ALICE LAUDISIO
UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

La gestione del paziente con OIC per l'ottimizzazione della terapia del dolore

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

Definizione

Comparsa o il peggioramento dei sintomi da costipazione, associati all'inizio o conseguenti alle modifiche della terapia

Opioid-induced constipation (OIC)

- 60% to 90% of patients who take opioids for cancer pain
- approximately 40% to 60% of patients who take opioids for chronic non-cancer pain.
- Symptoms of OIC may lead to non-adherence with the prescribed opioid regimen.

Opioid-induced constipation (OIC)

- Patients with OIC report a significantly worse quality of life (QOL)
- OIC has been correlated to a poorer Eastern Cooperative Oncology Group (ECOG) performance status

Opioid-induced constipation (OIC)

Evidence suggests the risk of OIC rises with age.

OIC is underrecognized and undertreated in the older population often does not respond to conventional laxatives.

Studies of nursing home residents show that OIC is associated with worse physical and mental outcomes in older patients.

In particolare, la diagnosi di OIC contempla la presenza di sintomi nuovi o peggioramento della costipazione quando si inizia, si modifica o si aumenta la terapia oppioide che deve includere 2 o più dei seguenti segni:	
1a	sforzo durante più di un quarto (25%) delle evacuazioni
1b	feci grumose o dure in più di un quarto (25%) delle defecazioni
1c	sensazione di evacuazione incompleta in oltre un quarto (25%) delle defecazioni
1d	sensazione di ostruzione/blocco anorettale in oltre un quarto (25%) delle defecazioni
1e	manovre manuali per facilitare più di un quarto (25%) delle defecazioni o
1f	meno di 3 movimenti intestinali spontanei a settimana
2	necessità di ricorrere ai lassativi per ottenere feci normoformate

Diagnosi:

Criteri Roma IV

Simren M, et al. Curr Gastroenterol Rep. 2017;19(4):15.

Treatment

Peripherally acting μ-opioid receptor antagonists (PAMORAs) are a class of drugs that aim to reverse OIC without affecting opioid-mediated analgesia. PAMORAs minimally cross the blood–brain barrier and exert their therapeutic benefits by minimizing exogenous opioid actions at peripheral μ-opioid receptors, including the gastro-intestinal tract.

Table 8 Assessment scales for use in opioid-induced constipation (OIC)

Scale	Advantages	Disadvantages
Patient Assessment of Constipation—Symptoms (PAC-SYM)[a]		Not yet validated for OIC
		High number of questions → time-consuming and poor applicability in a clinical setting
Patient Assessment of Constipation—Quality of Life (PAC-QoL)		
Knowles–Eccersley–Scott Symptom Score		
Constipation Assessment Scale		
Stool Symptom Screener		Qualitative interviews
		Not sufficiently validated for comparative or sequential assessment of clinical status in patients with OIC [116]
Bowel Function Diary	Validated for OIC by the FDA	Not easy to use [114]
	Developed according to the methodology based on PRO	More suited to controlled clinical trials than to routine clinical practice [114]
	Assessment of both symptoms and their severity [115]	
Bowel Function Index	Validated and tested for OIC	
	Three simple questions	
	Subjective assessment of OIC	
	Administered by a physician or appropriately trained nurse/ nursing assistant	
	Uses numerical rating scales	
	Fast, effective and reliable	

FDA US Food and Drug Administration, *PRO* patient-reported outcomes
[a] A version of PAC-SYM is also available for patients with chronic low back pain and OIC

Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel

1. During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 means 'no difficulty' and 100 means 'severe difficulty'?

2. During the last 7 days, how would you evaluate your feeling of bowel evacuation on a scale from 0 to 100, where 0 means 'complete' and 100 means 'incomplete'?

3. During the last 7 days, how would you evaluate your constipation on a scale from 0 to 100, where 0 means 'absent' and 100 means 'severe'?

Add up the scores for Questions 1, 2, and 3, and divide the total by three.
Total score = _____ ÷ 3 = _____ = BFI
A BFI value >28.8 indicates the presence of pathological constipation.

De Giorgio R, et al. Adv Ther. 2021;38(7):3589-3621.

Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel

Table 9 Initial management of patients with an indication for, or already receiving, chronic opioid therapy

Indication for chronic opioid therapy	Already receiving chronic opioid therapy[a]
1. Inform the patient that opioid use may cause or worsen constipation, necessitating the use of laxatives	1. Administer a validated measurement scale before opioid therapy (baseline) and at regular intervals (e.g. once weekly) to facilitate the early detection of worsening bowel function
2. Assess bowel function before starting opioid therapy (baseline) using a validated measurement scale	2. If constipation is diagnosed, assess severity and possible causes
3. If bowel function is found to be abnormal, initiate appropriate treatment. The aim of such treatment is to avoid discontinuation of opioid treatment or a reduction in dosage that could lead to recurrence of pain	3. Initiate laxative treatment in patients not currently receiving it. In the case of worsening bowel function in patients already on laxative treatment, review and, if necessary, gradually intensify it. If possible, increase the dose of the medication(s) already in use. If necessary, add an additional agent with a complementary mechanism of action

[a] With or without concomitant laxatives

De Giorgio R, et al. Adv Ther. 2021;38(7):3589-3621.

