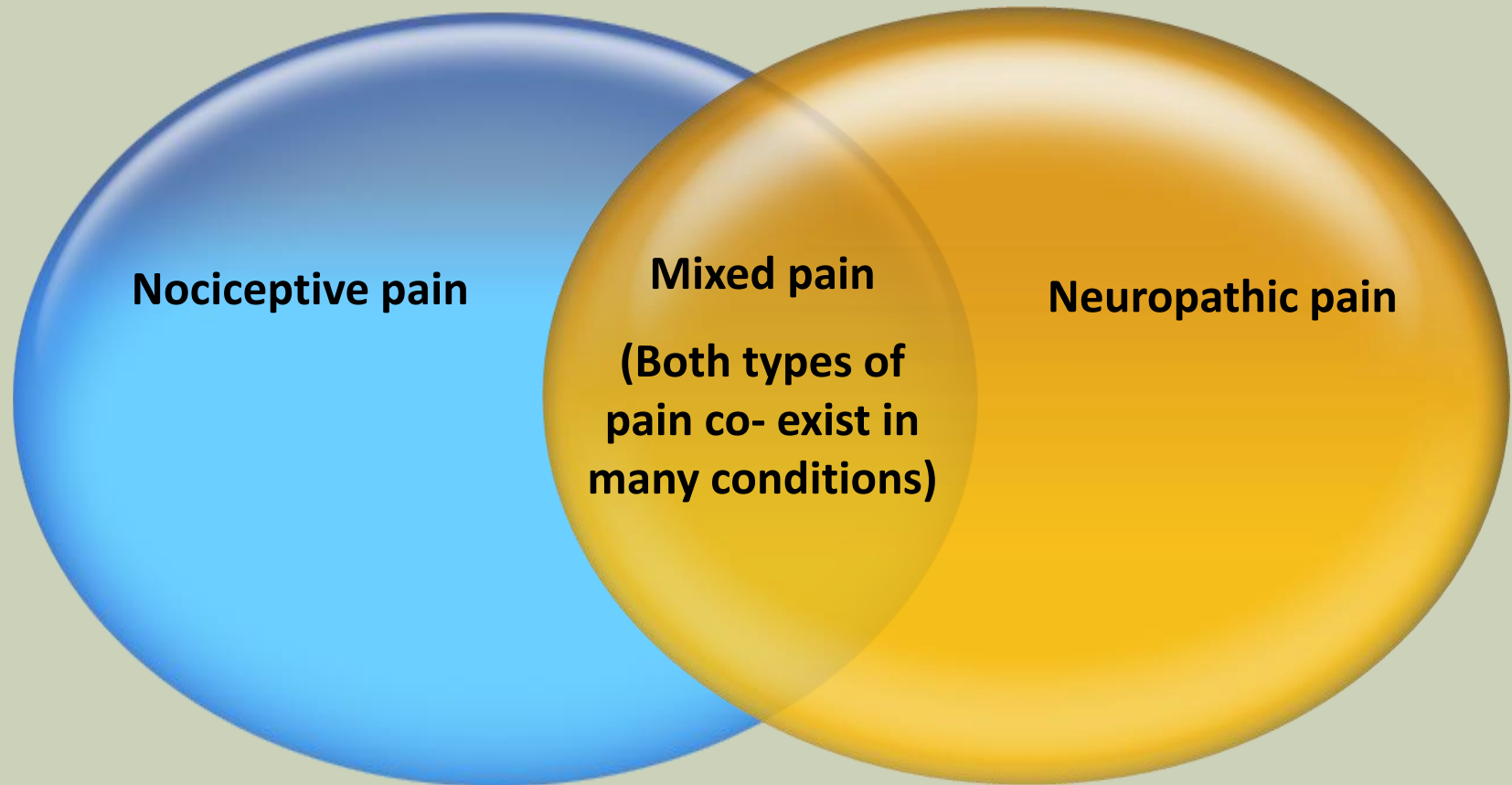


ROLE OF OPIOIDS IN INPATIENT REHABILITATION

A/Professor Arun Aggarwal
Neurology and Pain Medicine
Royal Prince Alfred Hospital, SYDNEY,
AUSTRALIA



TYPES OF PAIN



NOCICEPTIVE PAIN

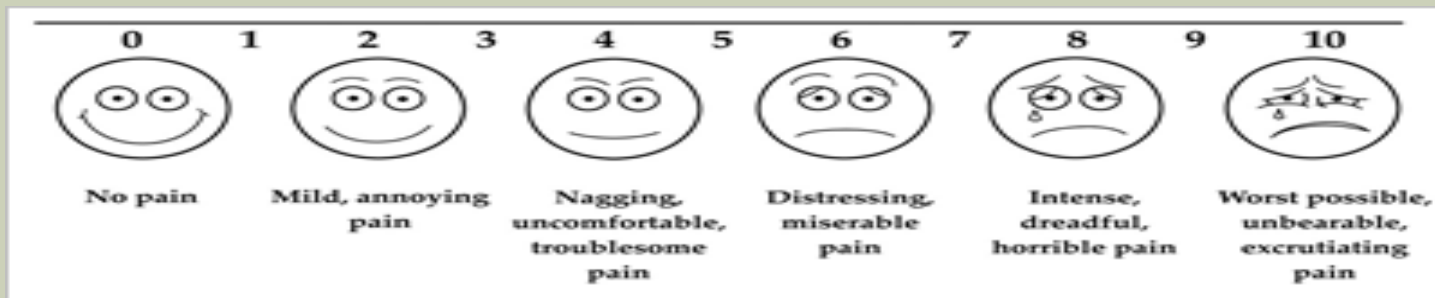
- A sensory and emotional experience that occurs when specific peripheral sensory neurons (nociceptors) respond to noxious stimuli
- Painful region is typically localised at the site of injury
 - Throbbing, aching or stiffness
 - Aggravated by movement
- Usually time-limited and resolves when damaged 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”



