The ROYAL MARSDEN
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Managing constipation in palliative care patients

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NHS

Managing constipation in palliative care patients

1. Constipation in palliative care:
   a complex issue

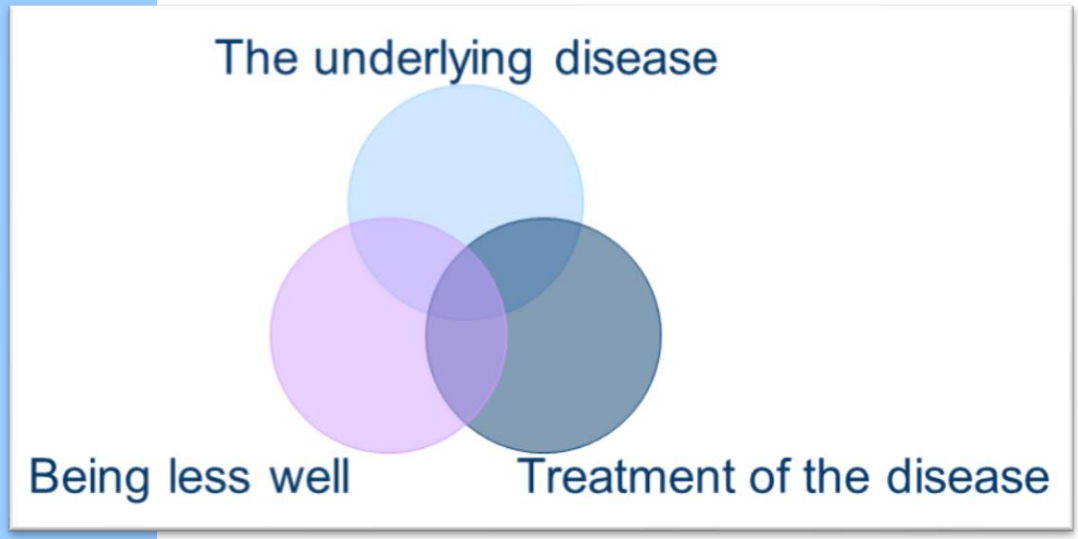
2. Oral laxatives and rectal preparations

3. Non-laxative agents

4. Opioid-induced constipation and PAMORAs

Constipation in palliative care patients: Complex pathophysiology

- A symptom, not usually a primary disorder



Alterations in

- Gut Transit
- Luminal fluid balance

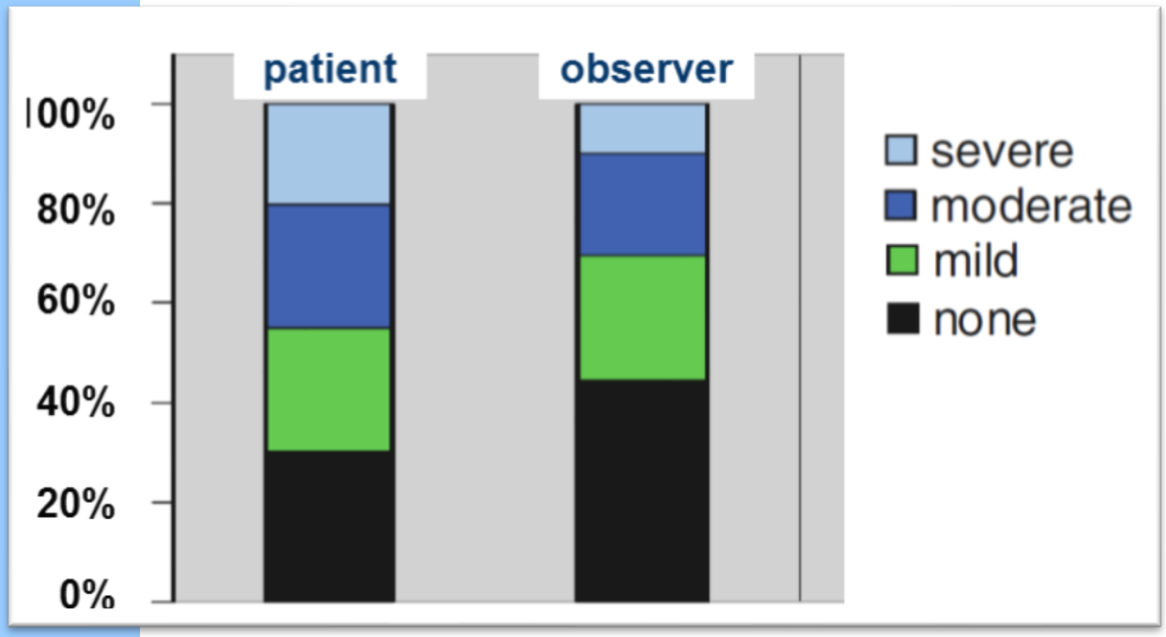
Larkin PJ, Sykes NP et al. Palliat Med 2008
Argoff C 2015 Pain Medicine 16: 2324–37

Constipation in palliative care patients: Complex patients

- **Patients are embarrassed to talk about it**
- Co-morbidities
- Poly pharmacy
- Frail

Larkin PJ, Sykes NP et al. Palliat Med 2008
Sue Gale Michael Sobell House 2007
Argoff C 2015 Pain Medicine 16: 2324–37

Constipation in palliative care patients:
Poor clinician assessment



- No standardised assessment tool
- Subjective versus objective assessment

Constipation means different things to different people

Laugsand et al Supportive Care in Cancer 2011
Argoff C et al. 2015 Pain Medicine 16: 2324–2337

Constipation in palliative care patients: Poor management

Support Care Cancer
DOI 10.1007/s00520-010-1051-2

ORIGINAL ARTICLE

Inadequate symptom control in advanced cancer patients across Europe

Eivor A. Laugsand · Gunnhild Jakobsen · Stein Kaasa · Pål Klepstad

- 70% constipated (N=1344/1938)
- >50% patients on no laxatives in past 24 hours
  - 41% of patients with moderate constipation
  - 27% with severe constipation
- **60% inadequate treatment**

Constipation in palliative care patients: Poor management

Support Care Cancer
DOI 10.1007/s00520-010-1051-2

ORIGINAL ARTICLE

Inadequate symptom control in advanced cancer patients across Europe

Eivor A. Laugsand · Gunnhild Jakobsen · Stein Kaasa ·
Pål Kleps

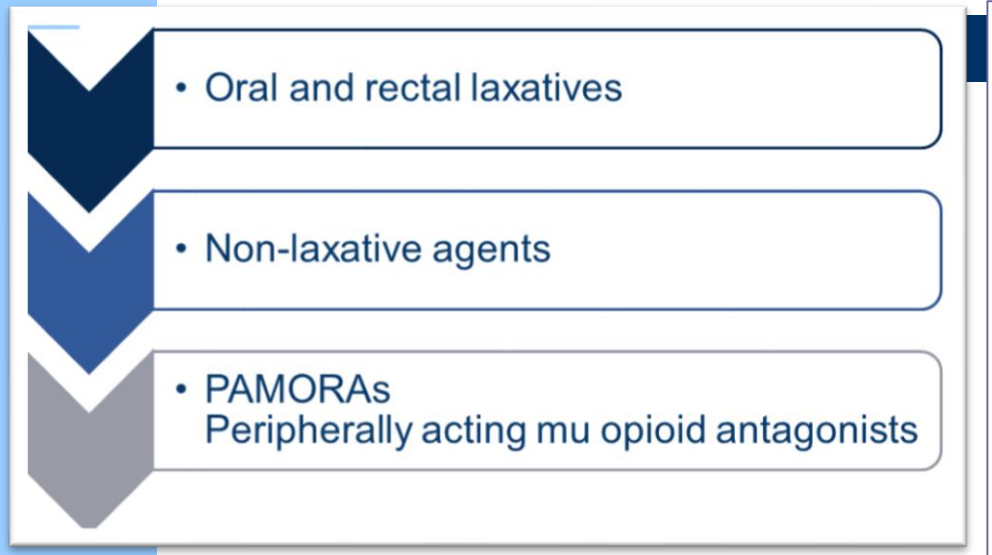
RMH data 2008

N=274 cancer patients taking morphine

63% constipated and inadequately treated

Droney J et al, Support Care Cancer 2008

Pharmacological management of constipation in palliative care



Aim of treatment:

