

CHRONIC PAIN.

**TARGIN®: INTEGRATING AGONISTS AND ANTAGONISTS IN
PAIN MANAGEMENT**

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26/01/2010



MEETING AGENDA

- Pain management principles
- Opioid-induced constipation (OIC)
- TARGIN® tablets
 - Mode of action
 - Pharmacokinetic studies
 - Clinical evidence
 - Analgesic efficacy
 - Bowel function benefits
- CASES STUDIES
 - Sovenor
 - Targin
- Questions and discussion



PAIN

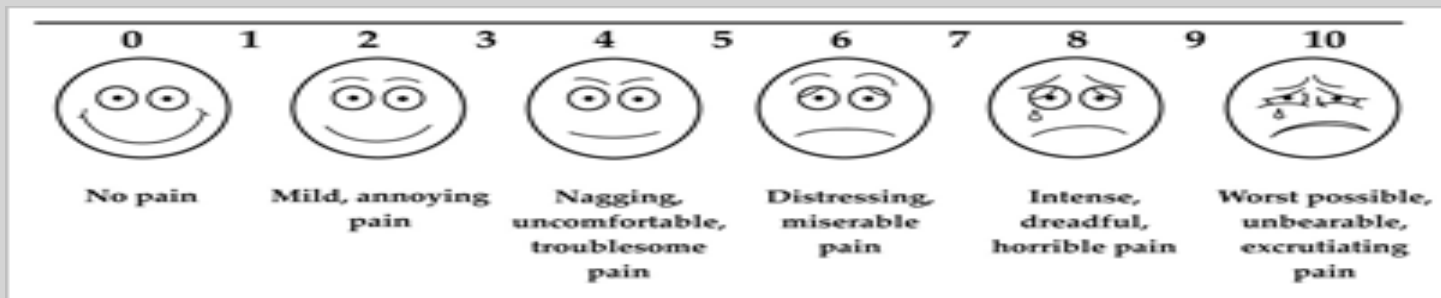
IASP Definition (1979)

‘an unpleasant sensory and emotional experience, associated with actual or potential damage or described in terms of such damage’

- **Pain is a complex process**
 - Pain involves thoughts and feelings
 - Whatever the experiencing person says it is
 - Exists whenever the experiencing person says it does
- **All pain is real**
 - Regardless of whether the biological cause is known

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”



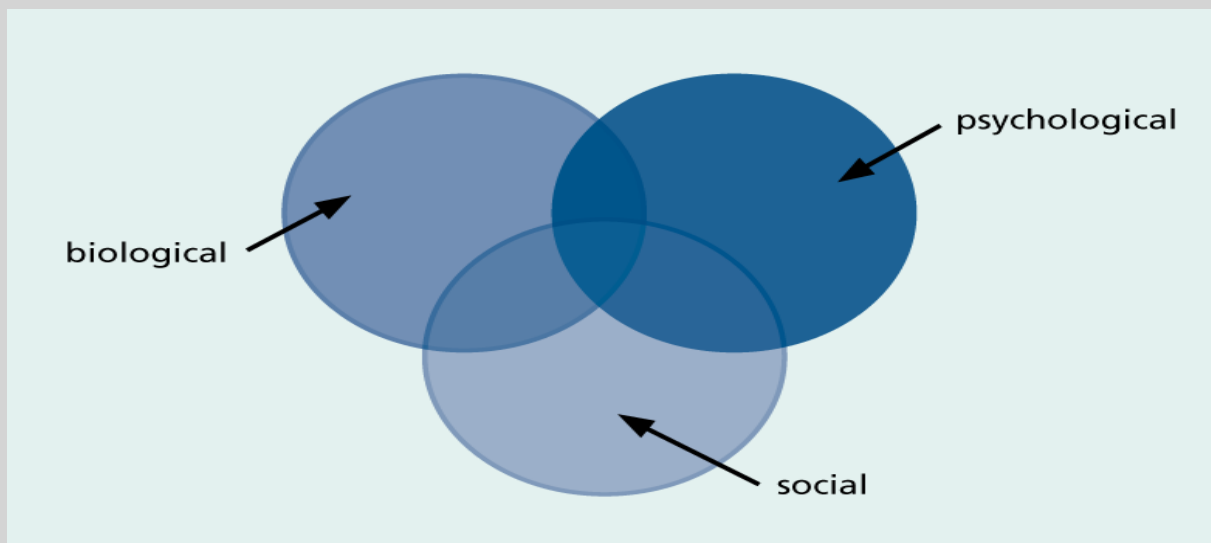


CHRONIC (Persistent) PAIN

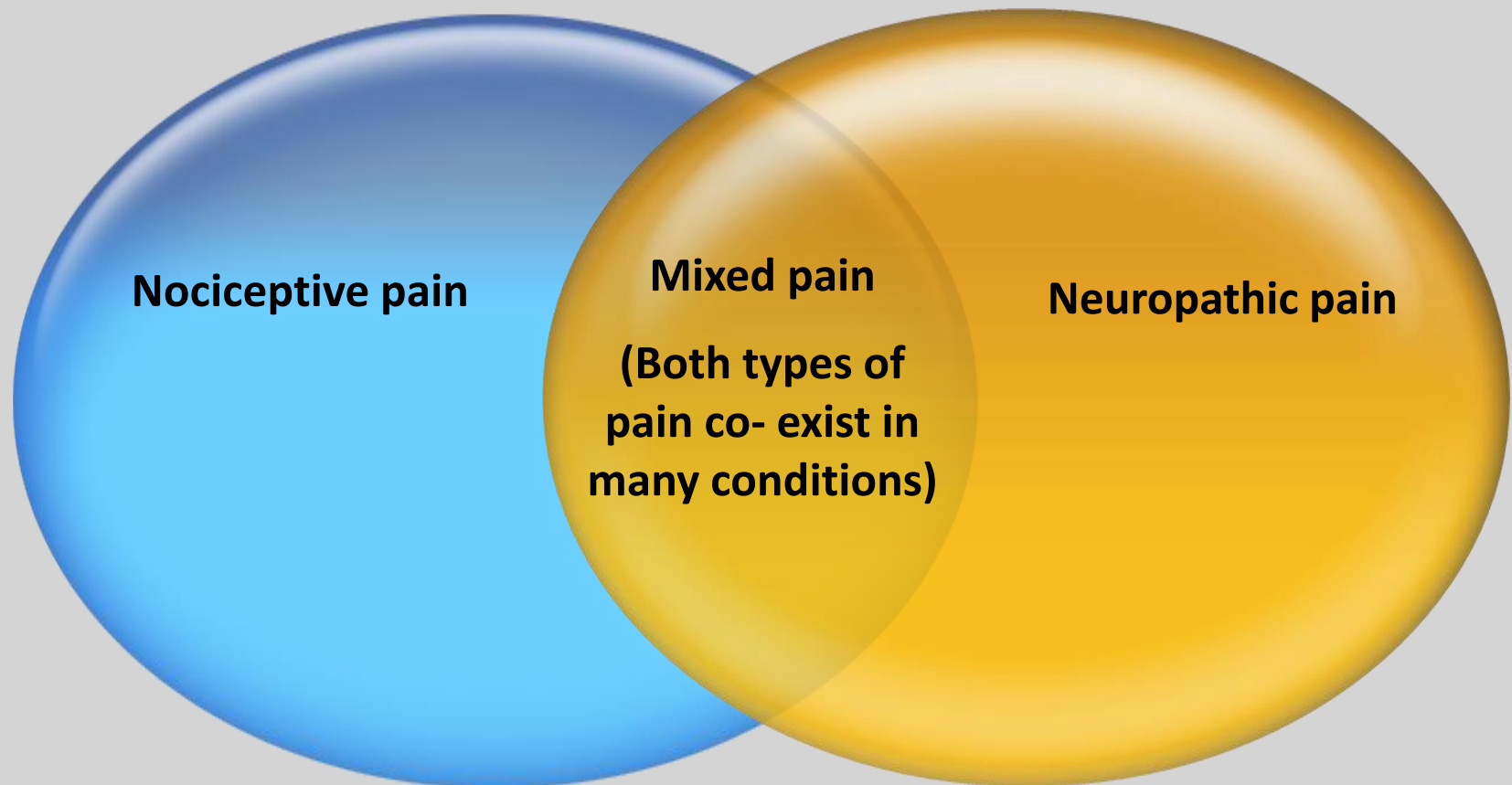
- **Pain persists beyond expected recovery time**
 - Pain continuous or recurrent beyond 3-6 months
 - Up to 33% persistent back pain at 1 year
 - 20% substantial limitations in activity
- **Pain interferes with life**
 - Pain affects self-esteem, well-being and relationships
 - Pain can lead to avoidance, depression and irritability
 - Physical disabilities, psychological distress
 - Unable to work

UNDERSTANDING PAIN

- **Effective pain management** requires comprehensive assessment which incorporates:
 - Biological – nociceptive or neuropathic
 - Psychological – anxiety, depression, negative thoughts
 - Social factors - litigation, cultural, financial, isolation



TYPES OF PAIN

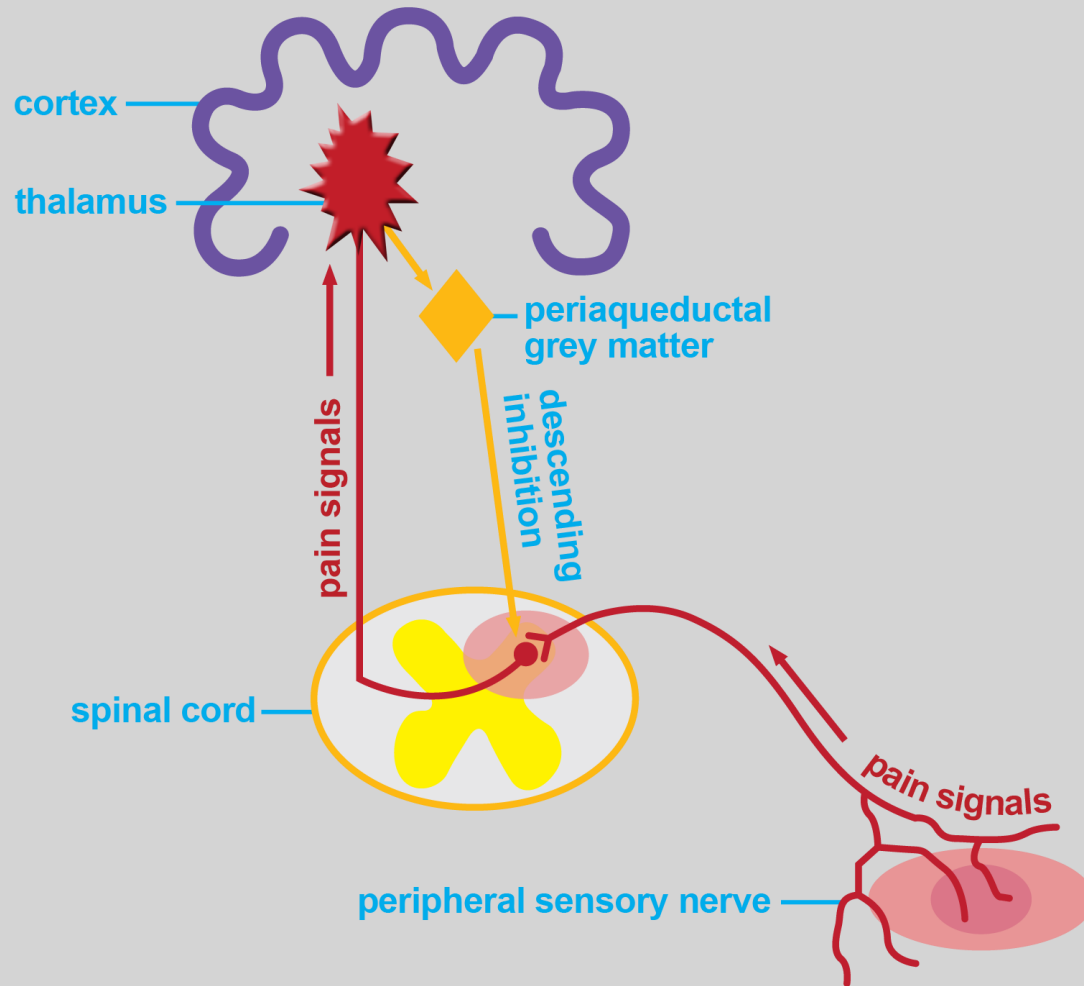




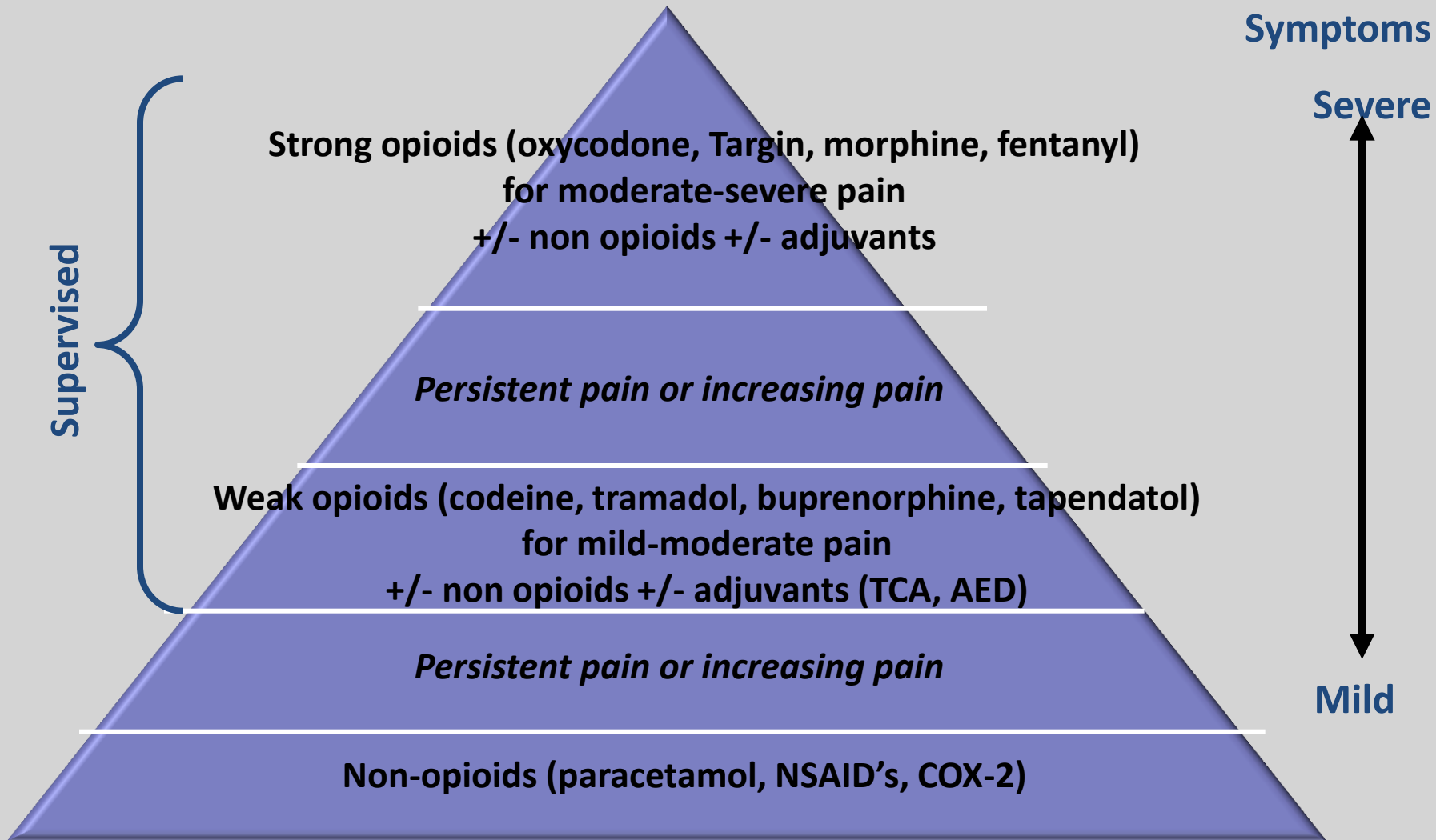
NOCICEPTIVE PAIN

- 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

NEURAL PAIN PATHWAYS



WHO ANALGESIC LADDER (GENERALLY FOR NOCICEPTIVE PAIN)





