Systematic review and meta-analysis of peripherally acting opioid receptor antagonists (oxycodone/naloxone combinations, methylnaltrexone, naloxegol and other PAMORA's) for opioid induced constipation during opioid treatment in patients with chronic pain

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ABSTRACT

Background

Opioid-induced constipation (OIC) is a common and dominant adverse effect of opioid treatment. Current treatment standards of OIC advice general non-pharmacological measures, like dietary advices and exercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. Over the last decade peripherally acting mu-opioid receptor antagonists (PAMORAs) and other agents have been developed for the treatment and prevention of OIC. Currently approved agents by the European Medicines Agency (EMA) for OIC are methylnaltrexone (MNTX), naloxegol, alvimopan, naldemedine and prolonged release oxycodone/naloxone (PR OXN).

Objectives

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. Therefore we performed a systematic literature review to describe the current evidence for the efficacy of opioid receptor antagonists in the treatment of opioid induced constipation caused by opioid treatment in patients with chronic pain.

Methods

A systematic review and analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was performed. Medline, the Cochrane Central Register of Controlled Trials, Embase, Web of Science and Google Scholar were searched, without language restrictions. Included studies were randomized controlled trials as well as prospective observational studies, we excluded animal studies, review studies and retrospective analyses.

Selection criteria

The studied population was adult patients on opioids for treatment of pain. The interventions used should be peripherally acting (locally or non-systemically acting) opioid receptor antagonists (like oxycodone/naloxone combinations, methylnaltrexone, naloxegol, alvimopan and other PAMORA's). Exclusion criteria were studies including subjects treated for addiction in methadone maintenance programs or with buprenorphine/naloxone combinations, studies on healthy volunteers with opiate- or opioid-related constipation as a model to mimic the condition of patients on opioids, animal studies and basic laboratory-based research.

Data collection and analysis

For the data synthesis and the statistical analysis Review Manager (RevMan) and the GRADEpro Guideline Development Tool were used.

Main results

We included 57 articles in the meta-analysis clustered them based on unique studies, as for some studies multiple papers appeared. This resulted in the identification of 38 unique studies (13 RCTs and 25 observational studies). For all unique studies outcomes were extracted. The proportion of patients obtaining normal bowel function (according to ROME-3 criteria) was evaluated in 12 RCTs (2 naloxegol, 2 PR OXN, 2 MNTX, 3 alvimopan and 3 naldemedine RCTs). In these trials, 2812 patients received a drug and 2042 received control treatment. Treatment with opioid antagonists resulted in a statistically significant improvement of bowel function compared with rescue laxative use when looking at the proportion of patients with normal bowel movements according to ROME 3-criteria (RR:1.56; 95% CI 1.37-1.76; P<0.00001), although there was significant heterogeneity between the RCTs. The quality of the evidence varied from low too high, overall the risk difference of the proportion of patients with normal bowel function on opioid antagonist treatment was 206 (136 to 280) more per 1,000 treated patients. Besides the proportion of patients with normal bowel function all other assessed parameters were in favor of opioid antagonist treatment.

Analysis of observational study data showed that the vast majority of observational study data were generated for PR OXN. For PR OXN 15 studies were identified that included patients with OIC at study start (n=17085). The studies mainly differed in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity. Despite the heterogeneity the mean weighted improvement in BFI was -29.22 95 % CI [-35.22, -23.22] (p<0.00001) similar to the improvement seen in the RCTs -27.4 95%CI [-19.1 to -35.7]. Another 10 studies with PR OXN were identified that included patients without OIC at study start (n=4693). The mean weighted improvement was -3.38 95% CI [-10.37, 3.61]. The studies differed substantially, mainly in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity (I2=96%, Chi2=215.39, df=9).

Conclusion

Opioid antagonists, have been approved for the treatment of opioid induced constipation for a decade (first approval in EU dating from 2008 for PR OXN and MNTX). Despite approval and growing consensus with regard to using these agents in clinical practice the uptake in formal guidelines is still minimal. Together with the study by Nee et al. 2018

(describing the safety and efficacy with regard to non-responders on opioid antagonists) this study provides further evidence on the efficacy with respect to bowel function and pain of opioid antagonists, like naloxegol, alvimopan, naldemedine, PR OXN and MNTX, in the treatment of OIC in patients with opioid treatment for chronic pain.

BACKGROUND

Opioid-induced constipation (OIC) is a common and dominant adverse effect of opioid treatment affecting up to 80% of patients treated with opioids[1-4]. OIC is frequently reported to be the most bothersome side effect associated with opioid therapy [2,5-7]. OIC has a negative impact on patients' quality of life, and has also been shown to be associated with lower work productivity, absenteeism and significant utilization of healthcare resources[2,6-9].

In the gastro-intestinal (GI) tract mu-opioid receptors are located throughout the entire enteral nervous system[10,11]. At a physiological level opioids cause inhibition of GI emptying by delaying GI transit, stimulating nonpropulsive motor activity, increasing intestinal tone, increasing fluid absorption by prolonging contact time, and decreasing the secretion of electrolytes and water into the intestinal lumen.[10-12]. Pancreatic, biliary, and intestinal secretions are depressed by opioid administration. The combined inhibition of intestinal fluid secretion and the enhancement of absorption contribute to the constipating effect of opioids[11,12]. At the tissue level, opioids exert effects on the smooth muscle located along the GI tract[4,11,12]. At the molecular level binding of opioids to GI-localized mu-opioid receptors inhibits gut motility. Opioids inhibit the firing of secretomotor and submucosal neurons as well as the release of vesicular-stored presynaptic neurotransmitters from these neurons[11,12]. Opioids inhibit the effects of the autonomic nervous system on GI smooth muscle and, thereby, decrease propulsive motility along the GI tracts[11,12]. Opioids further suppress GI motility by increasing autonomic nervous system sympathetic activity, which is mediated by enhanced release of vesicular-stored norepinephrine (noradrenaline) that subsequently acts on presynaptic α2-adrenoceptors located on enteric neurons[11,12]. The combined inhibition of enteric nerve activity, inhibition of propulsive motor activity and the inhibition of ion and fluid secretion all contribute to the development of constipation by opioid analgesics[11,12].

Current treatment standards and guidelines of OIC advice general non-pharmacological measures, like dietary advices and exercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. However, about half of all opioid treated patients requiring laxatives do not achieve satisfactory relief from OIC, as most used laxative treatments for OIC are non-specific and do not

target the underlying cause of OIC[13-15]. Furthermore, laxatives themselves may lead to gastrointestinal adverse events and complications[4,13,15].

Over the last decade peripherally acting mu-opioid receptor antagonists (PAMORAs) and other locally, non-systemically acting agents have been developed for the treatment and prevention of OIC. In this review PAMORAs like methylnaltrexone (MNTX), naloxegol, alvimopan and naldemedine were considered as was as the locally, non-systemically acting prolonged release combination of oxycodone and naloxone (PR OXN)[12].

Peripherally-acting opioid receptor antagonists and the prolonged release combination of oxycodone and naloxone (PR OXN) block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility[10,12]. By blocking μ-opioid receptors in the gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis[10,12].