Use of Peripheral μ-Opioid Receptor Antagonists for Treating Opioid-Induced Constipation among US Medicare Beneficiaries from 2014 to 2018

Measurements: The annual spending, number of beneficiaries, number of claims, and spending per beneficiary and claim for each PAMORA. The distribution by prescriber specialty using PAMORA. ***Results:*** From 2014 to 2018, aggregate spending on PAMORAs increased, from $13.6 to $150.9 million, and use increased, from 4221 to 72,592 beneficiaries… the most common specialties/professions were family practice (20.2%), internal medicine (18.0%), and nurse practitioner (15.4%). ***Conclusions:*** Our findings-significant and increasing expenditure on PAMORAs, and broad use across specialties-serve as a call for defining and implementing appropriate use of PAMORAs.

Premnath N, et al. J Palliat Med. 2021;24(8):1236-1239.

PAMORAs

Methylnaltrexone	2008
Naloxegol	2014
Naldemedina	2017

Subcutaneous Methylnaltrexone for Treatment of Opioid-Induced Constipation in Cancer versus Noncancer Patients: An Analysis of Efficacy and Safety Variables from Two Studies

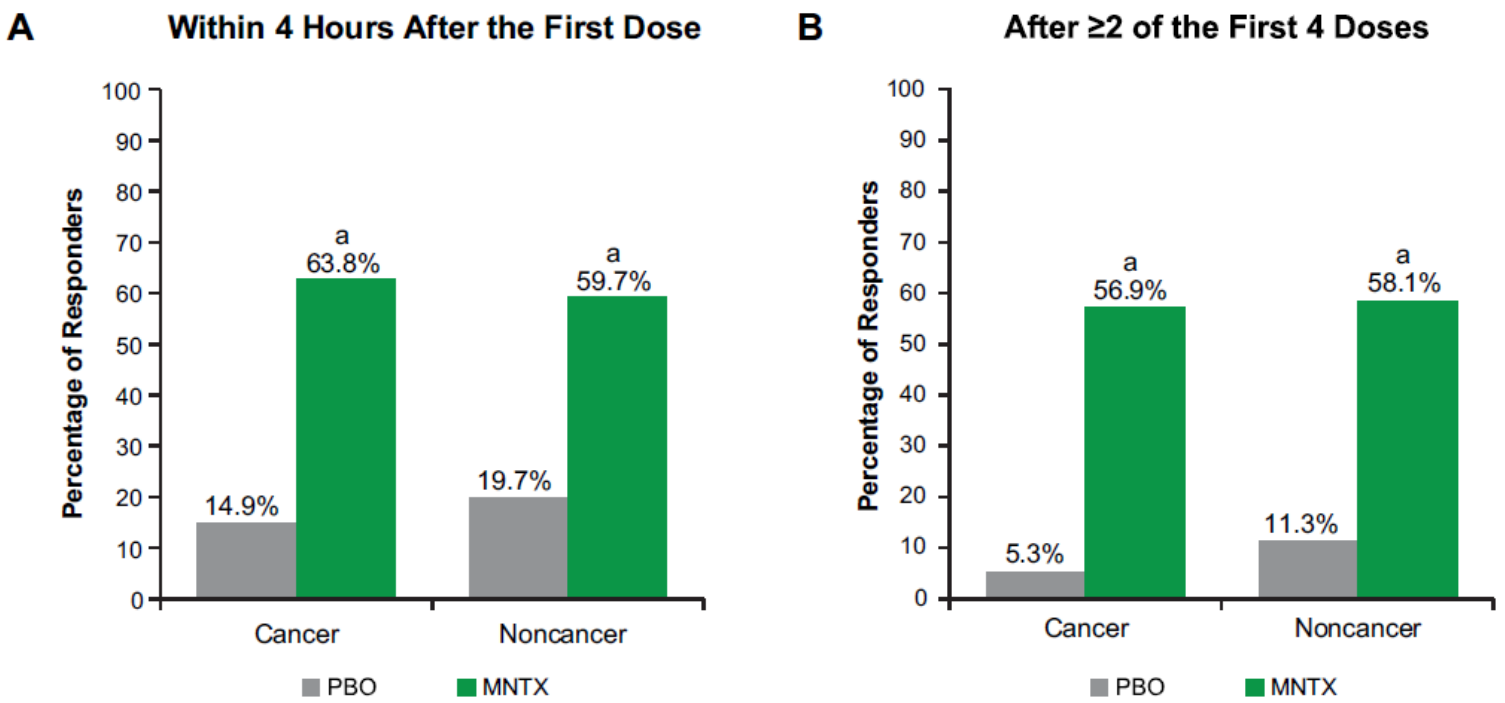
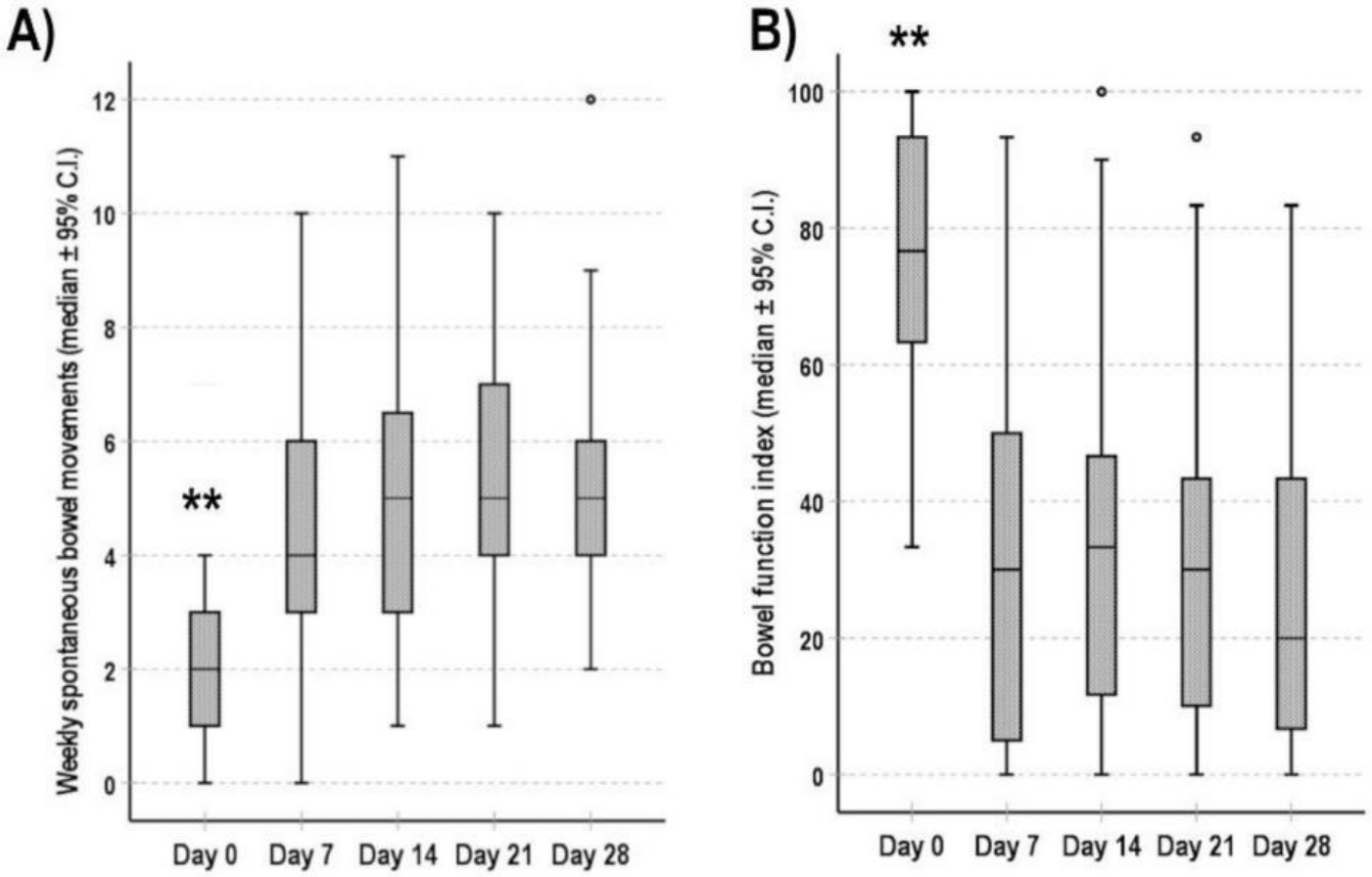


