

**CONGRESSO  
NAZIONALE SIGG**

**GLI ANZIANI:  
LE RADICI DA PRESERVARE**

ROMA 28 novembre  
01 dicembre 2018 Auditorium della Farnesina, Roma



# ***Il problema della stipsi nel paziente anziano oncologico in trattamento con oppiacei***

***Massimo Bellini***

***Resp. Sez. Fisiopatologia Digestiva  
U. O. Gastroenterologia Universitaria  
(Dir. prof. S. Marchi)***



## Table 1. Functional Gastrointestinal Disorders

### C. Functional bowel disorders

- C1. Irritable bowel syndrome
- C2. Functional constipation
- C3. Functional diarrhea
- C4. Functional abdominal bloating/distension
- C5. Unspecified functional bowel disorders
- C6. Opioid-induced constipation

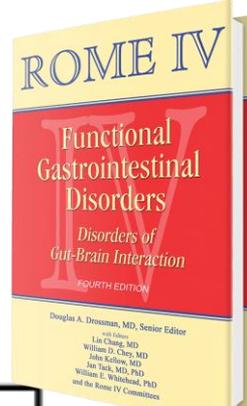
***“As opiate use has increased....”***

It has not be considered a distinct FGID, but rather should be categorized as an opioid-induced adverse effect

- Bloating
- Nausea
- Vomiting
- Diarrhea/constipation

### C6. Diagnostic Criteria for Opioid-Induced Constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following:
  - a. Straining during more than one-fourth (25%) of defecations
  - b. Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
  - c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
  - d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
  - e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
  - f. Fewer than three spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives



2016

Opioid-induced constipation is probably the most common adverse effect of these agents and can significantly impact the quality of life *(Webster, 2015)*

OIC ranges from **21% to 90%** depending on the type of opiate and length of usage. *(Sizar O, 2018)*

The prevalence of OIC is **41%** in patients with chronic **non cancer** pain taking opioids, *(Kalso E, 2004)*

In **cancer** patients taking opioids for pain, the incidence of constipation was approximately **94%** *(Sykes NP, 1998)*

Prevalence rates relate to the **instrument** used (520 pts.):

-59% according to the Bowel Function Index (BFI), *(Abramowitz L, 2013)*

-67% using the KESS score,

-86% according to the clinician's opinion

OIC is associated with significantly increased healthcare and economic burden in cancer patients; early and ongoing recognition and management of OIC are unmet needs in this population. *(Fine PG, 2018)*

# Impact of opioid-induced constipation on healthcare resource utilization and costs for cancer pain patients receiving continuous opioid therapy

Perry G. Fine<sup>1</sup> · Yen-Wen Chen<sup>2</sup> · Eric Wittbrodt<sup>3</sup> · Catherine Datto<sup>3</sup>

Supportive Care in Cancer

<https://doi.org/10.1007/s00520-018-4366-z>

**Table 3** Healthcare resource utilization during the 12 months postindex

Resource utilization	Cohort 1: opioid users with constipation (n = 1369)	Cohort 2: opioid users without constipation (n = 1369)	Odds ratios or differences in means (95% CI) <sup>a</sup>	P value
<b>All-cause resource utilization</b>				
<b>Inpatient hospitalizations</b>				
1 hospitalization, n (%)	993 (72.5)	707 (51.6)	2.47 (2.11–2.90)	< 0.0001
Number of hospitalizations, mean (SD) <sup>b</sup>	2.4 (1.7)	1.8 (1.3)	0.55 (0.39–0.72)	< 0.0001
Length of stay, days, mean (SD) <sup>b</sup>	14.9 (16.4)	10.8 (14.6)	4.03 (2.71–5.48)	< 0.0001
<b>Emergency room visits</b>				
1 visit, n (%)	547 (40.0)	398 (29.1)	1.62 (1.39–1.90)	< 0.0001
Number of visits, mean (SD) <sup>b</sup>	1.8 (1.3)	1.5 (1.2)	0.31 (0.13–0.50)	< 0.0001
<b>Outpatient and office visits</b>				
1 visit, n (%)				1.0000
Number of visits, mean (SD) <sup>b</sup>				< 0.0001
<b>Skilled nursing facility stays</b>				
1 stay, n (%)				0.0089
<b>Hospice care</b>				
1 hospice intervention, n (%)				< 0.0001
<b>Patients who died during follow-up, n</b>				
				< 0.0001
<b>Pain-related resource utilization</b>				
<b>Inpatient hospitalizations</b>				
1 visit, n (%)	536 (39.2)	315 (23.0)	2.15 (1.82–2.54)	< 0.0001
Number of visits, mean (SD) <sup>b</sup>	1.5 (0.8)	1.3 (0.8)	0.16 (–0.01–0.34)	0.0583
Length of stay, days, mean (SD) <sup>b</sup>	12.3 (15.8)	11.0 (15.8)	1.32 (–0.24–3.10)	0.1018
<b>Emergency room visits</b>				
1 visit, n (%)	205 (15.0)	141 (10.3)	1.53 (1.22–1.93)	0.0002
Number of visits, mean (SD) <sup>b</sup>	1.2 (0.6)	1.3 (0.8)	–0.05 (–0.26–0.21)	0.6771
<b>Outpatient and office visits</b>				
1 visit, n (%)	1023 (74.7)	921 (67.3)	1.44 (1.22–1.70)	< 0.0001
Number of visits, mean (SD) <sup>b</sup>	10.5 (16.7)	9.4 (12.2)	1.14 (0.19–2.18)	0.0181
<b>Hospice care</b>				
1 hospice intervention, n (%)	1 (0.1)	3 (0.2)	0.33 (0.04–3.20)	0.6247

- Hospitalizations (number and length)
- Emergency room visits
- Outpatients visits
- Pain related resource utilization

No difference in rates of OIC between morphine, hydrocodone, and hydromorphone (*Kalso E, 2004*).



OIC prevalence depends on the type of opiate and length of usage. (*Sizar O, 2018*)

Patients who developed OIC were more likely to be older, female, and unemployed (*Sizar O, 2018*)

Prevalence of OIC = 1:1.25 male:female (*Muller Lissner S, 2016*)

The longer patients take opioids, the intensity of constipation increases. About 50% have a history of constipation which worsened with the opioid.

OIC can also occur at both low and high doses and can present at any time once the treatment begins



Careful clinical history when prescribing opioids and also prescribe a laxative at the same time. This helps prevent constipation and distressful GI tract symptoms (*Sizar O, 2018*).

Three classes of opioid receptors in the GI enteric nervous system ( $\mu$ ,  $\kappa$  and  $\delta$ ): they are all G-protein coupled receptors that reduce **acetylcholine** release.

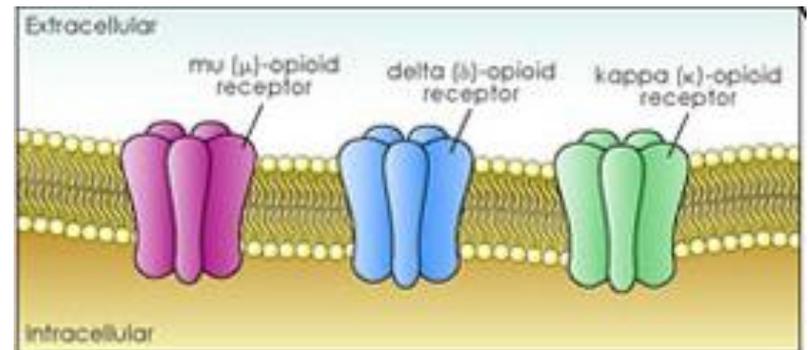
OIC develops when GI tract opioid receptors are activated by oral opioids leading to:

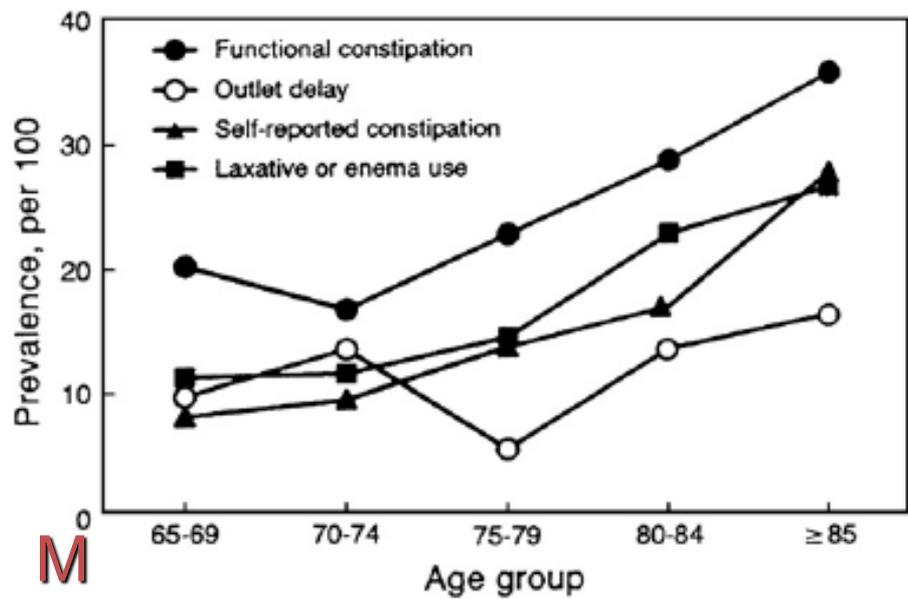
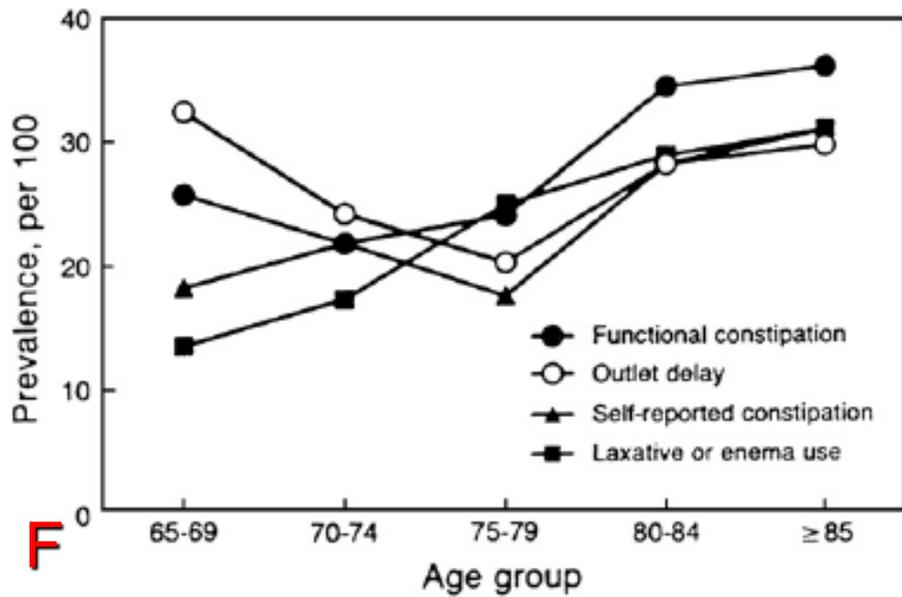
-a decrease in **propulsive activity** ( $\mu$ );

-an increase in **non propulsive contractions** ( $\mu$ ;  $\delta$ );

-a decrease in pancreatic, biliary, and gastric **secretions** ( $\mu$ ,  $\delta$ );

-an increase in **anal tone** ( $\mu$ ,  $\delta$ ).





# Restrizione idrica / disidratazione nell'anziano

***-Iatrogena***  
*epatopatie*  
*cardiopatie*  
*nefropatie*  
*vasculopatie*

*.....*

***-Volontaria***  
*-patologie urologiche*  
*-patologie neurologiche e/o*  
*-psichiatriche*

***-Pazienti istituzionalizzati***

# Farmaci e tossici

**Analgesici e Oppiacei**  
**Anestetici**  
**Antiacidi (Ca e Al)**  
**Anticolinergici**  
**Anticonvulsivanti**  
**Antidepressivi (TCA)**  
**Antiparkinsoniani**  
**Antistaminici**  
**Bario**  
**Bismuto**

**Ca-antagonisti**  
**Beta-bloccanti**  
**Colestiramina**  
**Calcio**  
**Diuretici**  
**Ferro**  
**I-MAO**  
**Lassativi (abuso)**  
**Metalli pesanti**  
**Sucralfato**

.....



# Consensus statement AIGO/SICCR diagnosis and treatment of chronic constipation and obstructed defecation (Part II: Treatment)

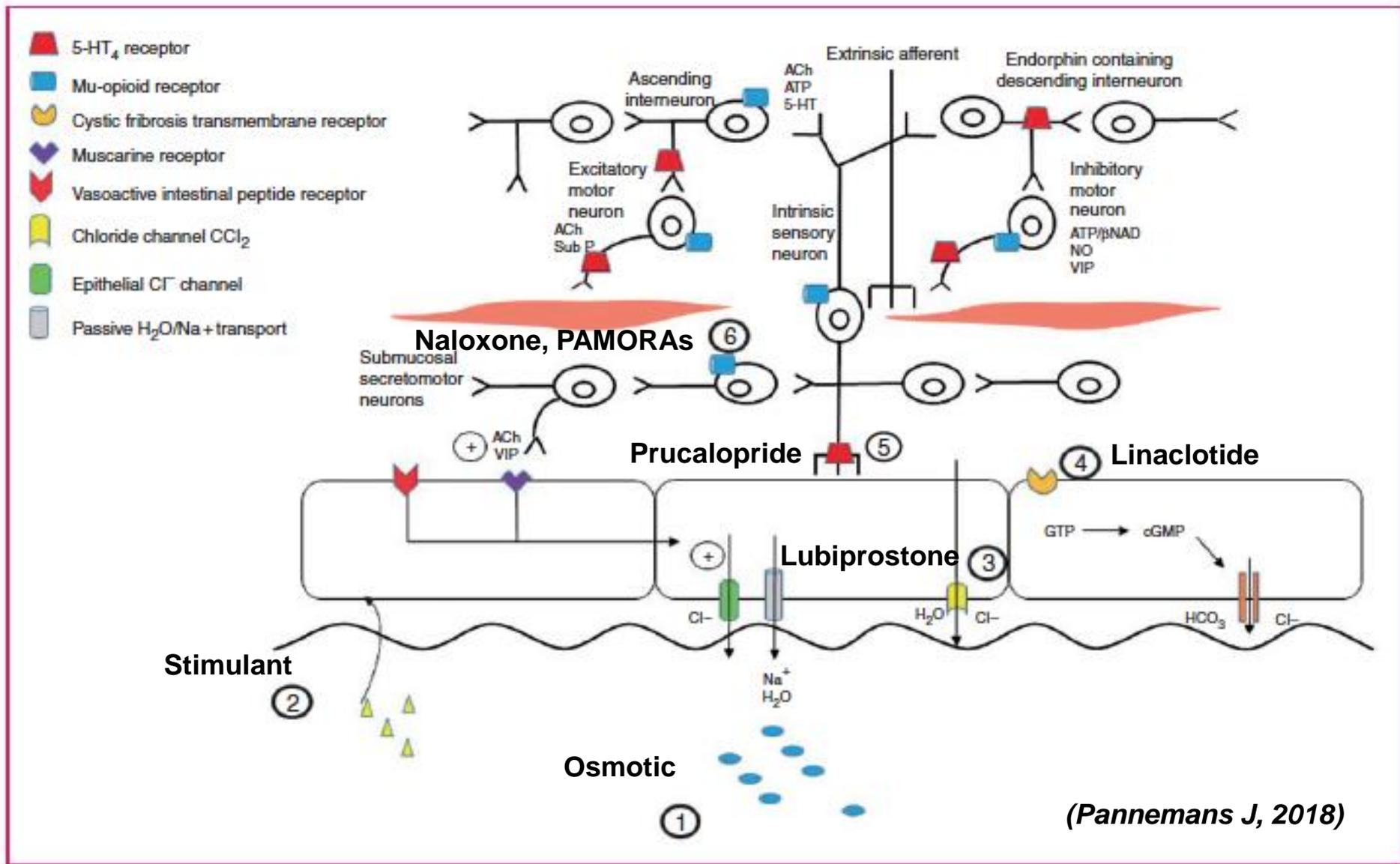
*World J Gastroenterol* 2012 September 28; 18(36): 4994-5013

Antonio Bove, Massimo Bellini, Edda Battaglia, Renato Bocchini, Dario Gambaccini, Vincenzo Bove, Filippo Pucciani, Donato Francesco Altomare, Giuseppe Dodi, Guido Sciaudone, Ezio Falletto, Vittorio Piloni



**Table 2** Levels of evidence and grades of recommendation of medical treatment in chronic constipation

	Level of evidence	Grade of recommendation
<b>Life style</b>		
Physical exercise	V	C
Toilet training	V	C
Increased fluid intake	V	C
<b>Bulking laxatives</b>		
Insoluble fibre	III	C
Soluble fibre: Psyllium	II	B
<b>Osmotic laxatives</b>		
Lactulose	II	B
Sorbitol	V	C
Magnesium hydroxide/magnesium salts	V	C
Polyethylene glycol	I	A
<b>Stimulant laxatives</b>		
Sodium picosulfate, bisacodyl	I	B
Senna, aloe, cascara	V	C
<b>Softening laxatives</b>		
Docusate	V	C
<b>Serotonergic enterokinetics</b>		
Tegaserod	I	A <sup>1</sup>
Prucalopride	I	A
<b>Prosecretory agents</b>		
Lubiprostone	I	B <sup>2</sup>
Linaclotide	I	B <sup>3</sup>
<b>Gastrointestinal <math>\mu</math>-opioid antagonists</b>		
Methylnaltrexone	I (no effect)	A (not used)
Alvimopan	I (no effect)	A (not used) <sup>2</sup>
<b>Probiotics</b>	V	C
<b>Colchicine</b>	III	C
<b>Procedures to empty the rectum-sigma</b>		
Peristeen <sup>®</sup>	V	C

