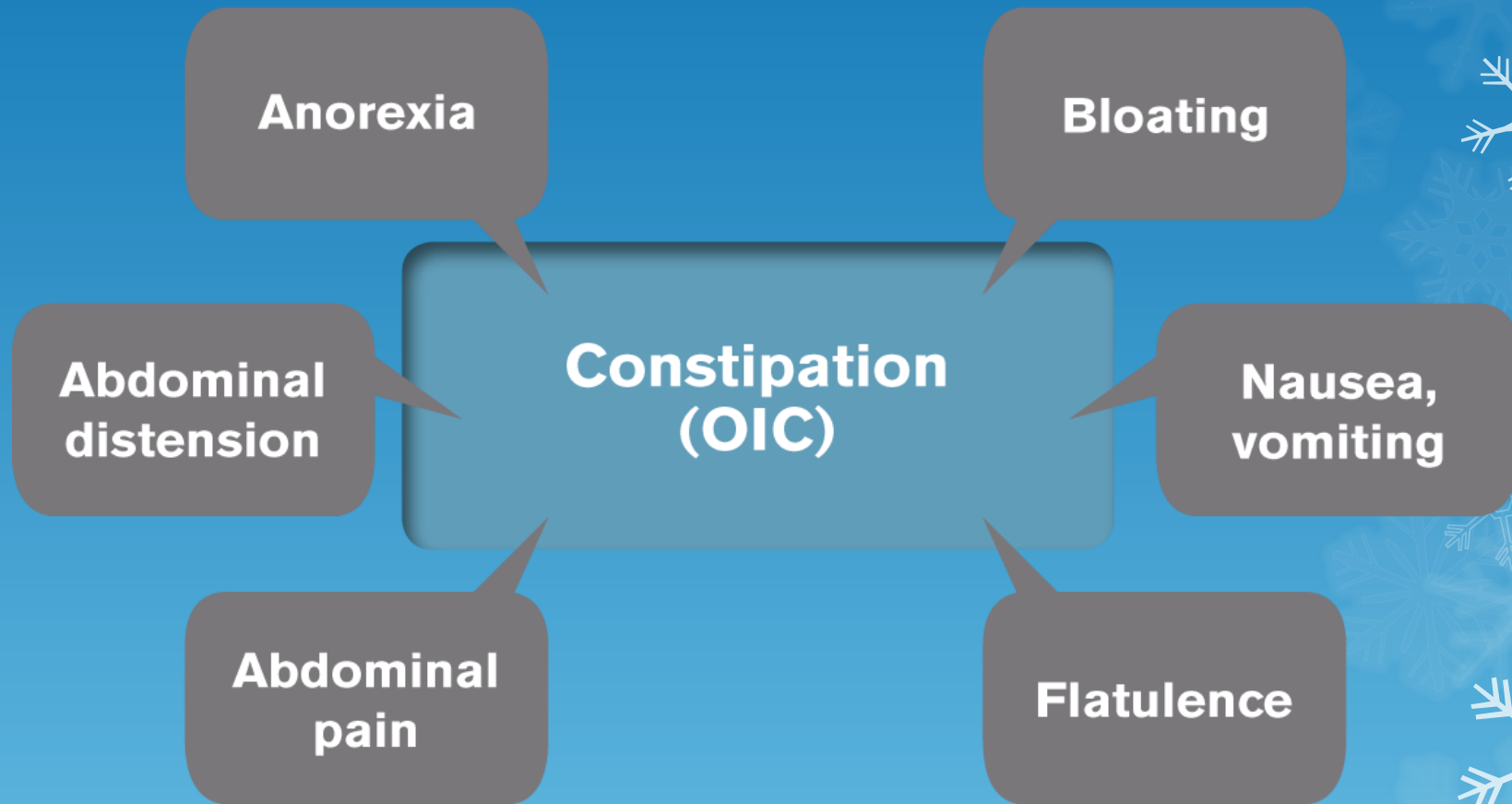
Adapted from Bell *et al.*⁴

OIC COMPROMISES PAIN MANAGEMENT^{4–6}

- OIC is one of the most common reasons chronic, moderate to severe pain patients avoid using opioids^{5,7}
- 1 in 3 patients with chronic pain* reduce or skip opioid doses specifically to facilitate a bowel movement⁵