Figure 1 Responders with laxation (**A**) within 4 hours after the first dose and (**B**) after ≥2 of the first 4 doses (pooled ITT population).
Notes: Among patients with cancer, n = 114 for PBO; n = 116 for MNTX. Among patients without cancer, n = 71 for PBO; n = 62 for MNTX. [a]$P < 0.0001$ vs PBO.
Abbreviations: ITT, intent to treat; MNTX, methylnaltrexone; PBO, placebo.

Chamberlain BH, et al. J Pain Res. 2021;14:2687-2697.

Can Naloxegol Therapy Improve Quality of Life in Patients with Advanced Cancer?



Evolution of bowel function during the 4 weeks of follow up. (A) Number of weekly spontaneous bowel movements, (B) BFI score. Data are shown as median (95% C.I.). ** $p < 0.001$ for the comparisons between values at day 0 and values at day 7, 14, 21 and 28.

Ostan R, Cancers (Basel). 2021;13(22):5736.

Can Naloxegol Therapy Improve Quality of Life in Patients with Advanced Cancer?

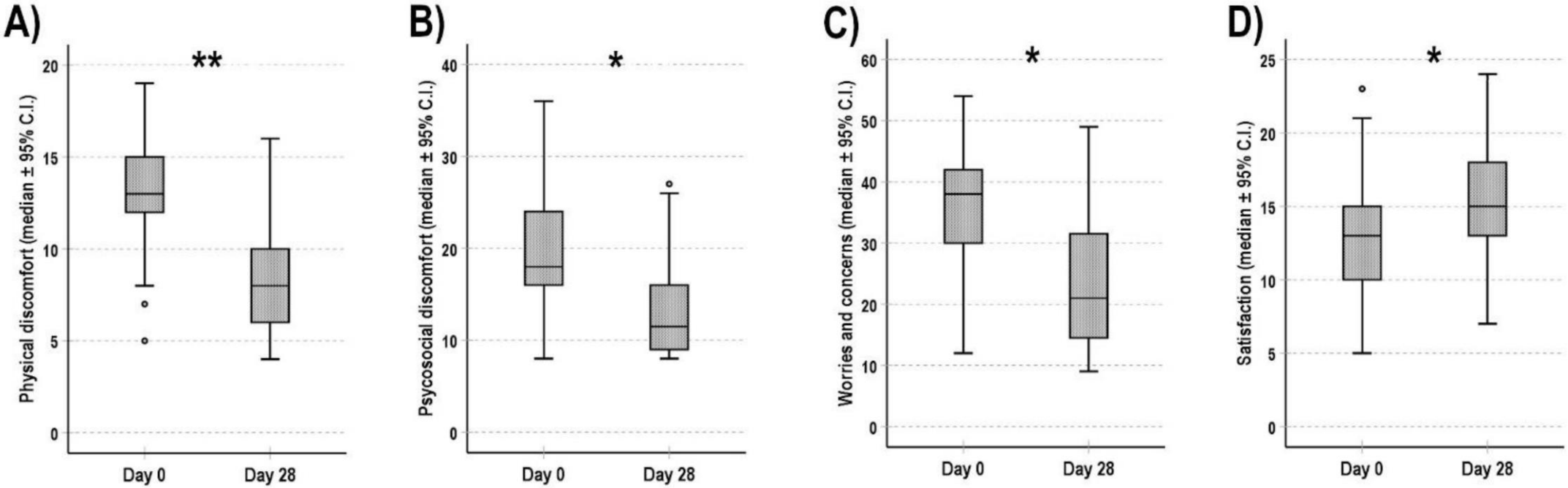


Figure 2. Constipation-related quality of life at the baseline (day 0) and after 4 weeks of follow up (day 28). The scores obtained in the four dimensions of PAC-QoL questionnaire ((**A**) physical discomfort, (**B**) psychological discomfort, (**C**) worries/concerns and (**D**) satisfaction) are shown as median (95% C.I.). * $p < 0.010$; ** $p < 0.001$.

Ostan R, Cancers (Basel). 2021;13(22):5736.

COMPOSE-1 and COMPOSE-2

Multicentre, phase 3, double-blind, randomised, parallel-group trials in adults with chronic non-cancer pain and OIC

- Age 18–80 years; did not use laxatives, and had a stable opioid regimen
- Patients were randomly assigned (1:1) to receive either oral naldemedine 0·2 mg or matching placebo once a day for 12 weeks.

Hale M, et al. Lancet Gastroenterol Hepatol. 2017;2(8):555-564

Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials

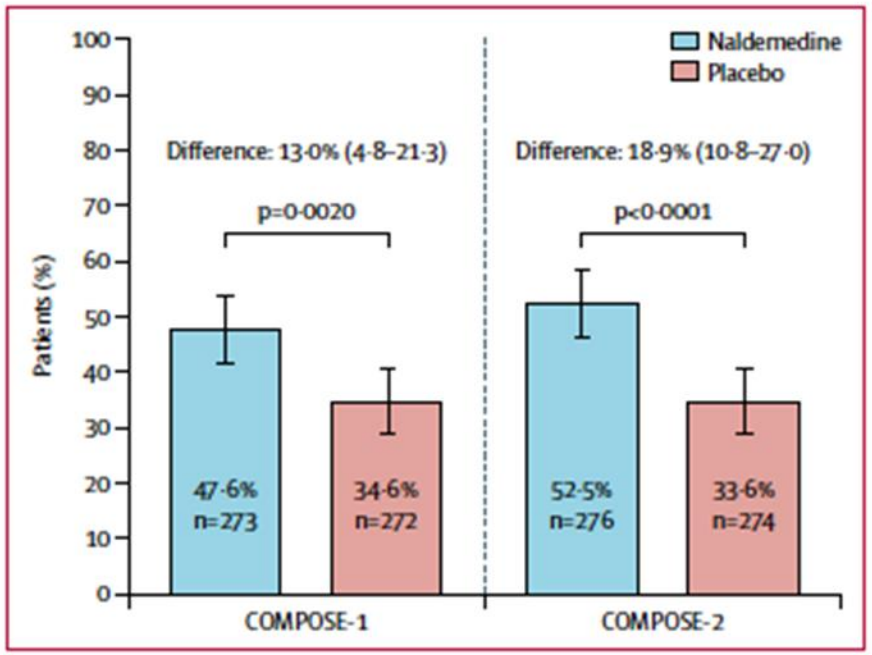


Figure 2: **Proportion of responders by treatment group (primary endpoint) in the intention-to-treat population**
Data presented in bars as proportion of responders with vertical lines representing 95% CI. Differences in proportion of responders with naldemedine compared with placebo are presented with 95% CI and p values.

The primary endpoint was proportion of responders. A responder had at least three spontaneous bowel movements (SBMs) per week with an increase from baseline of at least one SBM per week for at least 9 weeks of the 12-week treatment period including at least three of the last 4 weeks.

Hale M, et al. Lancet Gastroenterol Hepatol. 2017;2(8):555-564.