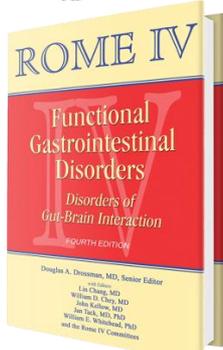


**Figure 1.** Summary figure of receptors and modes of action of agents used to treat opioid-induced constipation. (1): Osmotic laxatives. (2) Stimulant laxatives. (3) Lubiprostone. (4). Linaclotide. (5). Prucalopride. (6). Naloxone and peripherally acting mu-opioid receptor antagonists. 5-HT<sub>4</sub>: 5-hydroxytryptamine receptor 4; Ach: acetylcholine; ATP: adenosine triphosphate; cGMP: cyclic guanosine monophosphate; GTP: guanosine triphosphate; NDP: nucleoside diphosphate kinase; Sub P: substance P; VIP: vasoactive intestinal polypeptide.

**Table 7** Suggested therapies requested by the gastroenterologist after their visit

THERAPIES	878 pts.(%)	IBS-C (%)	FC (%)	NRC (%)	p-value <sup>1</sup>
Life style recommendations	722 (82.2)	84.7	81.8	74.1	ns
Dietary suggestions	749 (85.3)	85.5	85.8	79.6	ns

The initial treatment of OIC is similar in many ways to the treatment of Functional Constipation.



2016

Prucalopride	126 (14.4)	13.1	15.7	7.4	ns
Suppositories/micro-enemas	198 (22.6)	23.6	21.3	29.6	ns

THERAPIES	878 pts.(%)	IBS-C (%)	FC (%)	NRC (%)
Life style recommendations	722 (82.2)	84.7	81.8	74.1
Dietary suggestions	749 (85.3)	85.5	85.8	79.6
Fibre supplements	489 (55.7)	60.7	53.2	55.6

Pelvic floor rehabilitation	169 (19.3)	14.6	22.2 °	13.0	<0.05
Sacral neurostimulation	3 (0.3)	//	0.4	1.9	ns
Anorectal surgery	20 (2.3)	1.5	2.7	1.9	ns
Colectomy	1 (0.1)	//	//	//	
Other	18 (2.1)	2.2			

IBS-C irritable bowel syndrome with constipation, FC functional constipation, NRC patients do not a <sup>1</sup>p values are referred to the differences between IBS-C, FC and NRC groups, in particular # p < 0.0001 vs IBS-C and NRC; \* p < 0.0001 vs FC; \*\* p < 0.05 vs NRC; ^ p < 0.005 vs FC; § p < 0.05 v

Chronic constipation diagnosis and treatment evaluation: the "CHRO.CO.DI.T.E." study  
 BMC Gastroenterology (2017) 17:11



# I BUONI CONSIGLI.....

- Attività fisica
- Adeguato apporto idrico e calorico
- Non saltare il pasto (colazione, cena...)
- Non rimandare la defecazione...
- Dedicare tempo alla defecazione...
- Non ponzare inutilmente e a lungo (5 min.)
- Ritualizzare la defecazione (pasto, risveglio)



↓

*Risposta colica al pasto*  
*Riflesso ortocolico*

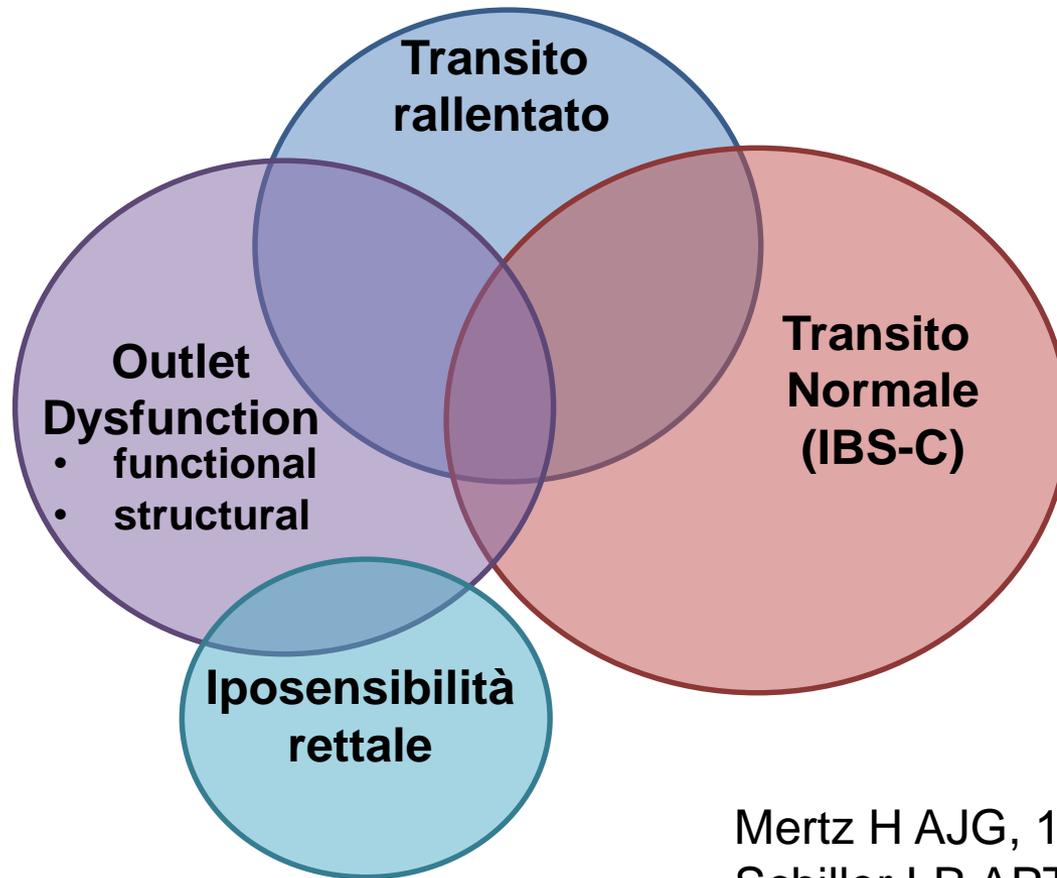
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**Movimenti di massa**

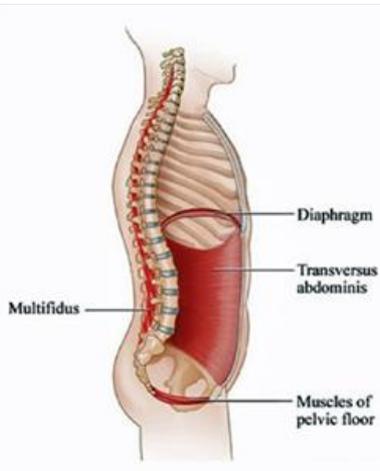
# Stipsi Cronica Primitiva



P.R. Renoir  
"Gli Ombrelli"  
1881-1886



Mertz H AJG, 1999;  
Schiller LR APT, 2001;  
Lembo NEJM, 2003;



Low efficiency of abdominal “press”

- Diafragma
- Paravertebral muscles
- Abdominal muscles



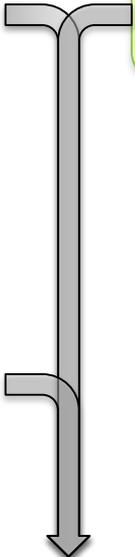
Inadequate defecatory propulsion

Lack of forces addressed toward the small basin > decreased or absent intrarectal pressure

Dyssynergic defecation

Contraction or inadequate relaxation of pelvic floor muscles

Rectal sensation (hyposensitivity)



Functional Defecation Disorder



# RIABILITAZIONE PELVI-PERINEALE



➔ **MULTIMODALE**

- Chinesiterapia
- Biofeedback
- Elettrostimolazione,
- Riabilitazione Volumetrica

➔ **DIECI SEDUTE (1 ora x 2/settimana)**

➔ **ESERCIZI DOMICILIARI**



• Anamnesi + Es. obiettivo

• colonscopia/clisma opaco/colonsc. virtuale

• Es. ematoch. (routine + RSO+ TSH)

(> 50 aa. o sintomi allarme)

## CORREZIONE DIETA E STILE DI VITA

MACROGOL, lattulosio

- Colonscopia/Clisma op./Colon.virtuale

(se non già eseguiti)

- Rx Transito colico

- Defecografia (Defeco-RMN, Ecodefecografia)

- Manometria anorettale

Salini, Lubrificanti,  
Stimolanti/Emollienti,  
Clismi, Supposte

↓ (+)

Procinetici  
Prosecretori



The conventional laxatives bisacodyl, sodium picosulfate, macrogol and senna: the first choice to treat OIC.