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. Therefore we performed a systematic literature review to describe the current evidence for the efficacy of opioid receptor antagonist in the treatment of opioid induced constipation caused by opioid treatment in patients with pain. The review questions of this publication is: What is the efficacy of opioid antagonists and PAMORA's with regard to improvement of OIC? Also the efficacy in special subgroups (e.g. laxative-refractory patients) was assessed when available.

METHODS

We conducted the systematic review and analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[16].

Data Sources and Searches

We searched Medline, the Cochrane Central Register of Controlled Trials, Embase, Web of Science and Google Scholar from inception to August 4th 2016, without language restrictions. The search strings for the different databases are depicted in table 1. We also manually checked reference lists of the identified reports and relevant reviews to identify potentially eligible articles. On February 8th, 2018 a PubMed search was performed searching published papers between August 4th 2016 to February 8th, 2018 to identify new RCT's using the PubMed search string depicted in table 1.

Table 1: Overview of used search strings per database.

Database	Search string
Embase.com	('narcotic analgesic agent'/exp OR (buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* OR (narcotic* NEXT/1 analgesic*)):ab,ti) **AND** ('constipation'/mj OR (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/3 (function* OR dysfunction*))):ab,ti) **AND** ('opiate antagonist'/exp OR (((opioid* OR opiate*) NEAR/4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*):ab,ti) **NOT** ([animals]/lim NOT [humans]/lim) **NOT** ('conference abstracts'/it)
Medline Epub (Ovid)	(exp "Analgesics, Opioid"/ OR exp "Morphinans"/ OR "Fentanyl"/ OR "Tramadol"/ OR (buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* OR (narcotic* ADJ1 analgesic*)).ab,ti.) AND ("Constipation"/ OR (constipat* OR obstipat* OR ((bowel* OR intestin*) ADJ3 (function* OR dysfunction*))).ab,ti.) AND (exp "Narcotic Antagonists"/ OR (((opioid* OR opiate*) ADJ4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*).ab,ti.) **NOT** (animals NOT humans).sh. **NOT** (abstracts).pt.
Cochrane Central	(buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* (narcotic* NEXT/1 analgesic*)):ab,ti AND (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/3 (function* OR dysfunction*))):ab,ti AND (((opioid* OR opiate*) NEAR/4 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*):ab,ti
Web of Science	**TS=(**(buprenorphine* OR fentanyl* OR hydromorphone* OR morphine* OR opioid* OR opiate* OR oxycodone* OR tapentadol* OR tramadol* (narcotic* NEAR/1 analgesic*)) **AND** (constipat* OR obstipat* OR ((bowel* OR intestin*) NEAR/2 (function* OR dysfunction*))) **AND** (((opioid* OR opiate*) NEAR/3 (antagonist*)) OR alvimopan* OR methylnaltrexone* OR naloxegol* OR naloxone* OR PAMORA*) **NOT (**animal* OR mice OR mouse OR rat OR rats **NOT** (human* OR patient*)**)) AND DT=**(Article)
Google Scholar	buprenorphine|fentanyl|hydromorphone|morphine|opioid|opiate|oxycodone|tapentadol|tramadol constipation|obstipation|"bowel|intestine function|dysfunction" antagonist|alvimopan|methylnaltrexone|naloxegol|naloxone|PAMORA
Additional PubMed search Feb 8th	(buprenorphine*[tiab] OR fentanyl*[tiab] OR hydromorphone*[tiab] OR morphine*[tiab] OR opioid*[tiab] OR opiate*[tiab] OR oxycodone*[tiab] OR tapentadol*[tiab] OR tramadol*[tiab]) AND ((constipat*[tiab] OR obstipat*[tiab]) OR ((bowel*[tiab] OR intestin*[tiab]) AND (function*[tiab] OR dysfunction*))) AND (alvimopan*[tiab] OR methylnaltrexone*[tiab] OR naloxegol*[tiab] OR naloxone*[tiab] OR naltrexone*[tiab] OR naldemedine*[tiab] OR PAMORA*[tiab]) NOT (animals[mesh] NOT humans[mesh])

Study Selection

Two reviewers (G. K. and Y. v. M.) independently assessed the eligibility of studies. Discrepancies, if any, were resolved by consensus by a third independent investigator (F.H.). Included studies were randomized controlled trials as well as prospective observational studies, we excluded animal studies, review studies and retrospective analyses. The prospective observational studies were divided in studies with prospective control arms and studies without control arms. All studies had to comply with predefined in- and exclusion criteria.

Study in- and exclusion criteria

Included studies had to comply with the following inclusion criteria. The studied population was adult patients on opioids for treatment of pain. The sample size (n) of each arm (or no. of included patients in case of uncontrolled studies) was set at n≥10. The interventions used should be peripherally acting (locally or non-systemically acting) opioid receptor antagonists (like opioid/naloxone combinations (PR OXN), methylnaltrexone (MNTX), naloxegol, alvimopan and other PAMORA's). Exclusion criteria were studies including subjects treated for addiction in methadone maintenance programs or with buprenorphine/naloxone combination, studies on healthy volunteers with opiate- or opioid-related constipation as a model to mimic the condition of patients on opioids, animal studies and basic laboratory-based research as well as studies with a group size of <10.

Outcome measures

The primary endpoint was opioid induced constipation (OIC). There is not one specific measure for OIC. A systematic review and consensus article by Gaertner et al.[17] has suggested that when measuring OIC a combination of outcomes should be measured, consisting of objective outcome measures, patient reported outcome measures and patient-reported global burden measures of OIC. Therefore the measures evaluated when looking at OIC consisted of a) objective measures of bowel movements (e.g. proportion of patients with normal bowel function based on ROME-3 criteria, complete spontaneous bowel movements [CSBM], spontaneous bowel movements [SBMs], rescue medication free bowel movements [RFBM], and bowel movements [BM], time to laxation, transit time, laxation within 4 hours and Brsitol Stool Form Scale [BSFS]) b) patient reported outcome measures (like Bowel Function Index [BFI], Patient Assessment of Constipation-symptom score [PAC-SYM], Global Clinical Impression of Change [GCIC]) c) patient-reported global burden measures of OIC (like Patient Assessment of Constipation-Quality of Life [PAC-QoL] and constipation distress) and d) additional laxative use. Secondary endpoint of the systematic search was pain relief measured with scales like Numeric Rating Scale (NRS), Numeric Analogue Scale (NAS), Verbal Rating Scale (VRS) or Verbal Analogue Scale (VAS).

Data Extraction and Quality Assessment

The predetermined outcome measures were extracted from each included study. The following items were recorded per study: registry number; registry number of extension study; treatment groups; study sample size; length of follow-up; and relevant patient characteristics including age, sex, predominant indication of pain. Two reviewers independently evaluated the potential risk of bias of each trial according to the GRADE-evaluation systematic.

Data Synthesis and Statistical Analysis

For the data synthesis and the statistical analysis Review Manager (RevMan) [Computer program]. (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the GRADEpro Guideline Development Tool [Software] (McMaster University, 2015, developed by Evidence Prime, Inc.., Available from gradepro.org) were used. As all data were prospectively generated relative risks (RR), were used as summary statistics for binary variables, resulting in more easily interpretable data. Weighted (standardized) mean differences (WMDs) were effect estimates for continuous variables. The RR with a 95% CI as well as the W(S)MDs with 95% were derived from published study data. No enquiries for missing variables were performed. .