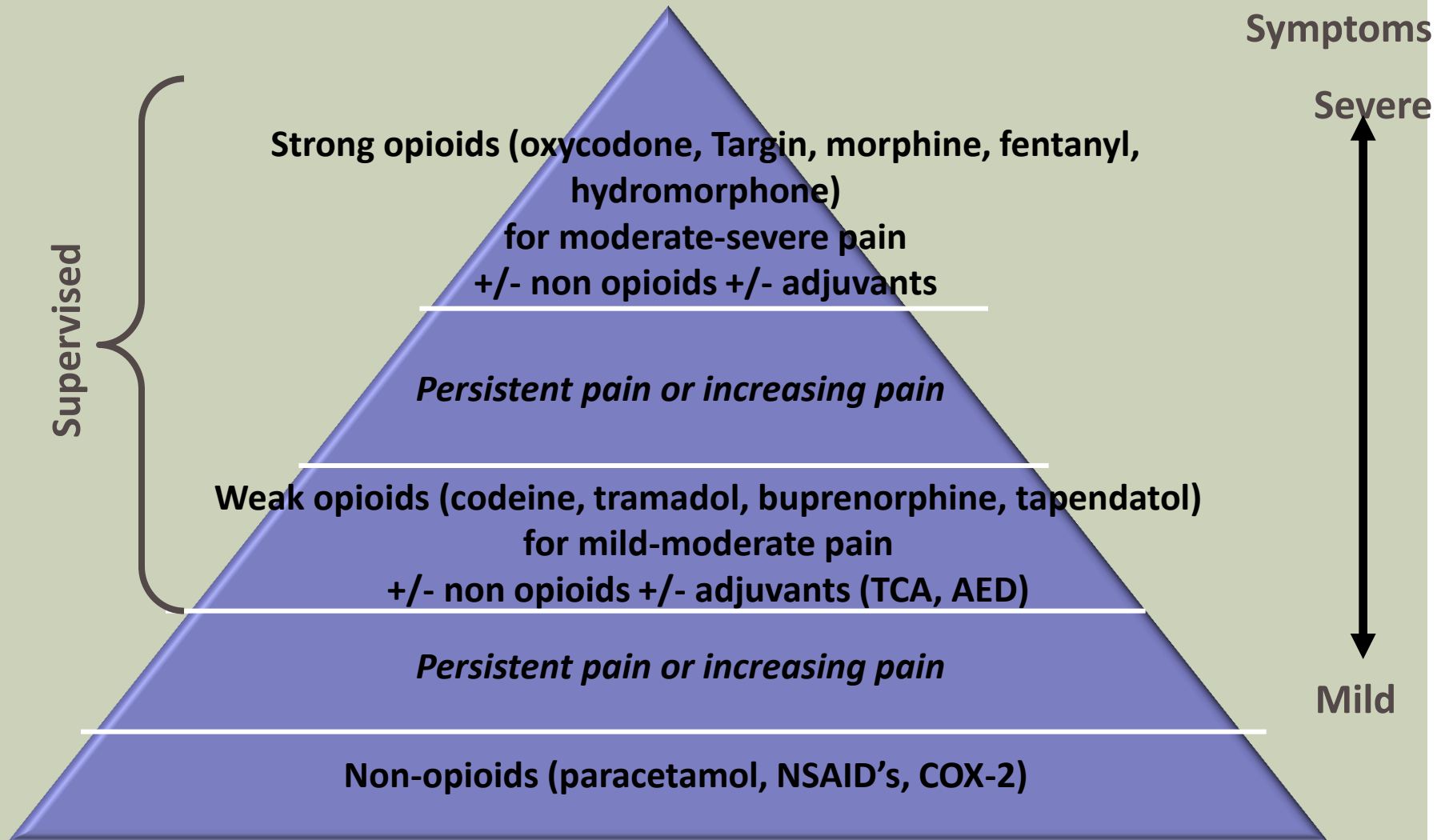
WHO LADDER

- The World Health Organization (WHO) analgesic ladder serves as a mainstay of treatment for the relief of pain, together with psychological and rehabilitative modalities
- This multi-dimensional approach offers the greatest potential to maximise analgesia and minimise adverse effects
- According to the literature, approximately 70-90% of cancer pain is relieved when clinicians apply the WHO ladder appropriately

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
 - PRN = PAIN RELIEF NEVER
- ***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)