(Muller Lissner S, 2016)

The new laxatives, linaclotide, lubiprostone and prucalopride, may also be effective in selected patients

# Prucalopride succinate for the treatment of constipation: an update

Gabrio Bassotti<sup>a</sup>, Dario Gambaccini<sup>b</sup> and Massimo Bellini<sup>b</sup>

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY, 2016

Prucalopride is a highly selective 5-HT<sub>4</sub> receptor agonist with proven efficacy for the treatment of constipation in adults, even in elderly people (1 mg/day), whereas the clinical efficacy in children is still debatable

Table 5. Phase III trials published as full papers.

Trial	Subjects	Primary end points Average $\geq 3$ SCBM/week (%)			Main secondary end points average $\uparrow \geq 1$ SCBM/week			Secondary end points average increase BM/week			Symptoms $\Delta$ PAC-SYM at week 12			QoL $\downarrow \geq 1$ on PAC-QoL at week 12 (%)		
		Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg
Camilleri et al.	620	12.0	30.9***	28.4***	25.8	47.3***	46.6***	0.8	2.2***	2.5***	-0.4	-0.6***	-0.7***	24.1	44.9***	48.7***
Quigley et al.	641	12.1	23.9**	23.5**	27.5	42.6***	46.6***	0.8	1.5***	1.5***	-0.5	-0.8***	-0.6*	26.0	43.5***	44.4***
Tack et al.	713	9.6	19.5**	23.6***	20.9	38.1***	44.1***	0.5	1.2***	1.4***	-0.4	-0.7***	-0.7***	16.4	33.5***	29.4***
Yiannakou Y et al.	374	17.7	37.9 <sup>†c</sup>	-	12.2 <sup>p=0.0002</sup>	27.7	-	-	-	-	-0.6	-0.8 (ns)	-	32.7	40.2	-
Kem et al.	501	10.3	33.3***	-	27.4	57.2***	-	1.1	2.4***	-	-0.4	-0.7***	-	16.2	36.9***	-

Modified from Camilleri and Deiteren [26].

\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, <sup>†c</sup>p < 0.005.

BM: bowel movements; PAC-QoL: Patient Assessment of Constipation Quality of Life; PAC-SYM: Patient Assessment of Constipation Symptoms; QoL: quality of life; SCBM: spontaneous complete bowel movement.

PRU increases **stool frequency**, reduces **constipation-related symptoms** and improves **quality of life**.

PRU is safe and well tolerated: no cardiac side effects, no effect on QT  
Headache and diarrhea are the most frequent adverse events.

High cost limited its diffusion in some countries.

A multicentre, phase 2, randomised, double-blind, placebo-controlled trial: 196 patients were randomised to placebo, prucalopride 2 mg or 4 mg for 4 weeks.

40.3% compared to 23.4% of patients achieved an increase of 1 SBM per week from baseline for prucalopride 4 mg compared to placebo, respectively (p. 0.002). )

*(Sloots CE, 2010)*



A 12-week RCT: 169 OIC pts. started in 2010, but **terminated early** based on a non-safety–related business priority decision.

Placebo and prucalopride 1 or 2 mg.

The percentage of participants with an average frequency of 3 SBMs did **not reach statistical significance** (p. 0.305).

*(ClinicalTrials.gov: NCT01117051)*

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# LINACLOTIDE (Constella®)

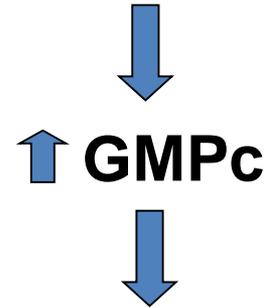
## Linaclootide for the treatment of chronic constipation

Gabrio Bassotti<sup>a</sup>, Paolo Usai-Satta<sup>b</sup> and Massimo Bellini<sup>c</sup>

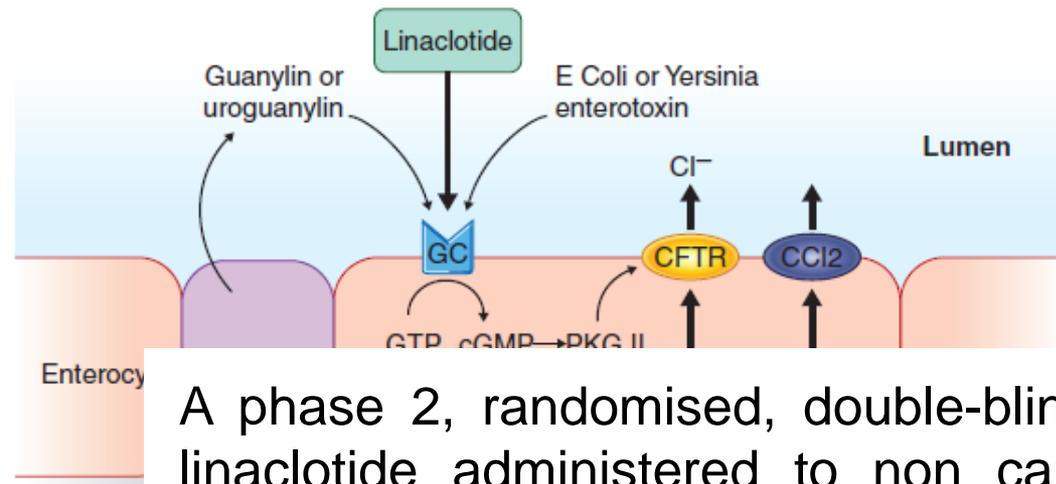
EXPERT OPINION ON PHARMACOTHERAPY

<https://doi.org/10.1080/14656566.2018.1494728>

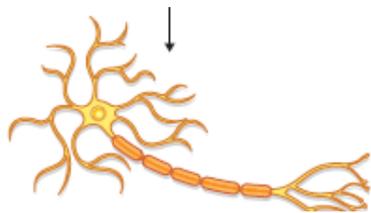
agonista recettore  
**Guanilato-ciclastasi C**  
(epitelio intestinale)



↑ secrez. Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>, H<sub>2</sub>O



A phase 2, randomised, double-blind, placebo controlled trial of linaclootide administered to non cancer patients with OIC was completed in 2016, but **no study results have been published.**



**Corsetti M, 2013**

**Figure 1.** Schematic representation of the actions of linaclootide and other ligands through the guanylate cyclase C receptor on enterocytes. EC cell: entero-endocrine cell; ST: heat-stable enterotoxin; CFTR: cystic fibrosis trans-membrane conductance regulator; CCl2: chloride channel type 2; GTP: guanosine triphosphate; cGMP: cyclic guanosine 3',5'-monophosphate; PKG: cGMP-dependent protein kinase.

# LUBIPROSTONE (Amitiza®)

- Chronic idiopathic constipation (FDA 2006)
- IBS-C women (FDA 2008)

Bicyclic functional fatty acid that acts as a selective type2 chloride channel (ClC-2) activator in the apical membrane of the gastrointestinal epithelium



**increases intestinal water and chloride secretion**  
(-restoration of **tight junctions** > recovery of mucosal barrier function)



**-increases intraluminal fluid in the gut**



Facilitates **transit** in the intestine and eases **stool passage**

*(Johanson JF, 2007)*

*(Mooser AJ, 2007)*

FDA approved lubiprostone *24 mcg twice daily* for treatment of OIC in patients with non-cancer pain in the US and Canada.

It also gained approval in several EU countries.



## Three RCTs; 12-weeks

Greater response rate for lubiprostone compared to placebo of 3.2 **SBMs/w** vs 2.4 SBMs/w (p. 0.001) (NNT: 13).

More patients in the lubiprostone group compared to the placebo group were **overall SBM** responders (27.1% vs 18.9%, respectively; p. 0.03).

Median **time to the first SBM** was significantly **shorter** after lubiprostone compared to placebo (23.5 vs 37.7 hours, respectively; p. 0.004).

**Higher portion of patients** with lubiprostone reported their **first SBM** within four, eight, 12 and 48 hours of the first dose (p 0.009). (*Jamal MM, 2015*)

Phase 3 trial 418 non-cancer pain patients with OIC

(Cryer B, 2014)

Lubiprostone: significant change in **SBM frequency**/week compared to placebo *at week 8* (mean, 3.3 vs 2.4 SBMs/week, respectively; p. 0.004).