- Regular soft bowel motion without difficulty
- Minimal medication burden
- Minimal drug side-effects / interactions
- Rational prescribing

Constipation assessment: Key to rational pharmacological management

Constipation is "the passage of (small), hard faeces, infrequently and with difficulty"

European Consensus Group on Constipation in Palliative Care
Larkin P et al, Palliative Medicine 2008 Oct; 22 (7): 796-807

Constipation assessment: Key to rational pharmacological management

Constipation is "the passage of (small), hard faeces, infrequently and with difficulty"

- Stool frequency
- Stool consistency
- Straining

→

Compared to usual pattern

Life-long constipation history

Subjective and objective assessment

"Do you think you are constipated?"

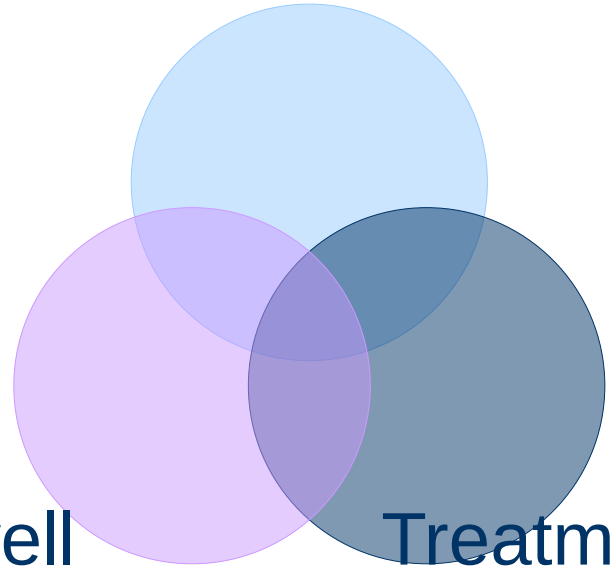
Constipation in palliative care: Workup

Rectal examination

The disease itself

Blood tests

Ca, renal, TFTs



Imaging

Endoscopy

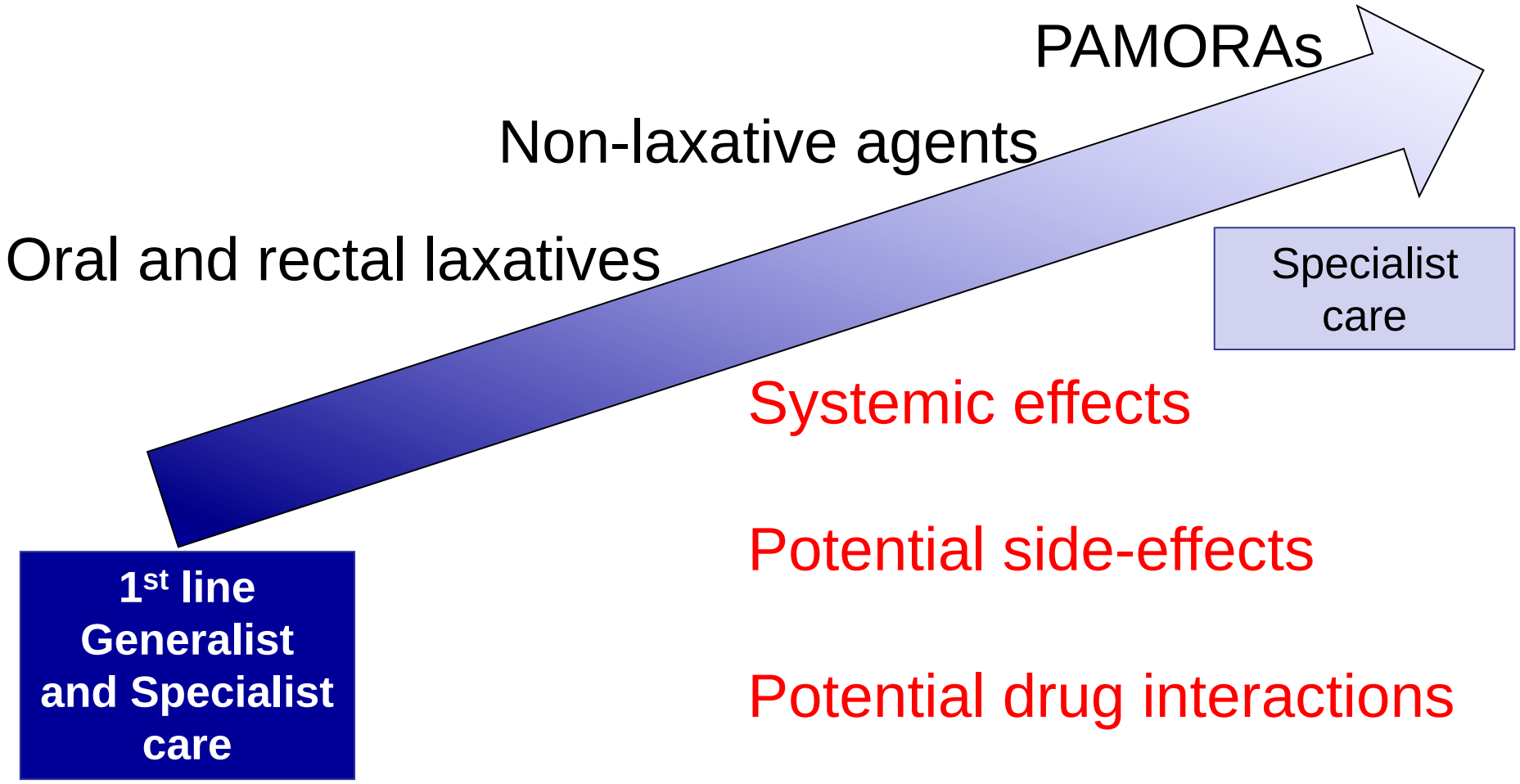
Surgical opinion

Being less well

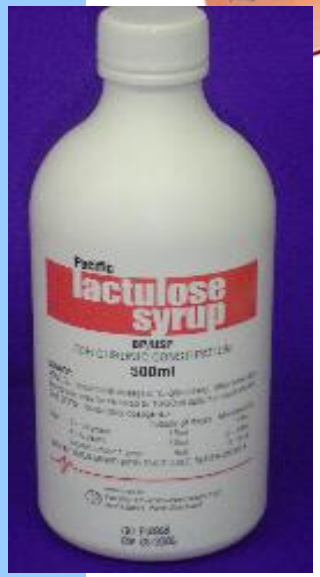
Treatment of the disease

Abdominal examination

Pharmacological management of constipation in palliative care



What laxative is best?



