PRC

New opioid analgesics for cancer pain. An addition for present guidelines?

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Norwegian Cancer Society Kreft foreningen

EAPC

Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Sanitario Regione Lombardia

From…

"USE OF OPIOID ANALGESICS IN THE TREATMENT OF CANCER PAIN: EVIDENCE-BASED RECOMMENDATIONS FROM THE EAPC"

A project of the European Palliative Care Collaborative (EPCRC) on behalf of the European Association for Palliative Care (EAPC)

Lancet Oncology, February 2012

….to

“PAIN MANAGEMENT IN CANCER PATIENTS: EVIDENCE BASED RECOMMENDATIONS FROM THE EAPC”

New topics

- In adult patients with moderate to severe pain directly due to cancer, which is the evidence that oral tapentadol is better than placebo, or other oral/transdermal opioids in the management of pain?

- In adult patients with moderate to severe pain directly due to cancer, which is the evidence that the combination of oxycodone with naloxone is better than placebo, or other oral/transdermal opioids in the management of pain and/or constipation?

Tapentadol
Embase Session Results

Number	Query	Results
#1	**'tapentadol'**/exp OR **tapentadol**	533
#2	**'cancer'**/exp OR **cancer**	3,846,999
#3	**'pain'**/exp OR **pain**	977,275
#4	**#1** AND **#2** AND **#3**	**94**

Tapentadol

- **Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain.**

  Imanaka K, Tominaga Y, Etropolski M, van Hove I, Ohsaka M, Wanibe M, Hirose K, Matsumura T.

  Curr Med Res Opin 2013 Oct; 29(10): 1399-409

- **Efficacy and safety of oral tapentadol extended release for the management of moderate to severe, chronic malignant tumor-related pain**

  Kress HG, Koch ED, Kosturski H, Steup A, Karcher K, Etropolski M, Eerdekens M

  Poster presented at the American Society of Regional Anesthesia and Pain Medicine (ASRA) 11th meeting, November 15-18, 2012, Miami , Florida.

Imanaka et al, 2013

- **<u>Study design</u>**:

  randomized, double-blind, active-controlled phase 3 non-inferiority study evaluated the efficacy and safety of oral tapentadol ER (25–200 mg bid) compared with oral oxycodone HCl CR (5–40 mg bid) in patients with moderate to severe, chronic malignant tumor-related cancer pain.

Imanaka et al, 2013

Patients' characteristics:

- Pain : average pain intensity score over the previous 24 hours of ***at least 4*** (NRS)
- Opioid naive

Study treatment:

- Starting dose: 25 mg of tapentadol bid or 5 mg of oxycodone bid
- Dose rescue: 5 mg of IR oral morphine (no limits of number doses and timing of doses per day)

Imanaka et al, 2013

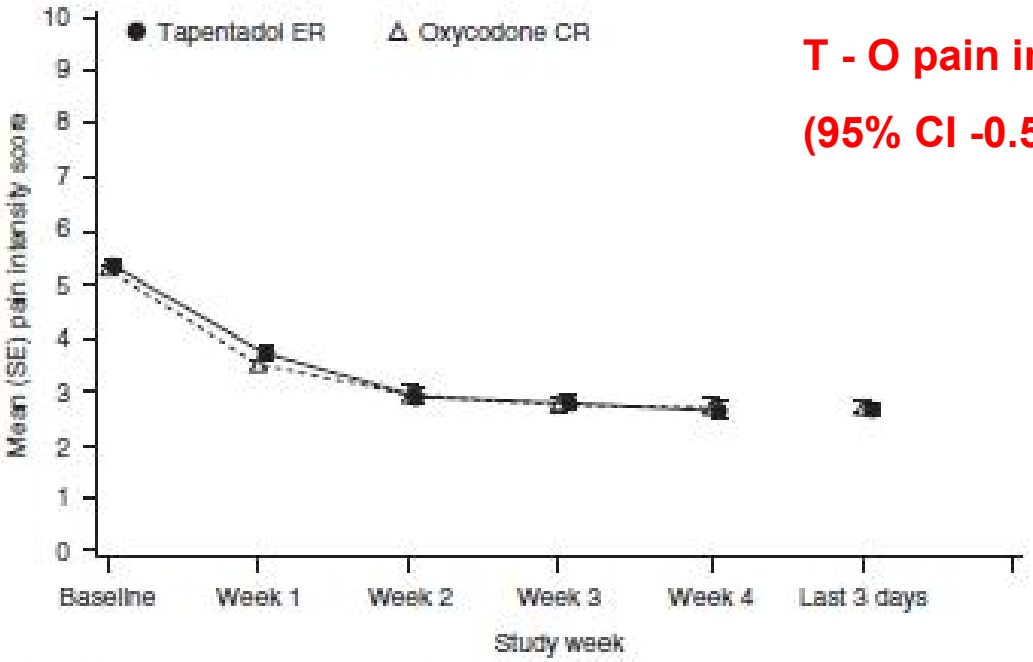
- The primary aim was to show non-inferiority of tapentadol ER to oxycodone CR for the change in average pain intensity from baseline to the last 3 days of study drug administration.