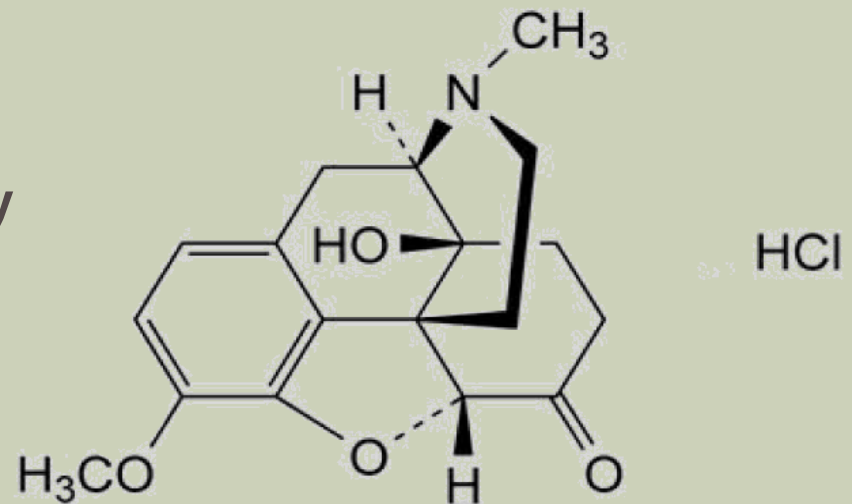
OPIOIDS PLACE IN PAIN MANAGEMENT

- 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

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

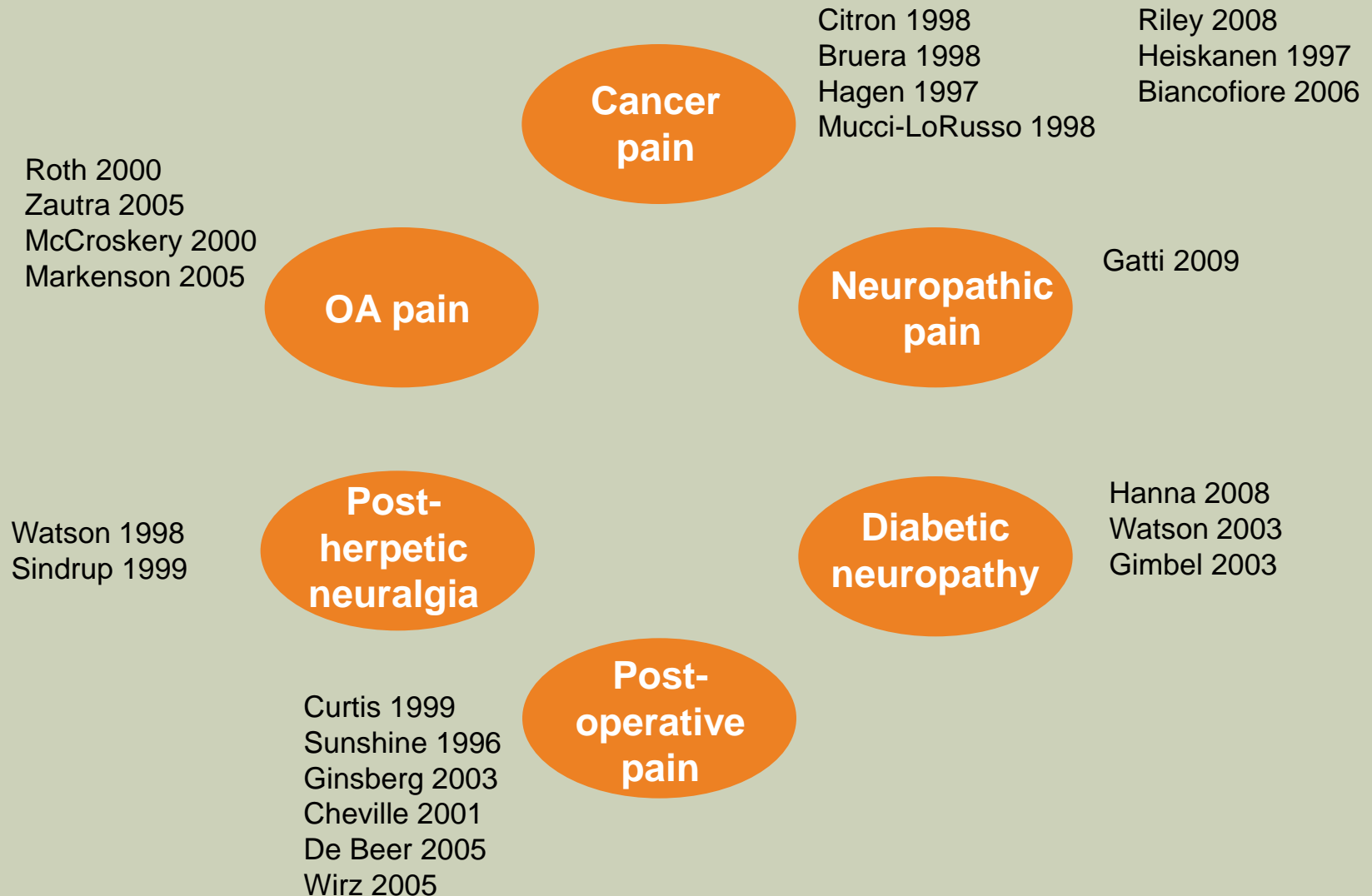
- Up to **87% oral bioavailability**
- Plasma protein binding is 45%



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



OPIOID BARRIERS

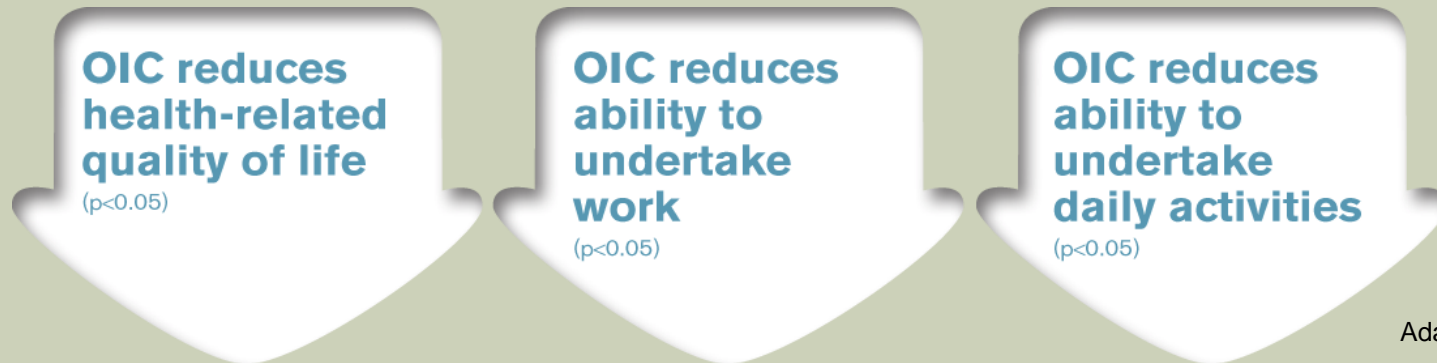
- Concerns about the use of opioids from healthcare practitioner,
 - family members and patients
 - Side-effects
 - Risk of dependence when using opioids
- Development of tolerance to the chronic use of opioids
- Successful pain management with opioids can be achieved by
 - balancing adverse effects and analgesia in each individual patient
- Newer available oral opioid formulations for the management of
 - Moderate-severe pain can assist in achieving effective levels of
 - analgesia in patients