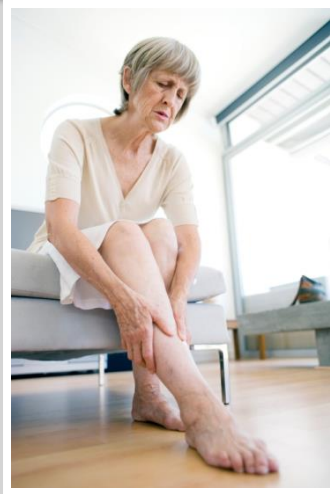
NEUROPATHIC PAIN

- 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

RECOGNITION OF NEUROPATHIC PAIN



Post-stroke pain



Diabetic peripheral neuropathy

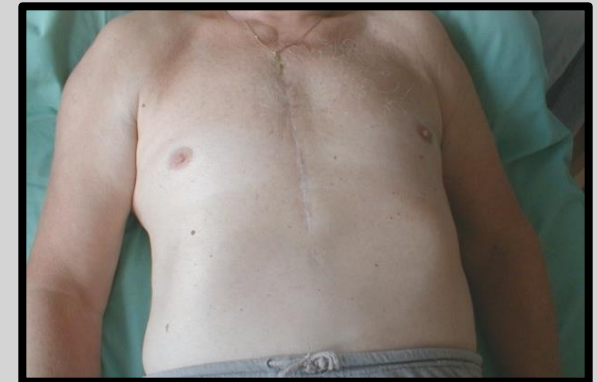


Post-herpetic neuralgia



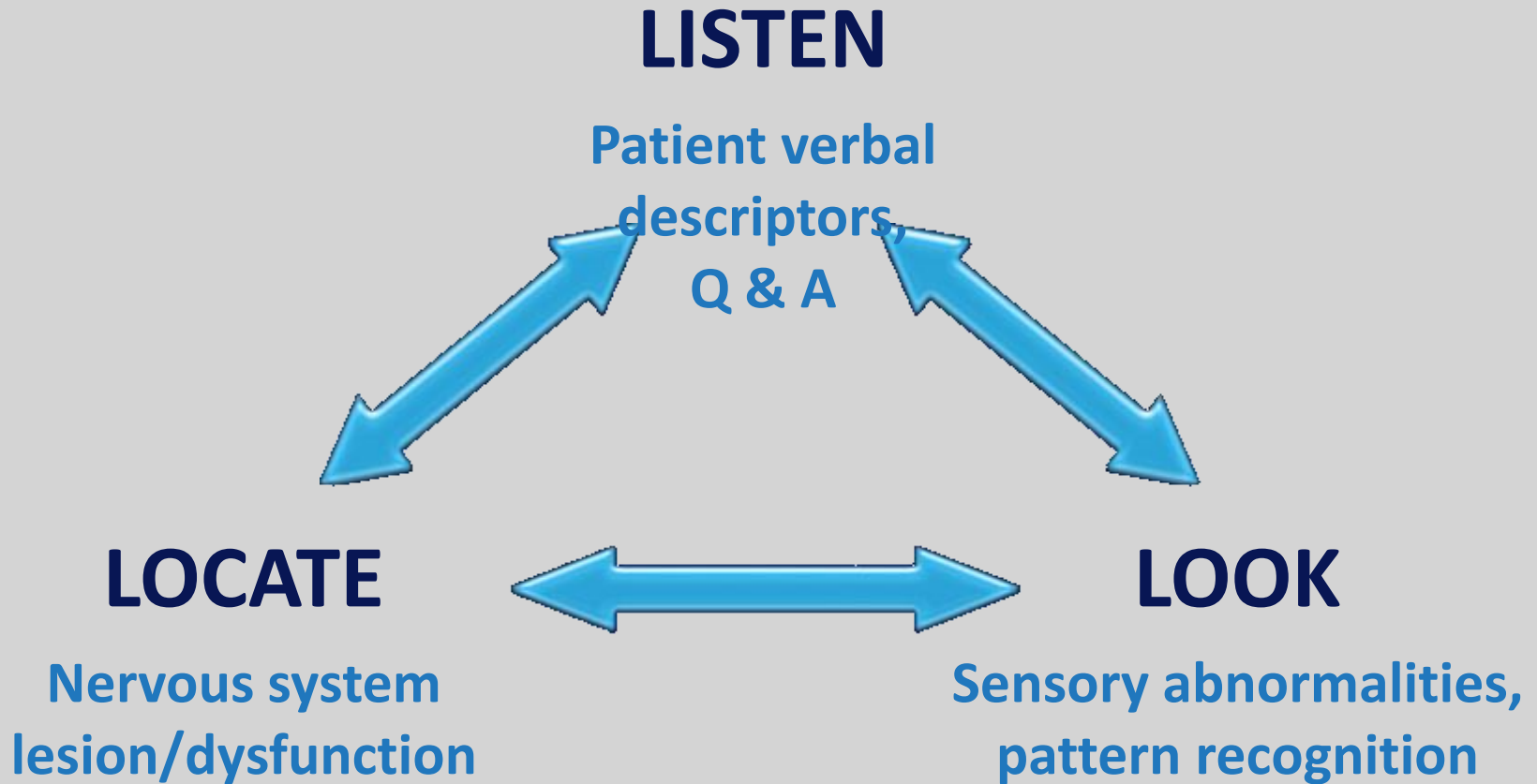
Lumbar radicular pain

**Common
descriptors**
Shooting
Electric shock-like
Burning
Tingling
Numbness



Chronic post-surgical pain

DIAGNOSING PAIN





BURNING

CRAWLING

STABBING

SHOCKING

FREEZING



TARGIN®
OXYCODONE/NALOXONE
CONTROLLED RELEASE TABLETS



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

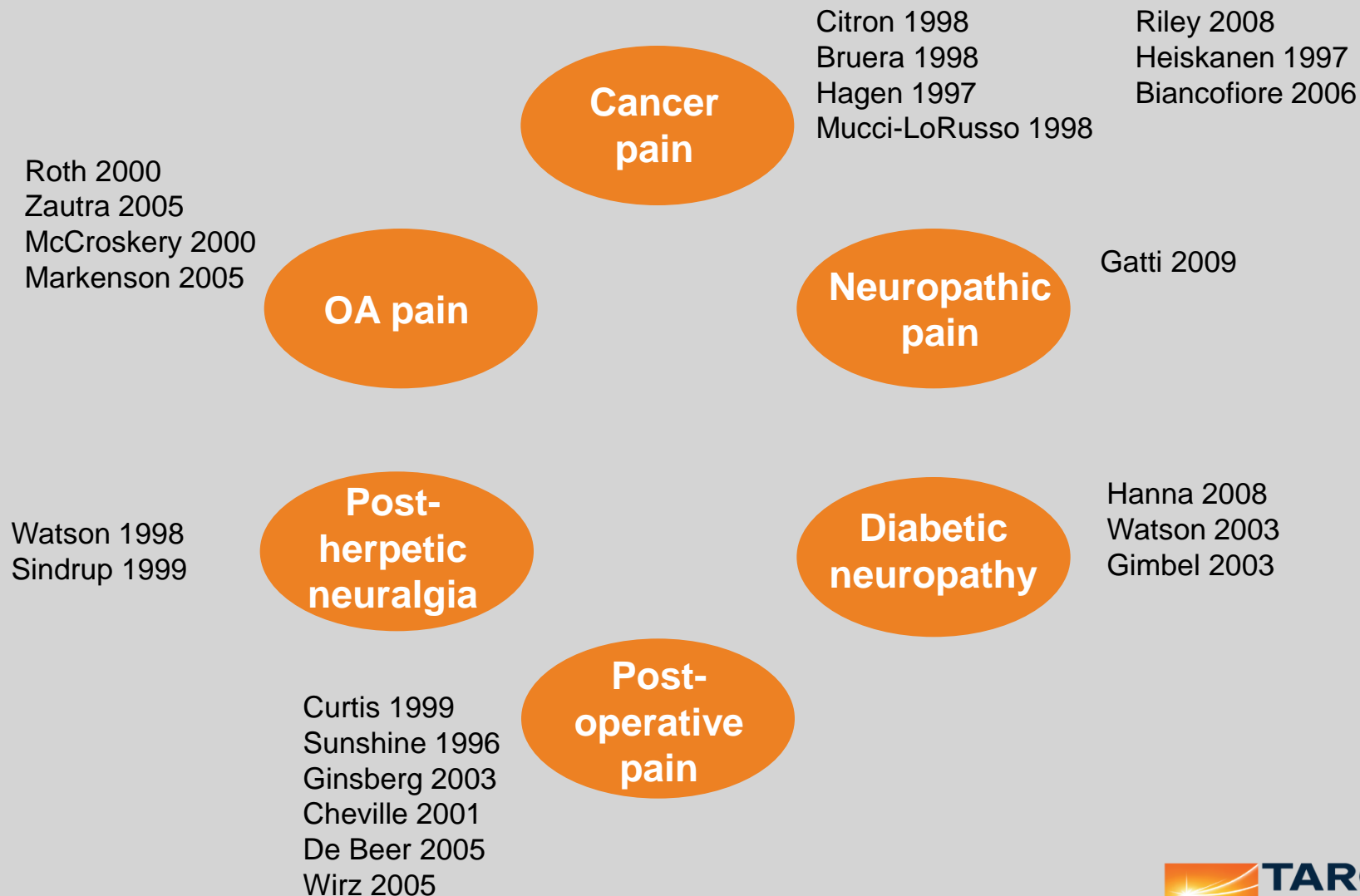


OPIOIDS PLACE IN PAIN MANAGEMENT

- Beneficial in some patients
 - Demonstrated good efficacy outcomes
 - Dose dependent response
 - Only moderate side effects
 - Low risk of abuse or addiction when used for pain
- Longer acting opioids are better than short-acting
- Patient selection and close follow-up important
- Most common side effects
 - Nausea and constipation - NNH was 4.2 (CI 3.2-5.6)
 - Followed by drowsiness, dizziness and vomiting