Cochrane Library

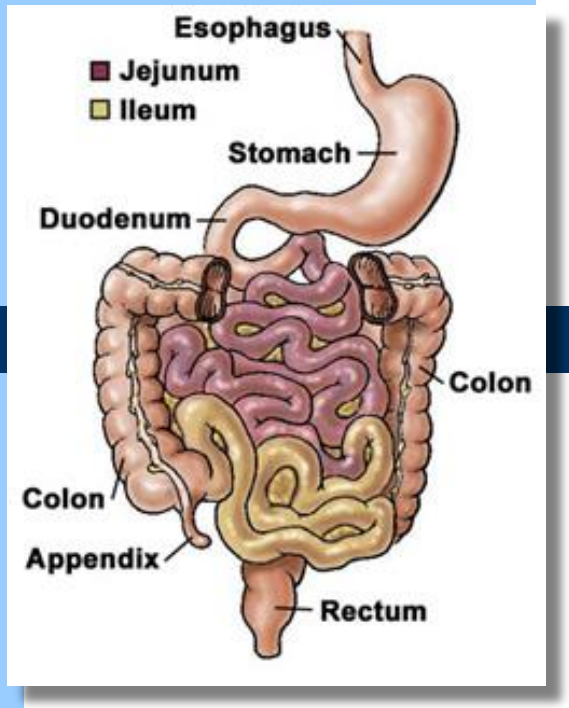
Cochrane Database of Systematic Reviews

2015
5 studies
370 participants

Laxatives for the management of constipation in people receiving palliative care (Review)

Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P

Lack of evidence regarding whether individual laxatives are more effective than others or cause fewer adverse effects



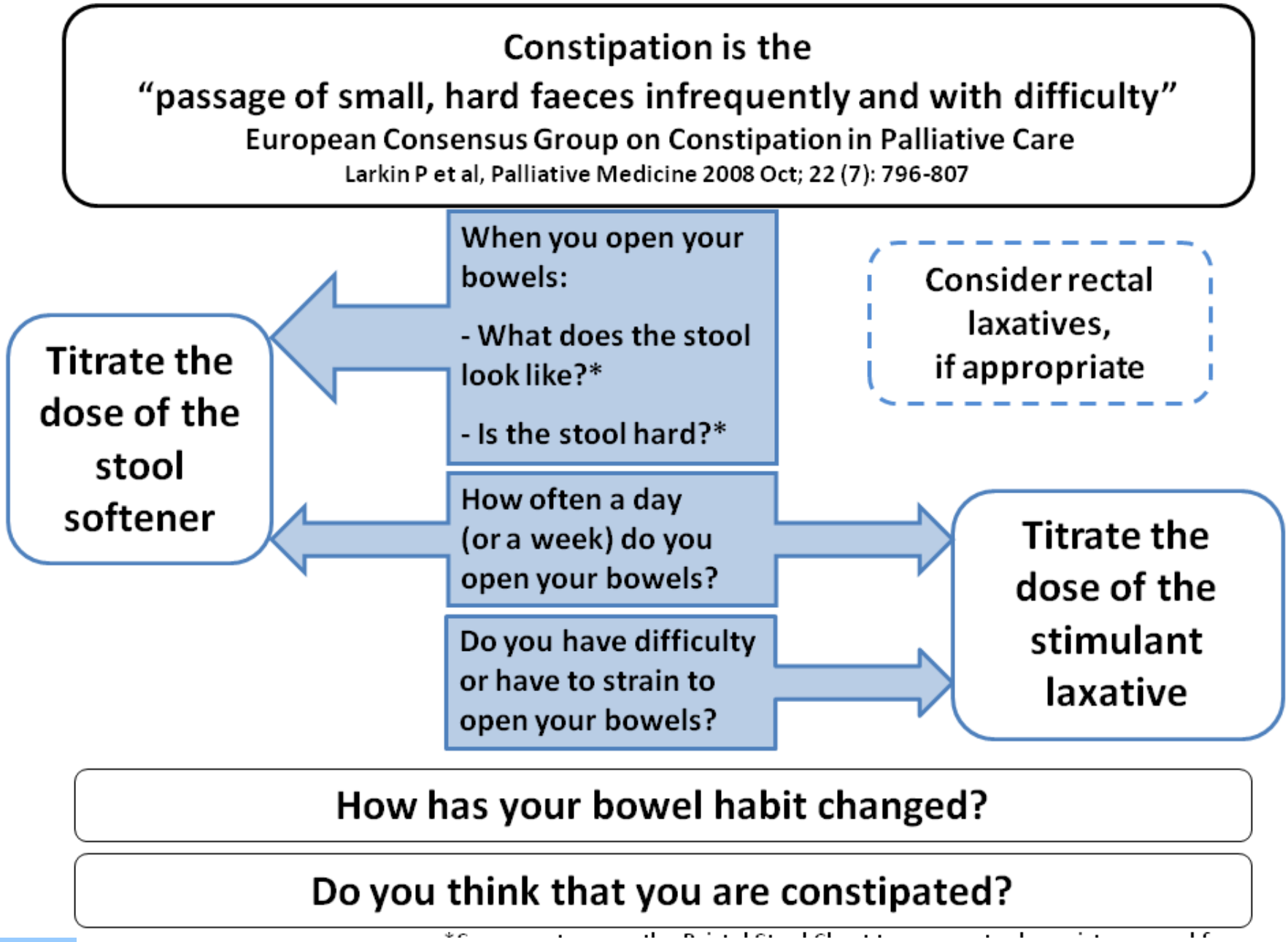
Aim of laxative therapy

Restore faecal water	Improve rectal evacuation
Reduce gut transit time	Improve faecal consistency
Increase faecal water	Promote peristalsis
Increase ability of faeces to retain water	

Oral laxatives

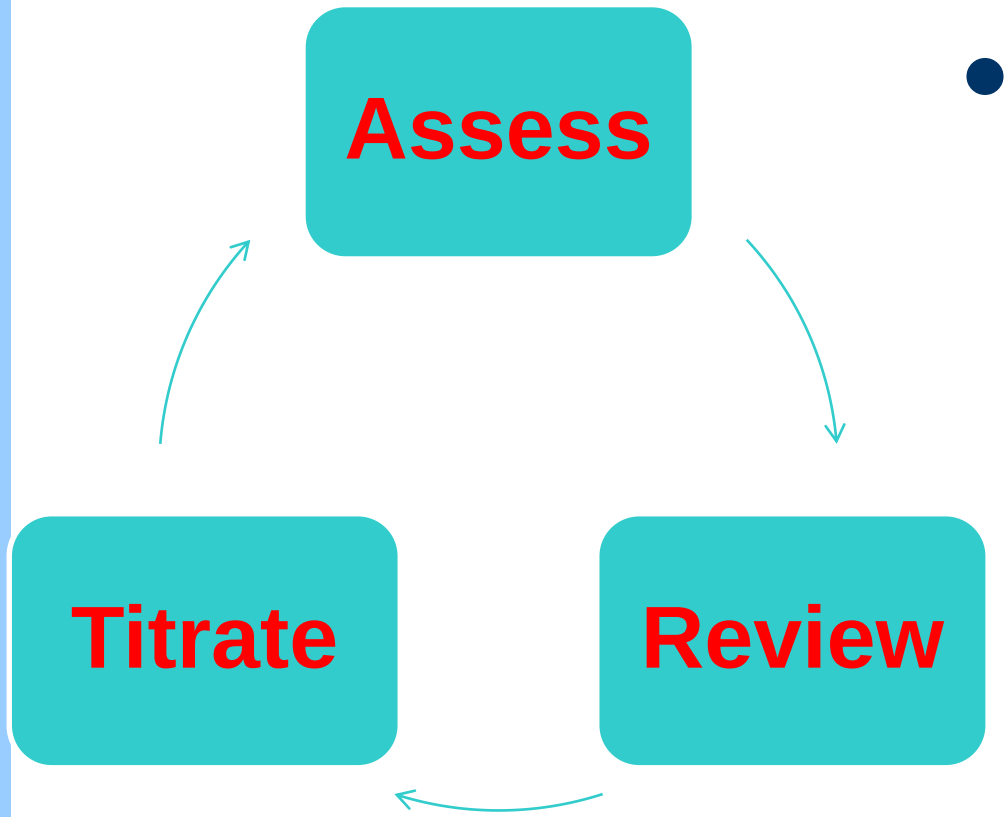
Predominantly softening	• liquid paraffin • bulk-forming (ispaghula) • macrogols • docusate sodium • lactulose
Predominantly stimulating	• senna • danthron • bisacodyl