*At week 12, however,* no significant difference was found (this study did not exclude patients taking methadone, which has a specific interaction with lubiprostone's mode of action: methadone, but not morphine, inhibits Cl<sup>-</sup> secretion by the CCl<sub>2</sub> channel)

Lubiprostone improved *abdominal discomfort, straining, constipation severity and stool consistency* better than placebo

A long-term safety and efficacy open-label extension study showed a mean SBM frequency increase of 4.9 up to 5.3 per week, compared to 1.4 per week at baseline (p < 0.001). Thereby, 67.0%–84.1% of patients did not need rescue medication. Lubiprostone was however not superior to senna,

(Spierings EL, 2016)

Additional treatment options for OIC involve the use of **opioid receptor antagonists** that block opioid actions either centrally or peripherally, combination of an opioid antagonist (**naloxone**) and an opioid agonist (oxycodone) (Targin®)



## **PAMORAs**

### **Peripherally acting mu-opioid receptor antagonists**

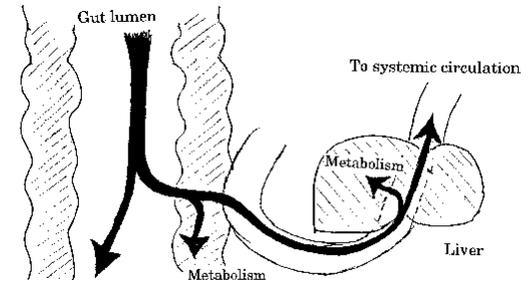
block opioid receptors in the GI tract, but not central receptors and thus do not lead to symptoms of withdrawal

**Methylnaltrexone, Naloxegol,**  
**Naldemedine**, Bevenopran, Axelopran, Alvimopan

European Association for Palliative Care guidelines recommend subcutaneous *methylnaltrexone* as a second-line treatment option for OIC in patients with chronic cancer pain when traditional laxatives are not effective (*Caraceni A, 2012*)

## Oxycodone and naloxone (2:1)

Naloxone, a relatively non-selective opioid antagonist, undergoes **first-pass metabolism** for the most part (>97%) in the **liver** > slow release to exert an effect only on the peripheral GI receptors without reversing central analgesic effects.



OXN reduced patients' BFI, improved SBMs, PAC-SYM and PAC-QoL. AEs: constipation, nausea, headache, vomiting and diarrhoea.

Tablets have to be swallowed as a whole: breaking them can cause rapid release of oxycodone > faster absorption and even fatality.

The combination tablet (FDA and EMA approved) to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for patients for whom alternative pain treatment options are inadequate.

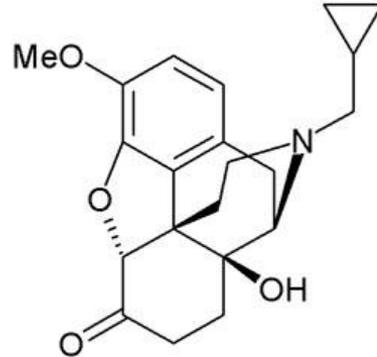
*(Simpson K, 2008)*

*(Lowenstein O, 2009)*

*(Mehta V, 2014)*

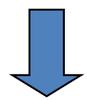
*(Sandner-Kiesling A, 2014)*

# METILNALTREXONE (Relistor®)

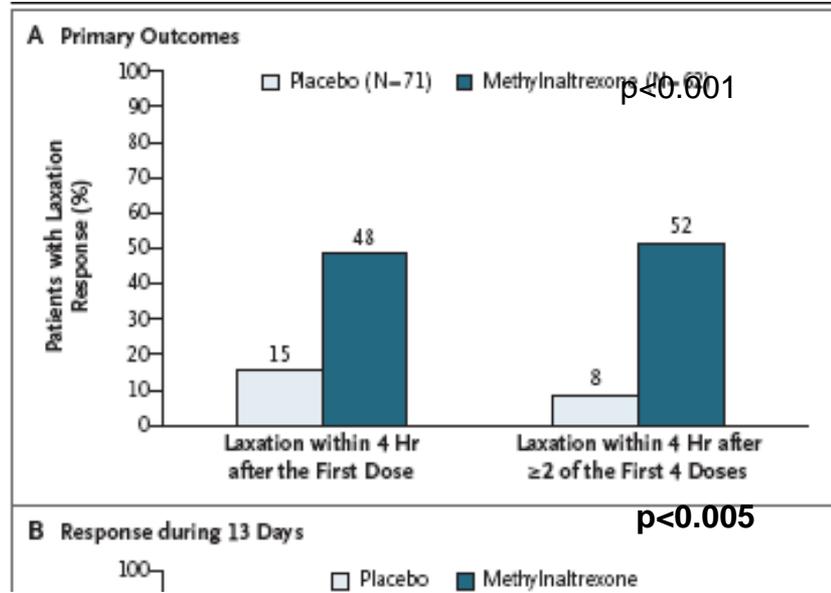


The **first** PAMORAs approved for OIC (FDA and EMA, 2008) (subcutaneous injection)

N-methyl group restricts the ability to **cross the blood-brain** barrier because of polarity and low lipid solubility.



non interferenza con analgesia da oppioidi



Three studies with patients with **cancer-related pain** had significantly **better results** in favor of the drug (RR = 0.51, 95% CI: 0.41-0.63) than studies with non-cancer related pain (RR = 0.75, 95% CI = 0.63-0.90;  $Q(1) = 7.44, p = .006$ ).

(Nee J, 2018)

Four week RCT once daily (QD) or every other day (QOD) vs placebo in non-cancer patients with OIC.

-QD group: improvement of **rectal and stool symptoms** and **global PAC-SYM**

-QOD group: improvement of **stool symptoms** and global **PAC-SYM**

*(Iyer SS, 2011)*

Four week RCT: 91 centres, 469 pts. with non-cancer pain and OIC.

Subcutaneous methylnaltrexone 12 mg QD, 12 mg QOD, or placebo

-34.2% in methylnaltrexone group: rescue-free bowel movement (**RFBM**) within four hours vs. 9.9% in placebo group ( $p < 0.001$ ).

**NNT**: 5 for QD and 14 for QOD to achieve 3 RFBMs per week.

*(Michna E, 2011)*

Most common AEs: abdominal pain, diarrhoea and nausea.

Seven cases of **bowel perforation**: causal relationship could not be ruled out nor established. Methylnaltrexone should be restrained in pts. at risk for GI perforation (peptic ulcer, Ogilvie's disease, diverticular disease, infiltrating malignancy).

*(Bader S, 2011)*

*(Mackey AC, 2010)*

Subcutaneous administration: limitations for clinical use



FDA approved the use of **oral methylnaltrexone**



Phase 3 RCT: 804 patients to 150, 300 or 450 mg or placebo QD for 4 weeks.

-Primary efficacy endpoint: **percentage of days with a Rescue Free BM within four hours** during weeks 1 to 4.

-Secondary efficacy endpoints: percentage of responders (**≥3 RFBMs per week**, with an increase of **≥1 RFBM** per week from baseline for at least three out of four weeks) during weeks 1 to 4, and change in weekly number of RFBMs from baseline during weeks 1 to 4.

Comparable results for the 450 mg tablet compared to sc methylnaltrexone.

24.3% with 300 mg and 26.2% with 450 mg: a RFBM within four hours vs. 19.2% with placebo (both  $p < 0.05$ ).

*(Rauck R, 2017)*

Oral tablets should not be used in patients who are at risk for GI perforation.

# Naloxegol (*pegylated naloxone*)

Pegylation prevents passage of the blood-brain barrier

Two multicentre phase 3 RCTs (KODIAC 4 and 5)

(*Chey WD, 2014*)  
(*Tack J, 2015*)

Response rate ( $\geq 3$  **SBMs/week** and  $\geq 1$  **SBM** over baseline for 9 of 12 treatment weeks and 3 of the final four treatment weeks) with naloxegol 12.5 or 25mg QD compared to placebo.

**Naloxegol 25mg:** significantly **higher response** in both trials (p.0.001 and p.0.02) but not 12.5mg dose

In both studies: greater improvements with 25mg for **straining, stool consistency** and **frequency** of days with complete SBMs.

KODIAC 8: 52-week, multicentre, open-label, phase 3 study: long-term safety and tolerability. Naloxegol was **safe and well tolerated**.

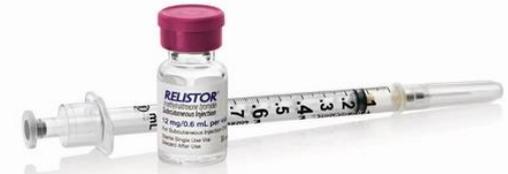
AEs: abdominal pain, diarrhoea and nausea e mostly mild and moderate.