RCTs and prospective observational studies were analyzed separately. Not all outcomes were present in all studies. Only outcomes that were identified for multiple substance were compared. Pooled analyses were calculated with fixed-effect models (Mantel–Haenszel method) or random-effect models (DerSimonian and Laird) according to the extent of heterogeneity. Heterogeneity was assessed with the I^2 statistic and the Chi^2-test (Cochran Q-test). A p-value < 0.10 indicates significant heterogeneity and I-squared of 0% to 40%, 30% to 60%, 50% to 90% and 75% to 100% represent heterogeneity that might not be important, moderate heterogeneity, substantial heterogeneity and considerable heterogeneity, respectively. To test the robustness of the findings, we performed, when available, subgroup analyses on laxative refractory patients. Publication bias was assessed visually by performing Funnel plot analyses.

RESULTS

Study Selection and Characteristics

The systematic literature review identified 1279 unique citations and the additional literature check in PubMed on February 8th retrieved another 77 citations resulting in 1356 citations of which the title/abstracts (tiab) were independently scanned by 2 researchers as described by Bramer et al. 2017 using EndNote[18]. 1004 abstracts were dismissed by both reviewers and another 54 articles were discussed between both authors and thereafter dismissed. Resulting in 1058 excluded citations. The resulting 298 articles were reviewed again on article type. A further 226 articles were dismissed for being review articles, articles that were not in English or German, articles that were cost-effectiveness studies or articles that were abstracts presented on congresses. Together this resulted in the definite inclusion of 72 articles in the systematic review (Figure 1)[4,15,19-89]. Although sample size was part of the inclusion and exclusion parameters none of the studies were dismissed solely based on this criterion.

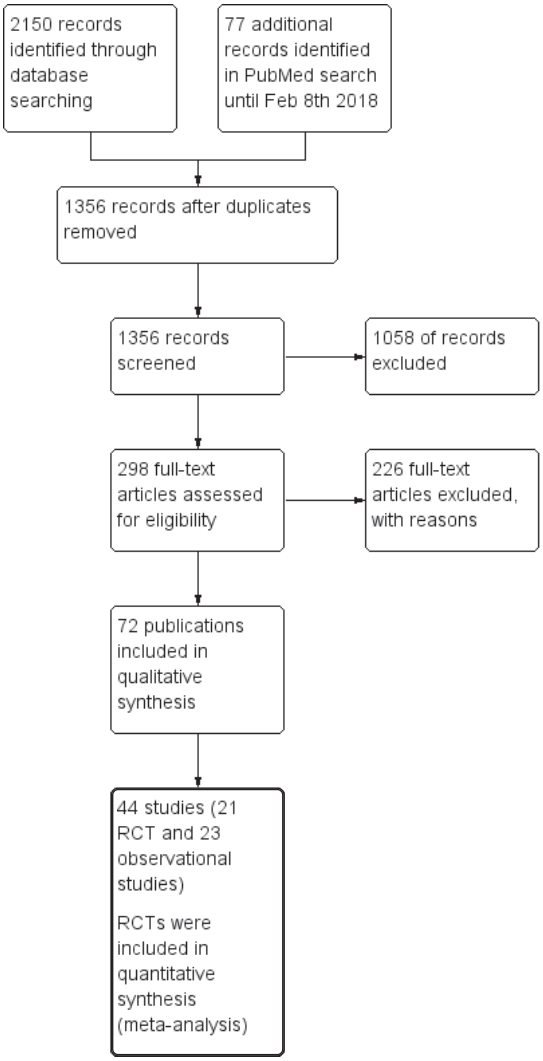

Figure 1: Flow diagram of studies identified, excluded, and finally included for the meta-analysis.

All 72 articles that were labelled as definite inclusion were uploaded in Review Manager (version 5.3) and clustered based on unique studies, as for some studies multiple papers appeared. This resulted in the identification of 44 unique studies (21 RCTs and 23 observational studies). For all unique studies outcomes were extracted. Detailed baseline characteristics as well as risk of bias assessment of included RCTs are presented in Table 2.

Table 2: Baseline characteristics and risk of bias assessment of included RCTs

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
Naloxegol						
KODIAC-04	NCT01309841	Australia, Germany, Slovakia, United States, 115 centers, outpatient	non-cancer-related pain, history of OIC (back pain 56.0%)	<3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC. Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the lectronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate,severe, or very severe straining; incomplete BM.	641 (61.3%)	12 weeks (open label extension data available)
KODIAC-05	NCT01323790	Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, United Kingdom, and the United States (US), 142 centers, outpatient	non-cancer-related pain, history of OIC (back pain 56.8%)	<3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and had a confirmed diagnosis of OIC. Confirmed OIC was defined as: documented <3 SBMs/week on average over the 2-week OIC confirmation period. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the bowel movements (BMs) recorded in the lectronic diary during the OIC confirmation period: Bristol Stool Scale stool type 1 or 2; moderate,severe, or very severe straining; incomplete BM.	696 (63.4%)	12 weeks (open label extension data available)
Naloxone (OXN)						
OXN2001	NCT00513656	UK, 1 center, outpatient	diagnosis of cancer and a documented history of moderate/severe, chronic cancer pain. (breast (19%), lung (13%) and prostate (10%) cancer)	No criteria for OIC at inclusion	184 (49%)	4 weeks (open label extension available)
OXN10-KR-002	NCT01313780	Korea, 7 centers, outpatient	moderate to severe cancer-related pain (colorectal cancer, 40.9%)	No criteria for OIC at inclusion	117 (29.9%)	4 weeks

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
-response rate with respect to bowel function -rescue laxative use -change from baseline number of SBMs per week -PAC-SYM score -pain relief	Response rate defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks.	*Chey 2014, Coyne 2017, Holzer 2015, Lawson 2016, Tack 2015, Webster 2014, Webster 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
-response rate with respect to bowel function -rescue laxative use -change from baseline number of SBMs per week	Response rate defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks.	*Chey 2014, Coyne 2017, Lawson 2016, Tack 2015, Webster 2014, Webster 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
-Bowel Function Index (BFI-score) -PAC-SYM total score -pain relief	The null hypothesis for BFI was a zero difference (on average) between treatment groups at the final visit. The null hypothesis for BPI-SF was a difference of -1 (on average) between treatment groups at the final visit, in favour of Oxy PR (OXN PR inferior to OxyPR).	*Ahmedzai 2012, Ahmedzai 2014, Koopmans 2014	LOW	LOW	LOW	LOW	HIGH	LOW	LOW
-pain relief	Change of pain intensity	Lee 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
OXN3001	NCT00412152	UK, Gemany, Spain, Czech Republic, 93 sites, outpatient	moderate-to-severe noncancer pain and constipation caused or aggrevated by an opioid (82.9% musculo-skeletal pain)	Citeria for constipation caused or aggrevated by an opioid not defined in publication	316 (unpublished)	12 weeks (open label extension data available)
OXN3006	NCTO0412100	Germany, Czech Republic, Finland, Hungary, Netherlands, UK, Spain, 172 centers, outpatient	moderate-to-severe, non-malignant pain and constipation (< 3 CSBMs/ week) caused or aggrevated by opioid therapy (back pain 61%)	constipation defined as <3 CSBMs/week	265 (68.3%)	12 weeks (open label extension data available)
OXN3506	NCT01438567	Australia, Czech Republick, Denmark, Finland, France, Germany, Israel, Poland, Romania, South Korea and UK, 66 centers, outpatient	cancer and non-cancer pain suffering from opioid-induced constipation caused or aggrevated by opioids.	Constipation caused or aggravated by opioids was confirmed by the patient and the investigator as an effect of the patient's pre-study opioid medication (at a comparable dose) and evidenced by a medical need of regular intake of laxatives to have at least three bowel evacuations per week or by having less than three bowel evacuations when not taking a laxative	243 (58.8%)	5 weeks (open label extension data available)
Kokki 2017	NCT02573922	Finland, 1 center, spinal surgery	patients scheduled to have an elective lumbar or cervical spinal surgery (spinal surgery, 100%)	No criteria for OIC at inclusion	180 (45%)	3 weeks