	COMPOSE-1		COMPOSE-2	
	Naldemedine group (n=271)	Placebo group (n=272)	Naldemedine group (n=271)	Placebo group (n=274)
Summary of TEAEs				
Total TEAEs	132 (49%)	123 (45%)	136 (50%)	132 (48%)
Treatment-related TEAEs	59 (22%)	45 (17%)	54 (20%)	31 (11%)
TEAE leading to discontinuation	13 (5%)	4 (2%)	14 (5%)	9 (3%)
Serious TEAEs	14 (5%)	5 (2%)	9 (3%)	13 (5%)
Treatment-related serious TEAEs	2 (1%)	0	2 (1%)	1 (<1%)
Serious TEAEs leading to discontinuation	3 (1%)	0	3 (1%)	3 (1%)
Major adverse cardiovascular events	..	..	..	..
Myocardial infarction	1 (<1%)	0	0	1 (<1%)
Deaths	0	0	1 (<1%)	0
TEAEs for ≥3% of participants for a preferred term (in any treatment group in either study)				
Infections and infestations SOC*	53 (20%)	48 (18%)	39 (14%)	53 (19%)
Urinary tract infection	7 (3%)	8 (3%)	6 (2%)	14 (5%)
Gastrointestinal disorders SOC*	58 (21%)	35 (13%)	58 (21%)	40 (15%)
Abdominal pain	17 (6%)	5 (2%)	14 (5%)	3 (1%)
Diarrhoea	18 (7%)	8 (3%)	24 (9%)	5 (2%)
Flatulence	3 (1%)	4 (2%)	6 (2%)	9 (3%)
Nausea	13 (5%)	7 (3%)	13 (5%)	9 (3%)
Musculoskeletal and connective tissue disorders SOC*	26 (10%)	29 (11%)	25 (9%)	20 (7%)
Back pain	6 (2%)	9 (3%)	10 (4%)	6 (2%)
TEAEs of opioid withdrawal or possible opioid withdrawal				
Patients with an opioid withdrawal TEAE†	2 (1%)	1 (<1%)	0	0
Patients with an event of possible opioid withdrawal‡	2 (1%)	1 (<1%)	5 (2%)	2 (1%)
Only non-gastrointestinal preferred terms§	0	0	0	0
Non-gastrointestinal and gastrointestinal¶ preferred terms‖	0	0	4 (2%)	2 (1%)

Data are number of patients (%). TEAEs with the same preferred term occurring more than once in a participant were only counted once. edDRA=Medical Dictionary for Regulatory Activities. SOC=system organ class. TEAE=treatment-emergent adverse event. * The data in the SOC row reflect all reported TEAEs, irrespective of the proportion of patients that experienced each preferred term within that SOC. †Opioid withdrawal based on standardised MedDRA query (drug withdrawal). ‡Possible opioid withdrawal based on opioid withdrawal terms of those patients with at least three preferred terms potentially related to opioid withdrawal syndrome that has onset on the same day or occurred within 1 day. §All non-gastrointestinal preferred terms with at least three preferred terms potentially related to opioid withdrawal syndrome. Gastrointestinal includes "gastrointestinal disorders" in MedDRA system organ class. ¶All gastrointestinal preferred terms with at least three preferred terms potentially related to opioid withdrawal syndrome. ‖At least one gastrointestinal preferred term and at least one non-gastrointestinal preferred term out of at least three preferred terms potentially related to opioid withdrawal syndrome.

Table 2: Summary of overall TEAEs, and TEAEs of opioid withdrawal or possible opioid withdrawal (safety population)

Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials

Naldemedine was generally well tolerated, despite resulting in a higher incidence of gastrointestinal adverse events than placebo. Gastrointestinal side-effects are expected with naldemedine because of its mechanism of action, which reverses the effect of opioids on μ-opioid receptors in the gastrointestinal tract.

Hale M, et al. Lancet Gastroenterol Hepatol. 2017;2(8):555-564.

Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study

This was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial (COMPOSE-3) that evaluated the long-term safety and tolerability once-daily oral naldemedine 0.2 mg for 52 weeks in patients with chronic noncancer pain, on a stable opioid therapy, and who could be on a routine laxative regimen but still had OIC

Webster LR, et al. *Pain*. 2018;159:987-994.