- Secondary endpoints included the Patient Global Impression of Change (PGIC) and the rescue medication use.

Imanaka et al, 2013

	Tapentadol ER	Oxycodone CR
Pts randomized (n)	171	172
Completed study (n)	110	121
Drop out rate (%)	34.5	29.7

Imanaka et al, 2013 Results



T - O pain intensity Δ=-0.06

(95% CI -0.51 to 0.38)

Figure 2. Mean (SE) pain intensity over time (LOCF; per protocol population). SE, standard error; LOCF, last observation carried forward; ER, extended release; CR, controlled release.

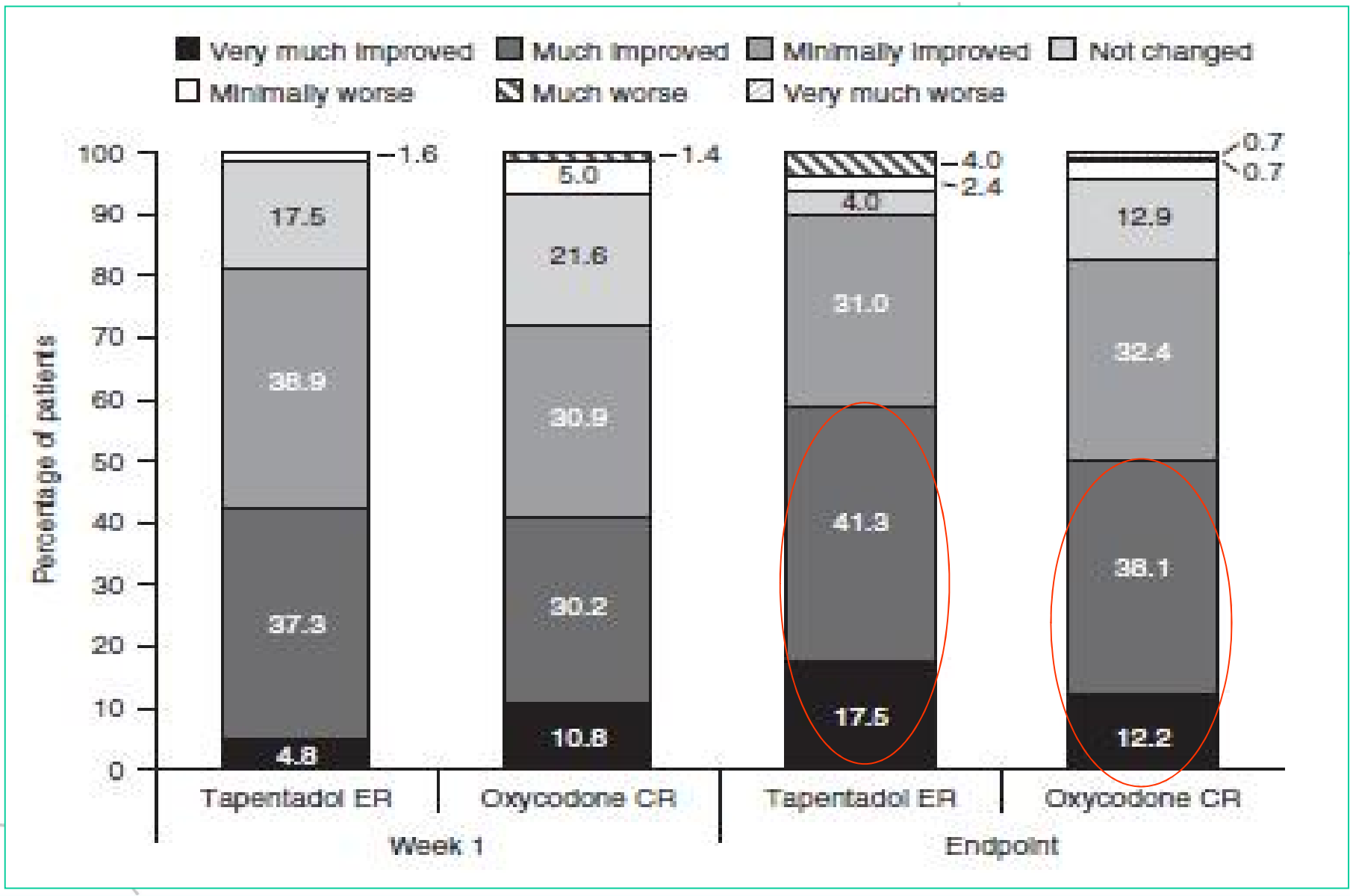
Imanaka et al, 2013 Results

- The median of the mean total daily dose (TDD) of study drug taken during double-blind treatment was **64.5 mg** for tapentadol and **13.8 mg** for oxycodone
- The median modal (or most frequently used) TDDs were **50.0 mg** for tapentadol and **10.0 mg** for oxycodone

Imanaka et al, 2013

- The mean of the average number of doses of morphine IR taken per day was **1.4** in the tapentadol group and **1.4** in the oxycodone group.

Results- patient global impression of change



Safety and tolerability

- The percentage of pts who experienced at least one TAE was 87.5% in tapentadol and 90.1% in oxycodone group
- The most common TAEs in both group were gastrointestinal (55.4% in tapentadol vs 66.4% in oxycodone)