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
-Bowel Function Index (BFI-score) -proportion of patients with laxative use -PAC-SYM total score -proportion of patients with normal number of CSBMs (≥3/ week) -pain relief	improvement in constipation as measured using the Bowel Function Index (BFI)	Blagden 2014, Koopmans 2014, Löwenstein 2010, Sandner-Kiesling 2010, *Simpson 2008	HIGH	HIGH	LOW	LOW	HIGH	LOW	LOW
-Bowel Function Index (BFI-score) -proportion of patients with laxative use -PAC-SYM total score -proportion of patients with normal number of CSBMs (≥3/ week)	improvements in symptoms of constipation, as measured by the Bowel Function Index (BFI)	Blagden 2014, Koopmans 2014, Löwenstein 2010, *Löwenstein 2009	LOW	HIGH	LOW	LOW	HIGH	LOW	LOW
-Bowel Function Index (BFI-score) -pain relief	improvement in symptoms of constipation as measured by the Bowel Function Index (BFI)non-inferiority of OXN PR compared with OxyPR with respect to the analgesic efficacy	*Dupoiron 2017a, Dupoiron 2017b	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-proportion of patients with laxative use	prevalence of constipation at 7 days after surgery	Kokki 2017	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
methylnaltrexone (MNTX)						
Michna 2011	NCT00529087	US, 78 centers, outpatient	chronic non-malignant pain and a history of constipation due to opioid use and fewer than 3 RFBMs per week (back pain, 60.4%)	Constipation during the screening period was defined as fewer than 3 RFBMs per week (no laxative use within 24 hours prior to any bowel movement) that were associated with one or more of the following: a) a Bristol StoolFormScale score of 1 or 2 for at least 25% of the bowel movements; b) straining during at least 25% of the bowel movements; c) a sensation of incomplete evacuation after at least 25% of the bowel movements.	460 (60.2%)	4 weeks
Rauck 2017	NCT01186770	US, 117 centers, outpatient	chronic non-malignant pain and a history of OIC (back pain, 68.2%)	OIC defined as having < 3 rescue-free bowel movements (RFBMs) per week that were associated with ≥ 1 of the following: ≥ 25% of RFBMs categorized as type 1 or type 2 on theBristol Stool Form Scale; straining during ≥ 25% of RFBMs or ≥ 25% of RFBMs with a sensation of incomplete evacuation.	803 (62.9%)	4 weeks, extended with 8 weeks (4 weeks results presented)
study 4000/4001	NCT00672477 and NCT00672139	US, Australia, Belgium, Brazil, Canada, France, Germany, Italy, Mexico, Spain, Sweden, UK, 60, outpatient	advanced illness (defined as a terminal illness [e.g., incurable cancer or other end-stage disease]), a life expectancy of ≥ 1 month, and OIC and were receiving stable doses of laxatives and opioids (cancer 66.0%)	OIC defined as < 3 bowel movements in the last week and no bowel movement in 24 hours or no bowel movement in 48 hours	230 (48.7%)	2 weeks (10 weeks open label extension) (4 week results presented)

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -No. of RFBMs/week -Rescue laxative use -Proportion of patients with normal bowel function -PAC-SYM score -pain relief	1) the proportion of subjects having a rescue-free bowel movement (RFBM) within 4 hours of the first dose, and 2) the percentage of active injections resulting in any RFBM within 4 hours	*Michna 2011, Iyer 2011	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
- RFBMs within 4 hrs of first dose -No. of RFBMs/week	mean percentage of dosing days that resulted in an RFBM within 4 hours of dosing during weeks 1 to 4	Rauck 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
- RFBMs within 4 hrs of first dose -No. of RFBMs/week -Rescue laxative use	percentage of patients with a rescue-free bowel movement (RFBM) within four hours after ‡ 2 of the first 4 doses (i.e., the first week of treatment).RFBMwas defined as a bowel movement without use of any rescue medication or procedure within four hours before the bowel movement.	Bull 2015	LOW	UNCLEAR	LOW	LOW	HIGH	LOW	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
Thomas 2008	NCT00402038	US, Canada, 27 , nursing homes, hospice sites, and palliative care centers.	advanced illness, which was defined as a terminal disease (incurable cancer or other end-stage disease) with a life expectancy and OIC (cancer, 58.2%)	opioid-induced constipation with either fewer than three laxations during the preceding week and no clinically meaningful laxation (as determined by the investigator) within 24 hours before the first study dose or no clinically meaningful laxation within 48 hours before the first study dose.	134 (56.7%)	2 weeks (3 month open label extension)
MNTX 301	NCT00401362	US, 17 centers, hospices and palliative care centers	advanced illness (life expectancy of 1-6 months) and OIC (cancer, 81.2%)	No clinically signifcant laxation within 48 hours prior to the frst study drug dose	154 (45.5%)	single-dose, 28 day open-label and 3 month extension
Alvimopan						
Paulson 2005		US, 22 centers, secondary and tertiary care	Patients on opioid therapy (88% chronic pain) with OIC (back pain, 38.7%)	<3 bowel movements per week without laxative use or enemas and at least one associated symptom: lumpy or hard stools, straining, sensation of anorectal obstruction, or sensation of incomplete evacuation	168 (58.3%)	3 weeks
SB767905/011		Australia, Germany, Greece, Italy, Portugal, US, Belgium, Canada, Denmark, 113 centers, outpatients	bowel dysfunction resulting from chronic opioid treatment for the management of pain of a non-cancer origin (back pain, 58.2%)	history of decreased bowel movement frequency since initiating opioid therapy and ≥1of the following symptoms: incomplete evacuation, hard stools, or straining, in ≥25% of bowel movements	522 (63.8%)	6 weeks
SB-767905/012		US, Canada, Europe, 148 centers, standalone research centers, pain centers, and non-pain practice external research centers.	persistent non-cancer pain and a recalled history of opioid-induced bowel dysfunction (back pain, 59%)	<3 spontaneous BMs (SBMs) per week and occurrence of at least 1 of the following symptoms for $25% of BMs— sense of incomplete evacuation after passing a stool, straining to pass a stool, or lumpy hard stools, or small pellets.	518 (63%)	12 weeks