*taking laxatives and daily oral opioids

OPIOID-INDUCED BOWEL DYSFUNCTION (OIBD) and OIC SYMPTOMS^{1,2}



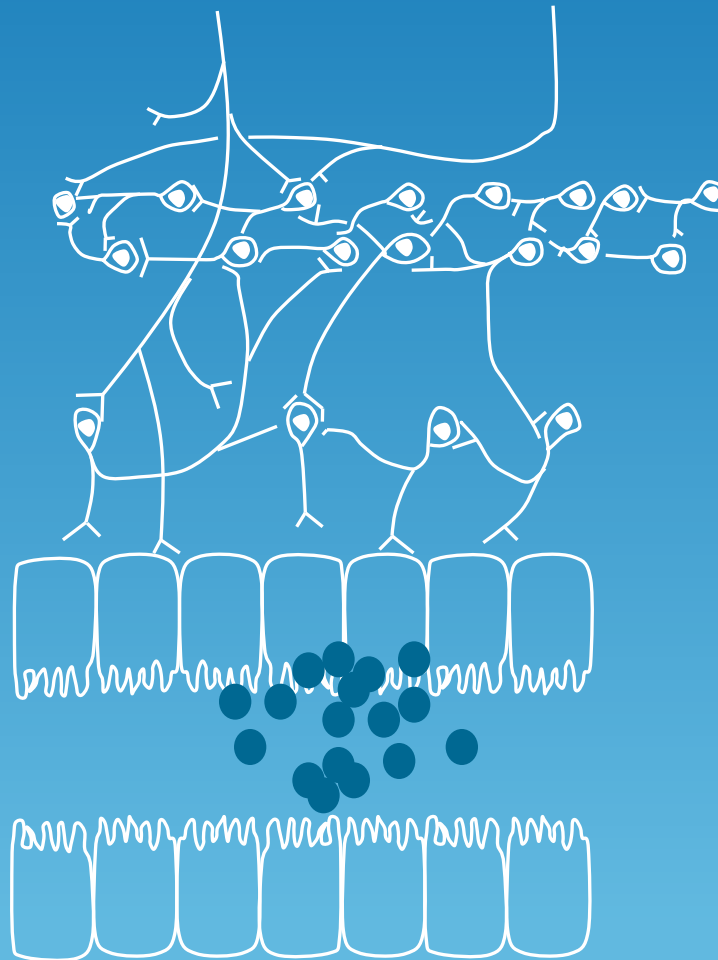
MECHANISM OF OIC

The primary cause of OIC is activation of opioid receptors in the gut¹⁻³

Normal bowel function requires co-ordinated motility, mucosal transport and defaecation reflexes

Gastrointestinal wall

Gastrointestinal lumen



Opioid receptors lie within the enteric nervous system of the GI wall

Epithelium

- Opioid molecule, binding to enteric opioid receptors to exert local effects

OIC=opioid-induced constipation.
GI=gastrointestinal. Adapted from: 1. Kurz A, Sessler DI. *Drugs* 2003;63:649–671. 2. Reimer K *et al.* *Pharmacology* 2009;83(1):10–17. 3. Pappagallo M. *Am J Surg* 2001;182(5A Suppl):11S–18S.

PATHOGENESIS OF CHRONIC CONSTIPATION

PRIMARY CONSTIPATION^{1,2}

- **Functional constipation (low fibre and fluid intake)**^{1,3,4}
- **Idiopathic (includes irritable bowel disease)**^{1,2,4}

SECONDARY CONSTIPATION^{1,2}

Iatrogenic → opioids, Ca²⁺ channel blockers, anti-cholinergics, TCA's, antacids¹⁻³

Metabolic & endocrine disorders → diabetes, thyroid disease,¹⁻³

Psychological → depression²

Neurologic and myopathic disorder → Parkinson's disease, multiple sclerosis, stroke¹⁻³

Structural obstruction → colon cancer, stricture, anal fissures and stenosis¹⁻³

CURRENT THERAPIES DO NOT ADDRESS THE CAUSE OF OIC¹⁻³

- Recommending laxatives for opioid-treated patients is considered best practice, however laxatives:
 - fail to address the underlying cause of OIC^{1,2}
 - are commonly associated with side effects^{1,3}
 - add to treatment costs for patients⁴
- OIC often persists despite laxative use^{1,3}

What is required is the blocking of opioid action at receptors in the gut, to prevent or reverse OIC^{4,5}

TARGIN® TABLETS (APRIL 2011)

OXYCODONE + NALOXONE



TARGIN® TABLETS 12-HOURLY CONTROLLED RELEASE¹

OXYCODONE

Opioid agonist with
central action¹



NALOXONE

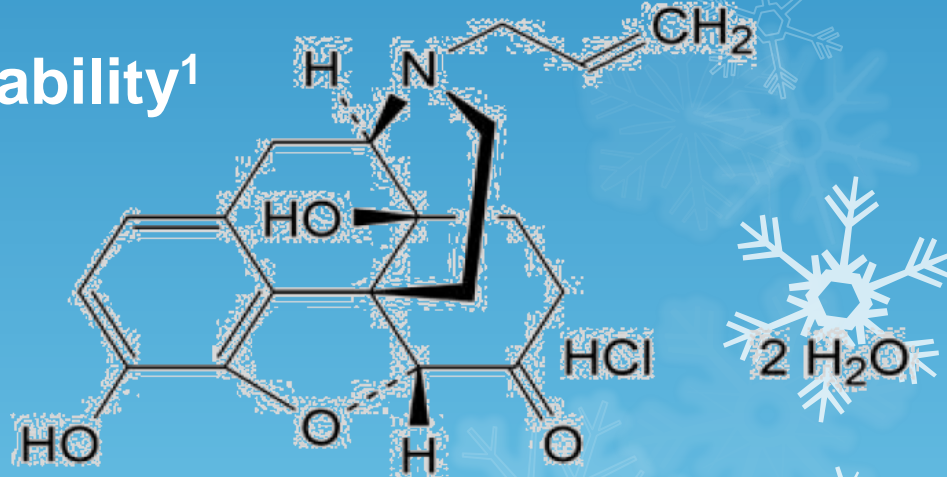
Opioid antagonist that
acts locally in the gut^{1,2}