OXYCODONE ANALGESIC EFFICACY





APPROPRIATE PATIENT SELECTION¹⁻³

- 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



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

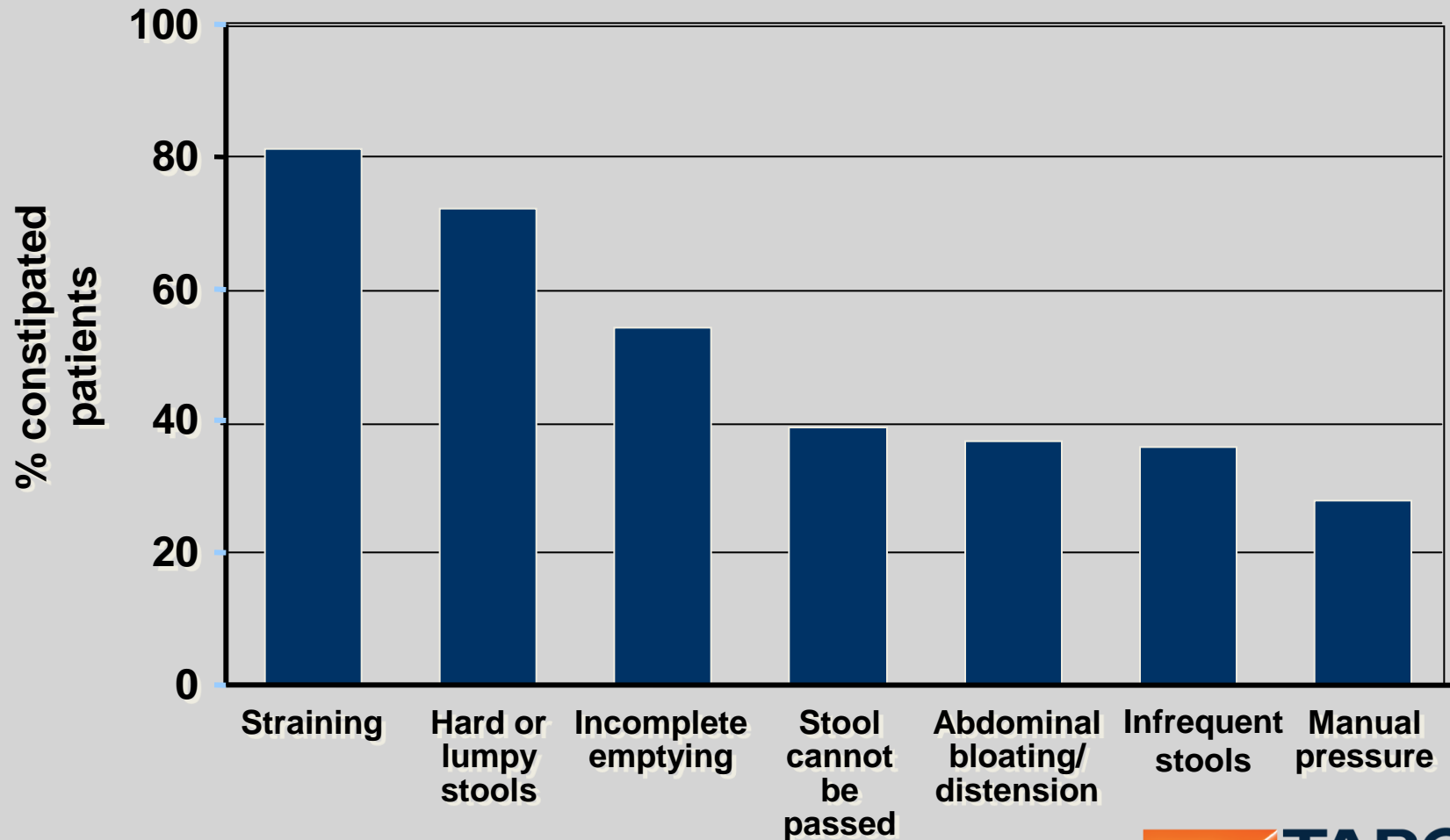
| OIC COMPROMISES PAIN MANAGEMENT^{4–6}

- 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

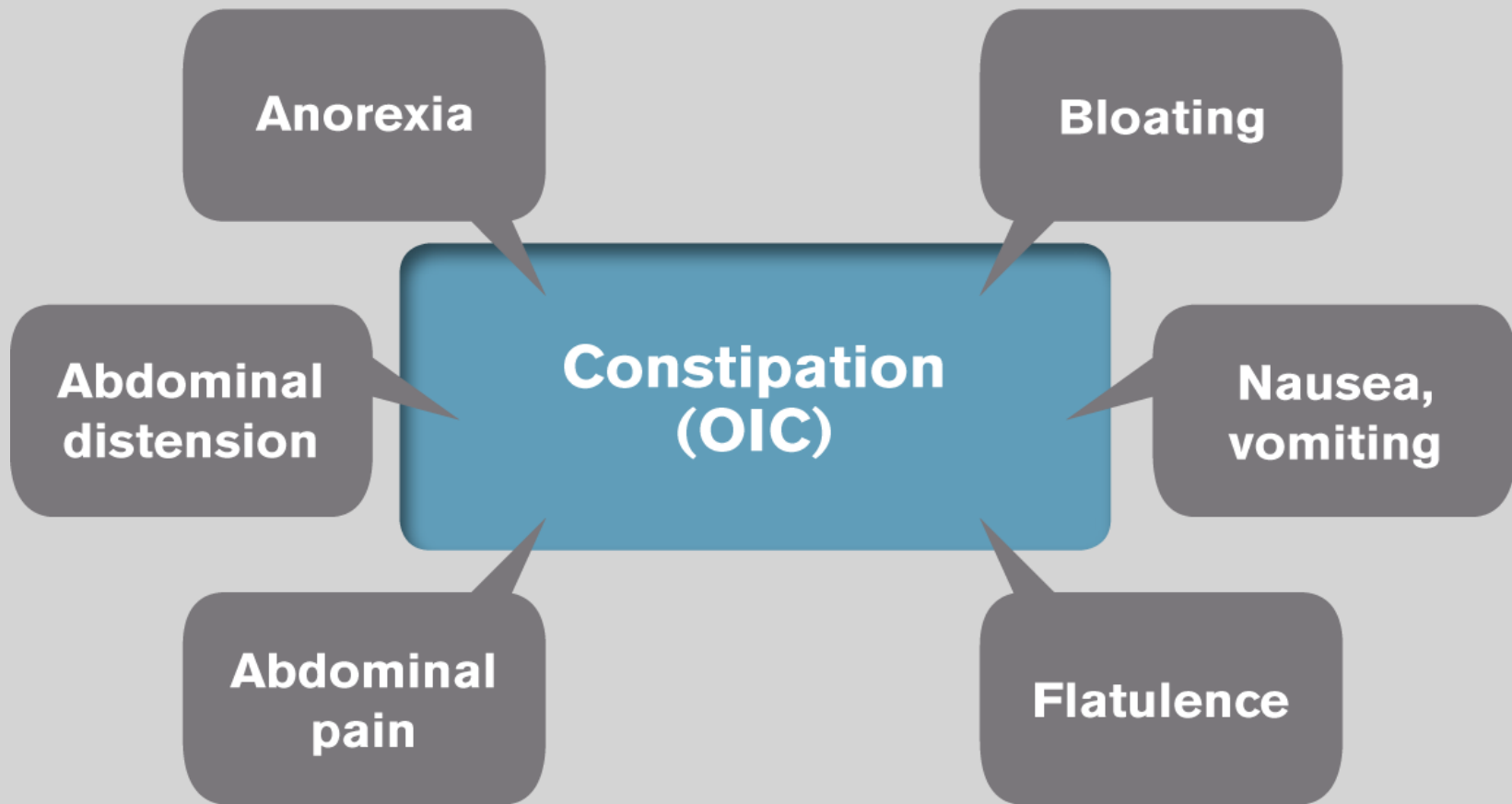
1. Benyamin R *et al.* Pain Physician 2008;11(2 Suppl):S105–120. 2. Tuteja AK *et al.* Neurogastroenterol Motil 2010;22(4):424–430, e496. 3. Roth SH *et al.* Arch Intern Med 2000;160(6):853–860. 4. Bell T *et al.* J Opioid Manag 2009;5(3):137–144. 5. Bell TJ, *et al.* Pain Med 2009;10(1):35–42. 6. Kurz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

CONSTIPATION: A VARIETY OF SYMPTOMS¹





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



MECHANISM OF OIC

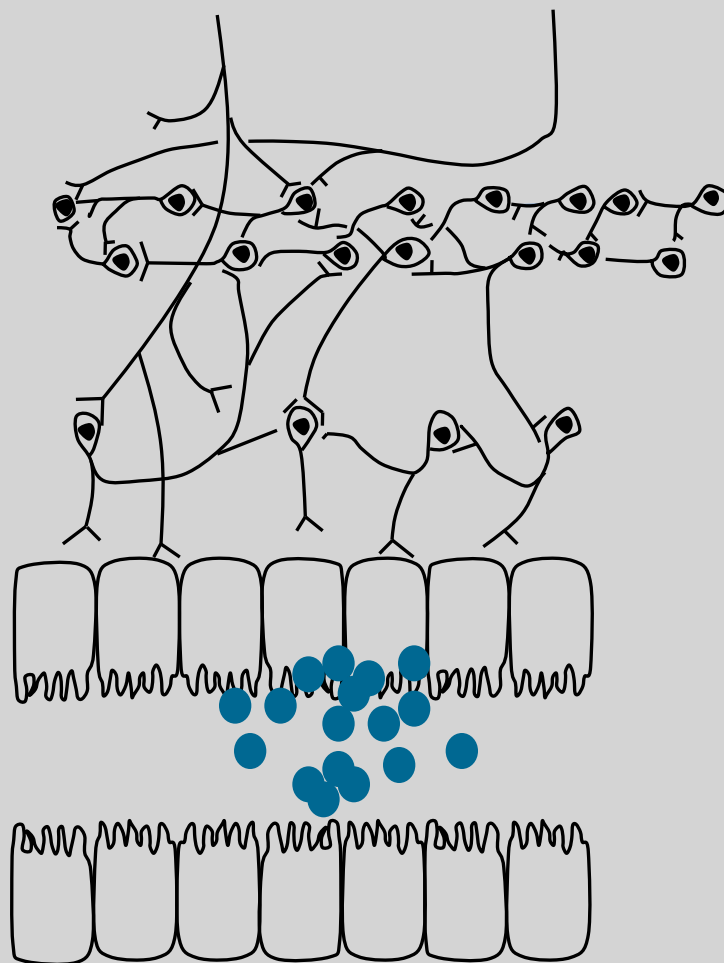
The primary cause of OIC is activation of opioid receptors in the gut¹⁻³

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

Gastrointestinal wall

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

Gastrointestinal lumen



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.



PHARMACOLOGIC EFFECTS OF OPIOIDS BINDING IN THE GUT resulting in OIBD^{1,2}

Site of action	Pharmacological action
Stomach	↓ gastric motility ↑ pyloric sphincter tone
Small intestine	↓ pancreatic, biliary and intestinal secretions ↓ intestinal secretion ↑ non-propulsive contractions ↑ fluid absorption
Large intestine	Above plus ↑ anal sphincter tone



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

STOOL CONSISTENCY CORRELATES WITH TRANSIT TIME and WATER CONTENT

BRISTOL STOOL FORM SCALE¹

Less

**water
content**

More

Type 1

Type 2

Type 3

Type 4

Type 5

Type 6

Type 7



Slower

**colon
transit**

Faster

TRADITIONAL THERAPY: LAXATIVES¹⁻⁴

Type	Mechanism of action	Treatment goal	Side effects
Bulk laxatives Fybogel, Metamucil	Water absorbing ↑ stool volume	Improve stool frequency and consistency	Bloating, flatulence
Stimulant laxatives Senakot, Movicol	↑ intestinal motility ↑ secretions	Improve stool frequency	Abdominal pain
Osmotic laxatives Lactulose, Movicol	Osmotic gradient Draws water into lumen to stimulate peristalsis	Improve stool frequency, consistency and straining	Bloating, nausea, abdominal pain
Stool softeners Coloxyl, Agarol, Movicol	Detergent Allow water to mix with stool to soften stool	Improve stool consistency	Inhibit fat-soluble vitamin absorption

1. Ramkumar D, Rao SS. Am J Gastroenterol 2005;100(4):936–971. 2. Tack J, Müller-Lissner S. Clin Gastroenterol Hepatol 2009;7(5):502–508. 3. Schaefer DC, Cheskin LJ. Am Fam Physician 1998;58(4):907–914. 4. Spinzi GC. Dig Dis 2007;25(2):160–165.



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}***



NOVEL THERAPIES FOR OIC

- **Methylnaltrexone injectable (Relistor) sub-cut¹**
 - Treatment of OIC in palliative care patients when response to laxatives has not been sufficient
 - Acts as a **mu opioid antagonist in gut**
 - Does not cross BBB (low lipid solubility)
 - **No analgesic effect**
 - Short term use
 - Less than 4 months
 - Side effects
 - Abdominal pain, flatulence, nausea, dizziness





TARGIN® TABLETS (APRIL 2011) **OXYCODONE + NALOXONE**

TARGIN® TABLETS 12-HOURLY CONTROLLED RELEASE¹

OXYCODONE

Opioid agonist with
central action¹



NALOXONE

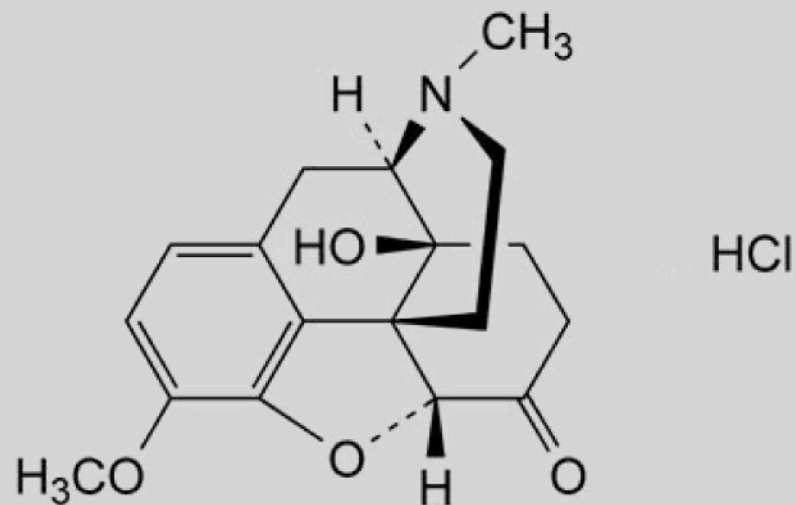
Opioid antagonist that
acts locally in the gut^{1,2}

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

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

OXYCODONE^{1,2}

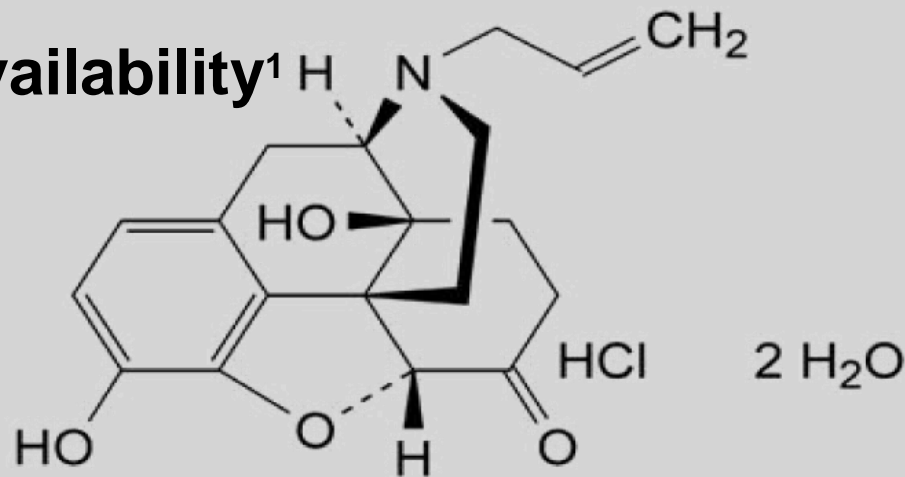
- Semi-synthetic derivative of a morphine alkaloid, thebaine
- Full opioid receptor agonist
- Therapeutic action is analgesia



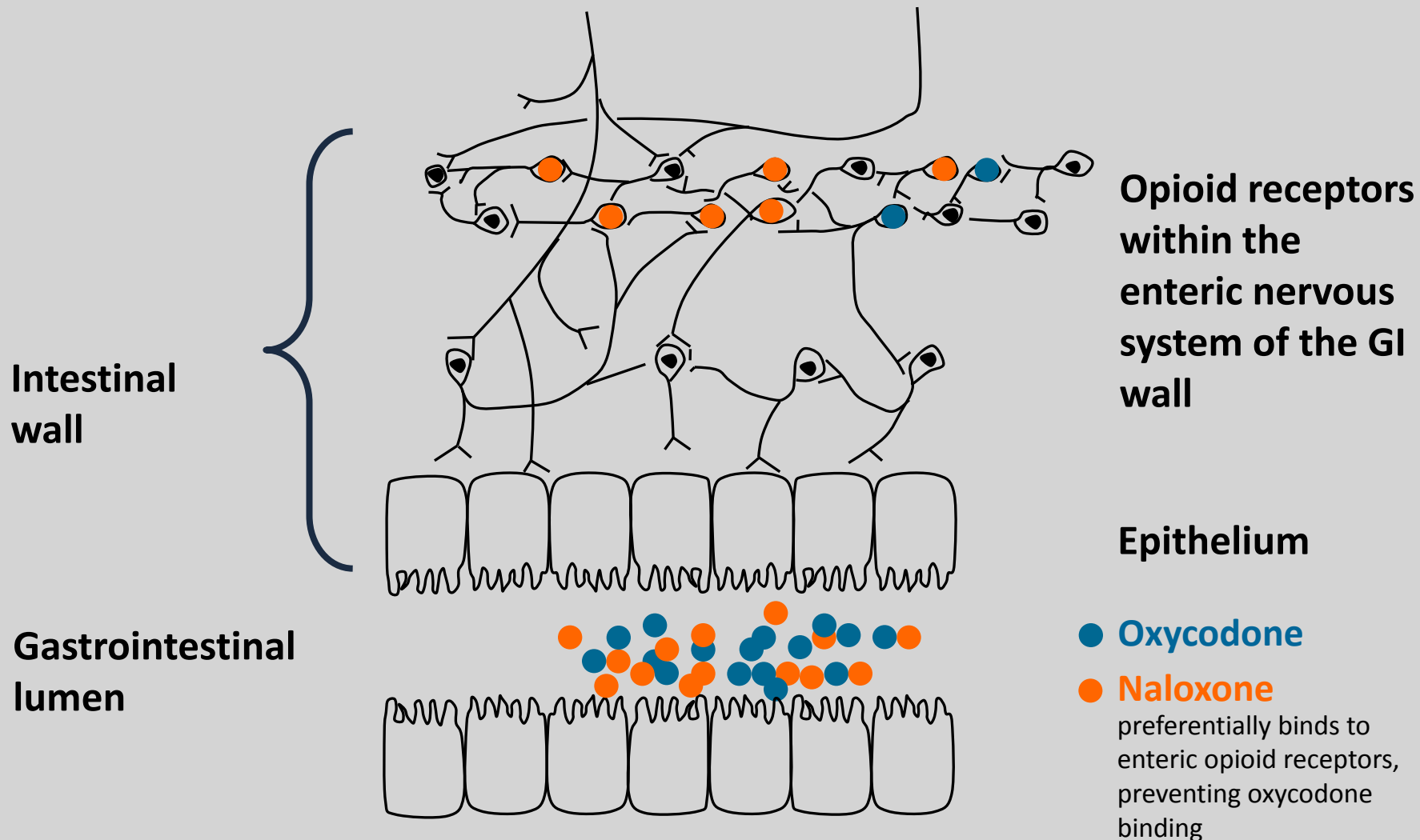
- Metabolised in the **liver** with no clinically significant metabolites
- Up to **87% oral bioavailability**