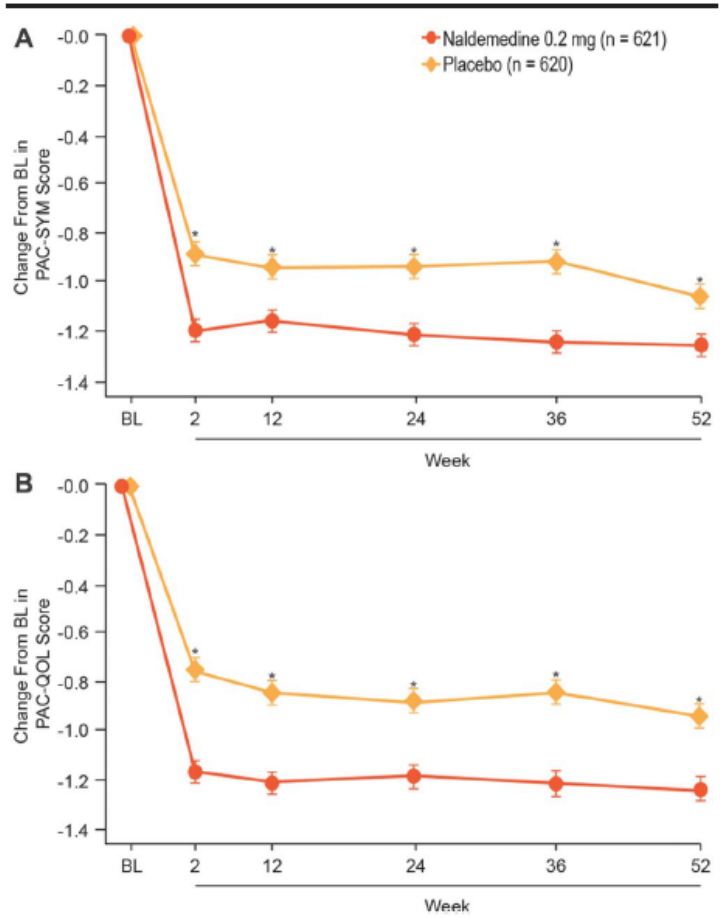


Figure 6. Change from baseline in (A) Patient Assessment of Constipation Symptoms and (B) Patient Assessment of Constipation Quality of Life scores (intent-to-treat population; least squares mean ± SE). *$P \leq 0.0001$ vs placebo. BL, baseline; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms.

COMPOSE-3

Long-term naldemedine treatment elicited significant and durable improvements in the frequency of bowel movements, constipation-related symptoms, and patient quality of life.

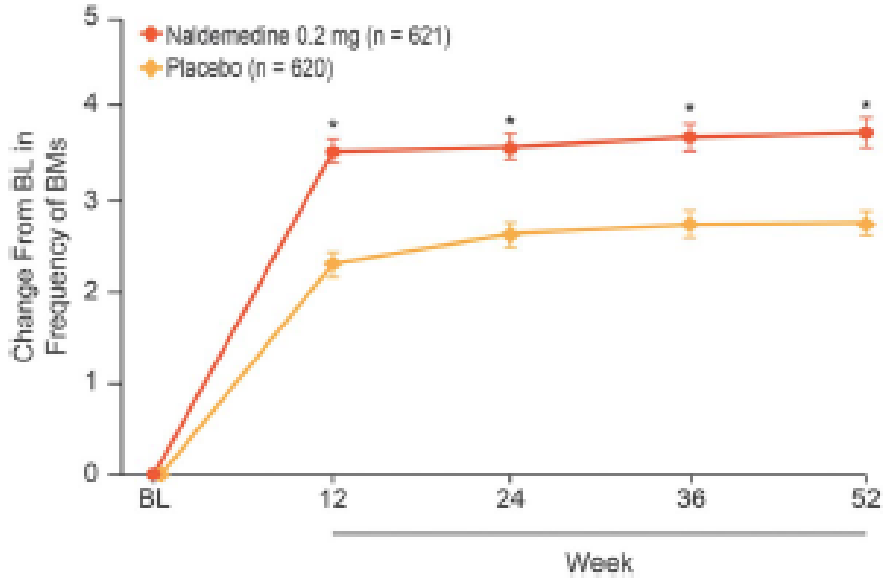


Figure 5. Changes from baseline in frequency of bowel movements (intent-to-treat population; least squares mean ± SE). *$P \leq 0.0001$ vs placebo. BL, baseline; BM, bowel movement. BL value for both treatment groups: 2.02 BMs per week.

Webster LR, et al. *Pain*. 2018;159:987-994.

Naldemedine is effective in the treatment of opioid-induced constipation in patients with chronic non-cancer pain who had a poor response to laxatives