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

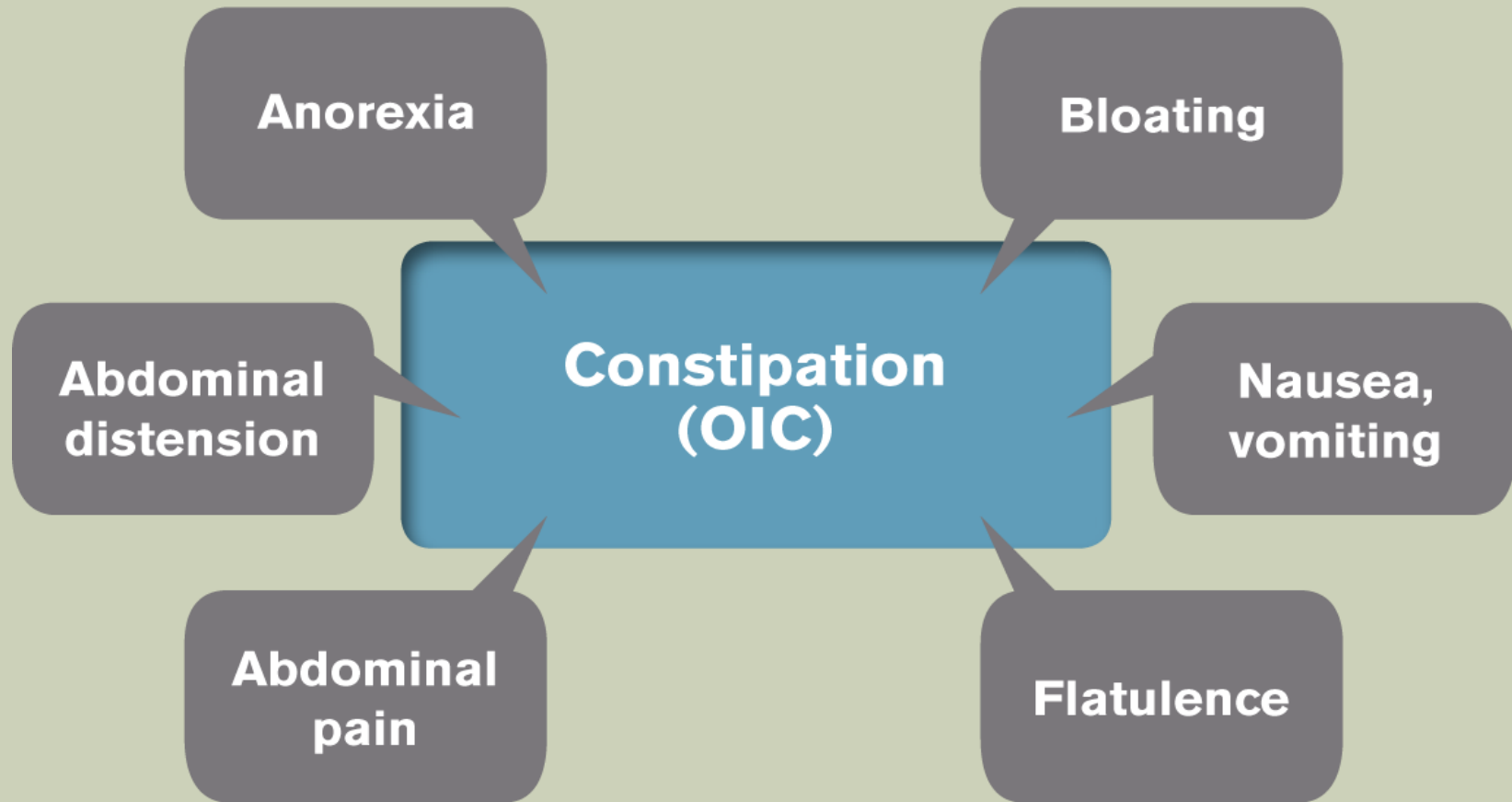
| OIC COMPROMISES PAIN MANAGEMENT^{4–6}

- 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

1. Benyamin R *et al.* Pain Physician 2008;11(2 Suppl):S105–120. 2. Tuteja AK *et al.* Neurogastroenterol Motil 2010;22(4):424–430, e496. 3. Roth SH *et al.* Arch Intern Med 2000;160(6):853–860. 4. Bell T *et al.* J Opioid Manag 2009;5(3):137–144. 5. Bell TJ, *et al.* Pain Med 2009;10(1):35–42. 6. Kurz A, Sessler DI. Drugs 2003;63(7):649–671. 7. Duensing L, *et al.* Curr Med Res Opin 2010;26(7):1579–1585.

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

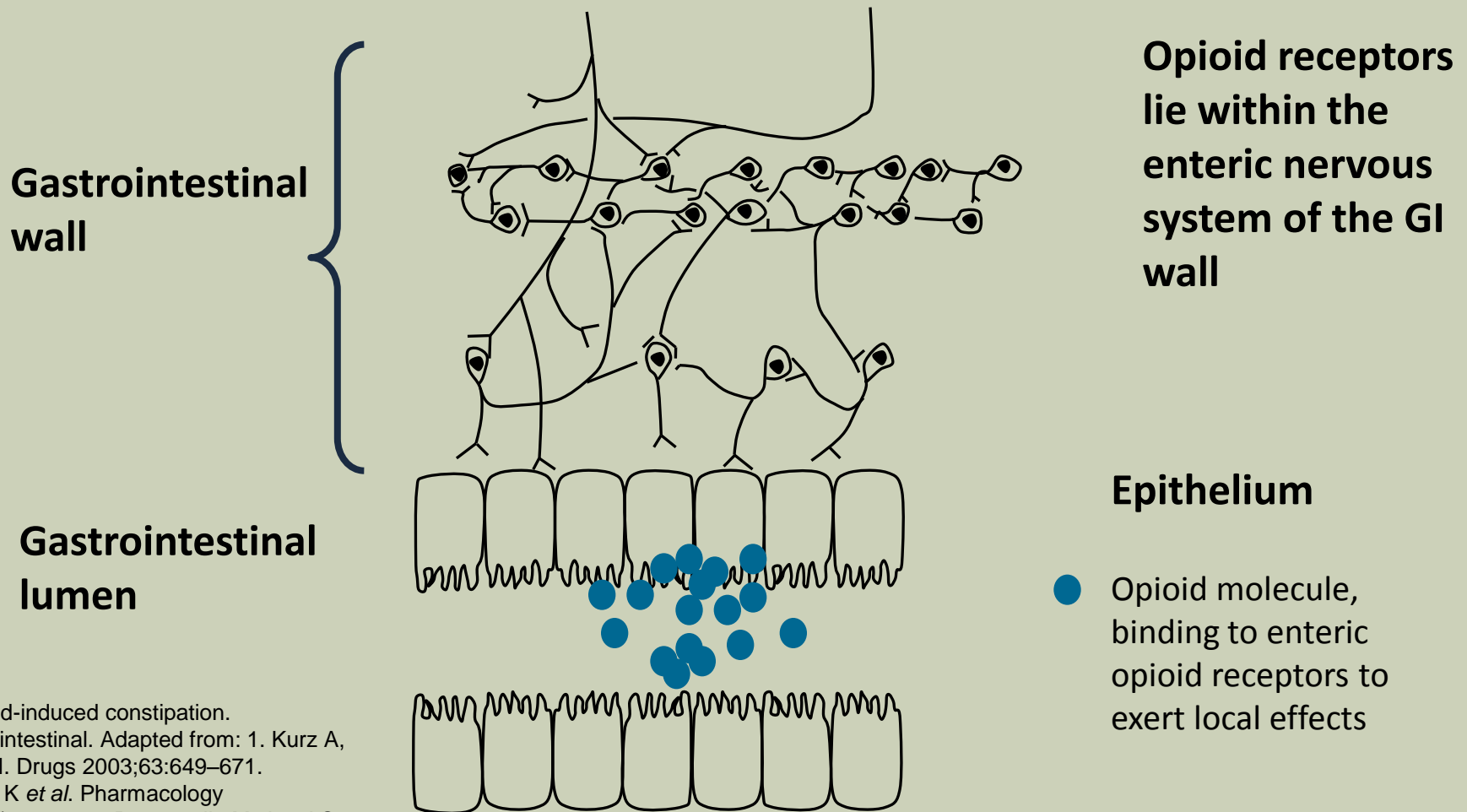


OIC=opioid-induced constipation. Adapted from 1. Reimer K *et al.* Pharmacology 2009;83(1):10–17. 2. Miles CL *et al.* Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003448. DOI: 10.1002/14651858.CD003448.pub2.