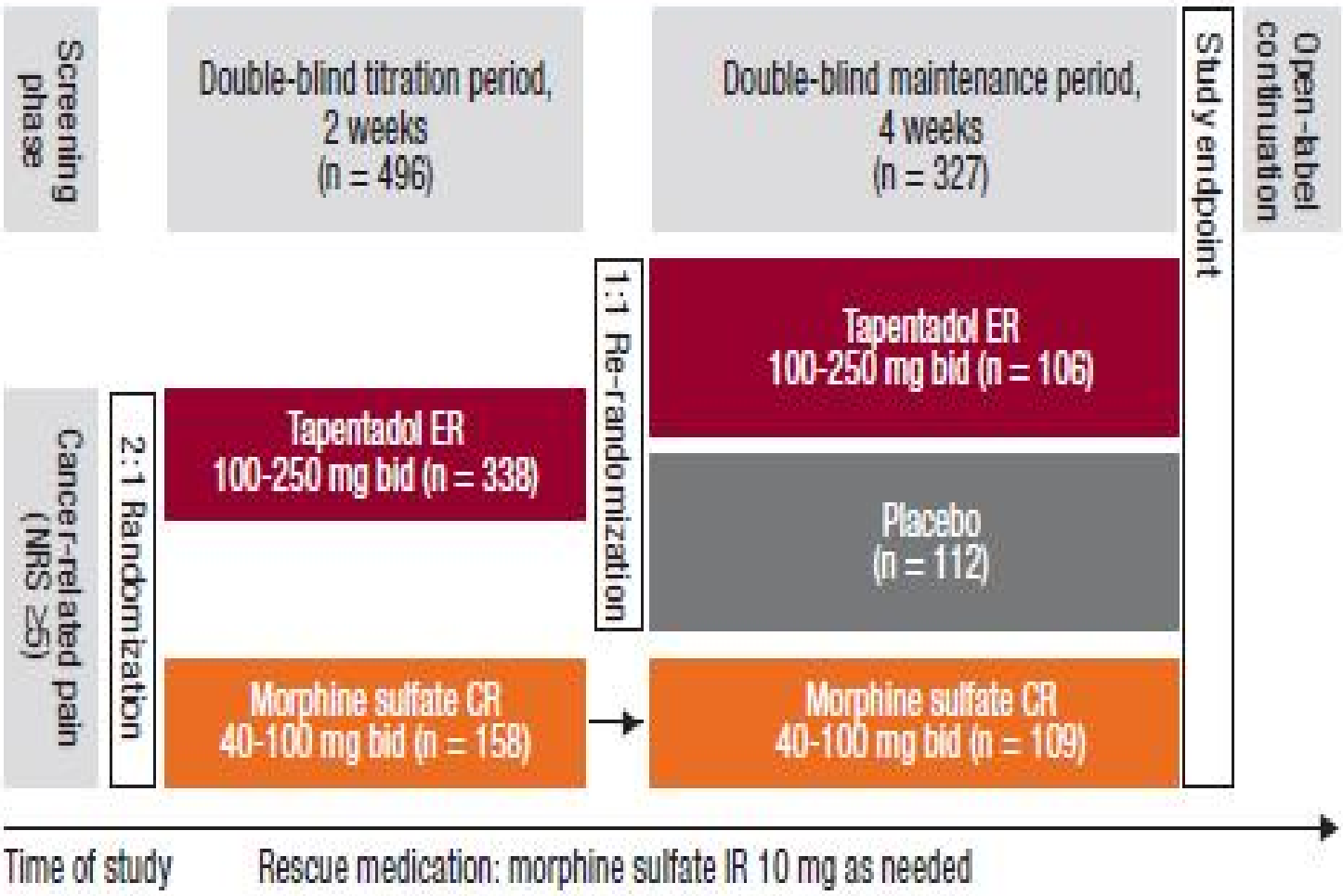
Authors' conclusion

- The results indicate that tapentadol provides analgesic efficacy non-inferior to oxycodone for the management of moderate to severe chronic cancer pain, with a better gastrointestinal profile.

Kress et al, 2012

Key inclusion criteria

- chronic, malignant tumor-related pain
- pain intensity ≥5 on an 11-point numerical rating scale at the start of titration
- no prior opioid treatment or opioid treatment with a dose equivalent of oral morphine ≤160 mg/day
- dissatisfaction with prior treatment



ER, extended release; bid, twice daily; CR, controlled release; NRS, numerical rating scale; IR, immediate release.