**TARGIN® TABLETS
EFFECTIVELY RELIEVE
MODERATE TO SEVERE
CHRONIC PAIN¹**

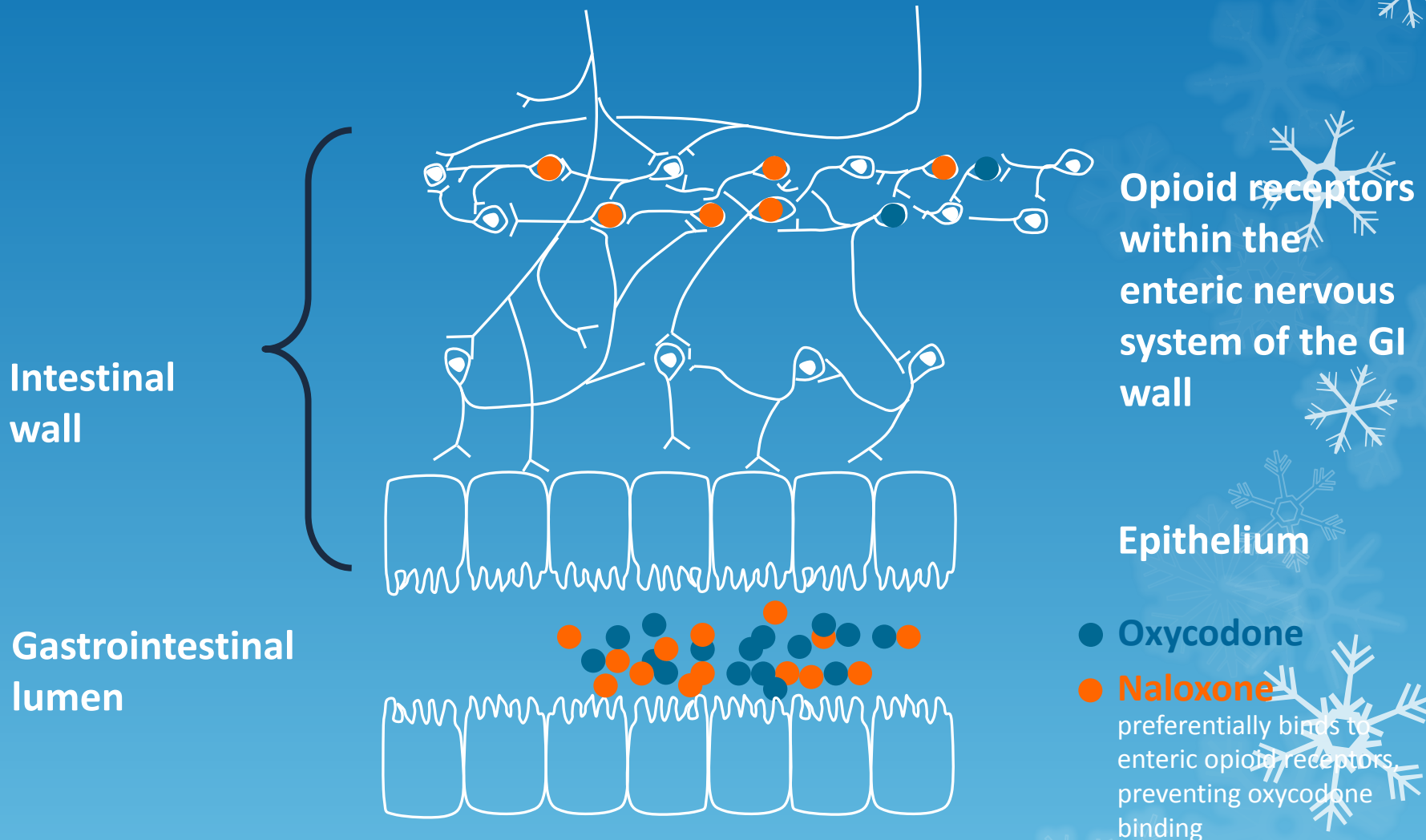
**TARGIN® TABLETS
HELP PREVENT OIC^{1,3}**

NALOXONE

- Synthetic congener of oxymorphone¹
- Pure antagonist at opioid receptors²
- Parenterally administered naloxone is used to reverse effects of opioids¹
- Metabolised extensively in the **liver**¹ during 1st pass metabolism
- **Less than 2% oral bioavailability¹**



TARGIN® TABLETS AND THE GI WALL¹⁻⁴



TARGIN® TABLETS

INITIATION and TITRATION



Opioid therapy should only be used as part of a multimodal pain management plan

USUAL STARTING DOSE

- Patients uncontrolled on weaker opioids



- 12-hourly oral dosing
- TARGIN® tablets must be swallowed whole and **must not be broken, chewed or crushed**
- Titrate cautiously, to achieve pain relief and functional improvement, and to minimise the risk of adverse events