MECHANISM OF OIC

The primary cause of OIC is activation of opioid receptors in the gut^{1–3}

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



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

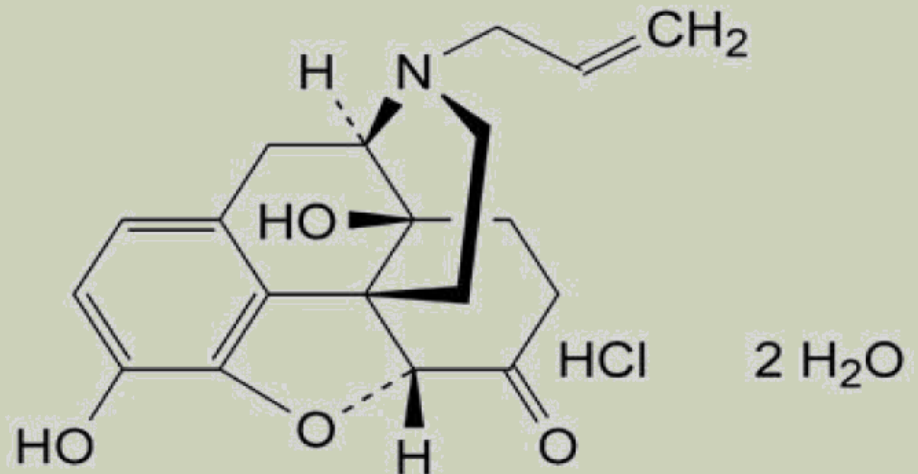
Opioid antagonist that
acts locally in the gut^{1,2}

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

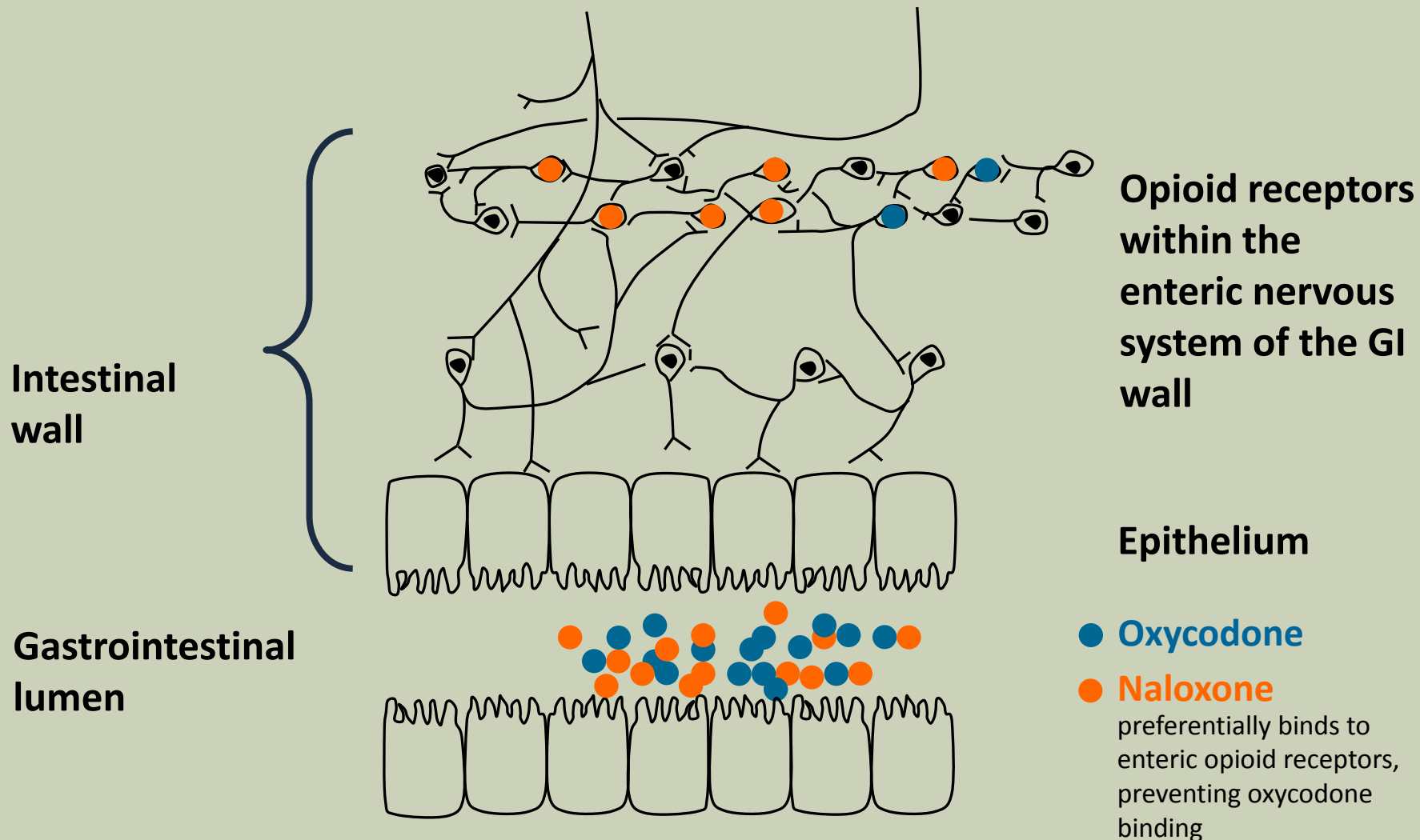
**TARGIN® TABLETS
HELP PREVENT OIC^{1,3}**