Figure 1. Study design and flowchart.

Kress et al, 2012

Primary efficacy end-point

To evaluate the proportion of patients who were classified as responders at the end of maintenance period

Kress et al, 2012

"RESPONDER" Definition

Based on:

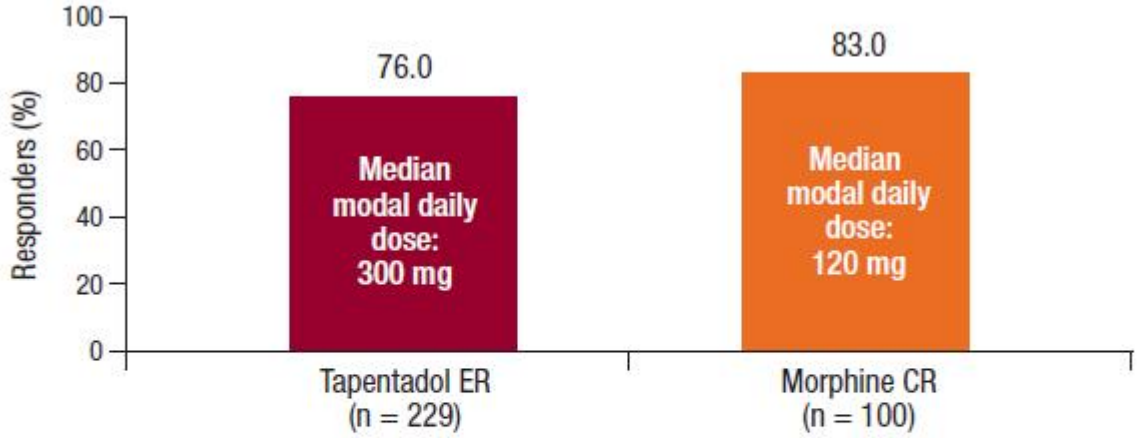
- study compliance
- mean pain intensity score <5 (NRS)
- mean consumption of rescue medication ≤20 mg/day of morphine

Kress et al, 2012

Titration Period		
	Tapentadol ER	Morphine CR
Randomized (n)	338	158
Drop out rate (%)	17.5	18.4

Results: Titration period

Lower bound of 95% CI of the between group difference in the responding rates=-15.5 %