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -Proportion of patients with normal bowel function -pain relief	proportion of patients with rescue-free laxation within 4 hours after the first dose of the study drug and the proportion of patients with rescue-free laxation within 4 hours after two or more of the first four doses.	Thomas 2008	LOW	LOW	LOW	LOW	HIGH	LOW	LOW
- RFBMs within 4 hrs of first dose -RFBMs within 24 hrs of first dose -pain relief	proportion of patients with laxation within 4 hours after administration of the double-blind dose.	Nalamachu 2015, *Slatkin 2009	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-number of bowel movements per week -pain relief	proportion of patients with at least 1 BM within 8 hours of study drug administration on each day during the 21-day treatment period, averaged across all patients.	Paulson 2005	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW
-Proportion of patients with normal bowel function -number of bowel movements per week	change in weekly spontaneous bowel movement frequency during the first 3 weeks of the 6-week treatment period.	Webster 2008	LOW	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW
-Proportion of patients with normal bowel function -number of bowel movements per week -proportion of patients using concomittant laxatives	proportion of 'responders', with responder defined as a patient experiencing 3 or more SBMs per week over the treatment period and an average increase from baseline of at least 1 SBM per week.	Jansen 2011	LOW	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW

Table 2: Baseline characteristics and risk of bias assessment of included RCTs (*continued*)

Study	Clinicaltrials.gov identifier	Country, # centers, setting	Patient group (main indication, %)	Criteria for OIC at inclusion	Total no. Pts (% female)	Treatment-duration
SB-767905/013		US, Canada, Europe, 153 centers, non–pain-practice research center extensions of clinical sites, research centers, and pain centers	persistent non-cancer pain and a recalled history of opioid-induced bowel dysfunction (back pain, 60%)	<3 spontaneous BMs (SBMs) per week and occurrence of at least 1 of the following symptoms for $25% of BMs— sense of incomplete evacuation after passing a stool, straining to pass a stool, or lumpy hard stools, or small pellets.	485 (64%)	12 weeks
Naldemedine						
COMPOSE-1	NCT01965158	USA, Austria, Czech Republic, Germany, Poland, Spain, UK, 68, outpatient	chronic non-cancer pain and OIC (unknown)	no more than four spontaneous bowel movements (SBMs) over the 14-day qualifying period with no more than three SBMs in a given week; at least one bowel symptom (presence of straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage) in at least 25% of bowel movements	547 (60.1%)	12 weeks
COMPOSE-2	NCT01993940	USA, Austria, Czech Republic, Germany, Poland, Spain, 69, outpatient	chronic non-cancer pain and OIC (unknown)	no more than four spontaneous bowel movements (SBMs) over the 14-day qualifying period with no more than three SBMs in a given week; at least one bowel symptom (presence of straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage) in at least 25% of bowel movements	553 (60.2%)	12 weeks
COMPOSE-4	JAPIC-CTI-132340	Japan, 70 sites	cancer pain and OIC (lung cancer, 45.1%)	five or fewer spontaneous bowel movements (SBMs; a bowel movement not induced by rescue laxatives) and experience with straining, incomplete evacuation, and/or hard stools in 25% or more of all BMs during the 2 weeks before random assignment.	193 (38.3%)	2 weeks (12 weeks open label extension study)

Outcome measures used in review	Primary endpoint	Associated publications	Random Sequence Generation	Allocation Concealment	Blinding of participants or personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting/ reporting bias	Other Bias
-Proportion of patients with normal bowel function -number of bowel movements per week -proportion of patients using concomittant laxatives	proportion of "responders," with responder defined as a patient experiencing 3 or more SBMs per week over the treatment period and an average increase from baseline of at least 1 SBM per week.	Irving 2011	LOW	UNCLEAR	LOW	LOW	HIGH	UNCLEAR	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of responders, with a responder defined as a patient having at least three SBMs per week and an increase from baseline of at least one SBM per week for that week (a positive response week) for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the 12-week treatment period.	Hale 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of responders, with a responder defined as a patient having at least three SBMs per week and an increase from baseline of at least one SBM per week for that week (a positive response week) for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the 12-week treatment period.	Hale 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW
-proportion of patients with normal bowel function -change in number of SBMs per week -change in number of CSBMs per week -pain relief	proportion of SBM responders during the 2-week treatment period. An SBM responder was defined as a patients with three or more SBMs/week who had an increase of one or more SBM/week from baseline.	Katakami 2017	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW

Pain relief

Pain relief was assessed in all randomized controlled trials. However, for a number of studies effects on pain relief were described in writing and no actual pain scores were reported. When assessing studies that did report on pain relief (either in numbers or graphs) the analysis showed that treatment with opioid antagonists did not interfere with pain relief. As expected there were no differences between treatments reflected by a standardized mean difference (95% CI) of 0.03 (-0.09, 0.03) and no heterogeneity was detected (I^2=0%) (see Figure 2).

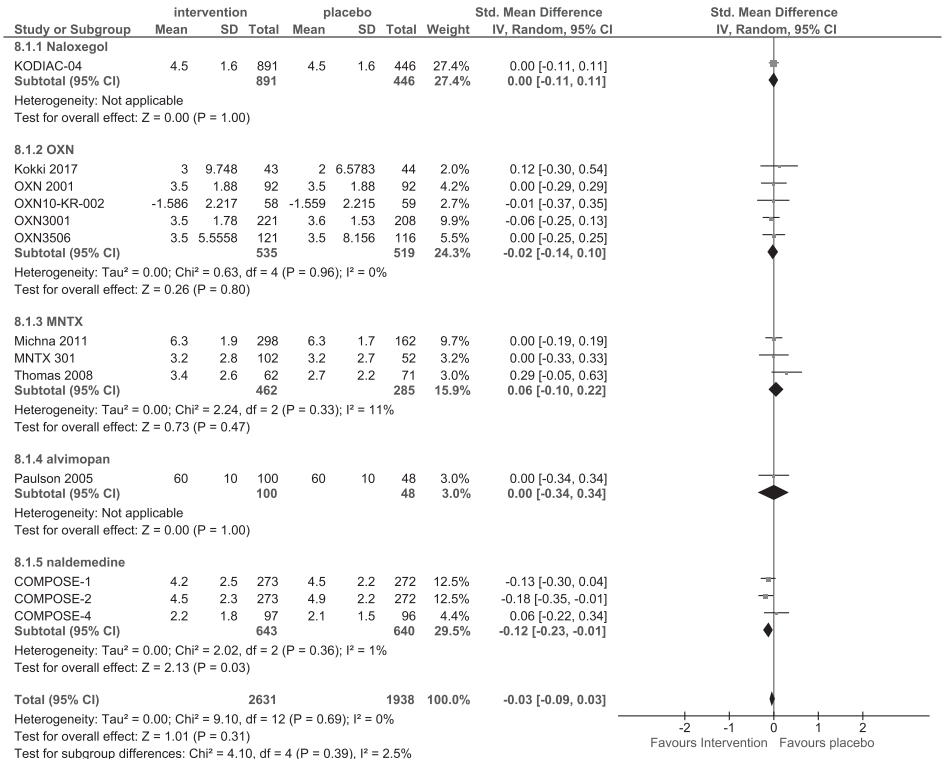

Figure 2: Forest plot of comparison: Effect of opioid antagonist treatment on pain relief (RCTs only).

The summary of findings table generated from the GradePro GDT platform for this parameter is presented in Table 3. The quality of the evidence varied from moderate to high.