Emmanuel A, Therapeutic Advances in Gastroenterology 2011
Palliative Care Formulary 5



Droney J and Cowap J Eur J Pall Care 2012

Oral laxatives for constipation



- Individualised management plan
  - Patient experience
  - Patient preference

Fallon M Pall Med 1999
Bennett M Pall Med 2003

Faecal softeners

- **Surface wetters**
  - **Docusate sodium**
  - Detergent
  - Water and fats penetrate hard dry faeces

- **Osmotic laxatives**
  - **Lactulose**
  - **Macrogol**
  - **Magnesium salts**
- Water is retained in gut lumen
- Not absorbed
- Cochrane 2011: macrogols > lactulose
  - (higher volumes)
- Magnesium: unpredictable effect

Lee-Robichaud H et al. Lactulose versus polyethylene glycol for chronic constipation. Cochrane reviews 2011

Lubricants

- Coat stool surface
  - Easier to evacuate
- Arachis oil
  - Peanut allergy

Liquid paraffin:

- Anal seepage/irritation
- Absorption with granulomatous formation
  - Higher risk with concommitant use of docusate sodium
- Pneumonia if aspirated
- Impaired absorption of fat soluble vitamins (A,D,E,K)

Stimulant laxatives

- Direct contact with submucosal and myenteric plexus
- (Increase water secretion into lumen)
- Dantron burns
- Dantron discoloration of urine
- Abdominal cramps

Senna

Sodium picosulfate

Bisacodyl

Dantron

Bowel preparations

- **Klean-Prep**: Macrogol 3350 (osmotic laxative)
- **Citramag**: Magnesium citrate (osmotic laxative)
- **Picolax**: Sodium picosulphate (stimulant) + magnesium citrate (osmotic laxative)

Stimulant + softener?

- Common advice
- Minimise adverse effects (cramping)
- **Lack of evidence regarding efficacy**

- Not unreasonable to start with stimulant alone

Twycross R et al. Stimulant laxatives and opioid induced constipation, JPSM 2012

Tarumi et al, JPSM 2012

The North West London Hospitals NHS
NHS Trust

Colonoscopy bowel preparation Instructions for Senna tablets and two packets of Citramag or Picolax

If you are having a AM procedure (up to 11am) please follow below:

- **At 2pm** take the 10 senna tablets and drink plenty of water.
- **At 5pm** dissolve the contents of **one** packet of Picolax or Citramag in 200mls (eight fluid ozs) **of hot water in a large wide mouthed measuring jug**, as the mixture may fizz over when the powder is added. Allow to cool for at least half an hour before pouring into a suitable glass and drink.

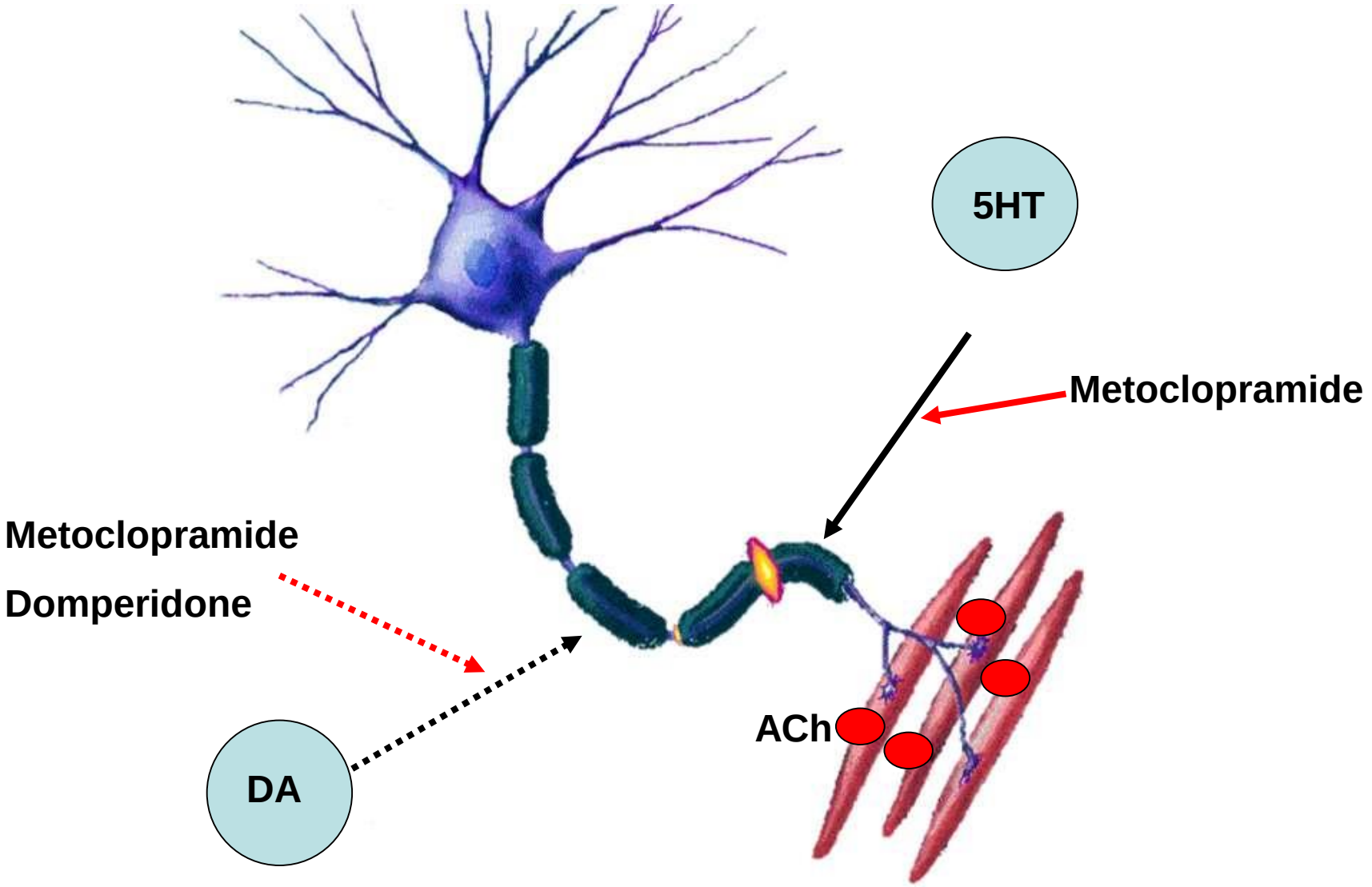
- **At 7pm** dissolve the second packet of Picolax or Citramag in 200mls (eight fluid ozs) **of hot water in a large wide mouthed measuring jug**, as the mixture may fizz over when the powder is added. Allow to cool for at least half an hour before pouring into a suitable glass and drink.
- During the rest of the evening, drink at least one and a half litres of water.