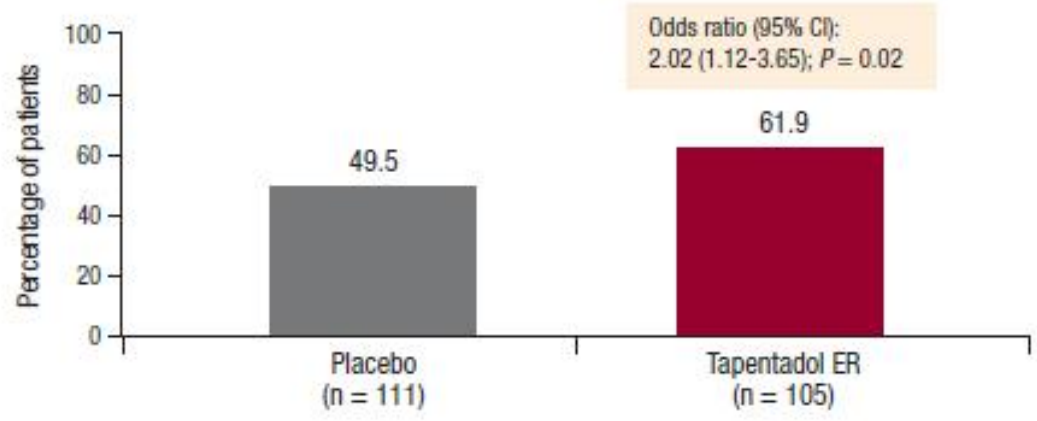
ER, extended release; CR, controlled release; NRS, numerical rating scale.
[a]Analyzed using the Farrington-Manning method.
[b]A responder at the end of the titration period was defined as a patient who completed titration, had a mean pain intensity score <5 (11-point NRS) during the last 3 days of titration, and used ≤20 mg/day of rescue medication on average during the last 3 days of titration.

Figure 4. Responder rates and median modal daily doses at the end of the titration period (per protocol population).[a,b]

Kress et al, 2012

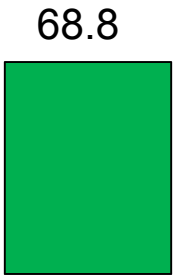
Characteristic	Placebo (112)	Tapentadol (106)	Morphine (109)
Start-of-maintenance pain intensity Mean (SD)	2.88 (1.19)	3.14 (1.16)	2.83 (1.39)