Bowel function efficacy outcomes

The outcomes proportion of patients with normal bowel movements were available for naloxegol, MNTX, alvimopan, PR OXN and naldemedine, the proportion of patients with additional laxative use were available for naloxegol, MNTX, alvimopan and PR OXN, PAC-SYM total scores were available for naloxegol, MNTX and PR OXN. All other identified

Table 3. The effect of opioid antagonist treatments compared to placebo on pain relief in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Pain relief	4569 (13 RCTs)	-	-	-	SMD **0.03 lower** (0.09 lower to 0.03 higher)
Naloxegol	1337 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0** (0.11 lower to 0.11 higher)
PR OXN	1054 (5 RCTs)	⊕⊕⊕◯ MODERATE [a]	-	-	SMD **0.02 lower** (0.14 lower to 0.1 higher)
MNTX	747 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.06 higher** (0.1 lower to 0.22 higher)
Alvimopan	148 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0** (0.34 lower to 0.34 higher)
Naldemedine	1283 (3 RCTs)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.12 lower** (0.23 lower to 0.01 lower)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **SMD:** Standardised mean difference

Explanations: a. Risk of bias was identified in 4 out of 5 studies with regard to: random sequence generation and treatment allocation (OXN3001 and OXN3006), blinding (Kokki 2017 and KF5503/60), incomplete outcome data (all but Kokki 2017 and OXN10-KR-002).

bowel function parameters were analyzed per active ingredient and are presented in supplementary figure S1-S7.

Proportion of patients with normal bowel movements

The proportion of patients with normal bowel function (>3 bowel movements per week) was reported in 12 RCTs, 2 studies with naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]), 2 studies with MNTX (Michna 2011[34,37,54,55] and Thomas 2008[41,53,60,83]), 2 studies with PR OXN (OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]), 3 studies with alvimopan (SB-767905/011, SB-767905/012, SB-767905/013[35,68,70]) and 3 studies with naldemedine (COMPOSE-1, COMPOSE-2 and COMPOSE-4[27,29]). None of the observational studies reported proportion of patients with normal bowel function based on ROME-3 criteria, subsequently all studies were RCTs. Treatment with opioid antagonists resulted in a statistically significant improvement of bowel function compared with rescue laxative use when looking at the proportion of patients with normal bowel movements according to ROME 3-criteria (RR:1.56; 95% CI 1.37-1.76; P<0.00001; Figure 3). Considerable heterogeneity was detected (I^2=73%, Chi2=7.12 df=11).

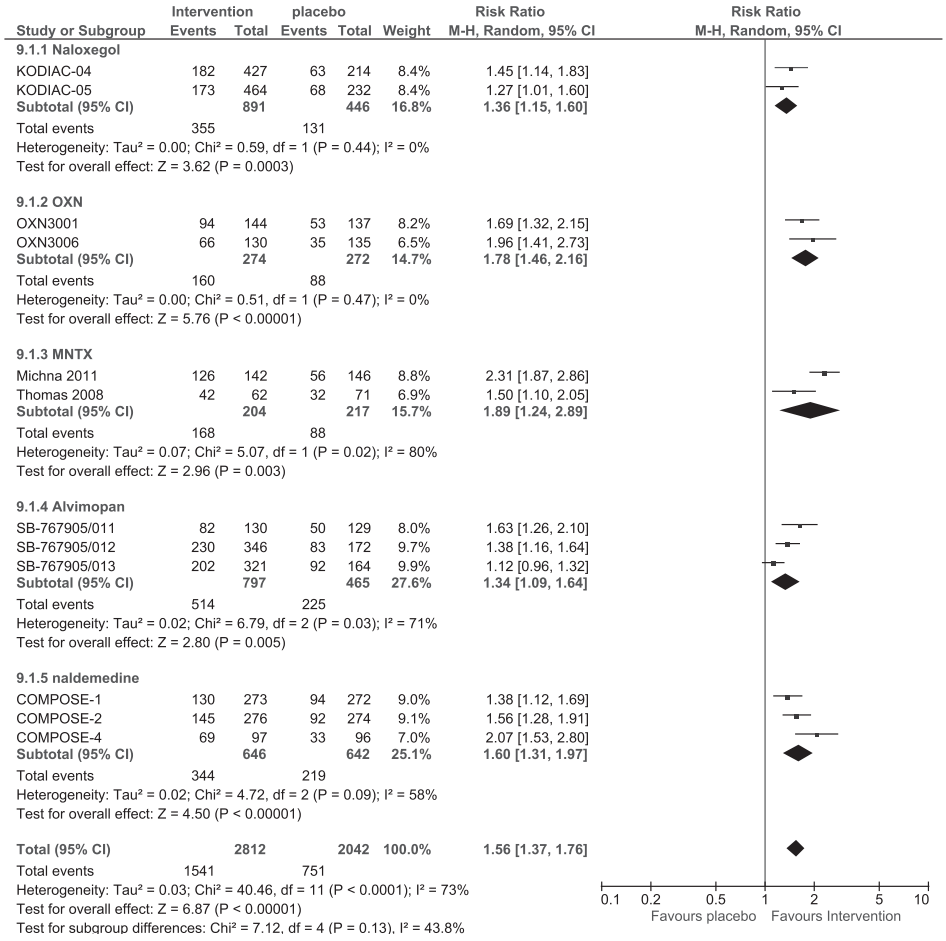

Figure 3: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the proportion of patients with normal bowel function (>3 bowel movements per week).

The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 4. The quality of the evidence varied from low to high, overall the risk difference of the proportion of patients with normal bowel function on opioid antagonist treatment was 206 (136 to 280) more per 1,000 treated patients.

Proportion of patients with additional laxative use

The proportion of patients with additional laxative use was reported in 9 RCTs, 2 studies with naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]), 2 studies with MNTX (Michna 2011[34,37,54,55] and study 4000/4001[84]), 3 studies with PR OXN (Kokki 2017[26], OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]) and 2 studies with alvimopan (SB-767905/012, SB-767905/013[68,70]. Treatment with opioid antagonists suggested a significant improve-

Table 4. The effect of opioid antagonist treatment compared to placebo on the proportion of patients with normal bowel function in patients with opioid treatment for pain and opioid induced constipation

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Proportion of patients with normal bowel function	4854 (12 RCTs)	-	**RR 1.56** (1.37 to 1.76)	368 per 1,000	**206 more per 1,000** (136 more to 280 more)
Naloxegol	1337 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.36** (1.15 to 1.60)	294 per 1,000	**106 more per 1,000** (44 more to 176 more)
PR OXN	546 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 1.78** (1.46 to 2.16)	324 per 1,000	**252 more per 1,000** (149 more to 375 more)
MNTX	421 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 1.89** (1.24 to 2.89)	406 per 1,000	**361 more per 1,000** (97 more to 766 more)
Alvimopan	1262 (3 RCTs)	⊕⊕◯◯ LOW [c,d]	**RR 1.34** (1.09 to 1.64)	484 per 1,000	**165 more per 1,000** (44 more to 310 more)
Naldemedine	1288 (3 RCTs)	⊕⊕⊕◯ MODERATE [e]	**RR 1.60** (1.31 to 1.97)	341 per 1,000	**205 more per 1,000** (106 more to 331 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio.