NALOXONE

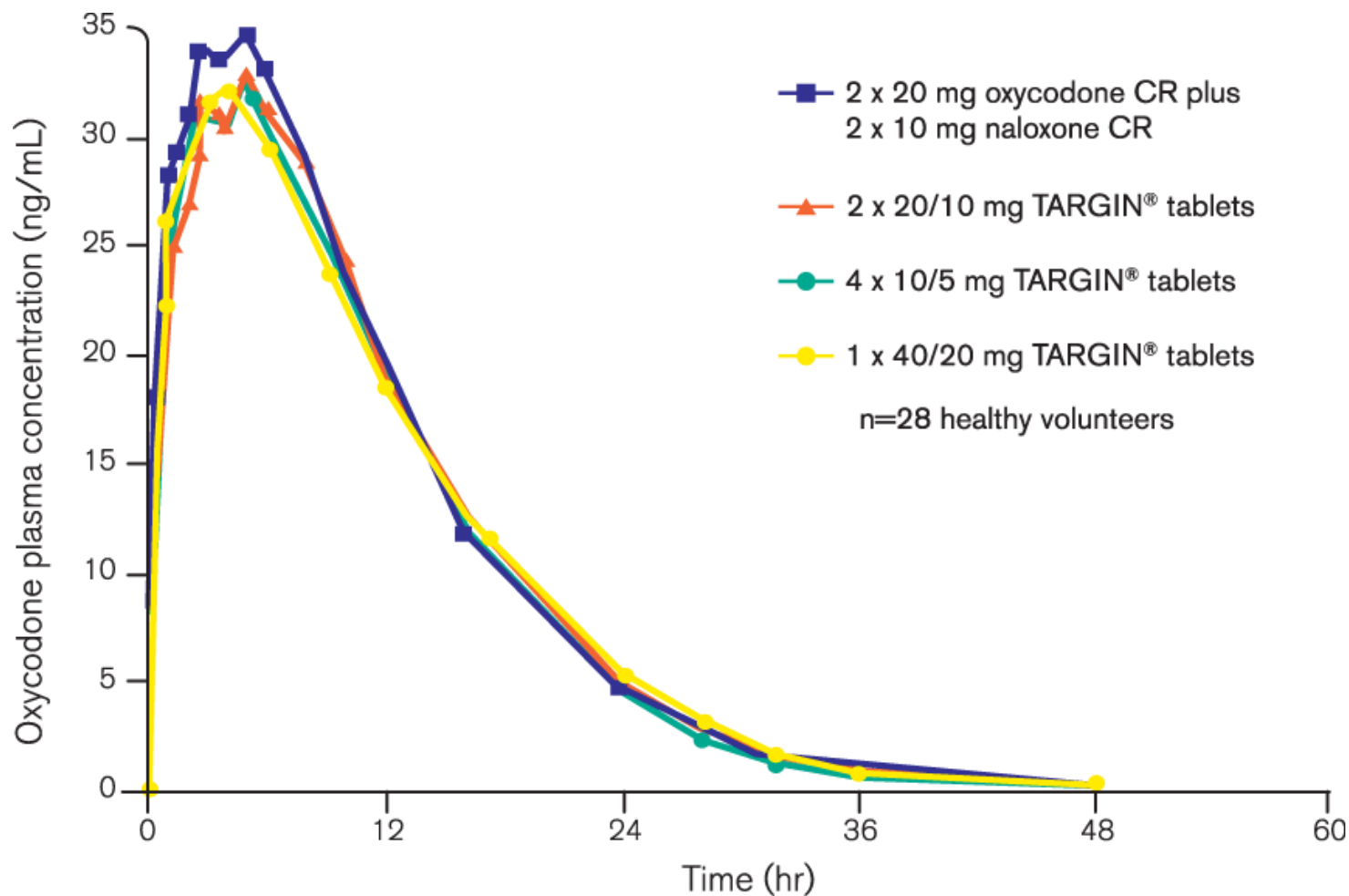
- Synthetic congener of oxymorphone¹
- Pure antagonist at opioid receptors²
- Parenterally administered naloxone is used to reverse effects of opioids¹
- Metabolised extensively in the **liver**¹ during 1st pass metabolism
- **Less than 2% oral bioavailability**¹