Non-laxative agents for constipation

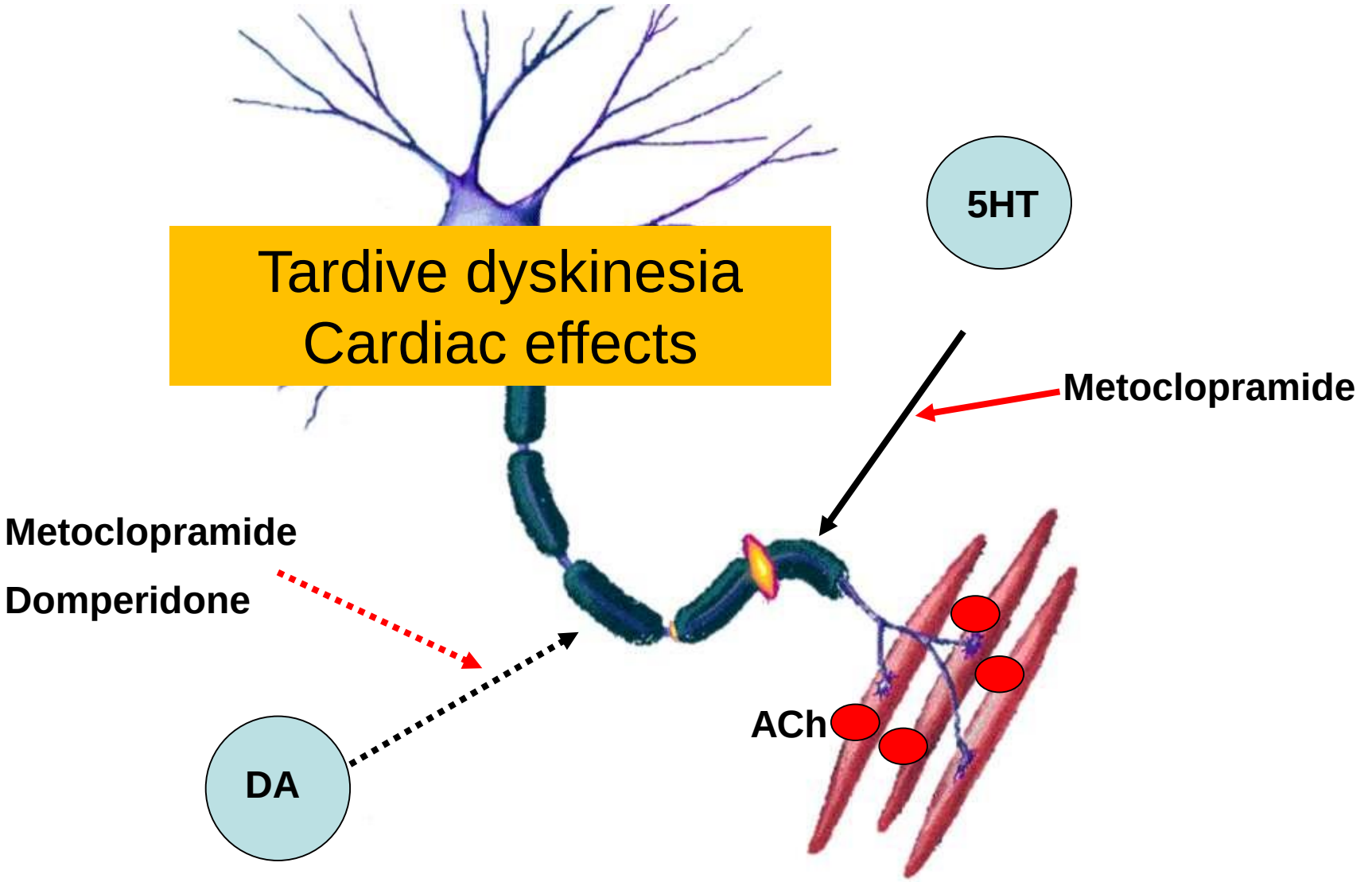
- Prokinetics (metoclopramide, domperidone)

- Pro-motility: erythromycin
- Prostones: Lubiprostone
- 5HT-agonists: Prucalopride

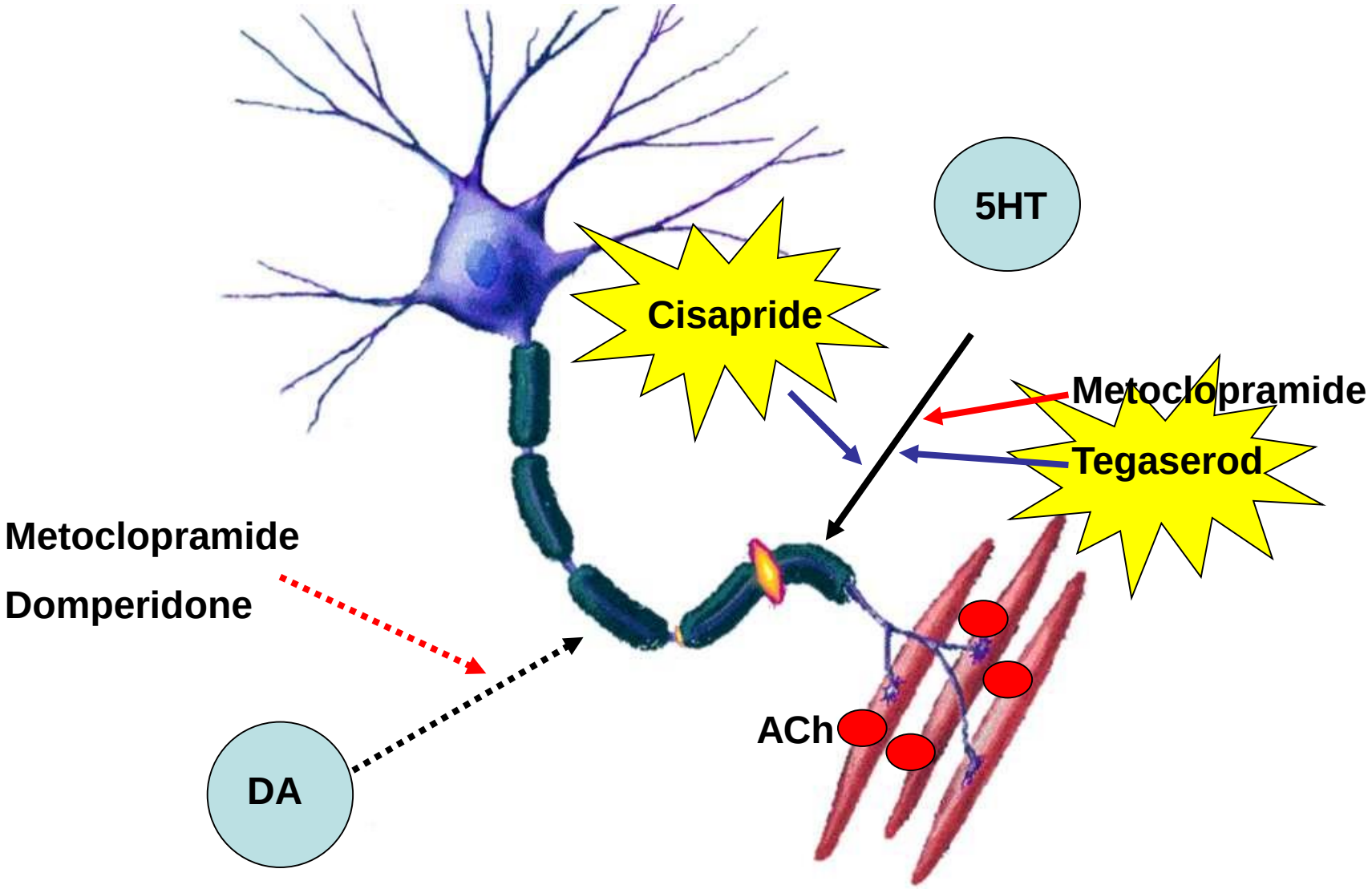
Prokinetic agents



Prokinetic agents



Prokinetic agents



Other agents in the pipeline

- **Amidotrizoate**
  - Water-soluble contrast medium
  - Wetting agent
  - Prospective study (N=99): 44% BM within 24hours

Mercadante et al JPSM 2010

- **Lubiprostone**
  - prostaglandin activates chloride channel to stimulate gut lumen secretion
  - counteracts the anti-secretory effects of morphine

Sun X Dig Dis Sci 2011

- **Prucalopride**
  - selective 5-HT4 receptor agonist - stimulates colonic motility