(*Webster L, 2014*)



*Agenzia Italiana del Farmaco*

**AIFA**



**30 Marzo 2017:** nuova versione **nota 90 dell'Aifa:** autorizza la **prescrizione a carico del SSN di Metilnaltrexone e Naloxegol.**

Rimborsabilità limitata a soggetti con malattia in stato terminale che siano in terapia continuativa con oppiacei da almeno due settimane e mostrino resistenza al trattamento con lassativi ad azione osmotica per più di 3 giorni.

**Metilnaltrexone bromuro (Relistor): 12 mg (0,6 mL) 7 f: 287.25 euro**  
per via sottocutanea; almeno 4 dosi settimanali > fino a una volta al giorno.

**Naloxegol: naloxone pegilato (Moventig) 30 Cpr Riv 25 mg : 98.75 euro**  
25 mg per os una volta al giorno



# Naldemedine

FDA approved for orally OIC treatment in adult patients.

Two randomised, controlled, *phase 3 trials* patients with chronic non-cancer pain.

In the COMPOSE I and II trial, 47.6% compared to 34.6% (p. 0.002), and 52.5% compared to 33.6% (p< 0.0001) in the naldemedine vs placebo group, respectively, were found to have **≥3 SBMs** per week and an increase of **≥1 SBM** per week.

*(Hale M, 2017)*

GI-related **AEs** such as diarrhoea, nausea and abdominal pain were more prevalent in the naldemedine group but were *mild to moderate* in nature.

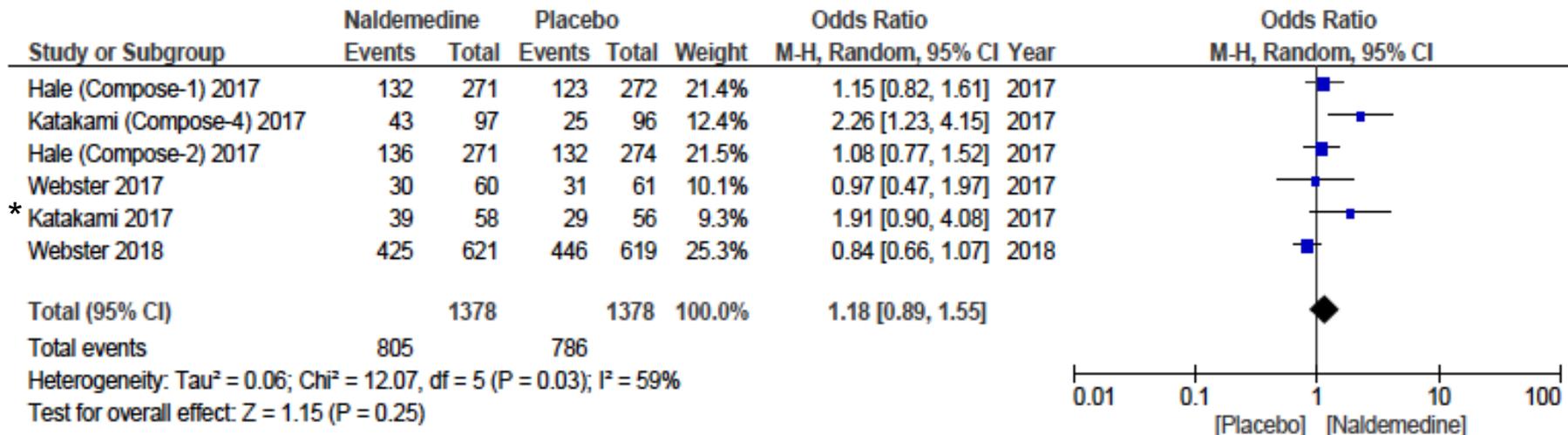
**Long-term safety:** a *52-week*, randomised, double-blind, *phase 3 study*. 1246 patients were equally randomised to receive naldemedine or placebo.

The proportion of patients with **AEs** (*mild to moderate*) was *similar* across both treatment groups, with diarrhoea being the most prevalent AE in the naldemedine group.

*Webster LR, 2018*

## 6 RCTs: 2672 pts *(Hewlett A, submitted JGLD, 2018)*

primary and secondary outcomes of Naldemedine compared to placebo.



**SBM responders** was significantly higher in Naldemedine group (56.4%) versus placebo group (34.7%) ( $p < 0.0001$ ). Change in **SBM frequency** was higher in Naldemedine group versus placebo group ( $P < 0.0001$ ).

\*phase III RCT in 193 cancer-related OIC patients: 71% responded to 0.2 mg/day compared with 34% percent of the placebo group (using the same response criteria as used in the COMPOSE I and II trials).

**Bevenopran (CB-5945):** Two phase 3 clinical trials and one safety study were **terminated prematurely in 2014** because of difficulties with enrolment.

**Axelopran (TD-1211)** once-daily, oral PAMORA  
Four phase 2 trials have been completed: > 400 OIC patients.  
Data have been published in **only one abstract**: three oral doses of axelopran were evaluated in a five-week, double-blind, placebo controlled, and parallel-group study conducted in 217 chronic non-cancer pain OIC patients.  
At week 5, the mean change from baseline in weekly complete SBMs for axelopran patients with < 5 years of OIC ranged from 1.7 to 2.3 vs 0.7, and 1.2 to 3.3 vs 0.6, respectively, for axelopran vs placebo with OIC 5 years.





THE COCHRANE  
COLLABORATION®

2008

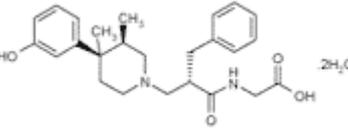
Taguchi	2001
Wolff	2004
Delaney	2005
Viscusi	2006
Herzog	2006
Ludwig	2006

(Entereg/Entrareg®)

## ALVIMOPAN for postoperative ileus

### Endpoint

- Time to tolerance of regular diet
- Recovery of gastrointestinal function
- Time to passage of first stool
- Length of hospital stay
- Time to passage of first flatus

- 
- Placebo
  - **A** 6 mg per os

### Two phase 3RCTs in OIC.

Alvimopan 0.5 mg BID vs. placebo (3.51 vs 2.01 SBMs frequency increase per week;  $p < 0.001$ ) (Jansen JP, 2011)

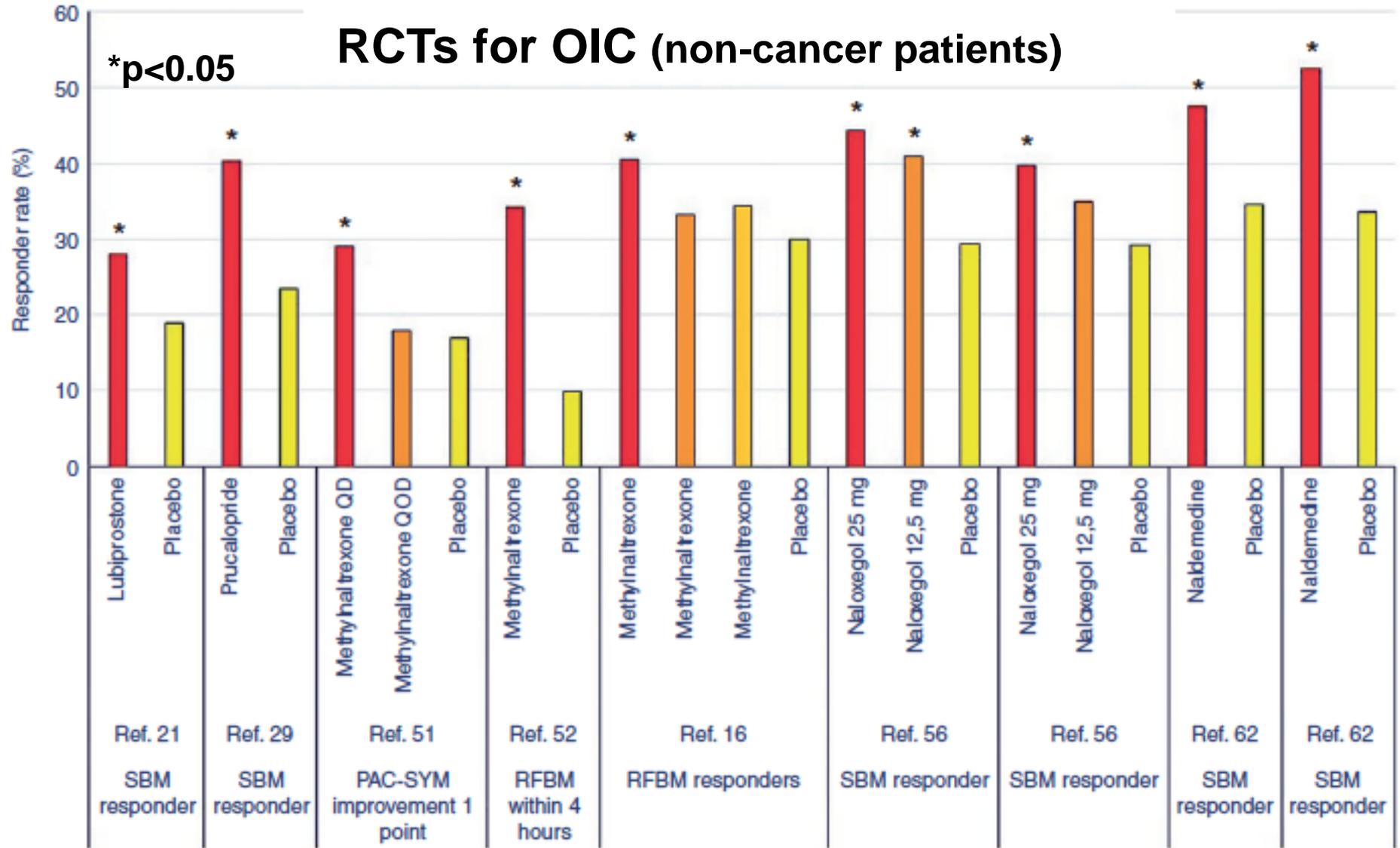
The result was not confirmed by the other study: an unexpectedly high placebo response (56%) and reduced efficacy of alvimopan.