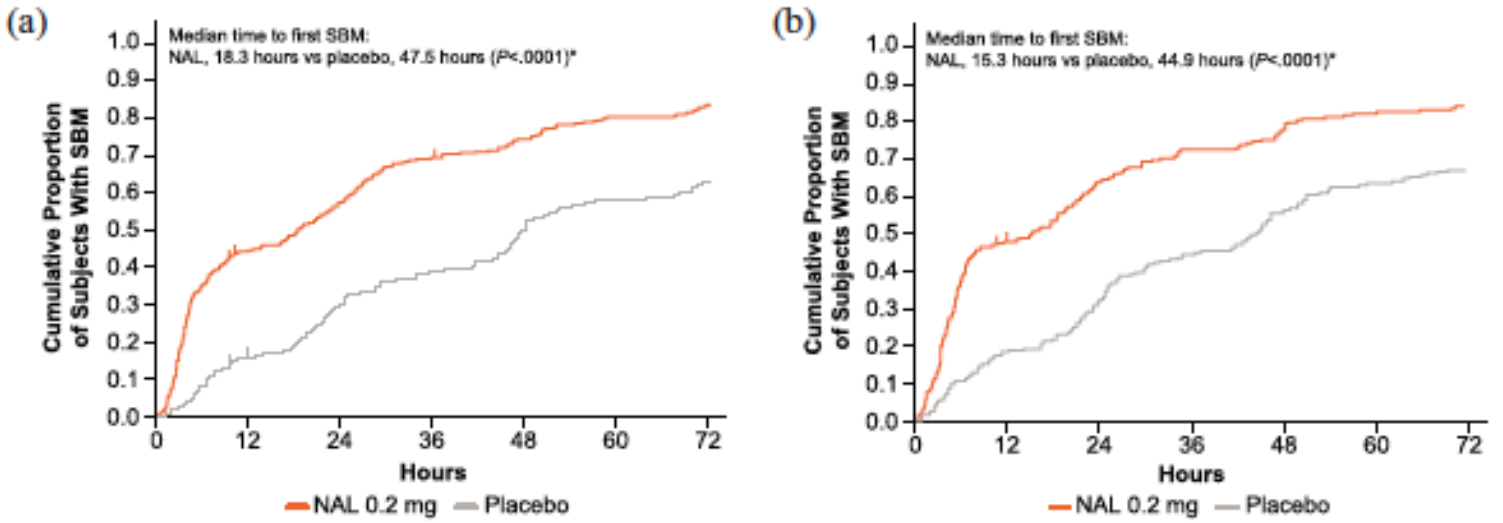


Figure 5. Kaplan–Meier estimate of time to first spontaneous bowel movement in (a) PLR and (b) non-PLR subgroups

Conclusion

Data from this integrated analysis further support the efficacy and tolerability of naldemedine in the treatment of OIC and demonstrate that naldemedine has a consistent effect regardless of whether or not a patient had a poor response to laxatives.

Hale ME, et al. *Therap Adv Gastroenterol*. 2021;14:17562848211032320.

COMPOSE- 4 COMPOSE- 5

Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer

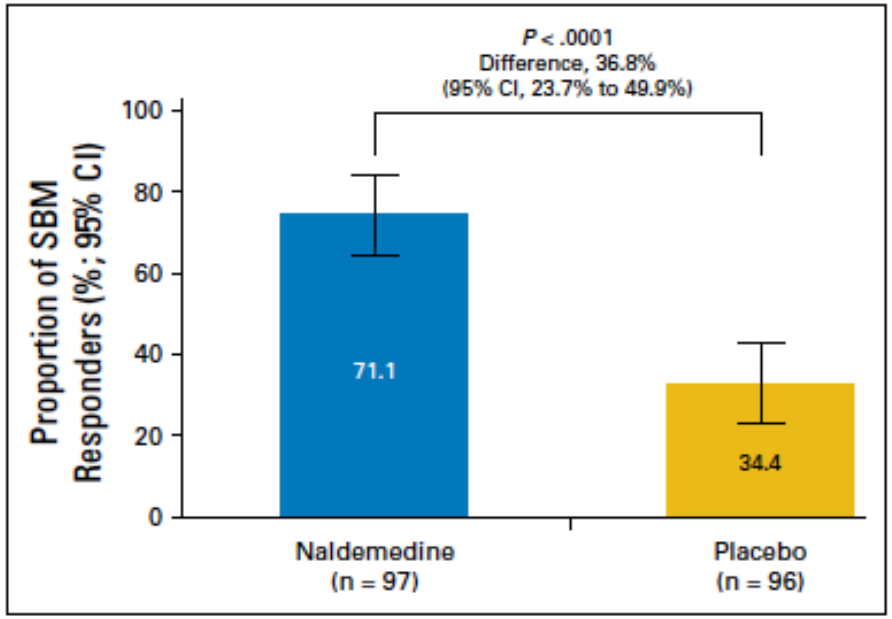


Fig 2 Proportion (± standard error) of spontaneous bowel movement (SBM) responders in the naldemedine and placebo groups during the 2-week treatment period of COMPOSE-4 (full analysis set).

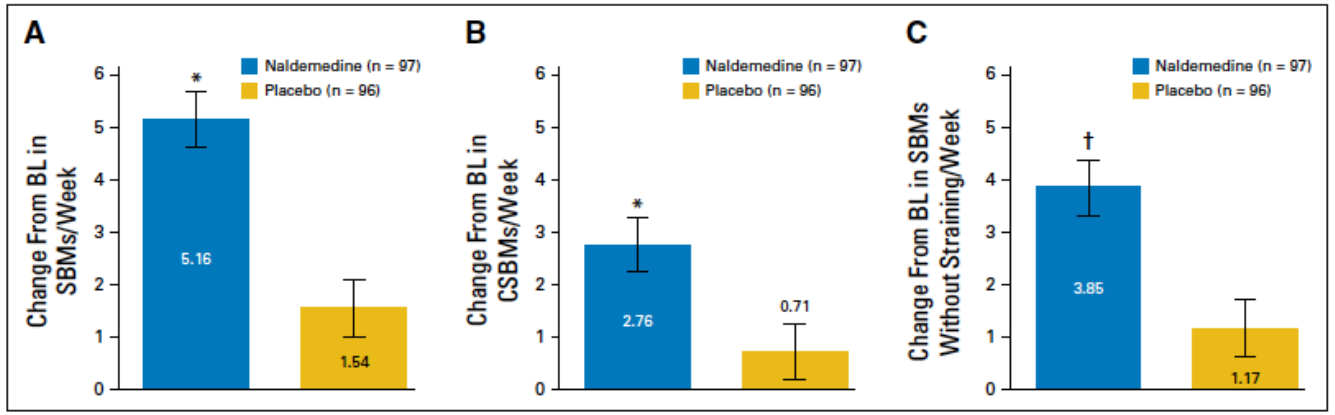


Fig 3. Change from baseline (BL) in least squares (LS) mean of the frequency of (A) spontaneous bowel movements (SBMs)/week, (B) complete SBMs (CSBMs)/week, and (C) SBMs without straining/week in COMPOSE-4 (full analysis set; LS mean ± standard error). (*) $P < .0001$ versus placebo; (†) $P = .0005$ versus placebo.