TARGIN® TABLETS

INITIATION and TITRATION

50% STARTING DOSE IN:¹

- Patients with mild hepatic impairment
Bil to 45, Alb to 28, INR 2.3
- Patients with renal impairment
Clcr <60mL/min
- Debilitated elderly patients



MAXIMUM RECOMMENDED DOSE¹



- A maximum recommended dose exists due to limited exposure of patients receiving doses beyond 40/20 mg 12-hourly
- If longer-term treatment is anticipated, careful and regular assessment and monitoring is required to establish the clinical need for ongoing opioid treatment

TARGIN® TABLETS

BREAKTHROUGH or INCIDENT PAIN¹

OxyNorm® capsules
5-10 mg q4hr

- Reassess non-pharmacological treatment adjuncts such as pacing and coping techniques, physical exercise and TENS^{1,2}
- If clinically necessary, treat with **oxycodone IR (OxyNorm / Endone) rescue medication³**
- If more than two doses of rescue medication are required per day reassess the patient and, if appropriate, adjust the dosage of TARGIN® tablets³
- If incident pain can be predicted, consider rescue medication prior to activity causing pain⁴
- If pain persists, consider neuropathic component to pain

TARGIN® TABLETS

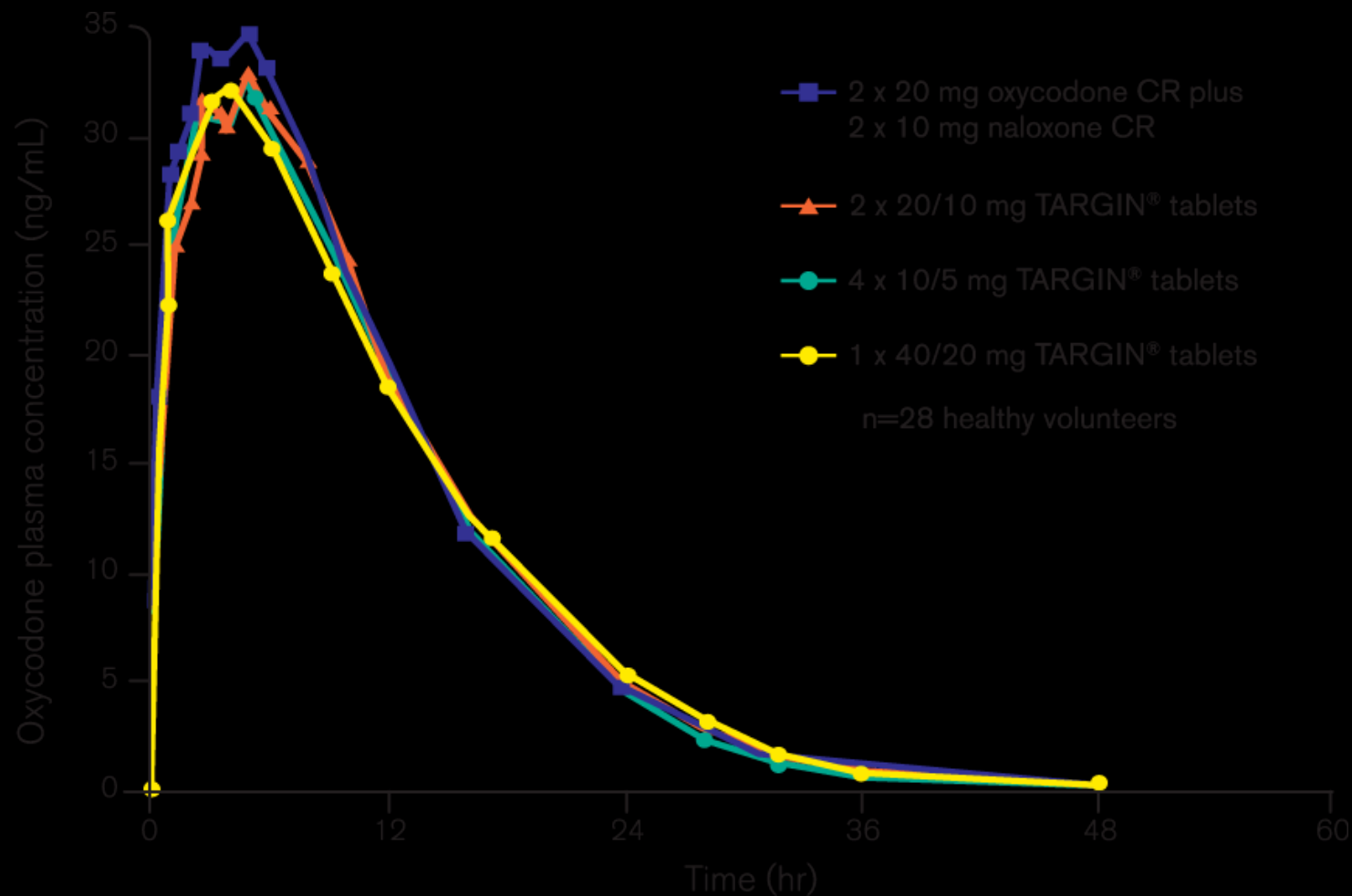
SAFETY PROFILE

CONTRAINDICATIONS (similar to OXYCONTIN):