(Irving G, 2011)

The sponsor decided to discontinue.

# RCTs for OIC (non-cancer patients)

\*p<0.05



(Pannemans J, 2018)

QD: once daily; QOD: once every other day;

RFBM: rescue-free bowel movement; SBM: spontaneous bowel movement

# Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care

seven RCTs: 976 participants

Bridget Candy<sup>1</sup>, Louise Jones<sup>2</sup>, Victoria Vickerstaff<sup>1</sup>, Philip I Larkin<sup>2</sup>, Patrick Stone<sup>3</sup>

2018, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Oxycodone/naloxone prolonged release tablets compared with oxycodone prolonged-released tablets for opioid-induced bowel dysfunction

**Patient or population:** people with cancer and people receiving palliative care with opioid-induced bowel dysfunction

**Settings:** cancer care

**Intervention:** oxycodone/naloxone prolonged-release tablets

**Comparison:** oxycodone prolonged-released tablets

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oxycodone	Oxycodone/naloxone				
Laxation response within 24 hours of dose	-	-	-	-	-	Not reported
Laxation response between day 1 and day 14	-	-	-	-	-	Not reported
Effect on analgesia: opioid withdrawal <sup>c</sup>	-	-	Intervention group: mean 6.64 (SD 5.97) comparison group: mean 7.29 (SD 4.59) at 7 days	184 (1 study)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Effect on analgesia: pain intensity <sup>a</sup>	-	-	Intervention group: mean 3.50 (SD 1.88) and comparison group: mean 3.52 (SD 1.80) at 4 weeks	184 (1 study)	⊕⊕⊕○ Moderate <sup>b</sup>	Another study, <a href="#">Dupouiron 2017</a> also found outcome to be similar between trial arms, but did not provide any data
Serious adverse events	43 per 1000	87 per 1000 (27 to 279)	RR 2.00 (95% CI 0.62 to 6.41)	184 (1 study)	⊕⊕○○ Low <sup>b,d</sup>	-
Adverse events	754 per 1000	815 per 1000 (709 to 935)	RR 1.08 (95% CI 0.94 to 1.24)	234 (2 studies)	⊕⊕⊕○ Moderate <sup>b</sup>	-

# Methylnaltrexone compared to placebo for opioid-induced bowel dysfunction in cancer and people receiving palliative care

**Patient or population:** people with cancer and people receiving palliative care with opioid-induced bowel dysfunction

**Setting:** palliative care

**Intervention:** methylnaltrexone

**Comparison:** placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with methylnaltrexone				
Laxation response within 24 hours of dose <sup>a</sup>	195 per 1000	568 per 1000 (431 to 695)	RR 2.77 (1.91 to 4.04)	287 (2 studies)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Laxation response between day 1 and day 14 (specifically within 4 hours after 4 or more of the 7 doses) <sup>a</sup>	52 per 1000	517 per 1000 (330 to 699)	RR 9.98 (4.96 to 20.09)	305 (2 studies)	⊕⊕⊕○ Moderate <sup>b,c</sup>	-
Effect on analgesia: opioid withdrawal <sup>d</sup>	Study 1: day 1: MD 0.00 (-0.46 to 0.46); day 14: MD 0.10 (-0.63 to 0.83) Study 2: median change to day 2 = 0 in both trials arms			236 (2 studies)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Effect on analgesia: pain intensity <sup>e</sup>	Study 1: at 4 hours (methylnaltrexone 0.15 mg/kg: MD -0.76 (-1.47 to 0.05); methylnaltrexone 0.3 mg/kg: MD -0.25 (-0.91 to 0.41) Study 2: at day 1 and 14 (day 1: MD 0.20 (-0.62 to 1.02); day 14: MD -0.70 (-1.52 to 0.12))			287 (2 studies)	⊕⊕○○ Low <sup>b,f</sup>	Another study, <a href="#">Bull 2015</a> , found similar pain intensity experienced in trial arms, full data not provided
Serious adverse events	238 per 1000	142 per 1000 (88 to 219)	RR 0.59 (0.38 to 0.93)	364 (2 studies)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Adverse events	700 per 1000	815 per 1000 (745 to 869)	RR 1.17 (CI 0.94 to 1.45)	518 (3 studies)	⊕⊕○○ Low <sup>b,g</sup>	Heterogeneity was substantial (74%). It was explained in sensitivity analysis by omitting the trial at a high risk of bias because of small

# Naldemedine compared to placebo for opioid-induced bowel dysfunction in cancer and people receiving palliative care

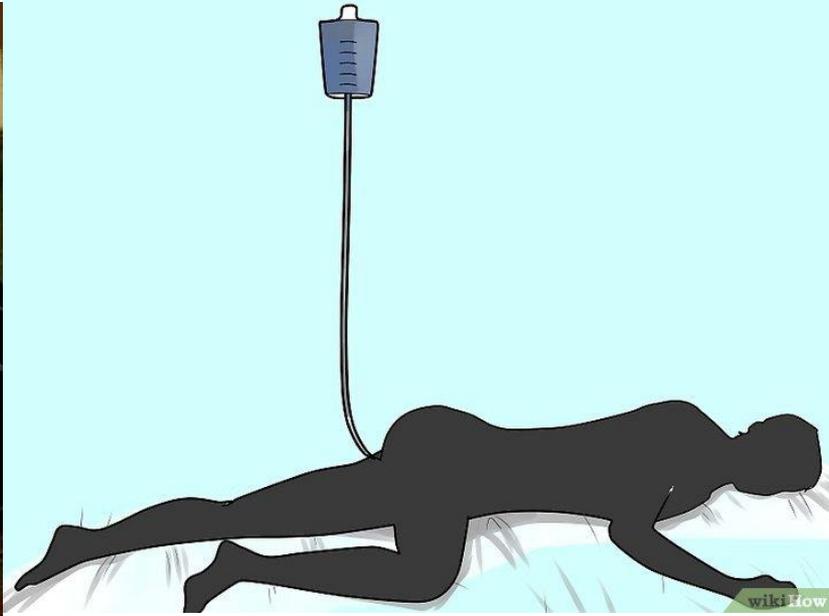
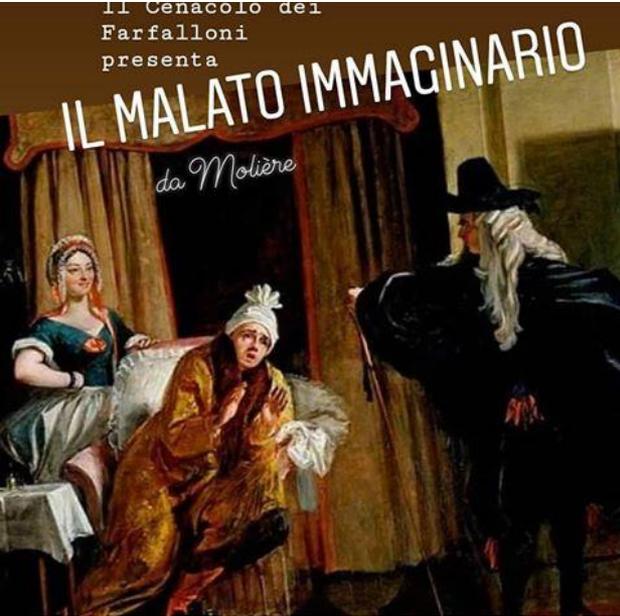
**Patient or population:** people with cancer and people receiving palliative care with opioid-induced bowel dysfunction