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

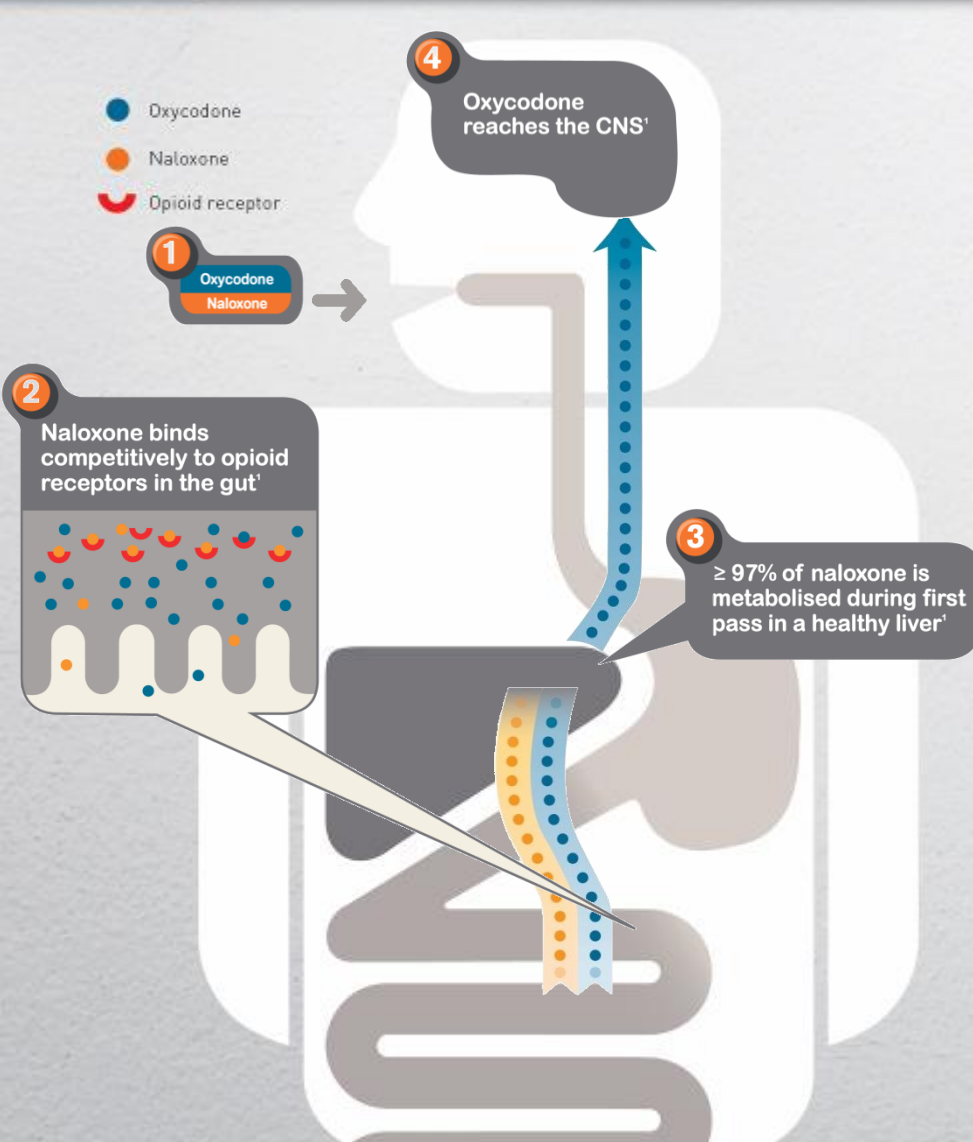


TARGIN® TABLETS AND THE GI WALL¹⁻⁴



TARGIN® TABLETS

MODE OF ACTION



1 12-HOURLY OXYCODONE AND NALOXONE¹

- Oral TARGIN® tablets deliver oxycodone CR and naloxone CR¹

2 NALOXONE BINDS COMPETITIVELY TO OPIOID RECEPTORS IN THE GUT¹

- Due to its high binding affinity, naloxone prevents or reverses the effects of oxycodone in the GI tract, reducing OIC¹

3 NALOXONE IS METABOLISED DURING FIRST PASS¹

- During first pass, at least 97% of naloxone is metabolised in the healthy liver, (low oral bioavailability while up to 87% of oxycodone passes into the circulation unchanged¹

4 OXYCODONE REACHES THE CNS¹

- The oxycodone in TARGIN® tablets exerts a central analgesic effect equivalent to oxycodone administered alone¹

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
Clcr <60mL/min
- Debilitated elderly patients



5/2.5 mg TARGIN®
tablet 12-hourly

MAXIMUM RECOMMENDED DOSE¹



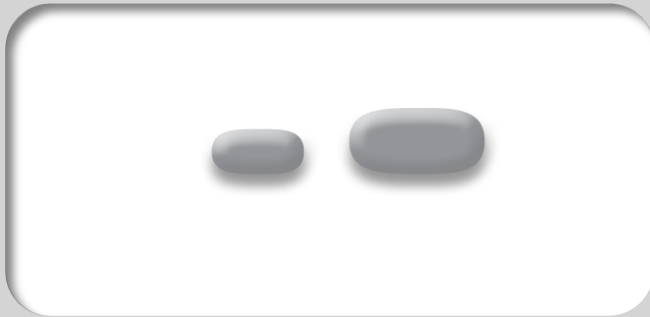
40/20 mg TARGIN®
tablet 12-hourly

- 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

ASYMMETRIC DOSING and DISCONTINUATION

ASYMMETRIC DOSING¹



- Morning and evening doses can be adjusted individually to help manage day–night variations in pain severity

DISCONTINUATION¹

**Gradually reduce dose to
minimise withdrawal
symptoms**

- TARGIN® tablets should not be prescribed or taken for longer than absolutely necessary to manage pain
- After complete discontinuation of TARGIN® tablets and a subsequent switch to another opioid, a worsening of bowel function can be expected



TARGIN® TABLETS

BREAKTHROUGH PAIN 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 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



CONSENSUS FOR A CLINICALLY APPROPRIATE DAILY DOSE RANGE IN GENERAL PRACTICE¹⁻³

Below 120 mg
of oral morphine
or equivalent per day
ie **80 mg** of oxycodone

A consensus exists for a clinically appropriate daily dose range in most patients with chronic non-cancer pain in general practice¹⁻³

- Before increasing the daily opioid dose above this range, consider:
 - if pain is opioid-responsive
 - if the patient has demonstrated sustained improvements in both function and pain
 - the possible risks/benefits of higher opioid doses^{3,4}
- If daily doses exceed the equivalent of 120 mg morphine (oxycodone 2:3 morphine), it is strongly recommended that the treating doctor considers discussion with or **referral to a pain specialist**.^{1-3,5}



TARGIN[®] TABLETS

SUPPLEMENTAL DOSING



OxyContin[®]
tablet 12-hourly to
achieve pain relief

- Beyond the TARGIN[®] tablets maximum recommended daily dose of 40/20 mg 12-hourly, **administer OXYCONTIN at the same time interval**
- The beneficial effect of naloxone in TARGIN[®] tablets on bowel function may be impaired by supplemental oxycodone dosing



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 <20mL/min
- Severe respiratory depression
- Pregnancy and lactation

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



CLINICAL TRIALS

**TARGIN® : THE ONLY OPIOID ANALGESIC THAT HELPS
PREVENT OPIOID-INDUCED CONSTIPATION (OIC)¹⁻³**

A/Professor Arun Aggarwal



TARGIN® TABLETS

ANALGESIC EFFICACY and BOWEL FUNCTION BENEFITS

- Will naloxone interfere with the analgesic effect of oxycodone??
- Will TARGIN demonstrate significant bowel function benefits regarding opioid-induced constipation (OIC) vs oxycodone alone??¹
- What is the effect of naloxone on analgesia and bowel function, long-term??²

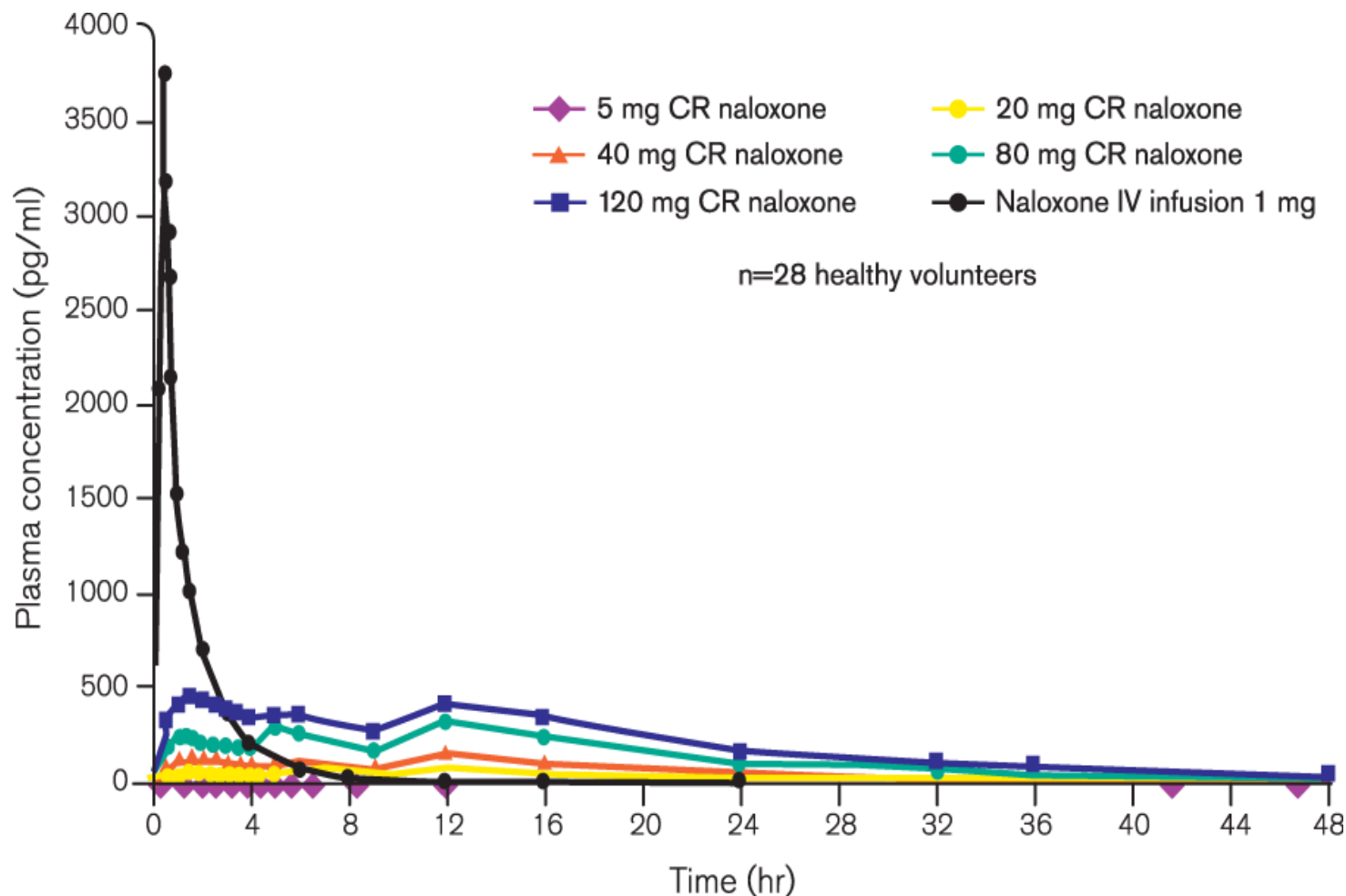


PHARMACOKINETIC STUDIES – Phase 1

- Single-dose and absolute bioavailability of naloxone¹
- Single-dose^{2,3} and steady-state pharmacokinetic^{2,4} comparison of TARGIN[®] tablets with oxycodone CR and naloxone CR

SINGLE DOSE

MEAN NALOXONE PLASMA CONCENTRATIONS¹

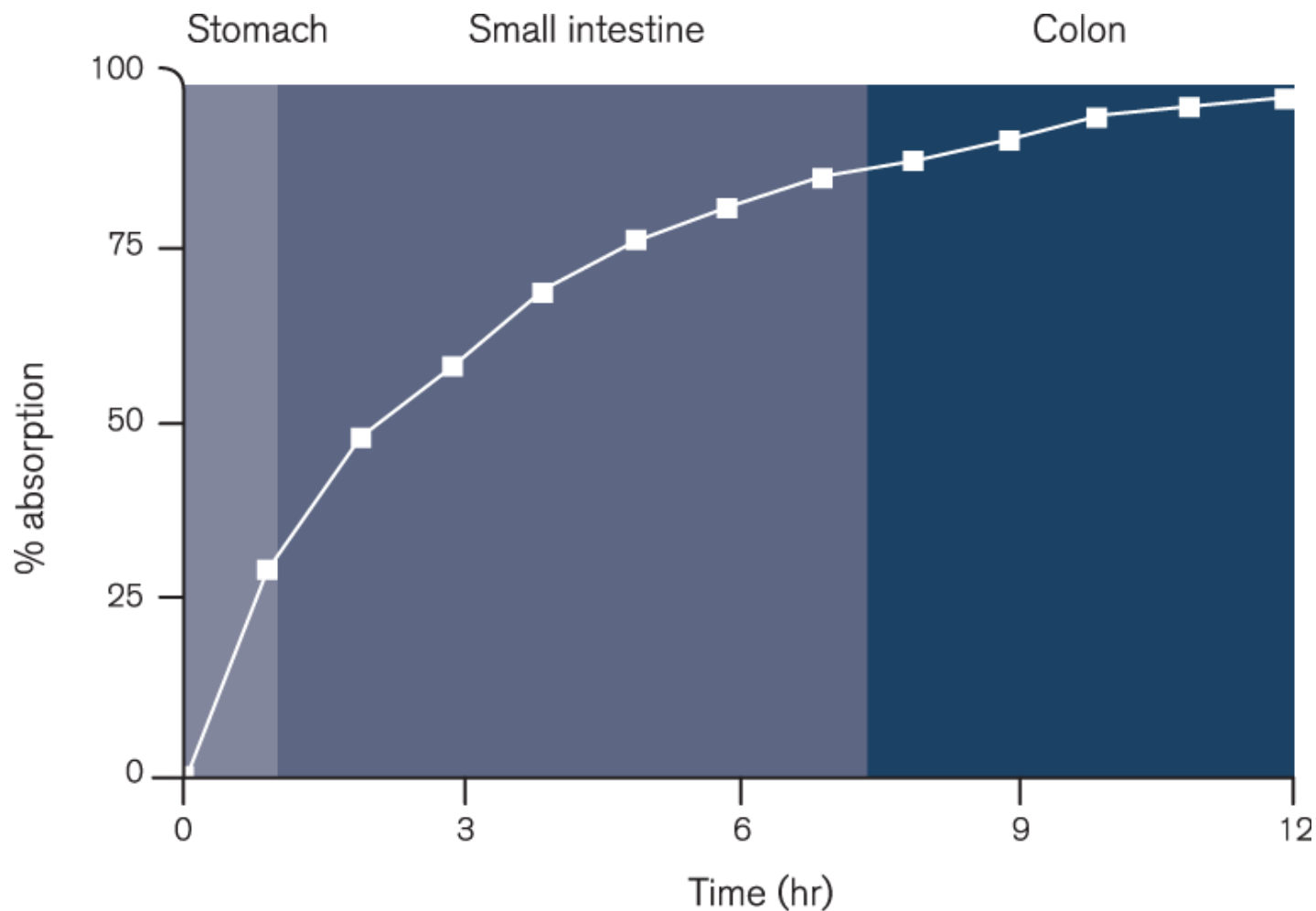




ABSOLUTE BIOAVAILABILITY OF ORAL NALOXONE

Dose naloxone CR	Mean absolute bioavailability
5 mg	0.9%
20 mg	1.8%
40 mg	2.0%
80 mg	2.0%
120 mg	2.0%