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN3001 and OXN3006) b. Downgraded because of significant heterogeneity between studies (I^2=80%). c. Downgraded because of uncertainty about treatment allocation (all three studies) and uncertainty about handling of incomplete outcome data (all three studies) d. Downgraded because of significant heterogeneity between studies (I^2=77%) e. Downgraded because of uncertainty about handling of incomplete outcome data

ment of bowel function compared with rescue laxative use when looking at the proportion of patients using additional laxatives (RR:0.76; 95% CI 0.69-0.84; P<0.001; Figure 4).

However, substantial heterogeneity was detected (I^2=65%, Chi2=22.60 df=8). The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 5. The quality of the evidence varied from moderate to high, overall the risk difference of the proportion of patients using additional rescue laxatives on opioid antagonist treatment was 157 (202 to 104) fewer per 1,000 treated patients.

PAC-SYM total score

The PAC-SYM total score was reported in 5 RCTs, 1 study with naloxegol (KODIAC-04[32,36,42,64,82]), 1 study with MNTX (Iyer 2011[69]) and 3 studies with PR OXN (OXN2001[66,88,89], OXN3001[45,48,58,66,85] and OXN3006[58,59,66,85]). None of the observational

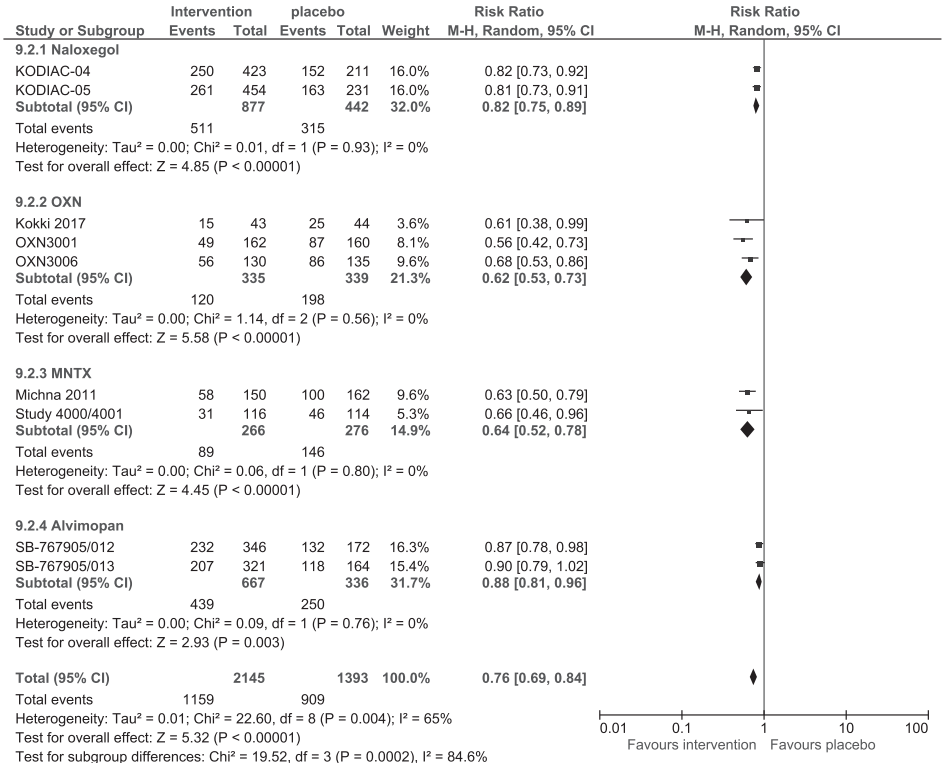

Figure 4: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the proportion of patients using rescue laxatives.

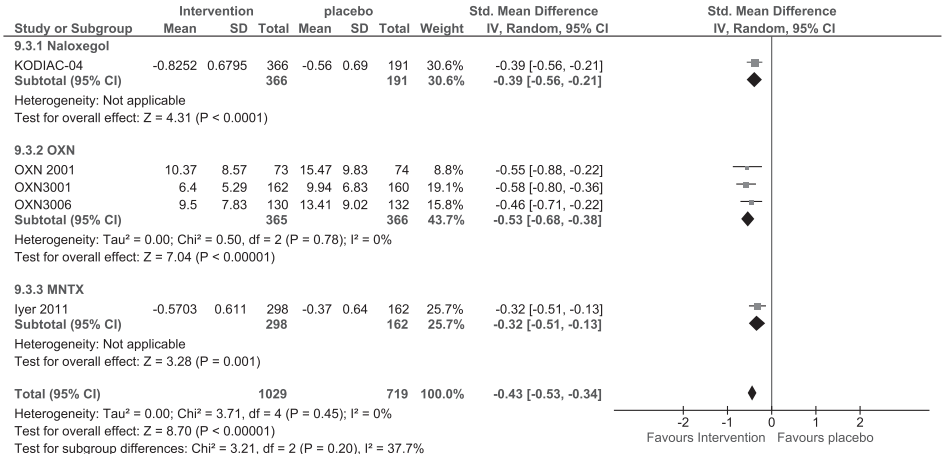

Figure 5: Forest plot of comparison: Effect of opioid antagonist treatment on bowel function (RCTs only), measured with the PAC-SYM total score.

Table 5. The effect of opioid antagonist treatments compared to placebo on the proportion of patients using rescue laxatives in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
Proportion of patients using rescue laxatives	3538 (9 RCTs)	-	**RR 0.76** (0.69 to 0.84)	653 per 1,000	**157 fewer per 1,000** (202 fewer to 104 fewer)
Naloxegol	1319 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.82** (0.75 to 0.89)	713 per 1,000	**128 fewer per 1,000** (178 fewer to 78 fewer)
PR OXN	674 (3 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.62** (0.53 to 0.73)	584 per 1,000	**222 fewer per 1,000** (275 fewer to 158 fewer)
MNTX	542 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.64** (0.52 to 0.78)	529 per 1,000	**190 fewer per 1,000** (254 fewer to 116 fewer)
Alvimopan	1003 (2 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 0.88** (0.81 to 0.96)	744 per 1,000	**89 fewer per 1,000** (141 fewer to 30 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio.

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN3001 and OXN3006) and uncertainty about blinding (Kokki 2017)

b. Downgraded because of uncertainty about treatment allocation (all studies) and uncertainty about handling of incomplete outcome data (all studies)

studies reported a PAC-SYM total score, subsequently all studies were RCTs. Treatment with opioid antagonists resulted in a statistically significant improvement of PAC-SYM total score compared with rescue (St. Mean Difference: -0.43; 95% CI -0.53, -0.34; P<0.00001; Figure 5).

No heterogeneity was detected (I^2=0%, Chi2=3.71 df=4). The summary of findings table generated from the GradePro GDT platform for this parameter is presented in table 6. The quality of the evidence varied from moderate to high.