TARGIN® TABLETS AND THE GI WALL¹⁻⁴

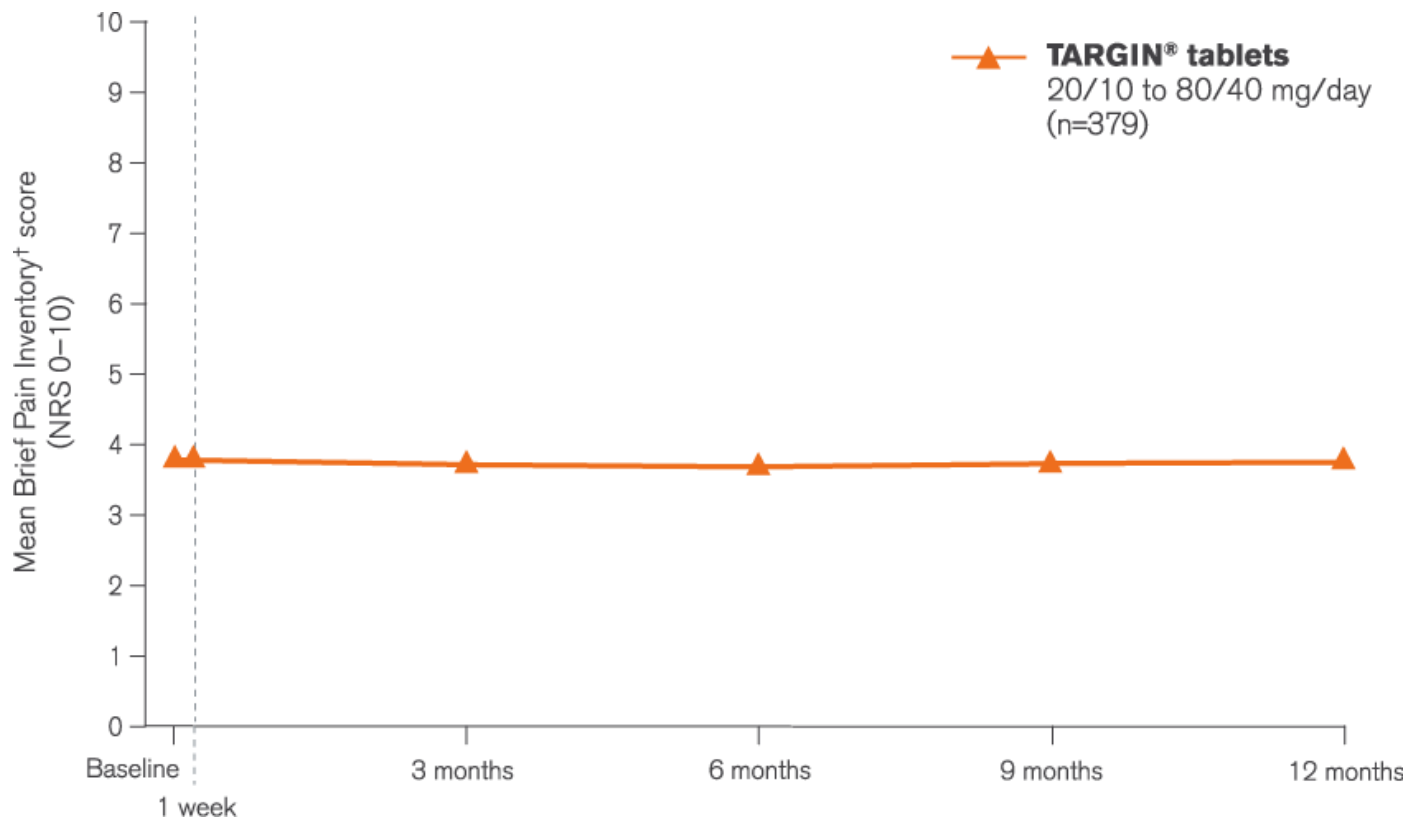


SINGLE DOSE MEAN OXYCODONE PLASMA CONCENTRATIONS^{1,2}



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**

TARGIN® TABLETS

INITIATION AND TITRATION



5/2.5 mg



10/5 mg



20/10 mg



40/20 mg

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

USUAL STARTING DOSE

- Patients uncontrolled on weaker opioids



10/5 mg TARGIN®
tablet 12-hourly

- 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 **Cl_{cr}**
<60mL/min
- Debilitated elderly patients



5/2.5 mg TARGIN[®]
tablet 12-hourly

MAXIMUM RECOMMENDED DOSE¹



40/20 mg TARGIN[®]
tablet 12-hourly

- 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 medication**³
- If more than two doses of rescue medication are required per day re-assess 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.

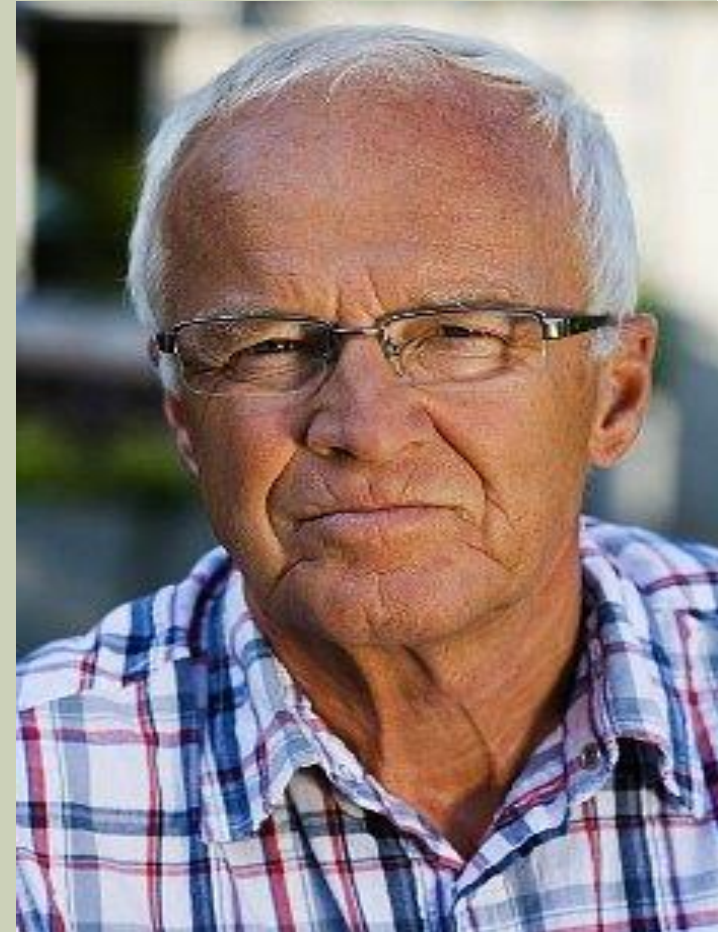
ROLE OF OPIOIDS IN INPATIENT REHABILITATION

CASE STUDIES



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

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



MRS MW

- 54 yo
- 8 year history of lower lumbar back pain
- Constant sharp shooting pain radiating down right leg 9/10
- CT Lumbar spine – severe degenerative facet joint disease and moderate disc bulge L4/5
- **Amitriptyline 10 mg nocte**
 - Improved sharp pain
- Ongoing dull ache 5-6/10
- Add **Tramadol SR 100 mg mane**
 - Improved pain and able to return to work

MRS MW

- Constant dull ache 5/10
- Increased Tramadol to 200 mg bd
- **Bone Scan**
 - Moderate facet joint uptake at multiple levels
- Started **Oxycontin 10 mg bd**
 - Excessive daytime drowsiness
 - 5 mg bd improved pain from 8/10 to 5/10
 - Drowsy during the day
 - “Sick of taking pills”

MRS MW

■ Fentanyl patch

- 12 – 25 – 37 mcg every 3 days but lasts only 2 days
- Drowsy throughout the day
- Constant pain - dull ache - 5/10

■ Constipation

- **Opening her bowels about once a week**
 - Drinking 2 litres of water a day
 - Tony Ferguson high fibre diet

■ Targin 10/5 mg bd increasing to 20/10 mg bd

- Pain manageable and tolerable 2/10
- Less drowsy during the day
- Less constipation – bowels opening 2-3 times a week

INITIATING OPIOID THERAPY

- **Opioid risk assessment** (Next slide)
- Set treatment goals, including increased participation in an exercise program
- Obtain patient consent and written or verbal treatment agreement
- Initiate 4–6 week strong opioid trial with weekly reviews
 - Discuss side effects
- Monthly review as per the **6 A's of pain medicine** (Next slide)
 - If pain opioid responsive, continue with monthly reviews for 3–6 mths
 - if there is reduction in pain and improvement in function, consider longer-term (until surgery)
 - Taper dose and cease opioid post surgery