NICE 2010 Prucalopride for the treatment of chronic constipation in women

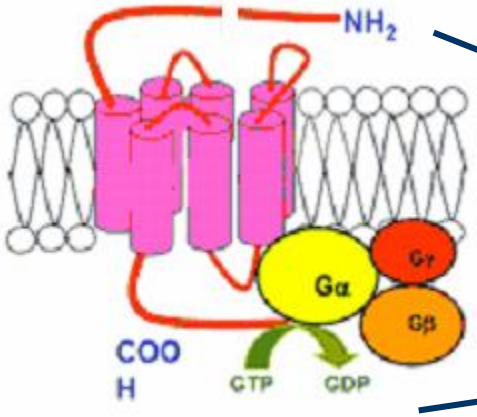
Opioid induced constipation

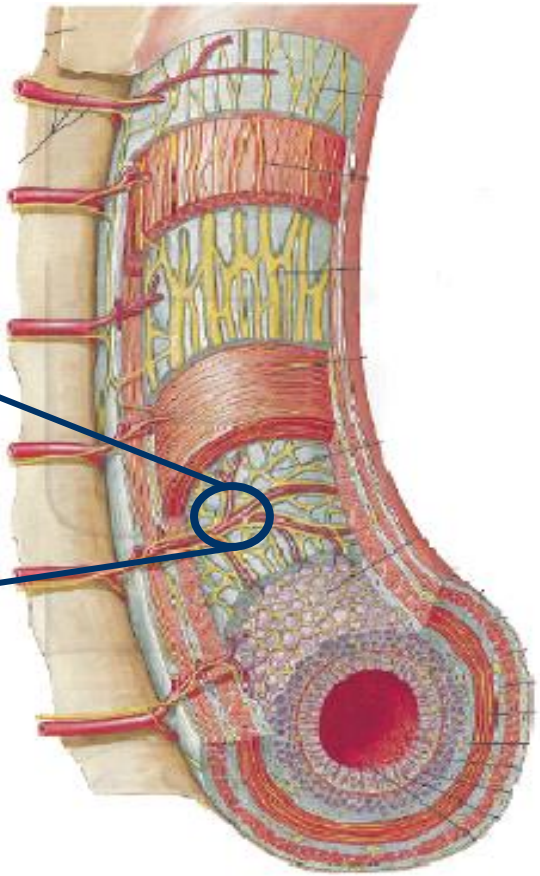
PAMORAs

(Peripherally acting mu-opioid receptor antagonists)

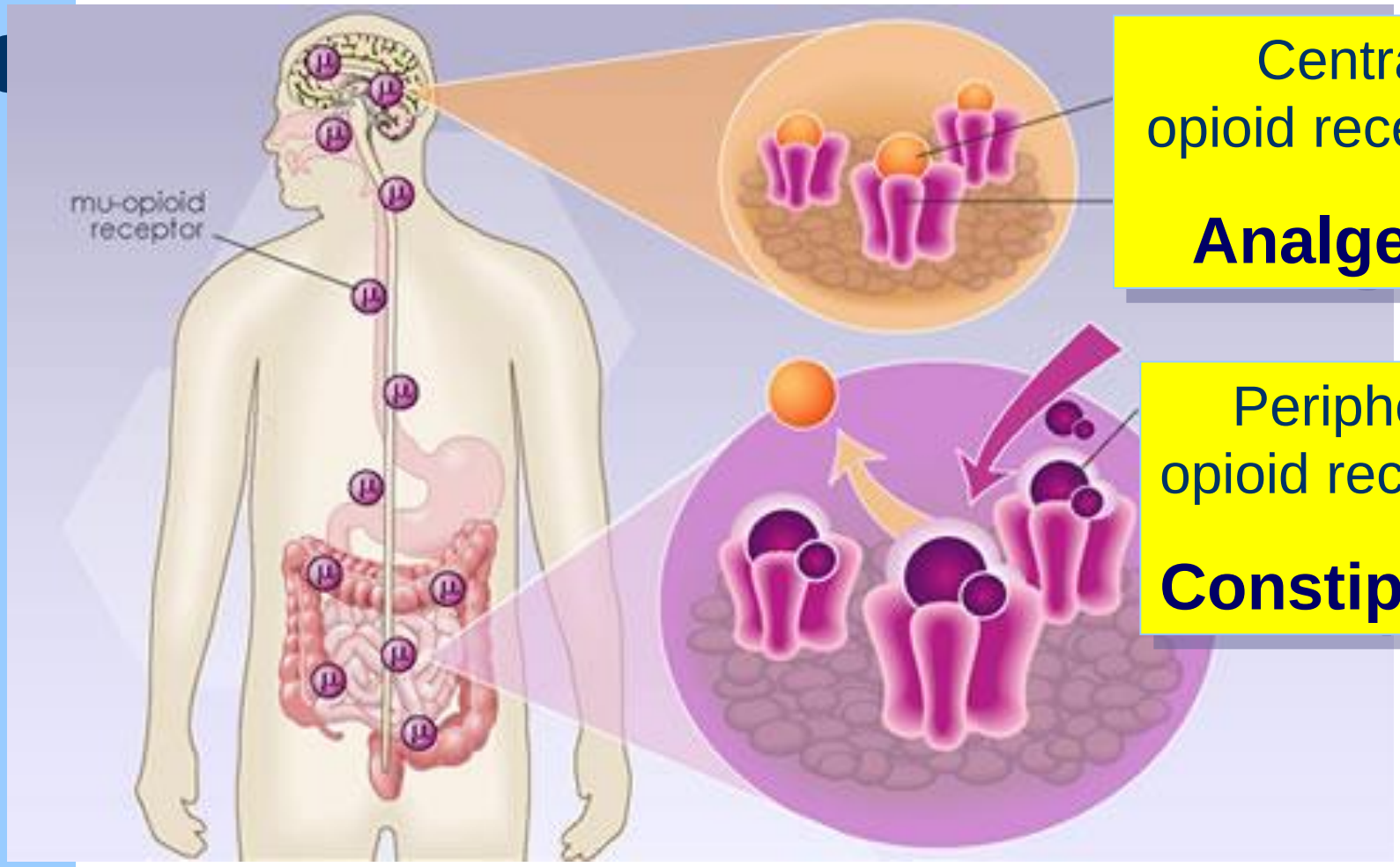
Physiological role of endogenous opioids

Opioid receptors





Opioid-induced constipation



Mechanism of opioid-induced constipation

↓gut transit

- ↓Neural activity
- ↓Propulsion

↓fluid in gut lumen

- Enhance fluid absorption
- Anti-secretory effect

↓ACh

Ideal treatment for OIC

- Acts directly at opioid receptors along GIT
- Does not cross blood brain barrier
- Does not interfere with opioid analgesia
- Cheap
- Few side-effects

PAMORAs

Peripherally acting mu-opioid receptor antagonists

PAMORAs

- Oral naloxone
- Methylnatrexone
- Targinact
- Naloxegol
- Alvimopan

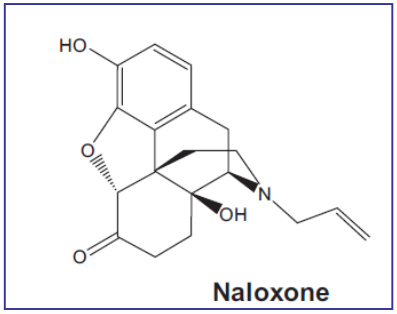
- Naldemedine

Reduce gut transit time in healthy volunteers

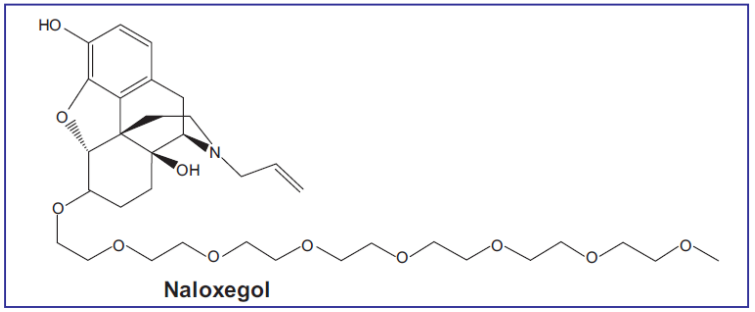
No comparisons with adequate laxative regimen