Results: Maintenance period

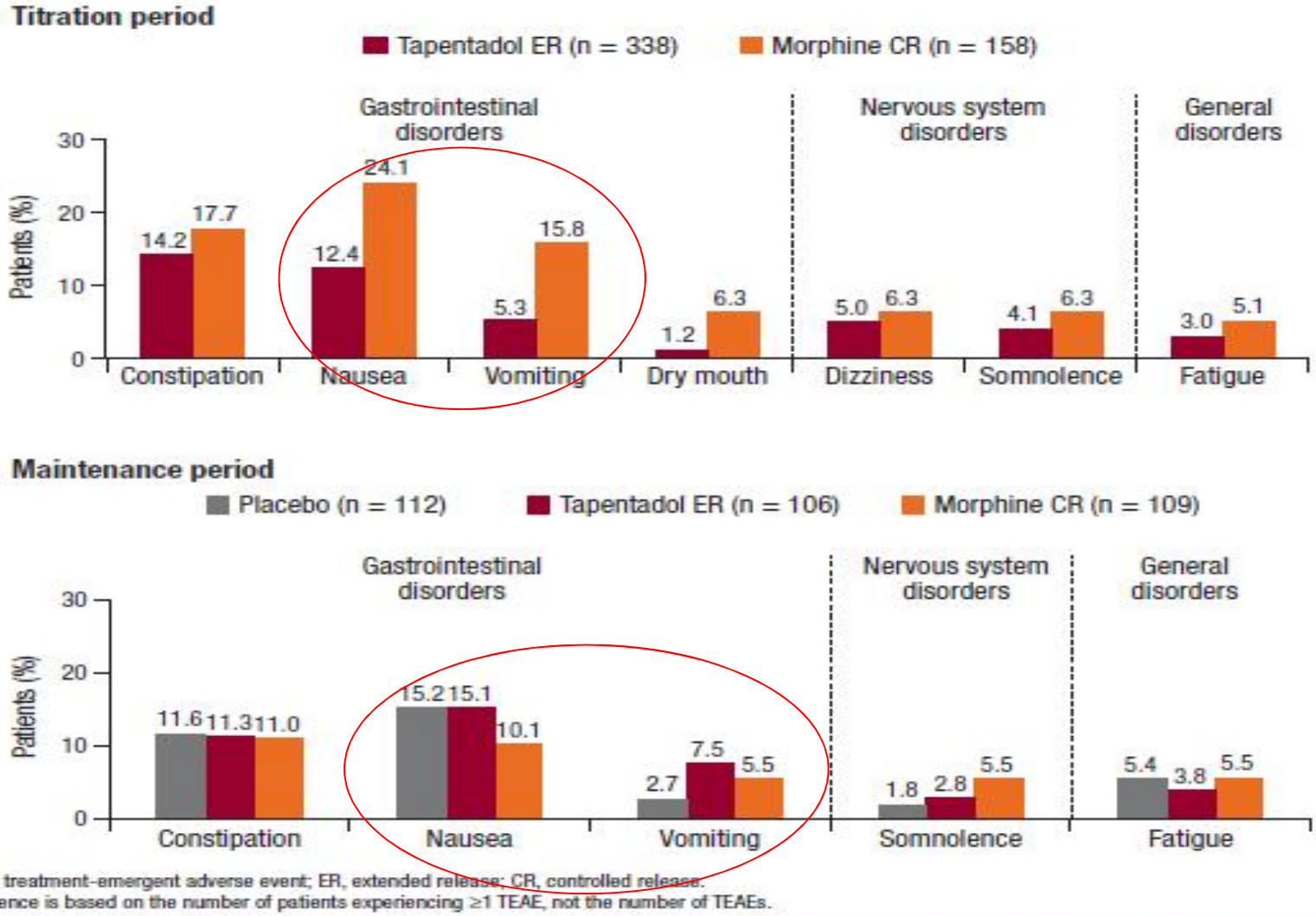


ER, extended release; CI, confidence interval; NRS, numerical rating scale.
[a]Analyzed using a logistic regression model, with treatment group and pooled center as factors and current pain intensity at the start of the maintenance period as a covariate.
[b]A responder was defined as a patient who completed ≥28 days of maintenance, had a mean pain intensity score <5 (11-point NRS) during maintenance, and used ≤20 mg/day of rescue medication on average during maintenance.

Figure 3. Responder rates during the maintenance period in the placebo and tapentadol ER groups (maintenance full analysis population).[a,b]



morphine (109)



TEAE, treatment-emergent adverse event; ER, extended release; CR, controlled release.
[a]Incidence is based on the number of patients experiencing ≥1 TEAE, not the number of TEAEs.

Figure 5. Selected TEAEs reported by ≥5% of patients in any treatment group during the A) titration period or B) maintenance period (safety populations).[a]

Authors' conclusion

- Based on responder rates at the end of titration, tapentadol ER demonstrated non-inferior efficacy compared with morphine CR in the per protocol population.
- For the primary efficacy endpoint, tapentadol ER was shown to be superior to placebo during the maintenance period in the titration responder patients.

Oxycodone + naloxone Embase Session Results

Number	Query	Results
#1	'oxycodone'/exp OR oxycodone	10,364
#2	'naloxone'/exp OR naloxone	39,549
#3	'cancer'/exp OR cancer	3,846,999
#4	'pain'/exp OR pain	977,275
#5	#1 AND #2 AND #3 AND #4	**309**

Oxycodone plus naloxone

A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain

Ahmedzai SH, Nauck F , Bar-Sela G, Bosse B, Leyendecker P, Hopp M

Palliat Med 2012, 26: 50

Ahmedzai et al, 2012

Study design

A 4-week, international, multicentre randomized, double-blind, active-controlled, double-dummy, parallel-group, Phase II study, designed to evaluate the safety and efficacy of OXN PR compared to OX PR in patients with moderate/severe chronic cancer pain.

Ahmedzai et al, 2012

Two primary objectives:

(i) To determine whether patients with moderate/severe cancer pain taking OXN PR experience an improvement in symptoms of constipation, as measured by the validated Bowel Function Index (BFI),compared with patients taking OxyPR alone;

(ii) To compare efficacy for management of chronic cancer pain, as assessed by the Brief Pain Inventory–Short Form (BPI-SF).

Ahmedzai et al, 2012

- Moderate/severe chronic cancer pain requiring opioid therapy (equivalent to 20-80 mg/day of OxyPR)
- patients were titrated up to a maximum of 120 mg/day of oxycodone PR
- oxycodone immediate-release were available to patients as rescue medication, up to a maximum of six doses per 24 h.