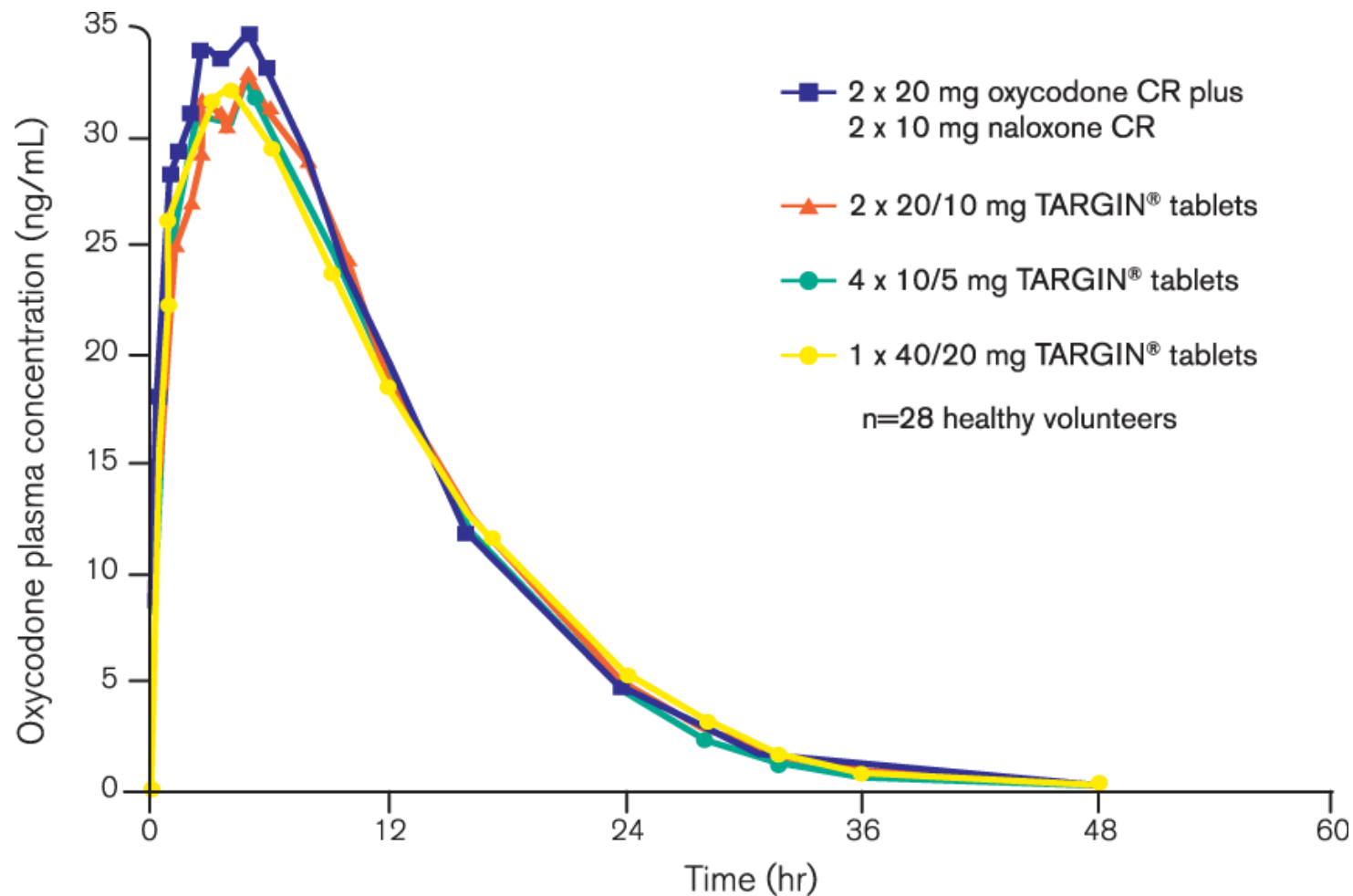
DISINTEGRATION OF TARGIN® TABLETS



Deconvolution results for the 20/10 mg TARGIN® tablet.

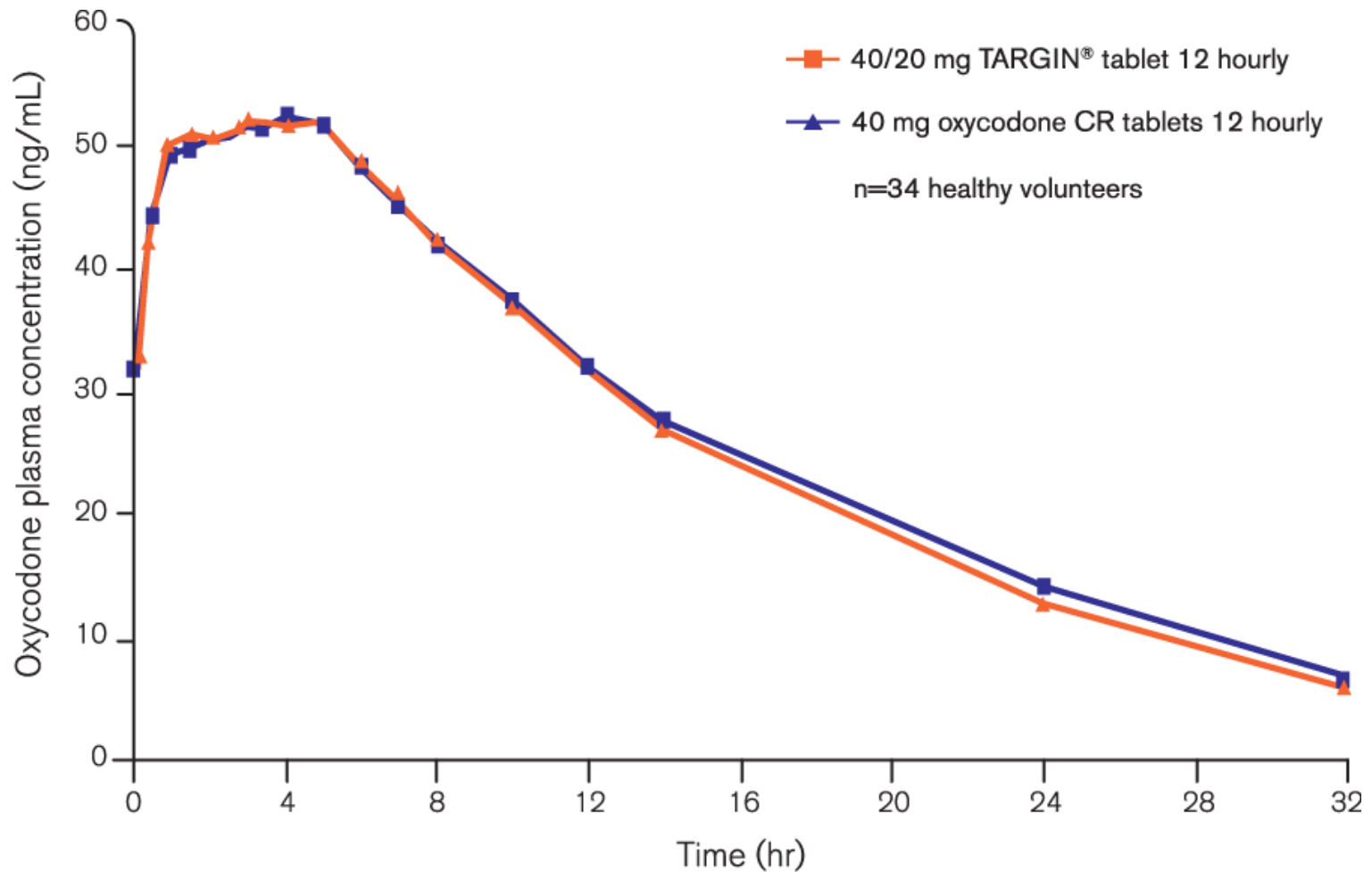
SINGLE DOSE

MEAN OXYCODONE PLASMA CONCENTRATIONS^{1,2}



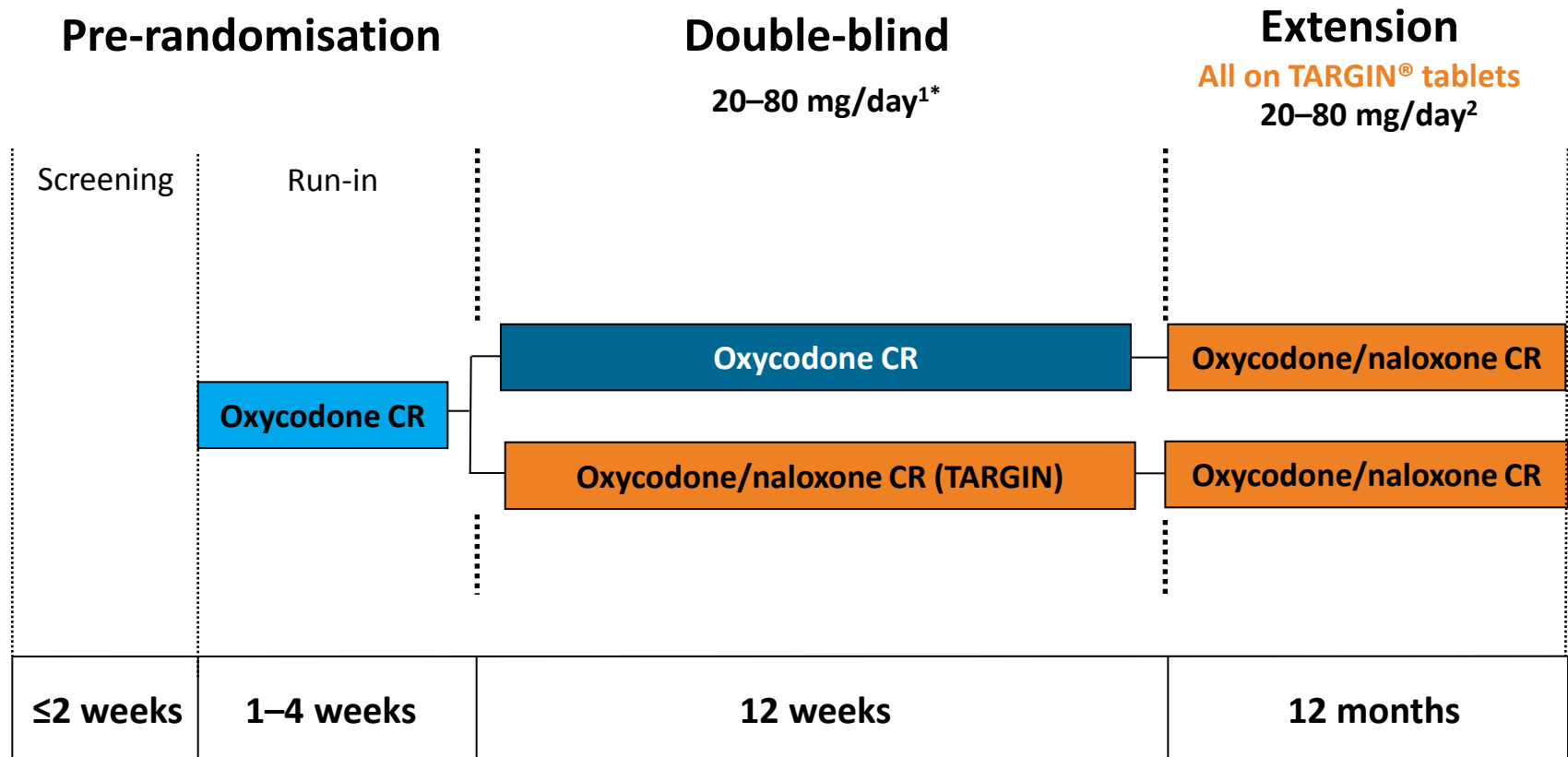
MULTIPLE DOSE (7 consecutive doses)

MEAN PLASMA OXYCODONE CONCENTRATIONS^{1,2}



STUDY DESIGN

ANALGESIC EFFICACY and BOWEL FUNCTION

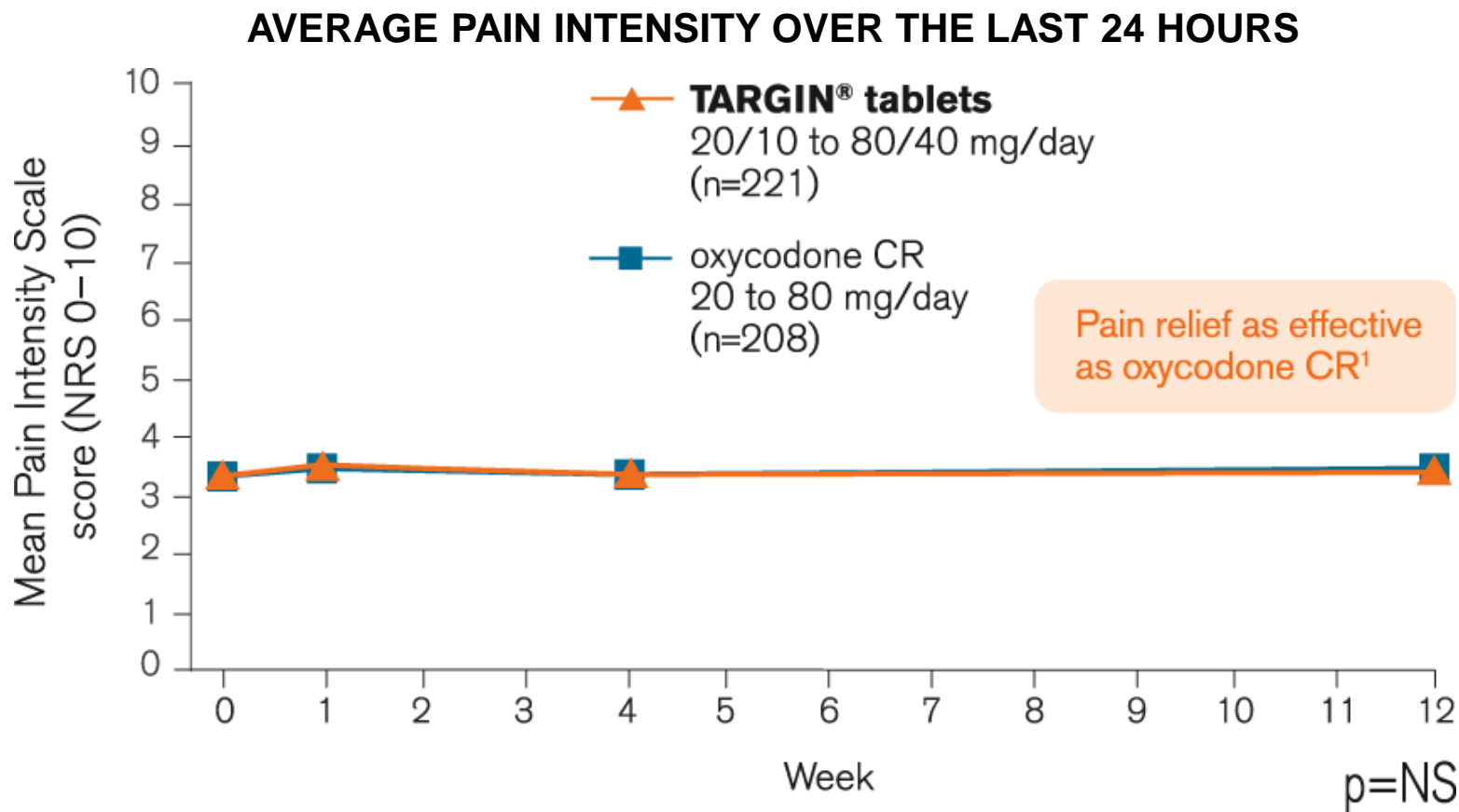


CR=controlled release. IR=immediate release. *Oxycodone dose, administered as either oxycodone CR or TARGIN[®] tablets.