Safety and Efficacy of Naldemedine for the Treatment of Opioid-Induced Constipation in Patients with Chronic Non-Cancer Pain Receiving Opioid Therapy: A Subgroup Analysis of Patients ≥ 65 Years of Age

Conclusions This integrated analysis confirmed that OIC treatment with naldemedine 0.2 mg was generally well tolerated and effective in patients aged ≥ 65 years with chronic non-cancer pain. Safety and efficacy results were consistent with the overall patient population.

Wild J, et al. Drugs Aging. 2020;37:271-279.

The Influence of Renal or Hepatic Impairment on the Pharmacokinetics, Safety, and Tolerability of Naldemedine

Conclusions

The $AUC_{0\text{-}inf}$ of naldemedine did not increase substantially (GMRs <138%) in subjects with renal or hepatic impairment. Naldemedine was well tolerated in subjects with renal impairment, hepatic impairment, and healthy subjects with normal renal or hepatic function.

Fukumura K, et al. Clin Pharmacol Drug Dev. 2020;9(2):162-174.

Table 11 Dosage and administration of peripherally acting mu (μ) opioid receptor antagonists (PAMORAs) [60, 139, 147]

Drug	Administration route	Initial dose	Maintenance dose
Methylnaltrexone	Subcutaneous	In adult patients with chronic pain (except palliative care patients with advanced illness):[a]	
		12 mg (0.6 mL) as needed, given as at least 4 doses weekly, up to once daily (7 doses weekly)	
		In adult patients with advanced illness (palliative care patients):[b]	
		8 mg (0.4 mL) for patients weighing 38–61 kg	
		12 mg (0.6 mL) for patients weighing 62–114 kg	
	Oral[c]	450 mg	450 mg/day
Naloxegol	Oral	25 mg[d]	25 mg/day[d]
Naldemedine	Oral	0.2 mg/day	0.2 mg/day

Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel

De Giorgio R, et al. Adv Ther. 2021;38(7):3589-3621.

Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel

Thus, patients with OIC should be appropriately managed with an integrated strategy based on improving dietary fibre, fluid intake, and exercise, as well as by restoring bowel function without altering the antinociceptive power of opioid drugs.

In line with the international recommendations, our panel indicates the use of either osmotic (i.e. polyethylene glycol) or stimulant laxatives (i.e. anthraquinone) as first-line pharmacological treatment for OIC. Should this approach be inadequate, a second laxative can be added.

For second-line treatment, peripherally acting μ opioid receptor antagonists (PAMORAs), i.e. methylnaltrexone, naloxegol or naldemedine, are recommended being target therapies for patients with OIC unresponsive to combination of laxatives.

Prokinetics or intestinal secretagogues, i.e. lubiprostone, are off-label for OIC in Italy and their use should be restricted to specialist centres and clinical trials.

De Giorgio R, et al. Adv Ther. 2021;38(7):3589-3621.

Prompt diagnosis of **idiopathic chronic constipation + OIC**

Diagnosis of **OIC**

Dietary and behavioural modification.
Prescription of laxatives, if not already taken, preferably PEG or stimulant laxatives, at the minimum effective dose

Review at 2 weeks (clinical and measurement scales) with possible intercurrent phone contact in the event of worsening symptoms/signs.
If ineffective, increase the laxative dose up to the highest tolerated level.
If constipation persists, introduce a second laxative with a complementary mode of action

RESPONSE TO LAXATIVES
Reduce and possibly discontinue laxatives.
Continue treatment and clinical monitoring

NO RESPONSE TO LAXATIVES after 3 days:
Introduce a **PAMORA**[a]
in combination with laxative treatment

RESPONSE TO PAMORA
Discontinue laxative treatment and maintain PAMORA.
Monitor treatment effectiveness

NO RESPONSE TO PAMORAs
Clinical specialist investigations (anorectal manometry, evaluation of transit time, pelvic MRI, or MRI enterography)[b]

Prescribe a **third-line agent** (prokinetics/secretagogues)[c]

Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel

De Giorgio R, et al. Adv Ther. 2021;38(7):3589-3621.

Tabella VII. La corretta indicazione ai PAMORA, secondo la Nota AIFA n. 90.

Metilnaltrexone Naldemedina Naloxegol	La prescrizione a carico del SSN è limitata alle seguenti condizioni: • soggetti in terapia cronica con oppiacei e diagnosi di costipazione indotta da oppiacei secondo i criteri di ROMA-IV che rispondano contemporaneamente alle seguenti caratteristiche: – terapia cronica e continuativa con oppiacei – resistenza al trattamento con almeno due lassativi di cui uno ad azione osmotica (la resistenza è definita come la mancata risposta dopo 3 giorni)

PRESCRIVIBILITA'