OPIOID RISK ASSESSMENT TOOL (ORT)¹⁻²

Factor	Males	Females
Family history of substance abuse		
- Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 1 point
- Illicit drugs	<input type="checkbox"/> 3 points	<input type="checkbox"/> 2 points
- Prescription drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
Personal history of substance abuse		
- Alcohol	<input type="checkbox"/> 3 points	<input type="checkbox"/> 3 points
- Illicit drugs	<input type="checkbox"/> 4 points	<input type="checkbox"/> 4 points
- Prescription drugs	<input type="checkbox"/> 5 points	<input type="checkbox"/> 5 points
Aged between 16 and 45	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point
History of preadolescent sexual abuse	<input type="checkbox"/> 0 points	<input type="checkbox"/> 3 points
Psychiatric disease		
- Attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	<input type="checkbox"/> 2 points	<input type="checkbox"/> 2 points
Depression	<input type="checkbox"/> 1 point	<input type="checkbox"/> 1 point

**8+
HIGH
RISK**

**4-7
MODERATE
RISK**

**0-3
LOW
RISK**

THE 6 AS OF PAIN MEDICINE¹⁻⁵

Activity	What progress has been made in the patient's functional goals?
Analgesia	How does the patient rate their average and worst pain over the last 24 hours? How much relief have pain medications provided?
Adverse effects	Has the patient experienced any adverse effects from medication?
Aberrant behaviour	Has the patient been taking medication as prescribed? Has the patient exhibited any signs of medication misuse/abuse?
Affect	Have there been any changes to the way the patient has been feeling? Is pain impacting on the patient's mood? Depressed? Anxious?
Accurate records	Document the initial evaluation and each follow-up, including current pain medication and any changes to the management plan.

1. Gourlay DL et al. Pain Med 2009;10:S115-23. 2. Gourlay DL et al. Pain Med 2005;6:107-12. 3. Hunter Integrated Pain Service. Opioid use in persistent pain, April 2012. 4. Jovey R. Practical pain management - optimizing outcomes, reducing risks. Personal communication, April 2010. 5. DeRemer CE et al. South Med J 2011;104(9):629-33.

POST-OP PAIN

- Study performed to identify the impact of pain on outcomes following hip fracture in older adults
- 411 consecutive cognitively intact patients admitted with hip fracture to 4 New York hospitals were enrolled in a prospective cohort study
- Post-operative pain on immediate post-operative outcomes
 - duration of stay,
 - physical therapy sessions missed or shortened
 - ambulation following surgery
 - post-operative complications and
 - outcomes 6 months following fracture (locomotion, mortality, return to the community, residual pain)
- Patients with higher pain scores at rest had:
 - Significantly longer hospital lengths of stay ($P=0.03$),
 - Significantly more likely to have physical therapy sessions missed or shortened ($P=0.002$),
 - Significantly less likely to be ambulating by post-operative day 3 ($P<0.001$),
 - Significantly longer to ambulate past a bedside chair ($P=0.01$) and
 - Significantly lower locomotion scores at 6 months ($P=0.02$).
- Pain at rest was not significantly associated with:
 - Post-operative complications
 - Nursing home placement
 - Survival at 6 months
 - Residual pain at 6 months
- Appropriate cautious opioid analgesics to older adults improves pain control and decrease length of stay, enhance functional recovery and improve long-term functional outcomes

POST –OP PAIN

PRN – PAIN RELIEF NEVER

- Study designed to determine whether controlled-release opioids enhance post-arthroplasty pain control and facilitate functional recovery during rehabilitation
- “As-needed” analgesia following TKR may lead to inadequate control of pain and delayed recovery of function
- Preemptive use of controlled-release opioids may:
 - Improve pain control,
 - Accelerate recovery and
 - Reduce the need for inpatient rehabilitative services
- 59 patients admitted for inpatient rehabilitation following unilateral TKR were randomized with 29 to receive OxyContin (controlled-release oxycodone) and 30 patients to receive placebo every twelve hours.
 - Both groups could receive on-request, immediate-release oxycodone (5 mg every four hours). The dose of study medication was increased on the basis of the frequency of requests for immediate-release oxycodone.
 - Pain rated using VAS (visual-analogue scale, changes in ROM, quadriceps strength and improvements in FIM
 - The duration of the hospital stay for rehabilitation also was compared between the two groups
- Patients who received OxyContin reported:
 - Significantly less pain as well as
 - Significantly greater range of motion of the knee (passive motion, $p = 0.036$)
 - Significantly greater active motion, $p < 0.001$)
 - Greater quadriceps strength ($p = 0.001$)
 - Discharged home on average 2.3 days earlier than the patients in the placebo group ($p = 0.013$)

NSAID'S

- Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly combined with intravenous morphine patient-controlled analgesia to relieve postoperative pain
- NSAIDs have a documented 30-50% sparing effect on morphine consumption
- A meta-analysis of randomized controlled trials was performed to evaluate the risk of morphine adverse effects in patients treated with NSAIDs
- 22 prospective, randomized, double-blind studies including 2,307 patients were selected
 - NSAIDs decreased significantly postoperative nausea and vomiting by 30%
 - Nausea alone by 12%,
 - Vomiting alone by 32% and
 - Sedation by 29%.
 - A regression analysis yielded findings indicating that morphine consumption was positively correlated with the incidence of nausea and vomiting.
 - Pruritus, urinary retention, and respiratory depression were not significantly decreased by NSAIDs

COX-2 INHIBITORS

- Use of a pre-emptive and scheduled dose of oxycodone and a selective COX-2 inhibitor was highly efficacious as compared to a postoperative patient-controlled anaesthesia regimen
- Multi-modal pre-emptive analgesia:
 - Decreased postoperative IV narcotic requirements
 - Increased the percentage of patients able to participate in rehabilitation therapy
 - Decreased length of hospital stay and
 - Decreased the percentage of patients requiring discharge to an extended care facility
- Although our data was combined from 2 populations (THR and TKR patients), the observed differences in length of hospital stay and missed therapies were consistent for both when examined separately



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 pain⁵⁻⁷

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.

THANK YOU



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), Tapendatol, Morphine, Fentanyl, Hydromorphone

- Baclofen, Mexilitene, Clonidine
- Capsaicin cream, Lignocaine 5% Dermal patch

- N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine

- Botulinum Toxin
- Vitamin B12