- Moderate to severe hepatic impairment
 - Bil >45, Alb <28 and INR >2.3
- Patients with moderate to severe renal impairment
 - Clcr <40mL/min
- Severe respiratory depression
- Pregnancy and lactation

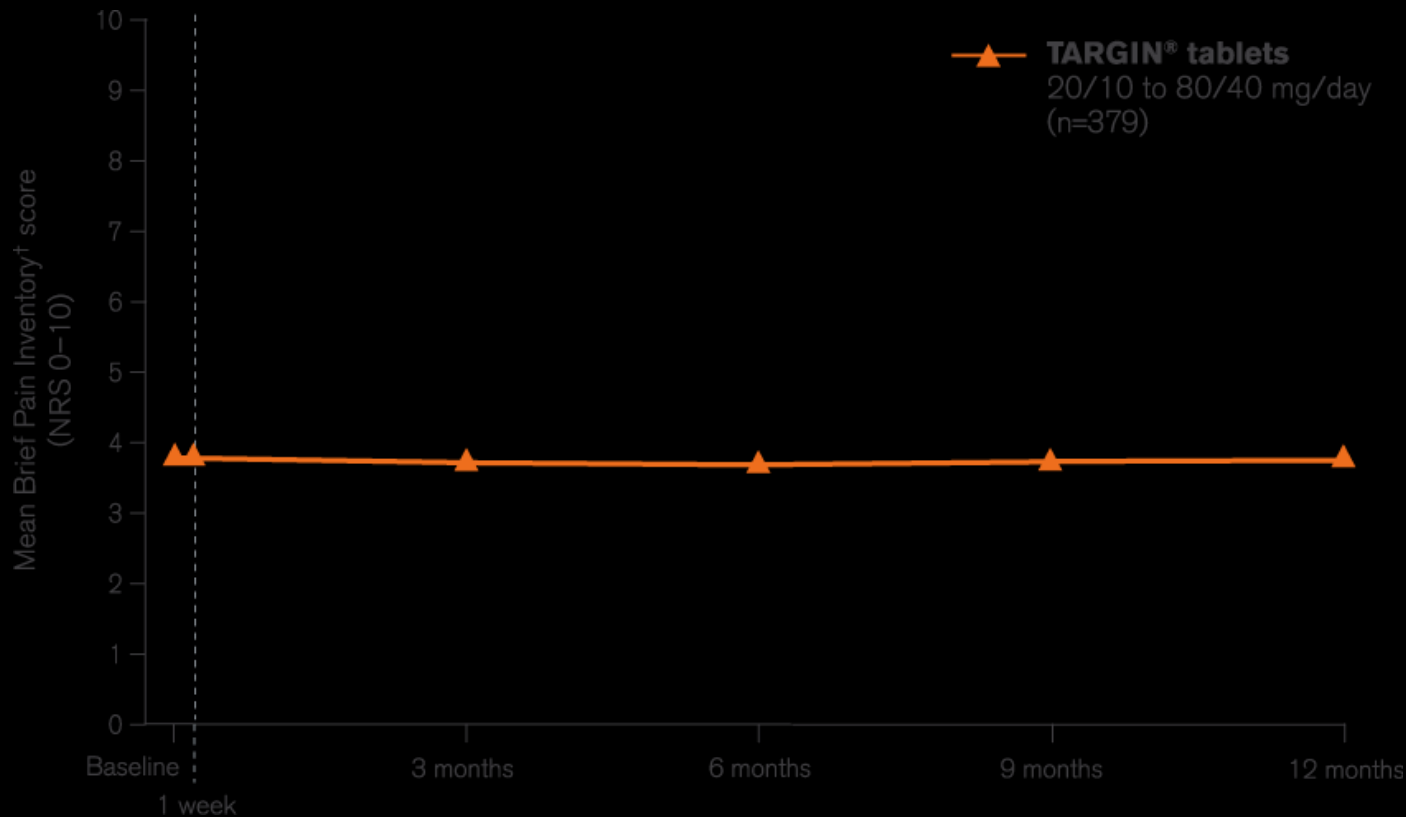
Please review Product Information for complete details of Adverse Reactions,
Contraindications and Precautions.

SINGLE DOSE MEAN OXYCODONE PLASMA CONCENTRATIONS^{1,2}



EFFECTIVE LONGER-TERM ANALGESIA

MEAN PAIN SCORES STABLE OVER 12 MONTHS (379 patients)



Mean oxycodone dose:

- 35.6 mg/day at week 2
- 40.9 mg/day for weeks 1-52

- The majority of patients remained on a TARGIN® tablets dose that was comparable with the dose they received during the double-blind phase

TARGIN® TABLETS

CLINICAL TRIAL SUMMARY

ANALGESIC EFFICACY

- Analgesic efficacy equivalent to oxycodone CR^{1,2}
- Mean pain scores remained low and stable throughout the 12-month extension with minimal dose escalations³

BOWEL BENEFITS

- Significant improvements in OIC were apparent after only 1 week²
- Significant improvements in OIC were maintained for the 12-week study period² compared with oxycodone CR²
- Improvements in OIC were maintained throughout the 12-month extension study³
- Fewer patients required laxatives compared with oxycodone CR²