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

TARGIN® TABLETS

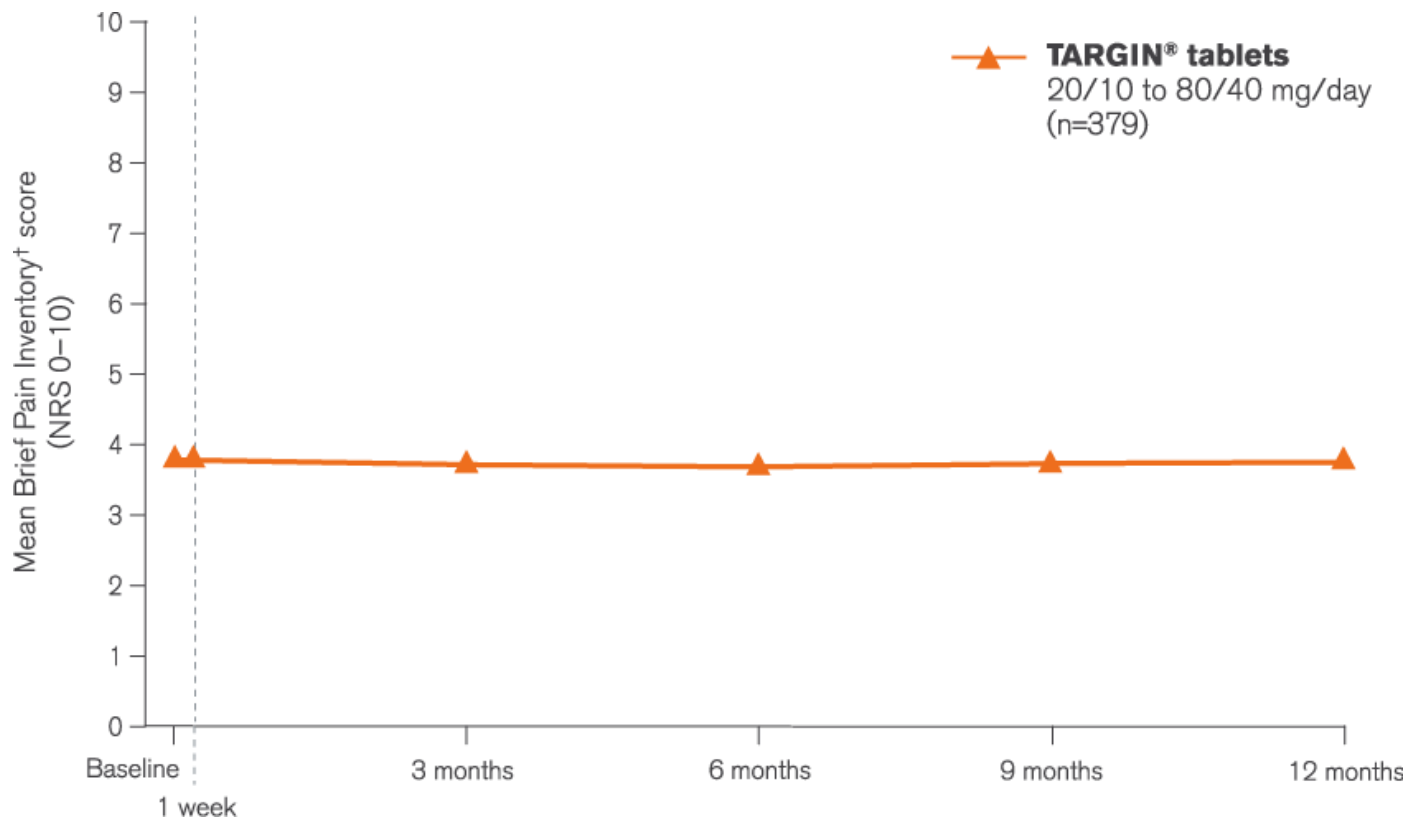
EFFECTIVE PAIN RELIEF OVER 12 WEEKS¹



- 86% of patients experienced pain associated with musculoskeletal & connective tissue disorders. 34% of patients reported neuropathic pain¹
- There was no statistically significant difference in mean daily use of rescue medication between the two groups¹

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



BOWEL FUNCTION INDEX (BFI)^{1,2}

- Evaluates constipation from the patient's perspective^{1,2}
- Clinician-administered, patient-reported, 3-item questionnaire^{1,2}
- The items measured by the BFI are:^{1,2}
 - Ease of defaecation
 - Feeling of incomplete bowel evacuation
 - Personal judgement of constipation
- The patient assesses the severity of each item using a 0–100 numerical analogue scale (NAS) where 0=no problems, 100=most severe problems and the 3 scores are averaged^{1,2}

A SCORE OF ≤ 30 IS CONSIDERED NORMAL BOWEL FUNCTION WITH RESPECT TO OIC^{1–4}

BFI SCORE CHANGE OF ≥ 12 POINTS IS CLINICALLY MEANINGFUL

OIC=opioid-induced constipation. 1. Rentz AM, *et al.* J Med Econ 2009;12(4):371–383. 2. Rentz AM *et al.* Curr Med Res Opin 2011;27(1):35–44. 3. Clemens KE, Mikus G. Expert Opin Pharmacother 2010;11(2):297–310. 4. Schutter U *et al.* Curr Med Res Opin 2010;26(6):1377–1387.

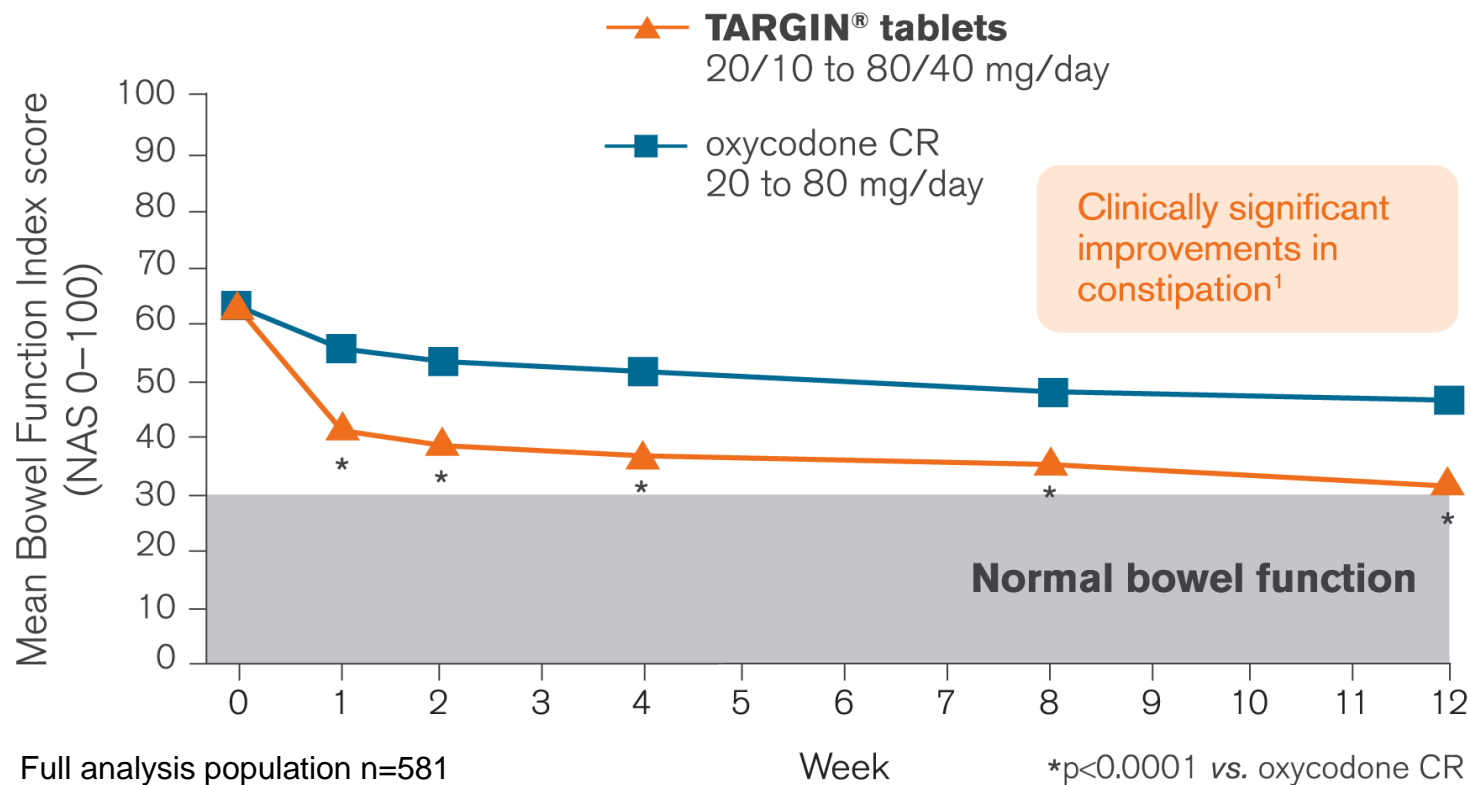
THE BOWEL FUNCTION INDEX (BFI)¹

ITEM	PATIENT QUESTION	SCORE
1. EASE OF DEFECATION during the last 7 days according to patient assessment	ASK YOUR PATIENT: <i>"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"</i>	<input type="text"/> /100 0 = easy / no difficulty 100 = severe difficulty
	IF THE PATIENT NEEDS CLARIFICATION, ASK: <i>"During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"</i>	
2. FEELING OF INCOMPLETE BOWEL EVACUATION during the last 7 days according to patient assessment	ASK YOUR PATIENT: <i>"During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"</i>	<input type="text"/> /100 0 = not at all 100 = very strong
	IF THE PATIENT NEEDS CLARIFICATION, ASK: <i>"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong."</i>	
3. PERSONAL JUDGEMENT REGARDING CONSTIPATION during the last 7 days according to patient assessment	ASK YOUR PATIENT: <i>"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong?"</i>	<input type="text"/> /100 0 = not at all 100 = very strong
	IF THE PATIENT NEEDS CLARIFICATION, ASK: <i>"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong?"</i>	
BFI	Calculate the BFI by finding the average of scores for items 1 to 3 BFI = <input type="text"/> + <input type="text"/> + <input type="text"/> = <input type="text"/>	<input type="text"/> /100 ≤30 = normal bowel function*

TARGIN® TABLETS

IMPROVED BOWEL FUNCTION FROM WEEK 1¹

BOWEL FUNCTION INDEX (BFI) SCORE OVER TIME



A score of ≤ 30 is considered normal bowel function with respect to OIC.²⁻⁵

A change of ≥ 12 points indicates a clinically relevant change in bowel function.²⁻⁵

Laxatives used in fewer patients on TARGIN during 1st 4 weeks

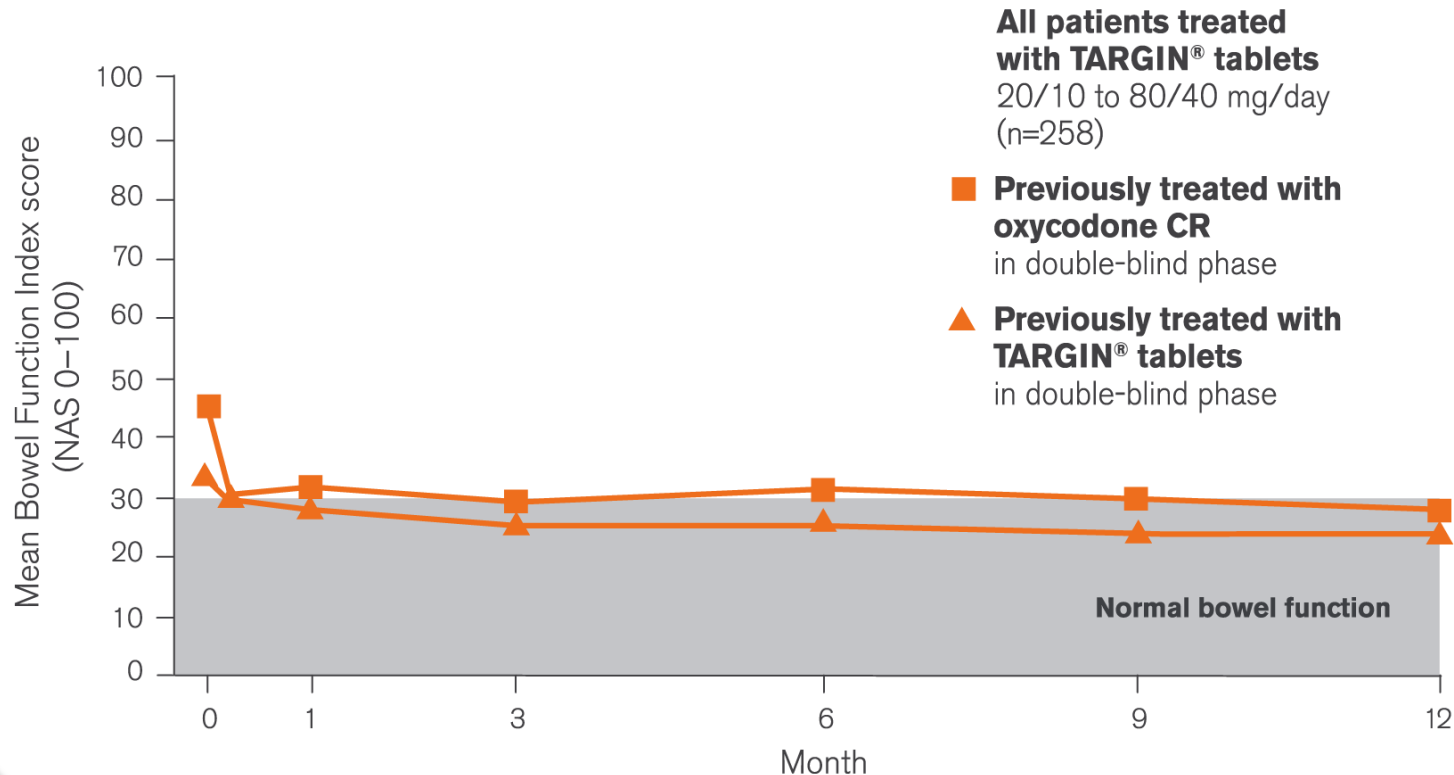
- Significantly fewer patients on TARGIN® tablets required laxatives during the first 4 weeks of treatment ($p<0.0001$ vs. oxycodone CR)

CR=controlled release. NAS=numerical analogue scale. 1. Löwenstein O *et al.* BMC Clin Pharmacol 2010;10:12. 2. Rentz AM *et al.* J Med Econ 2009;12(4):371-383. 3. Clemens KE, Mikus G. Expert Opin Pharmacother 2010;11(2):297-310. 4. Schutter U *et al.* Curr Med Res Opin 2010;26(6):1377-1387. 5. Rentz AM *et al.* Curr Med Res Opin 2011;27(1):35-44.



LONGER-TERM IMPROVEMENT IN BOWEL FUNCTION¹

MAINTAINED IMPROVEMENT IN OIC OVER 12 MONTHS OF THERAPY¹



Mean oxycodone dose:

- 32.8 mg/day with TARGIN[®] tablets in double-blind phase

- 34.0 mg/day with oxycodone CR in double-blind phase

- 38.3 mg/day with TARGIN[®] tablets in extension phase

- A score of ≤ 30 is considered normal bowel function with respect to OIC.^{2–5}

- A change of ≥ 12 points indicates a clinically relevant change in bowel function.^{2–5}

- **8.5% of patients reported regular laxative intake after the first week of the 12-month extension study¹**

OIC=opioid-induced constipation. CR=controlled release. NAS=numerical analogue scale. 1. Sandner-Kiesling A *et al.* Int J Clin Pract 2010;64:763–74. 2. Rentz AM *et al.* J Med Econ 2009;12(4):371–383. 3. Clemens KE, Mikus G. Expert Opin Pharmacother 2010;11(2):297–310. 4. Schutter U *et al.* Curr Med Res Opin 2010;26(6):1377–1387. 5. Rentz AM *et al.* Curr Med Res Opin 2011;27(1):35–44.



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**

CHRONIC PAIN.