Action not restricted to Gastro-intestinal tract

Study design and rationale



Naloxone



Naloxegol

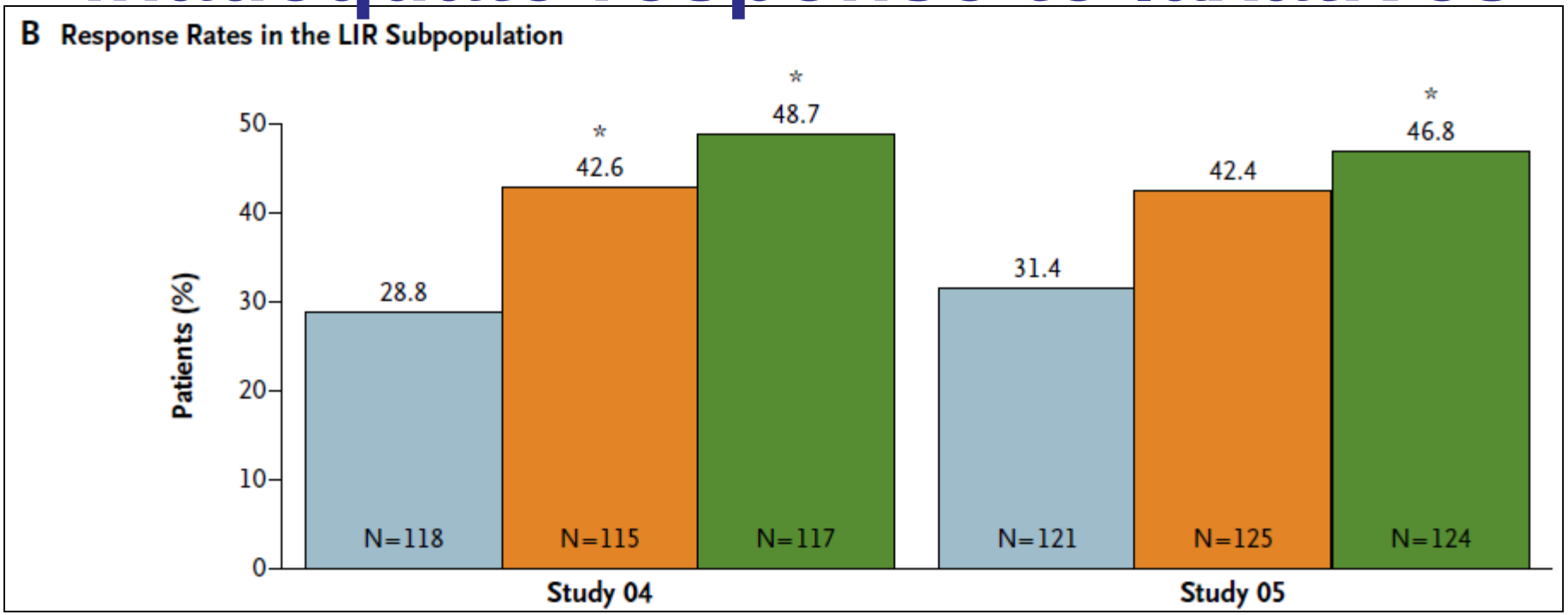
Oral naloxone

- High first pass hepatic clearance
  - 2% into systemic circulation
- Increasing doses may result in increased bioavailability)
  - Crosses BBB
  - Risk of opioid withdrawal

Naloxegol

- PEGylated naloxone
- Limits BBB crossing

Naloxegol in patients with inadequate response to laxatives



Patients taking medication from ≥ 1 class of laxative for at least 4 days within 2 weeks before screening with moderate- severe symptoms

Chey W NEJM 2014

"Inadequate response to laxatives" or Inadequate laxative regimen?

Naloxegol in palliative care: Potential for drug interactions

Table 1 – Selected P-glycoprotein (ABCB1) substrates, inhibitors, and inducers

Substrates	Inhibitors	Inducers
Amitriptyline	Amitriptyline	Amitriptyline
Carbamazepine	Carbamazepine	Nefazodone (chronic)
Chlorpromazine	Chlorpromazine	Phenothiazines
Citalopram	Desipramine	St John's wort
Doxepin	Disulfiram	Trazodone
Morphine	Fluoxetine	
Nortriptyline	Fluphenazine	
Olanzapine	Fluvoxamine	
Paroxetine	Haloperidol	
Phenobarbital	Imipramine	
Quetiapine	Methadone	
Risperidone	Nefazodone (acute)	
Sertraline	Paroxetine	
Topiramate	Midazolam	
Trimipramine	Paliperidone	
Venlafaxine	Phenothiazines	
	Propranolol	
	Risperidone	
	Sertraline	
	Thioridazine	
	Trifluoperazine	
	Trimipramine	
	Vitamin E	
	Grapefruit juice	
	Garlic	
	Green tea	
	Seville orange juice	

Adapted from Oesterheld J.[9]

Substrate for P-glycoprotein transporter

CYP3A4 metabolism

Increased bioavailability with food

Table 2. CYP3A4 Substrates, Inducers, and Inhibitors

CYP3A4 Substrates	Nevirapine	Atazanavir	Indinavir
Carbamazepine	Omeprazole	Chloramphenicol	Isoniazid
Ethosuximide	Oxcarbazepine	Cimetidine	Itraconazole
Felbamate	Phenytoin	Clarithromycin	Ketoconazole
Phenobarbital	Primidone	Cyclosporine	Nefazodone
Phenytoin	Rifabutin	Darunavir	Nelfinavir
Tiagabine	Rifampin	Dasatinib	Nifedipine
Zonisamide	St. John's wort	Delavirdine	Quinolones
		Diltiazem	Ritonavir
CYP3A4 Inducers	**CYP3A4 Inhibitors**	Erythromycin	Saquinavir
Carbamazepine	Allopurinol	Fluconazole	Tamoxifen
Corticosteroids	Amiodarone	Fluoxetine	Valproic acid
Efavirenz	Amprenavir	Grapefruit juice	Verapamil
Modafinil	Aprepitant	Imatinib	

Targinact

- Fixed dose PR oxycodone : PR naloxone
- Trialled in chronic pain and cancer pain