CR=controlled release. OIC=opioid-induced constipation. 1. Vondrackova D *et al.* J Pain 2008;9:1144–1154

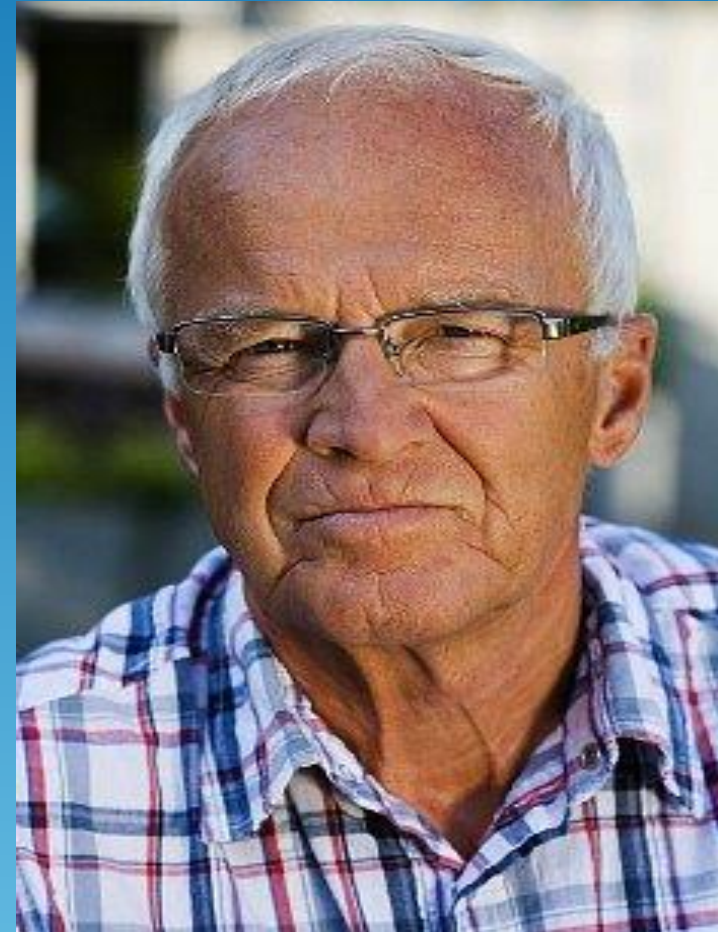
2. Löwenstein O *et al.* BMC Clin Pharmacol 2010;10:12. 3. Sandner-Kiesling A *et al.* Int J Clin Pract 2010;64:763–774.



MR JR



- 76 yo carpenter
 - Now manager at carpentry firm
 - Also likes working in garden
- 5 year history of right knee pain
- Maximum dose paracetamol/codeine (30 mg)
 - NSAID for breakthrough pain
- Has regular physiotherapy
 - Home-based exercise programme
 - Heat packs



POST – OP MANAGEMENT

- Right Total Knee Replacement
- Day 1 – 3 (Anaesthetist)
 - Patient Controlled Analgesia (PCA) - Morphine IV
 - Paracetamol IV or orally regularly
 - Celecoxib 200mg daily for 3 days
- Day 4 - 6 (Orthopaedic Surgeon)
 - Paracetamol 2 tablets every 4 hours regularly
 - Oxycodone 5-10 mg every 4 hours as required
 - Pain assessment NRS 8/10 = moderate to severe pain
 - Knee Flexion 60 degrees

NRS = Numerical rating scale

REHAB MANAGEMENT

- Day 7 - Transferred to Rehab
 - Targin 10/5 mg twice a day
 - Paracetamol 2 tablets every 4 hours regularly
 - Oxycodone 5-10 mg as required (2-4 times a day)
 - Movicol 2 sachets twice a day
 - Coloxyl with Senna 2 tablets twice a day
- Pain assessment NRS 8/10 = moderate to severe pain
 - Knee Flexion 60 degrees
- Commence Hydrotherapy and Physiotherapy

REHAB MANAGEMENT

○ Day 9

- Targin increased to 20/10 mg twice a day
- Paracetamol 2 tablets every 4 hours regularly
- Meloxicam 15 mg daily
- Oxycodone 5-10 mg every 4 hours as required (reduced to once a day)
- Coloxyl with Senna reduced to 2 at night and Movicol ceased
- Pain assessment NRS 2/10 and Knee flexion 90 degrees

○ Day 12

- Discharged home walking with 1 stick
- Targin reduced to 10/5 twice a day
- Pain 2/10 and Knee flexion 100 degrees

Mr EM

- 56 year old man
- L2-4 Lumbar laminectomy and Rhizotomy
 - Back pain resolved
 - Right leg sharp shooting pain resolved
 - Pregabalin 150 mg twice a day pre-op
- Developed LEFT FOOTDROP post-op
 - Secondary to neuropraxia from dural traction
 - Left leg pain 5/10
 - Oxycodone 10 mg twice a day
- Transferred to Rehab Day 3
 - Walking FASF