**Settings:** cancer care

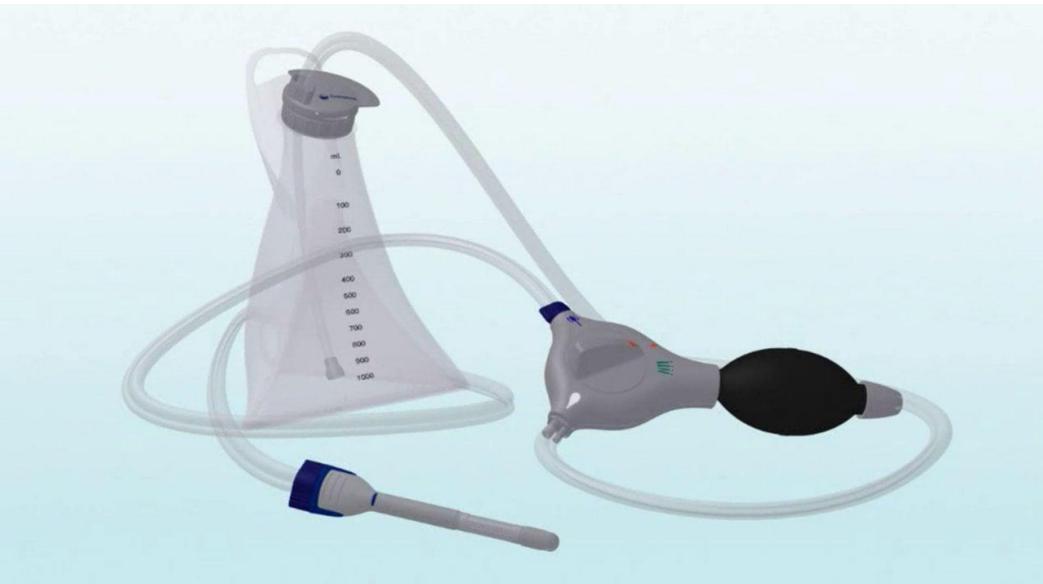
**Intervention:** naldemedine

**Comparison:** placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Naldemedine				
Laxation response within 24 hours of dose	-	-	-	-	-	Not reported
Laxation response between day 1 and day 14 <sup>a</sup>	375 per 1000	724 per 1000 (510 to 1000)	RR 1.93 (1.36 to 2.74) NNTB 2.88 (2.04 to 4.92)	225 (1 study)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Effect on analgesia: opioid withdrawal <sup>c</sup>	-	-	0.1 mg: MD -0.13 (-0.57 to 0.31); 0.2 mg: MD -0.40 (-0.87 to 0.07); 0.4 mg: MD -0.02 (-0.45 to 0.41)	225 (1 study)	⊕⊕⊕○ Moderate <sup>b</sup>	-
Effect on analgesia: pain intensity	-	-	-	-	-	Not reported
Serious adverse events <sup>a</sup>	-	-	5 SAEs occurred, all in naldemedine group.	225 (1 study)	⊕⊕○○ Low <sup>b,d</sup>	-
Adverse events <sup>a</sup>	518 per 1000	704 per 1000 (539 to 927)	RR 1.36 (1.04 to 1.79)	225 (1 study)	⊕⊕⊕○ Moderate <sup>b</sup>	-



## Transanal Irrigators





***Felice Evacuo***



# **Tolerance And Efficacy of Polyethylene Glycol 3350/Electrolyte Solution Versus Lactulose In Relieving Opiate Induced Constipation: A Double-Blinded Placebo-Controlled Trial**

*Michael D. Freedman, MD, FACP, FCP, H. Jeffrey Schwartz, MD, Robert Roby, MD, Steven Fleisher, MD*

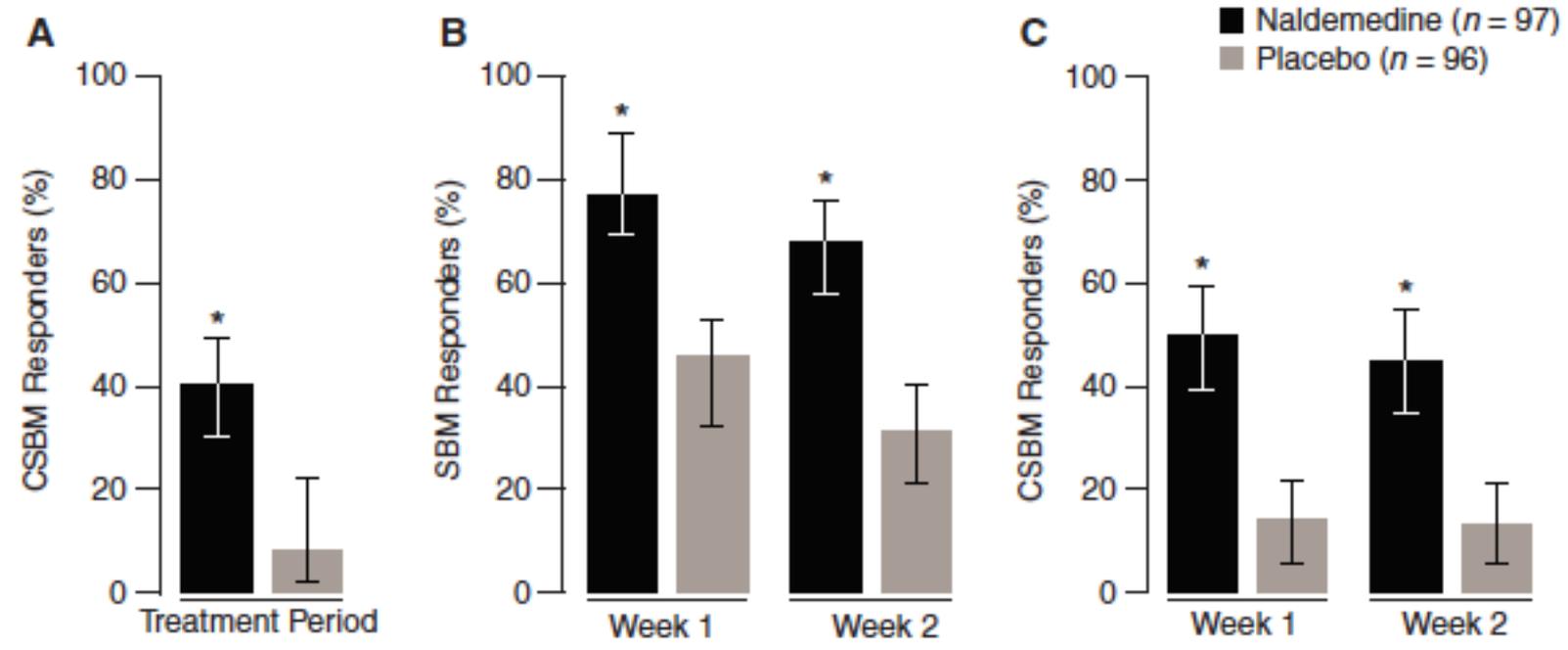
Methadone maintenance program in Baltimore, Maryland in 57 patients who are affected by opiate-induced constipation.

Self-reported frequencies, consistency, and ease of defecation during a 1 week run-in control period, followed by 3 treatment phases of 2 weeks each. Polyethylene glycol 3350/electrolyte solution and lactulose produced more “nonhard” stools than the placebo ( $P < 0.01$ ) and control ( $P < 0.003$ ). Polyethylene glycol 3350/electrolyte solution produced the loosest stool ( $P < 0.0001$ ) compared with the control, whereas lactulose had the most adverse effects. There were no significant differences in reducing hard stool formation in either experimental group, but both were better than having nothing or just the placebo.

# Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer

N. Katakami<sup>1\*</sup>, T. Harada<sup>2</sup>, T. Murata<sup>3</sup>, K. Shinozaki<sup>4</sup>, M. Tsutsumi<sup>5</sup>, T. Yokota<sup>6</sup>, M. Arai<sup>6</sup>, Y. Tada<sup>6</sup>, M. Narabayashi<sup>7</sup> & N. Boku<sup>8</sup>

*Annals of Oncology* 29: 1461–1467, 2018



## **Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care**

*seven RCTs: 976 participants*

Bridget Candy<sup>1</sup>, Louise Jones<sup>1</sup>, Victoria Vickerstaff<sup>1</sup>, Philip I Larkin<sup>2</sup>, Patrick Stone<sup>3</sup>

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There is moderate-quality evidence that methylnaltrexone improves bowel function in people receiving palliative care in the short term (24 hours) and over two weeks, and low-quality evidence that it does not increase adverse events

There is moderate-quality evidence in participants with cancer that have opioid-induced bowel dysfunction (OIBD), despite laxative use, that naldemedine, may improve bowel function within two weeks of the start of administration.

### **PAMORAs**

- rational treatment choice when conventional laxatives fail.
- are becoming more practical as tablet forms are emerging.