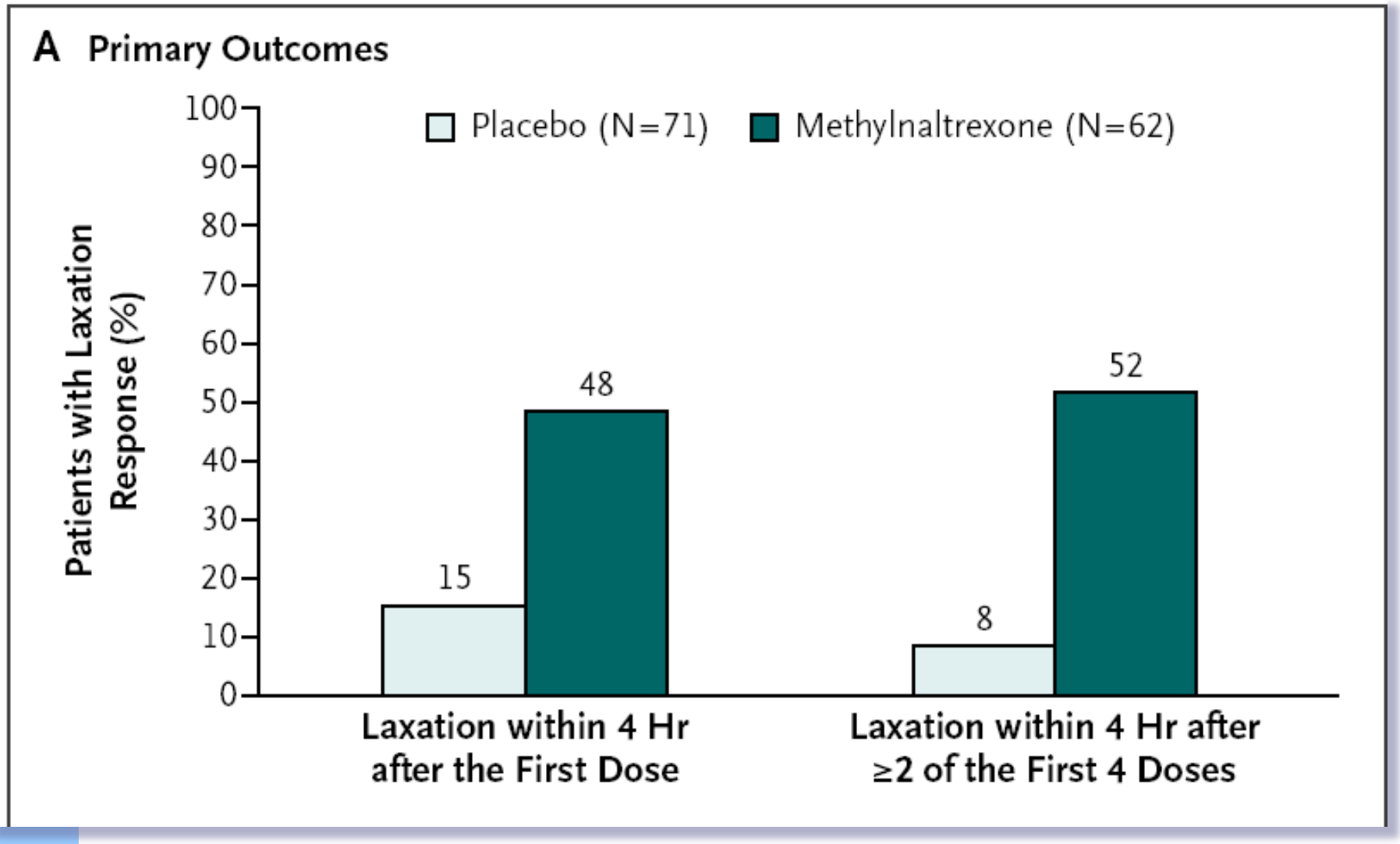
- Trial data: maximum oxycodone dose 120mg/24 hours
  - Need for safety monitoring at higher doses

– Case studies of opioid withdrawal / ineffectiveness

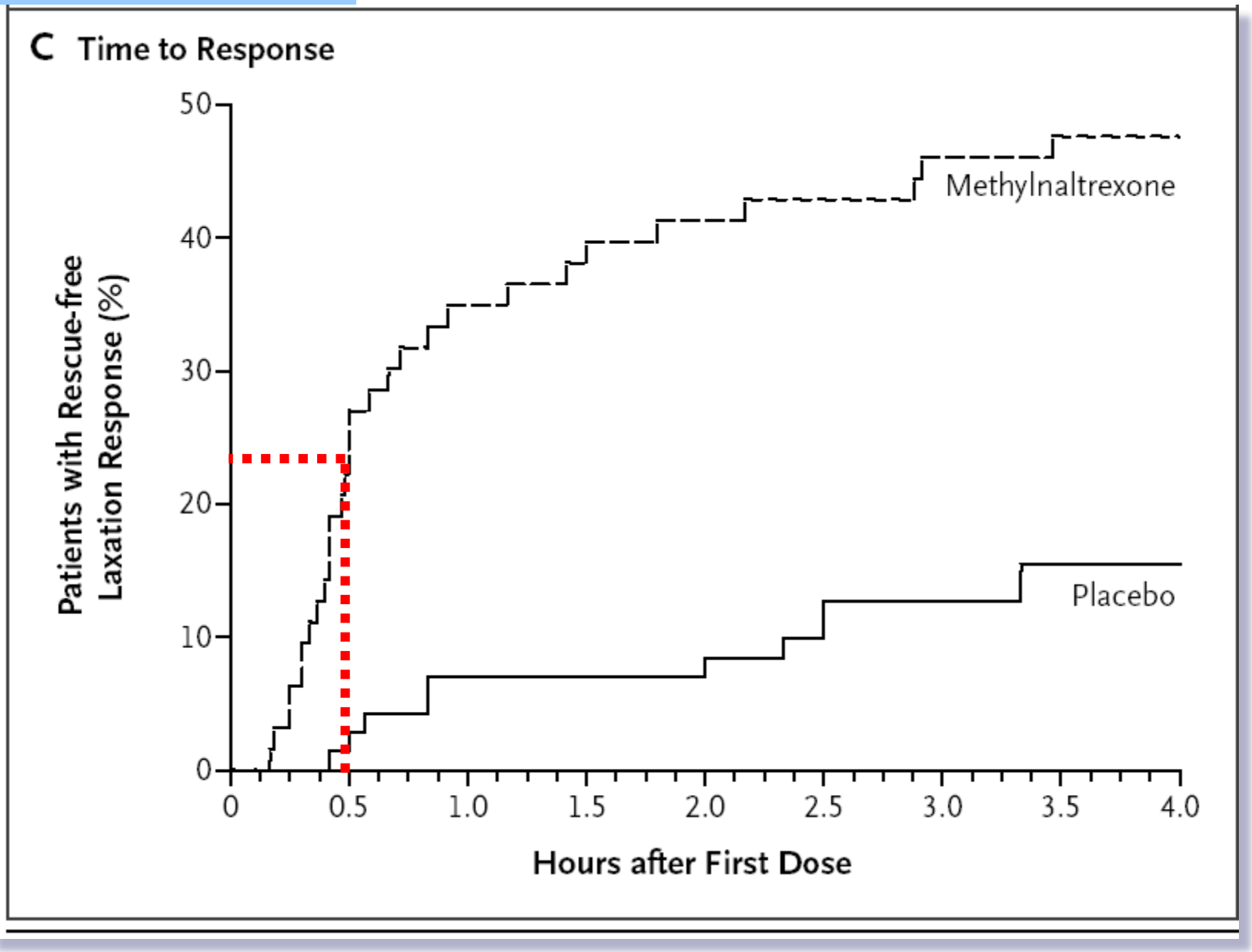
Mercadante S et al. Support Care Cancer 2011
Kang JH. JPSM 2013

MethylNaltrexone SC/IV

- Oral bioavailiability < 1%
- Does not cross blood-brain barrier
- Non-selective opioid antagonist



Thomas J et al. Methylnaltrexone for Opioid-induced constipation in advanced illness. NEJM May 2008


C Time to Response
Patients with Rescue-free Laxation Response (%)
50
40
30
20
10
0
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Hours after First Dose
Methylnaltrexone
Placebo

PAMORAs: possible uses in palliative care

- Patient unable to swallow oral medications
- Patient “in extremis” with constipation
- If adequately titrated conventional laxatives have failed
- Long term safety unclear

Mc Nicol ED. Cochrane 2008
Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Candy B. Cochrane 2011

Constipation: pharmacological management in palliative care

- Complex symptom
- Assessment and workup is key to optimising medical management
- Individualised management plans essential
- Titrate laxatives to response