REHAB MANAGEMENT

○ Day 4

- Targin 10mg twice a day
- Reduced Pregabalin to 75 mg twice a day
- Regular Paracetamol 2 tablets twice a day

○ Pain Free

○ Hydrotherapy

○ DICTUS BAND for footdrop

○ Day 7

- Targin reduced to 5/2.5 mg twice a day
- Ceased Pregabalin
- Walking with 1 stick



CONCLUSION

- ❖ Pain is a likely outcome of any surgical procedure
- ❖ In several countries the use of oxycodone has surpassed morphine in post-operative pain management
- ❖ Oxycodone is a strong opioid
 - ❖ Acts at mu- and kappa-opioid receptors
 - ❖ Greater analgesic potency to morphine
- ❖ Prolonged-release form of oxycodone
 - ❖ Fast onset of analgesia
 - ❖ Control pain for 12 hours
- ❖ It has relevant points of difference from other opioids and as such may be a suitable alternative to morphine

TARGIN® TABLETS

SUMMARY



- Opioids can be an important component of a multimodal pain management plan¹
- Pharmacokinetic properties of oxycodone in TARGIN® tablets are bioequivalent to oxycodone CR tablets^{6,7}
- Oxycodone in TARGIN® tablets is **bioequivalent** to oxycodone CR tablets³
- Effective in patients with **chronic moderate - severe osteoarthritis, back, neuropathic and cancer pain**⁵⁻⁷

OIC=Opioid-induced constipation. QoL=quality of life. CR=controlled release. 1. Govt of SA. Guidelines for SA GPs, Drug and Alcohol Services SA, 2008. 2. Bell T *et al.* J Opioid Manag 2009;5(3):137–144. 3. TARGIN® tablets Product Information. April 2011. 4. Löwenstein O *et al.* BMC Clin Pharmacol 2010;10:12. 5. Simpson K *et al.* Curr Med Res Opin 2008;24(12):3503–3512. 6. Löwenstein O *et al.* Expert Opin Pharmacother 2009;10(4):531–543. 7. Vondrackova D *et al.* J Pain 2008;9(12):1144–1154.

SUMMARY



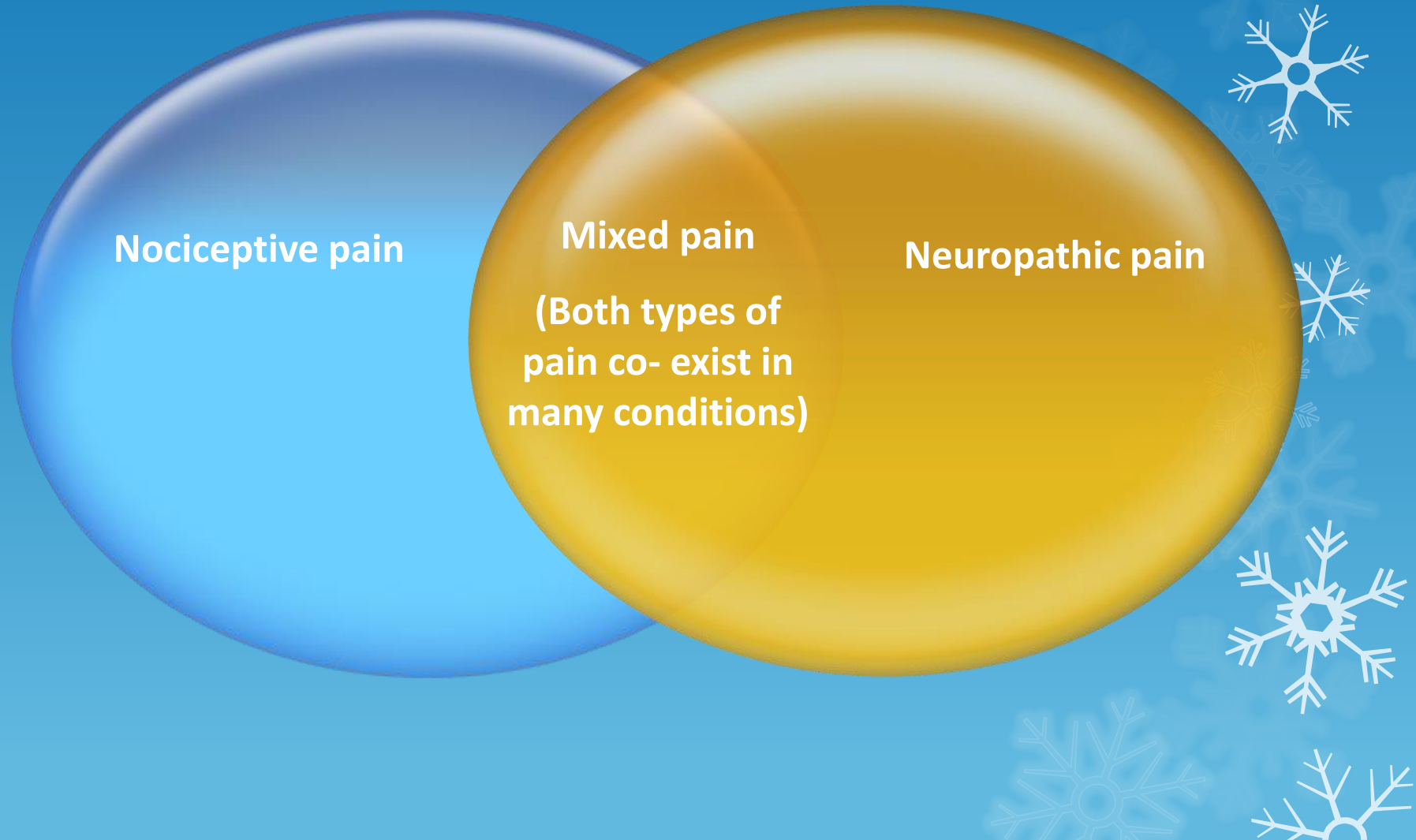
- TARGIN® tablets offer a specific mode of action in **PAIN MANAGEMENT** to help prevent OIC⁶
- There are many causes of constipation: **one of these is opioid-induced constipation (OIC)**, which is common and can be debilitating^{1,2}
- OIC can have a significant impact on health-related QoL²
- Laxatives fail to address the underlying cause of OIC³⁻⁵
- When administered orally, naloxone undergoes extensive first-pass metabolism resulting in negligible (<2%) systemic bioavailability^{6,7}