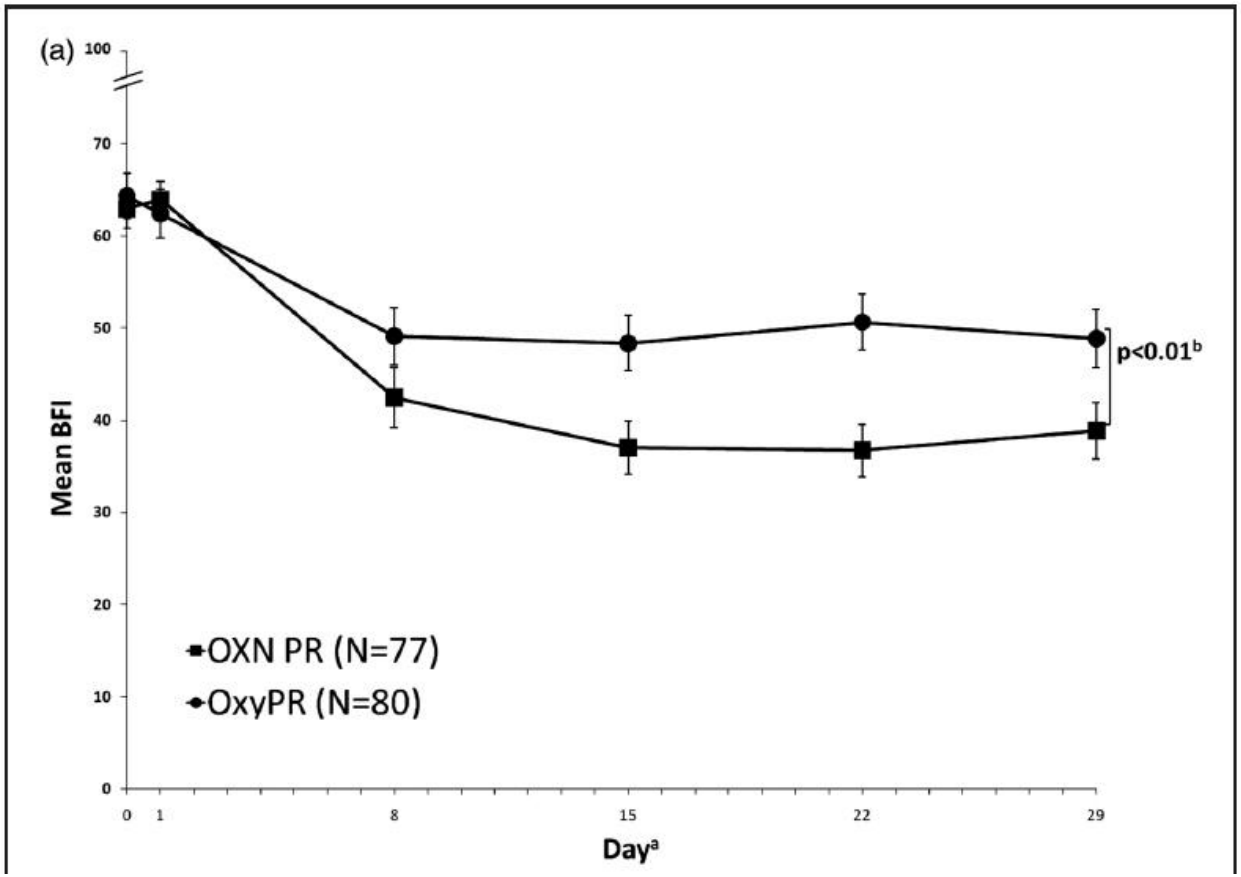
Ahmedzai et al, 2012

	OXN PR	OxyPR
Randomized (n)	92	92
Completed (n)	66	67
Drop out rate (%)	28.26	27.17

Ahmedzai et al, 2012

- The majority of patients in the OXN PR and OxyPR groups received study medication for 4 weeks (59.8 vs. 67.4%, respectively), and had similar mean durations of study participation (23.58 vs. 25.05 days, respectively) and **daily doses** (46.59 vs. 43.09 mg/day, respectively).