**TARGIN®: THE ONLY OPIOID ANALGESIC THAT HELPS
PREVENT OPIOID-INDUCED CONSTIPATION (OIC)¹⁻³**

A/Professor Arun Aggarwal
CASE STUDIES

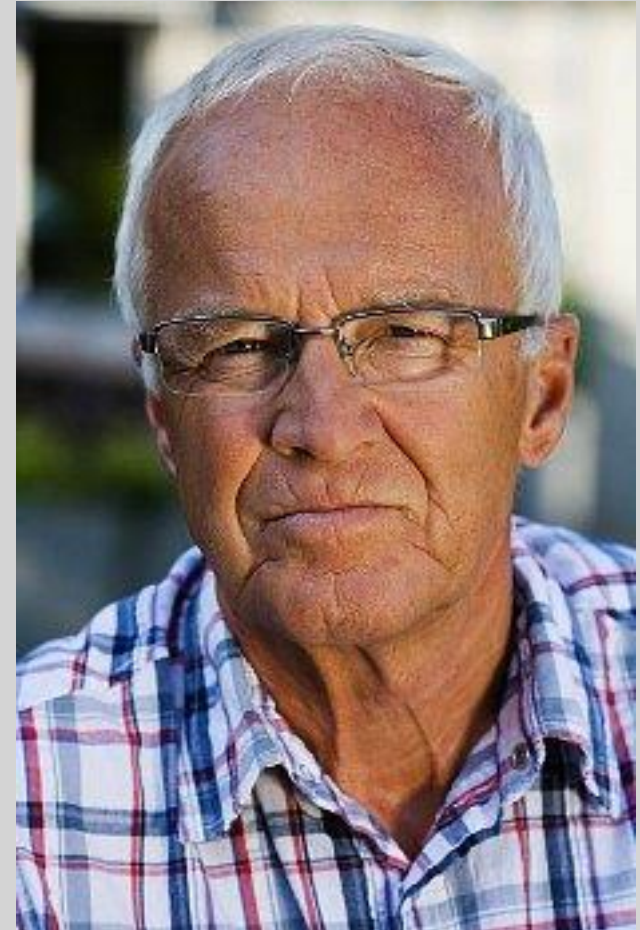


1. TARGIN® tablets Product Information. April 2011. 2. Australian Government, Department of Health and Ageing, Australian Register of Therapeutic Goods. 3. Meissner W *et al.* Eur J Pain 2009;13(1):56–64.



MR JR

- 76 yo carpenter,
 - now manager at carpentry firm
 - also likes working in garden
- History of right knee pain
- Currently on maximum dose paracetamol/codeine (30 mg)
 - NSAID for breakthrough pain
- Has regular physiotherapy
 - home-based exercise programme
 - heat packs





PRESENTATION

- Complains of worsening knee pain
 - pain assessment NRS **8/10** = moderate to severe pain
- Complains of impaired daily function
 - unable to work a full day due to knee pain
 - trouble with light household and gardening tasks
 - reduced tolerance for standing
 - disturbed sleep
- Experiences dyspepsia due to NSAID use

NRS = Numerical rating scale



WHAT IS YOUR TREATMENT PLAN FOR JOHN?

John may be a candidate for knee surgery.

How would you manage John's moderate to severe chronic pain between now and surgery?



OPIOIDS¹

Discussion point:
Which opioid would you trial for John's moderate to severe chronic pain and why?

- Buprenorphine 7-day patch (Sovenor)
- Tramadol / Tapendatol
- Oxycodone/naloxone CR (Targin)
- Oxycodone CR (Oxycontin)
- Fentanyl 3-day patch
- Morphine CR (MS Contin)
- Hydromorphone (modified release)



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 MEDICINE^{1–5}

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.



PROGRESS

- Commence **Buprenorphine 5 mcg/hr weekly patch (Sovenor)**
- Pain improved from **NRS 8/10 to 4/10**
 - Ceased regular paracetamol/codeine, but needs paracetamol 8/day
 - Able to work all day, without being limited by pain
 - Stand for as long as needed
 - Sleeping well at night
- Review in 4 weeks, **Sovenor increased to 10 mcg/hr weekly**
- Pain **improved to 2/10**
 - No additional analgesia required and functioning very well



Mrs PK

- 86 year old widow
- Lives alone
- Lumbar laminectomy 20 years ago
- Bleeding gastric ulcer 5 years ago
- Clinical and radiological diagnosis indicate:
 - Symptomatic osteoarthritis of knees
 - Lumbar spondylosis with central canal stenosis
- Independent ADL but difficulty walking up steps



CURRENT MEDICATIONS

- Consultation for repeat prescriptions for ***pain killers***
 - “*Not that they do a lot for me these days*”
- Analgesics
 - **Paracetamol 1000 mg 4/day**
 - **Tramadol 50 mg tds**
- Other medications
 - Doxepin
 - Amiloride/Hydrochlorothiazide (5 mg/50 mg) mane
 - Glucosamine sulphate 500mg tds
 - Antioxidant supplement for macular degeneration



PAIN ASSESSMENT

- Both knees are painful and stiff
 - Increasingly difficult to walk up stairs and hills (knee pain)
- Low back pain, radiating to her legs (no paraesthesiae)
 - Walking is limited to 10 minutes or 50 metres (back pain)
 - Prolonged sitting and standing are difficult
 - Able to sit for 10 minutes only
- Sleep interrupted by pain
- Background pain level is **6/10**
- Worst pain is **9/10**, which occurs with prolonged walking or walking up stairs



MANAGEMENT

- Tramadol providing short-term benefit
- Replace with:
 - **Slow release Tramadol – SR or XR**
 - Stronger opioid – **Transdermal buprenorphine (Sovenor)** due to potential compliance benefit
- Glucosamine discontinued
- Continue paracetamol as opioid sparer, but standard formulation replaced by modified release tablets to aid compliance
 - Panadol Osteo 2 tablets tds



PROGRESS

- Buprenorphine patch **5 mcg/hr weekly:**
 - Background pain **6/10 to 4-5/10**
 - Sleep has improved, not waking in pain
 - No change on pain during walking (rating 9/10)
 - No adverse effects reported
- Buprenorphine patch dose increased to **10 mcg/hr**
- Pain relief improved
 - Background pain reduced further to **3/10**
 - Incident pain improved with worst pain 5/10
 - Walking tolerance increased to 30 minutes
 - Buprenorphine is well tolerated
- **Continue buprenorphine patch at 10 mcg/h**



BUPRENORHINE (Sovenor)

- A potent partial agonist with a long duration of action
 - 30x as potent as morphine
- Low dose patches very useful in elderly patients with musculoskeletal degenerative disease
- Ceiling agonist effect at approximately 12mg/day in most adults
 - Full μ agonists are antagonised beyond this dose
 - Non-opiate analgesics will be required, eg amitriptyline



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**



Mrs PS

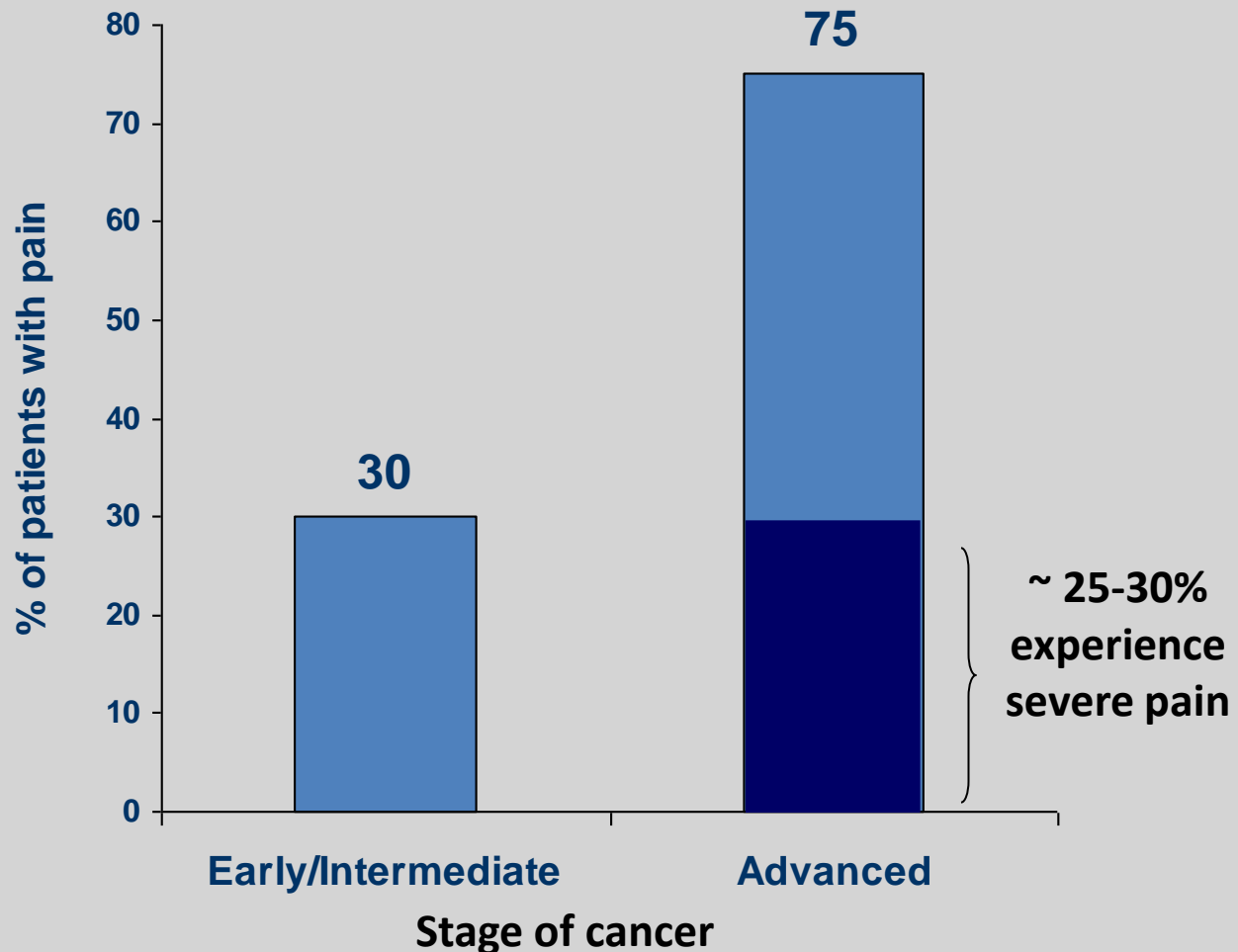
- 58 yo
- Self employed Occupational Therapist
- 2 year history of chronic generalised pain
- Lower lumbar pain radiating down both legs
- Constant dull ache with no sharp stabbing pain – 8/10
- MRI- degenerative disease or cervical and lumbar spine
- Responded initially to **Tramadol SR** 50 mg nocte
 - Improved pain on 100mg bd **8/10 to 2/10**



Mrs PS

- 12 months later pain increased back to **8/10**
 - Increased use of Mersyndol
- **Increased Tramadol SR to 200 mg bd**
 - Constipation – Movicol
- Changed to **Buprenorphine (Sovenor)**
 - Increased pain despite increasing patch to 20 mcg weekly – **8/10**
- **Targin 10/5 mg bd increased to 20/10 bd**
 - Pain improved **8/10 – 2/10**
 - No constipation
- Back to work as OT

Pain is the Most Common Treatable Symptom of Cancer





Mr RW

- 80 years old
- Diagnosed with **prostate cancer** 6 years ago
- Treated with radical radiotherapy with satisfactory results
- 2 years ago, increased prostate specific antigen
 - Hormone treatment
- History of **renal impairment** and **cardiac failure**
- Developed bone pain in several different sites
 - Pain levels generally **8-9/10**
- Bone scan shows **multiple bony metastases**



Analgesia for Bone Pain

- **NSAID**
 - Good for bone pain, but this patient's age and cardiac failure may preclude use
- **Paracetamol**
 - Probable central action, good for superficial pain but may not provide sufficient relief
- **Opioid**
 - Effective, manageable risks and easily titrated
 - Morphine has traditionally been the preferred agent for cancer pain
 - But morphine is far from ideal:
 - Oral bioavailability is highly variable
 - Pharmacologically active metabolites (morphine-6-glucuronide)



ALTERNATIVES to MORPHINE

- Oxycodone
 - Available in short and long-acting formulations
 - Quick onset of action
 - No significant active metabolites
- Fentanyl
 - Transdermal fentanyl is a good analgesic choice for patients with stable and infrequent episodes of breakthrough pain
- Methadone
 - Useful if pain is poorly controlled with standard opioids, but is difficult to titrate



PROGRESS

- Commenced **Targin 5/2.5mg twice a day**
- Regular Paracetamol 1000mg qid
 - No improvement in pain, but well tolerated
- **Targin increased to 10/5mg twice a day**
 - Pain improved from 8-9/10 to 6/10
- **Targin increased to 20/10mg twice a day**
 - Pain improved further to 3/10
 - Sleeping better
 - Walking longer distances
- **Targin increased to 40/20mg twice a day**
 - Virtually pain free 0-1/10
 - **No problems with constipation**



SUMMARY

- 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 OIC^{3–5}
- When administered orally, naloxone undergoes extensive first-pass metabolism resulting in negligible (<2%) systemic bioavailability^{6,7}
- TARGIN® tablets offer a specific mode of action in **PAIN MANAGEMENT** to help prevent OIC⁶



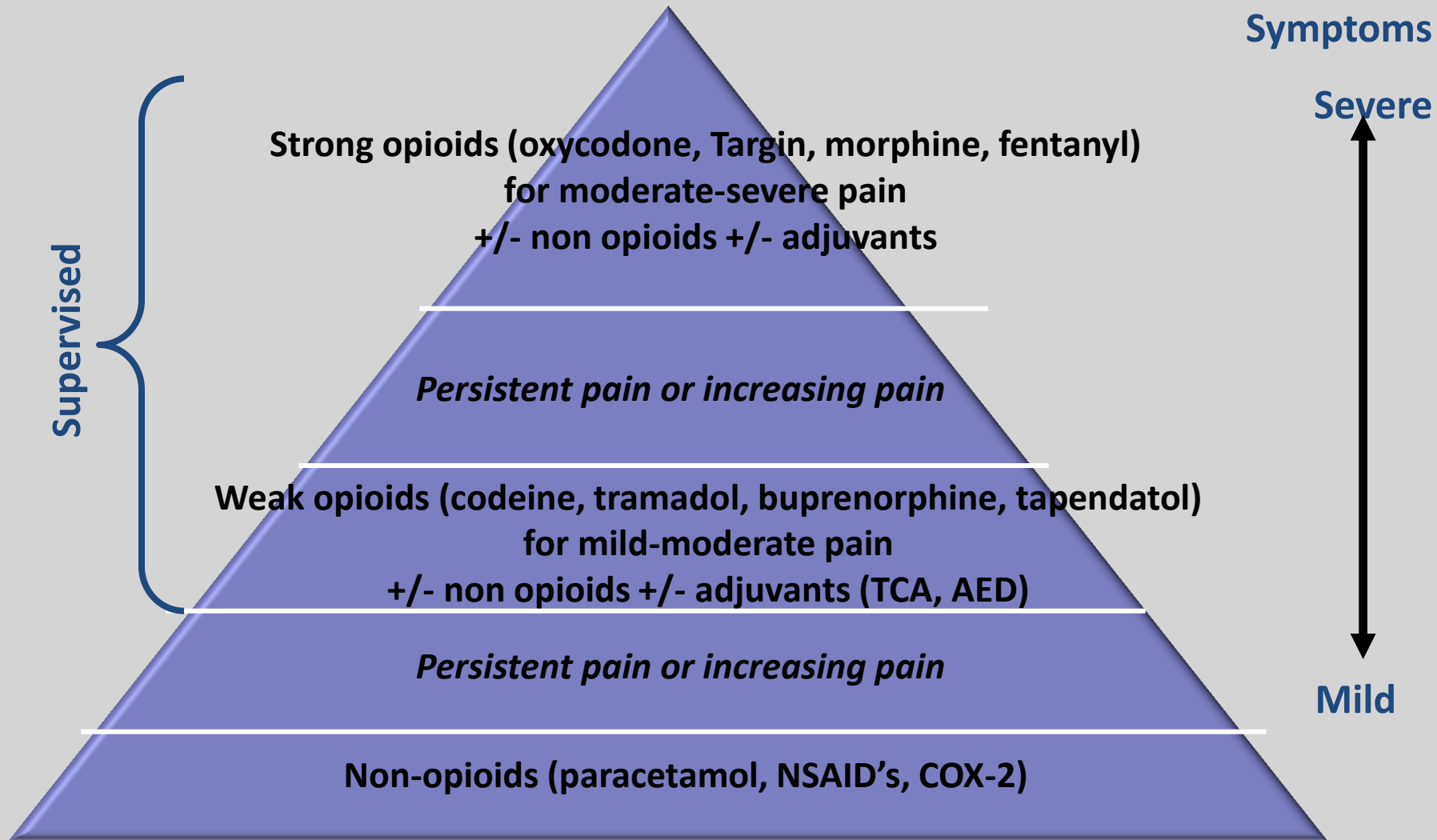
TARGIN[®] TABLETS

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.