1. Bell T *et al.* J Opioid Manag 2009;5(3):137-144 2. Benyamin R *et al.* Pain Physician 2008;11(2 Suppl):S105-120 3. Reimer K *et al.* Pharmacology 2009;83:10-17 4. Kurz A, Sessler DI. Drugs 2003;63(7):649-671. 5. Pappagallo M. Am J Surg 2001; 182(5A Suppl):11S-18S. 6. TARGIN® tablets Product Information. April 2011. 7. Smith K *et al.* Clin Ther 2008;30:2051-2068.

THANK YOU



TYPES OF PAIN



NOCICEPTIVE PAIN

- A sensory and emotional experience that occurs when specific peripheral sensory neurons (nociceptors) respond to noxious stimuli
- Painful region is typically localised at the site of injury
 - Throbbing, aching or stiffness
 - Aggravated by movement
- Usually time-limited and resolves when damaged tissue heals (e.g. bone fractures, burns and bruises)
- Can be chronic (e.g. osteoarthritis)
- Responds to conventional analgesics

NEUROPATHIC PAIN

- Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system
- Pain often described as shooting, electric shock-like, burning – commonly associated with tingling or numbness
- Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain) – typically distant from the site of injury
- Commonly a chronic condition (e.g. Post-herpetic neuralgia, post-stroke pain), but can occur with acute nerve injury (e.g. spinal cord injury, sciatica or surgery)
- Responds poorly to conventional analgesics

PAIN SCALES

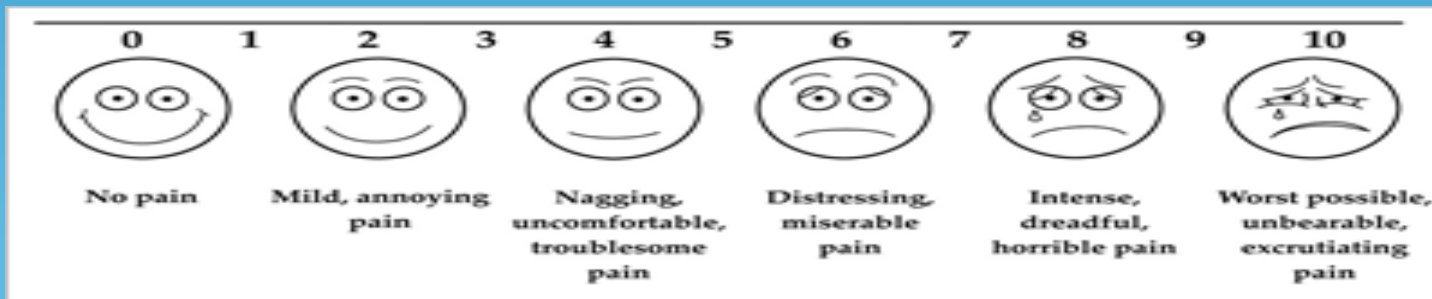
- Subjective experience - rely on self reporting

- **Verbal Rating Scale**

- no pain, mild, moderate and severe (0-3)







- **Visual Analogue Score**

- 10cm line from “no pain” to “worst pain”



NEUROPATHIC PAIN THERAPY 2013



- Carbamazepine (NNT to obtain 50% relief - 1.7)
 - Valproate, Phenytoin, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine
 - Pregabalin, Levetiracetam, Tiagabine
 - Lacosamide (Vimpat), Zonisamide
 - Clonazepam
 - Amitriptyline, Nortriptyline, Imipramine
 - Duloxetine
 - Opioids – Tramadol, Buprenorphine, Oxycodone (Targin), Tapendadol, Morphine, Fentanyl, Hydromorphone
 - Baclofen, Mexilitene, Clonidine
 - Capsaicin cream, Lignocaine 5% Dermal patch
 - N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine
 - Botulinum Toxin
 - Vitamin B12
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