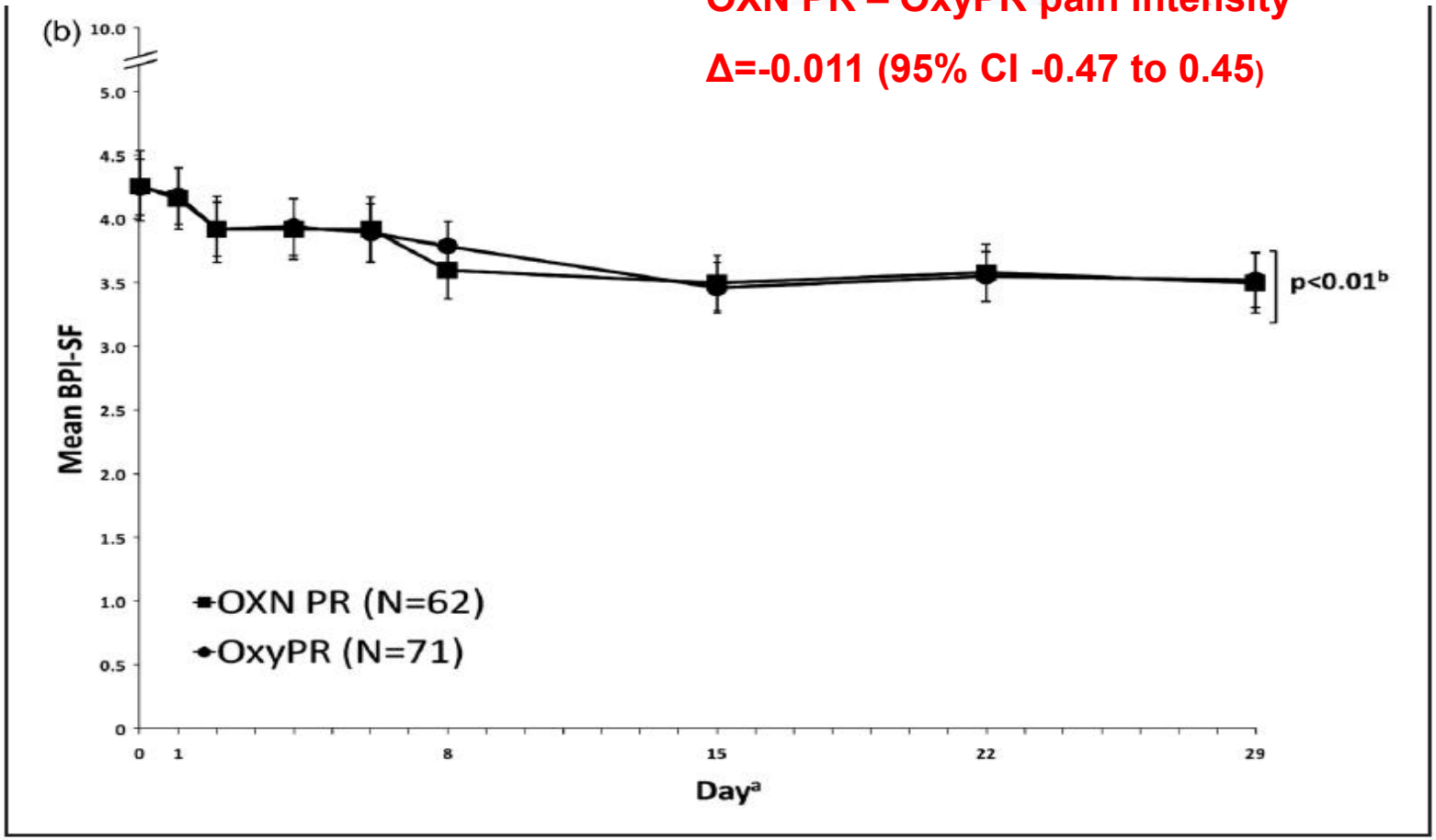
Results- Bowel function index



Results-pain (BPI-SF)

OXN PR – OxyPR pain intensity

Δ=-0.011 (95% CI -0.47 to 0.45)



Safety and tolerability

- The percentage of pts who experienced at least one TAE was 38% in OXN PR and 34.9% in Oxy PR group
- Also gastrointestinal TAEs were more common in OXN PR group (37%) than OxyPR group (30%)

Authors' conclusion

- OXN PR provides better bowel function in cancer pain patients, compared with OxyPR, without compromising analgesic efficacy or safety.

Some general considerations

- Multicenter studies (adequate sample size, no center related results)
- Drop-out rate may have biased the results and/or reduced their generalizability
- Target population definition is not always corresponding to the study aim or conclusions drawn
  - Tapentadol step II or step III?
  - Tapentadol vs morphine on “responders”
  - OXN P efficacious for controlling bowel function in pts already suffering from OIC
- Sponsorship

RECOMMENDATIONS?

TIMELINE

31 March 2015

submission of the guidelines manuscript to a peer reviewed journal