WHO ANALGESIC LADDER (GENERALLY FOR NOCICEPTIVE PAIN)



THANK YOU





TARGIN® TABLETS

SAFETY PROFILE and GI TOLERABILITY

- Common side effects are typical of those expected with other strong opioids and include:¹

Nausea	Constipation	Dry mouth	Dizziness
Vomiting	Diarrhoea	Pruritus	Headache

GI TOLERABILITY

- Fewer GI side effects such as constipation, nausea, vomiting, abdominal pain compared with oxycodone CR administered alone^{2,3}
- Diarrhoea may be a possible effect of naloxone, especially at the beginning of treatment, but tends to be transient¹

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



TARGIN® TABLETS

SAFETY PROFILE

OPIOID WITHDRAWAL

- When taken orally, the naloxone component in TARGIN® tablets is unlikely to result in a clinically relevant systemic effect due to naloxone's pronounced first-pass metabolism and low oral bioavailability (<3%)¹

ABUSE

- If abused parenterally or intranasally by individuals dependent on opioid agonists, TARGIN® tablets are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone¹

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



PRESCRIBING CONSIDERATIONS IN CHRONIC NON-CANCER PAIN

| UNIVERSAL PRECAUTIONS IN PAIN MEDICINE¹⁻¹¹

As with all opioid analgesics, the following universal precautions must be applied when considering initiating TARGIN[®] tablets in chronic non-cancer pain patients

- Undertake a comprehensive personal and family risk assessment of past and current substance and alcohol abuse¹⁻⁴
- All other conservative treatment options, including the non-pharmacological, must have been tried and failed before considering a trial of a strong opioid. Opioids should not be used in isolation but as part of a multimodal pain management plan^{1,2,5,6}
- Set clear treatment goals and consider a written or verbal treatment agreement or contract for initiation, continuation and termination of treatment^{1,3,7}
- Initiate an opioid trial of 4 to 6 weeks for first-time patients⁸⁻¹⁰
- If longer-term pain treatment is anticipated, regularly assess the 4+2As of pain medicine^{3,4,7-9,11}
- Prepare a protocol to be implemented for eventual opioid treatment discontinuation^{1,7}

Please refer to the Mundipharma Opioid Prescribing Requirements and participant's workbooks for more information and list of references, available from Mundipharma.



TARGIN® TABLETS

PRODUCT INFORMATION

PBS Information: Restricted benefit. Chronic severe disabling pain not responding to non-narcotic analgesics. Authority required for increased maximum quantities and/or repeats. Refer to PBS schedule for full restricted benefit and authority information.

Before prescribing any product mentioned in this presentation, please refer to Product Information and to State and Federal regulations.

OPIOID THERAPY SHOULD ONLY BE USED AS PART OF A MULTIMODAL PAIN MANAGEMENT PLAN. TARGIN® tablets MINIMUM PRODUCT INFORMATION. INDICATIONS The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation. **CONTRAINDICATIONS** Hypersensitivity to opioids, naloxone and any of the excipients or any situation where opioids are contraindicated; moderate to severe hepatic impairment; severe respiratory depression with hypoxia; elevated carbon dioxide levels in the blood; *cor pulmonale*; cardiac arrhythmias; uncontrolled bronchial asthma; severe chronic obstructive pulmonary disease; non-opioid induced paralytic ileus; pregnancy; lactation; severe CNS depression; increased cerebrospinal or intracranial pressure; brain tumour or head injury (due to the risk of increased intracranial pressure); uncontrolled convulsive disorders; suspected surgical abdomen; delayed gastric emptying; alcoholism; *delirium tremens*; concurrent administration of MAO-inhibitors and for 2 weeks after their cessation. **PRECAUTIONS** Most important hazard of opioid preparations is respiratory depression; occurs most frequently in overdose situations, the elderly, the debilitated and in those suffering from conditions accompanied by hypoxia when even moderate doses may be dangerous. Use with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, chronic obstructive pulmonary disease. Use with caution in hypothyroidism (may need to reduce dose); elderly, infirm or debilitated patients; mild hepatic impairment; renal impairment; severely impaired pulmonary function; opioid dependence; hypotension; hypertension; hypovolaemia; biliary tract disease; pancreatitis; inflammatory bowel disorders; prostatic hypertrophy; adrenocortical insufficiency (Addison's disease); toxic psychosis; myxoedema; opioid-induced paralytic ileus; pre-existing cardiovascular disease; epileptic disorder or predisposition to convulsions; patients on long-term high dose opioid treatment switching to TARGIN® tablets; chronic non-cancer pain; prior history of substance abuse. Not recommended in patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption; for the treatment of withdrawal symptoms; patients with cancer associated with peritoneal carcinomatosis or sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Tolerance and physical dependence tend to develop upon repeated administration. Withdraw gradually. Parenteral or intranasal abuse in opioid-dependent individuals is expected to produce marked withdrawal symptoms. Parenteral venous administration may be fatal. Reduce dosage to 1/3 to 1/2 of the usual dose in elderly patients who are infirm or debilitated and in patients with renal failure or mild hepatic impairment. May impair ability to drive and operate machinery. May produce positive results in sports agency drug testing procedures. Not recommended for immediate pre-operative use and post-operative for 24 hours after surgery. Do not use within 24 hours of cordotomy or other pain-relieving surgery. **INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (antidepressants, sedatives, hypnotics, general anaesthetics, phenothiazines or other tranquilizers, alcohol, other opioids, anti-histamines, anti-emetics, neuroleptics etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed agonist/ antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6). **ADVERSE EFFECTS** Typical of full opioid agonists and tend to reduce with time. Common side effects (incidence $\geq 1\%$) include agitation, anorexia, asthenic conditions, abdominal pain, bronchospasm, chills, constipation, diarrhoea, dizziness, drug withdrawal syndrome, dry mouth, dyspepsia, faintness, fever, gastritis, headache, hepatic enzymes increased, hiccup, hyperhidrosis, hypotension, mood changes, muscle spasms, muscle twitching, myalgia, nausea, orthostatic hypotension, pharyngitis, pruritus, rash, ureteric spasm, urinary abnormalities, urinary tract infection, vertigo, voice alteration, vomiting. **DOSAGE AND ADMINISTRATION** **Must be swallowed whole and not broken, chewed or crushed. Taking broken, chewed or crushed TARGIN® tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone that could be fatal.** Adults: Usual starting dose (opioid-naïve patients, or patients with moderate to severe chronic pain uncontrolled by weaker opioids): one TARGIN® 10/5 mg tablet 12-hourly. Patients with renal or mild hepatic impairment: one TARGIN® 5/2.5 mg tablet 12-hourly. Titrate cautiously (every 1–2 days if necessary) to achieve pain relief. Maximum recommended daily dose: 80/40 mg (TARGIN® 40/20 mg tablets 12-hourly). Children: Not recommended in patients below 12 years of age. **DATE OF FIRST INCLUSION ON ARTG** 12 May 2010. **DATE OF MOST RECENT AMENDMENT** 14 April 2011.



TARGIN®
OXYCODONE/NALOXONE
CONTROLLED RELEASE TABLETS



OxyContin[®] TABLETS

PRODUCT INFORMATION

PBS Information: *OxyContin[®]* tablets.

Restricted Benefit: Chronic severe disabling pain not responding to non-narcotic analgesics.

Authority Required (increased maximum quantities and/or repeats).

Refer to PBS Schedule for full restricted benefit and authority required information.

Before prescribing any product mentioned in this presentation, please refer to
Product Information and to State and Federal regulations.

OxyContin[®] tablets (5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 80mg) MINIMUM PRODUCT INFORMATION. INDICATIONS The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. **CONTRAINDICATIONS** Hypersensitivity to opioids or to any constituents of *OxyContin[®]* tablets, acute respiratory depression, *cor pulmonale*, cardiac arrhythmias, acute asthma or other obstructive airways disease, paralytic ileus, suspected surgical abdomen, severe renal impairment (creatinine clearance <10 mL/min), severe hepatic impairment, delayed gastric emptying, acute alcoholism, brain tumour, increased cerebrospinal or intracranial pressure, head injury (due to risk of raised intracranial pressure), severe CNS depression, convulsive disorders, *delirium tremens*, hypercarbia, concurrent administration of monoamine oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of their use, pregnancy. Not recommended for pre-operative use or for the first 24 hours post-operatively. **PRECAUTIONS** The major risk of opioid excess is respiratory depression. Use with caution in patients with hypothyroidism (may need to reduce dose), debilitated elderly or infirm patients, opioid-dependent patients, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, chronic pulmonary, renal or hepatic disease, myxoedema, following abdominal surgery (discontinue use if paralytic ileus is suspected or occurs), chronic, non-malignant pain, a prior history of substance abuse. Oxycodone should not be used during pregnancy or lactation unless clearly needed (Category C). Tolerance and physical dependence tend to develop upon repeated administration. Withdraw gradually. Parenteral venous injection of the tablet constituents may be fatal. Reduce dosage in elderly, debilitated patients and in patients with renal impairment or hepatic impairment (one-third to one-half of usual starting dose). May affect driving or operating machinery. Do not use in immediate pre-operative period, or within 24 hours of cordotomy or other pain-relieving surgery. **INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquilisers, alcohol, other opioids, neuroleptic drugs, etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed agonist/antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6). **ADVERSE REACTIONS** Typical of full opioid agonists and tend to reduce with time, except constipation. Common side effects (incidence ≥1%) include abdominal pain, abnormal dreams, anxiety, asthenic conditions, bronchospasm, chills, confusional state, constipation, diarrhoea, dizziness, dry mouth, dyspepsia, dyspnoea, faintness, fever, gastritis, headache, hiccup, hyperhidrosis, insomnia, nausea, nervousness, orthostatic hypotension, pharyngitis, pruritus, rash, sedation, somnolence, thinking abnormal, twitching, voice alteration, vomiting. **DOSAGE AND ADMINISTRATION** Must be swallowed whole and not broken, chewed or crushed. Taking broken, chewed or crushed *OxyContin[®]* tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. Alcohol should be avoided while the patient is being treated with *OxyContin[®]* tablets. *Adults, elderly and children over 12 years:* Dose at 12-hourly intervals. Usual starting dose (opioid-naïve patients or patients with severe pain uncontrolled by weaker opioids): one *OxyContin[®]* 10 mg tablet 12-hourly. Patients with renal or hepatic impairment: one *OxyContin[®]* 5 mg tablet 12-hourly. Titrate carefully (as frequently as once a day if necessary) to achieve pain relief. 10 mg oral oxycodone is equivalent to 20 mg oral morphine. *OxyContin[®]* 80 mg tablets should only be used in opioid-tolerant patients. In opioid-naïve patients, this tablet strength may cause fatal respiratory depression. *Children:* Not recommended in patients under 12 years of age. **TGA APPROVAL DATE** 15 July 1999. **DATE OF MOST RECENT AMENDMENT** 17 Feb 2011. ©: OXYCONTIN is a Registered Trademark. Product Information and further information are available from Mundipharma Pty Limited ABN 87 081 322 509, 50 Bridge Street, Sydney, NSW 2000. Phone 1800 188 009.



OxyNorm[®] CAPSULES and LIQUID

PRODUCT INFORMATION

PBS Information: OxyNorm[®] Capsules, OxyNorm[®] Liquid

Restricted Benefit: Severe disabling pain not responding to non-narcotic analgesics.

Authority Required (increased maximum quantities and/or repeats).

Refer to PBS schedule for full restricted benefit and authority required information.

Before prescribing any product mentioned in this presentation, please refer to
Product Information and to State and Federal regulations.

OxyNorm[®] Capsules (5mg, 10mg, 20mg), OxyNorm[®] Liquid (5mg/5mL) MINIMUM PRODUCT INFORMATION. INDICATIONS The management of opioid responsive, moderate to severe pain. **CONTRAINDICATIONS** Hypersensitivity to opioids or constituents of **OxyNorm[®]** capsules or liquid; acute respiratory depression; *cor pulmonale*; cardiac arrhythmias; acute asthma or other obstructive airways disease; paralytic ileus; suspected surgical abdomen; severe renal impairment (creatinine clearance < 10 mL/min); severe hepatic impairment; delayed gastric emptying; acute alcoholism; brain tumour; increased cerebrospinal or intracranial pressure; head injury; severe CNS depression; convulsive disorders; *delirium tremens*; hypercarbia; pregnancy; concurrent administration of monoamine oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use. **PRECAUTIONS** The major risk of opioid excess is respiratory depression. Use with caution in patients with hypothyroidism (may need to reduce dose); opioid dependence; hypotension; hypovolaemia; diseases of the biliary tract; pancreatitis; inflammatory bowel disorders; prostatic hypertrophy; adrenocortical insufficiency; toxic psychosis; chronic pulmonary, renal or hepatic disease; myxoedema; following abdominal surgery; debilitated elderly or infirm patients; non-malignant pain; a prior history of substance abuse. Not recommended in pregnancy (Category C); lactation. As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of oxycodone. There is potential for abuse of the drug and for development of strong psychological dependence. **OxyNorm[®]** capsules or liquid should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential. Withdraw gradually. Discontinue use if paralytic ileus is suspected or occurs. Parenteral venous administration may be fatal. Reduce dosage in elderly, debilitated patients and in patients with renal or hepatic impairment (one-third to one-half of usual starting dose). May affect driving or operating machinery. Do not use 6 hours prior to cordotomy or other pain relieving surgery. **INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (sedatives, hypnotics, general anaesthetics, phenothiazines or other tranquilizers, alcohol, other opioids, neuroleptics etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed opioid agonist/antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6). **ADVERSE REACTIONS** Typical of full opioid agonists and tend to reduce with time, except constipation. Immediate release formulations such as **OxyNorm[®]** capsules or liquid may have a higher incidence of some adverse reactions than controlled release formulations. The most frequently observed side effects with an incidence $\geq 1\%$ include abdominal pain, abnormal dreams, anorexia, anxiety, asthenic conditions, bronchospasm, chills, confusional state, constipation, diarrhoea, dizziness, dry mouth, dyspepsia, dyspnoea, faintness, fever, gastritis, headache, hiccup, hyperhidrosis, increased hepatic enzymes, insomnia, miosis, nausea, nervousness, orthostatic hypotension, pharyngitis, pruritus, rash, sedation, somnolence, thinking abnormal, twitching, vertigo, visual impairment, voice alteration, vomiting. **DOSAGE AND ADMINISTRATION** **OxyNorm[®]** capsules must be swallowed whole and not opened, chewed or crushed. Alcohol should be avoided while the patient is being treated with **OxyNorm[®]** capsules or liquid. **OxyNorm[®]** oral dosage forms are not interchangeable with Endone tablets. *Adults, elderly and children over 18 years:* Dose at 4-6 hourly intervals. Usual starting dose (opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids): 5 mg 4-6 hourly. Titrate carefully (once a day if required) to achieve pain relief. 10 mg oral oxycodone is equivalent to 20 mg oral morphine. Dose conservatively in mild to moderate renal impairment and mild hepatic impairment. Absorption of oxycodone from an oral solution may be significantly increased by food. *Children:* Not recommended in patients under 18 years of age. **TGA APPROVAL DATE** 13 November 2001 **DATE OF MOST RECENT AMENDMENT** Feb 2010. ©: OXYNORM is a Registered Trademark. Product Information and further information are available from Mundipharma Pty Limited ABN 87 081 322 509, 50 Bridge Street, Sydney, NSW 2000. Phone 1800 188 009.