Bowel function efficacy within the laxative refractory population

For naloxegol (KODIAC-04 and KODIAC-05[32,36,42,64,82]) and PR OXN (OXN2001, OXN3001 and OXN3006[66]) efficacy data with respect to bowel function were available. However, the reported data were not suitable for inclusion in the meta-analysis. For laxative refractory patients using naloxegol the proportion of patients responding to therapy

Table 6. The effect of opioid antagonist treatments compared to placebo on the PAC-SYM total score in patients with opioid treatment for pain and opioid induced constipation

Outcome	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with opioid antagonist treatments
PAC-SYM total score	1748 (5 RCTs)	-	-	-	SMD **0.43 lower** (0.53 lower to 0.34 lower)
Naloxegol	557 (1 RCT)	⊕⊕⊕⊕ HIGH	-	-	SMD **0.39 lower** (0.56 lower to 0.21 lower)
PR OXN	731 (3 RCTs)	⊕⊕⊕○ MODERATE [a]	-	-	SMD **0.53 lower** (0.68 lower to 0.38 lower)
MNTX	460 (1 RCT)	⊕⊕⊕○ MODERATE [b]	-	-	SMD **0.32 lower** (0.51 lower to 0.13 lower)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

Explanations: a. Downgraded because of uncertainty about Random Sequence Generation and treatment allocation (OXN3001 and OXN3006) as well as uncertainty about incomplete outcome data handling (OXN2001, OXN3001 and OXN3006) b. Downgraded because of uncertainty about treatment allocation and incomplete data handling

significantly improved in line with results in the total study population (RR: 1.50; 95% CI [1.21, 1.86]; p=0.0003; Supplementary figure S8).

For patients using PR OXN a significant improvement in BFI-score was seen similar to the improvement seen in the total population (WMD: -8.93; 95%CI [-16.26, -1.59]; P=0.02; supplementary figure S7). However, the lower patient numbers result in uncertainty about the results.

Bowel function efficacy in observational studies

Most identified published observational studies were performed with PR OXN (22 unique studies). One prospective uncontrolled study with MNTX was identified[34]. In this phase 3, multicenter, open-label trial, adults with chronic noncancer pain (n=1034) received subcutaneous methylnaltrexone 12 mg once daily for 48 weeks. 64.7% of included patients were female and the most common indication for pain treatment was back pain 53.8%. The median number of weekly methylnaltrexone injections was 5.98 (range 0.05–7.14), with the greatest number of patients (49.6%) requiring more than six or seven doses per week. A statistically significant increase in mean weekly BM rate from baseline (mean=1.5 BM/wk) was observed throughout the entire 48-week period (mean=5.3 BMs; mean change=1.5 BM/wk;P<0.001). After 48 weeks 34.1% of the 1034

injections resulted in a BM within 4 hrs, which is comparable to the values found in the RCTs, suggesting that effects seen in daily practice resemble the effects seen in RCTs.

For PR OXN 15 studies (17 publications) included patients with OIC at study start (n =17085)[4,28,33,38,46,49,56,61,62,67,71-73,77-79,81]. The studies mainly differed in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity, Despite the heterogeneity the mean weighted improvement in BFI was -29.22 95 % CI [-35.22, -23.22] (p<0.00001) similar to the improvement seen in the RCTs -27.4 95%CI[-19.1 to -35.7] (see supplementary figure S9), suggesting that effects seen in daily practice resemble the effects seen in RCTs. Patients with laxative refractory OIC (3 studies, n=110) had the largest improvement in BFI-scores, mean weighted improvement in BFI was -49.03 95% CI [-53.63, -44.42] (P<0.00001). This improvement. is greater than mean weighted improvement seen in the laxative refractory subpopulation of the RCTs (-20.1; 95% CI [-13.6 to -26.6]). Together this suggests that effects seen in daily practice are at least comparable to the effects seen in RCTs.

In 10 studies (14 publications) patients without OIC at study start were included (n =4693)[21,24,38-40,46,50,57,63,71-75]. The mean weighted improvement was -3.38 95% CI [-10.37, 3.61]. The studies differed substantially, mainly in the included pain population (e.g. non-malignant pain, malignant pain, elderly, neuropathic pain and laxative refractory pain patients), resulting in considerable heterogeneity (I^2=96%, Chi^2=215.39, df=9) (see supplementary figure S10). Within these heterogeneous studies three groups of studies could be identified, studies reporting no change in BFI, studies reporting an improvement in BFI and studies reporting a worsening of BFI, where all individual publications reported no significant and clinically relevant changes in BFI (a clinically relevant change in BFI is defined as a change of 12 points or more). Five studies showed a substantial improvement of BFI-score and mean weighted improvement of BFI in this group was -11.83 95% CI [-13.25, -10.41](p<0.00001) with no important heterogeneity in this subgroup (I^2=0%). Two studies showed a worsening of the BFI score with mean weighted worsening of 11.25 95% CI [8.13, 14.37] (p<0.00001), with no important heterogeneity (I^2= 6%). Another 3 studies did not show a difference in BFI-score and mean weighted improvement in this subgroup was -0.17 95% CI [-2.85, 3.19] (p=0.91), with no important heterogeneity (I^2=4%). Results of these analyses suggest that there appeared to be no significant clinically relevant changes in the bowel function index (a change in BFI of 12 points or more) even when the data are analyzed in the defined subgroups, suggesting that patients do not develop OIC during treatment with an opioid (supplementary figures S10-S13).

DISCUSSION

This study aimed to demonstrate that treatment with opioid antagonists is a valuable treatment option in patients that experience OIC when using opioid treatment for pain. Moreover, available observational data were analyzed to provide insight in to usage of opioid antagonist treatment in daily practice.

Despite significant heterogeneity between studies all identified randomized controlled trials showed that the efficacy of opioid antagonist treatment was superior to control treatment with respect to the proportion of patients achieving normal bowel function, the proportion of patients needing additional laxatives as well as the PAC-SYM total score. The Number Needed to Treat (NNT) to obtain normal bowel function is ~5 (~3.5-7; the reciproke of the anticipated absolute risk difference with opioid antagonist treatments), which is comparable to the meta-analysis by Nee et al. Also variables that were not studied for all agents, like (change in) BFI and (change in) number of bowel movements, showed that opioid antagonist treatments were superior to control treatment.

With respect to pain relief the RCTs showed that treatment with opioid antagonists did not significantly interfere with pain relief (13 RCTs, 4569 participants, SMD 0.03 lower (0.09 lower to 0.03 higher). The quality of the evidence using the GRADE-systematic was rated low for alvimopan, moderate for PR OXN, MNTX and naldemedine and high for naloxegol.

A further indication on the efficacy of opioid antagonist treatment in daily practice could be derived from prospectively designed observational studies predominantly performed with PR OXN. When analyzing the Bowel Function Index at start of opioid antagonist treatment and at final study visit it was shown that the BFI decreased significantly with 29.2 points (ΔBFI=-29.9 95% CI -35.2to -23.2; n=8524) in patients with OIC at study entry, a decrease that is considered to be clinically relevant (a change in BFI of 12 points or more is considered clinically relevant) indicating that bowel function improves significantly and that the improvement is also clinically relevant. For patients without OIC at study start the BFI did not significantly change (ΔBFI -3.4 95%CI -10.4 to 3.6; n=2341), indicating that treatment with PR OXN might prevent worsening of bowel function usually seen on opioid treatment.

An interesting population with respect to opioid induced constipation is the laxative refractory population. Therefore we also included analyses for the subgroup of laxative refractory patients. Five RCTs (KODIAC-4, KODIAC-5, OXN2001, OXN3001 and OXN3006) were identified that reported on bowel function efficacy in laxative refractory patients or laxative inadequate responders.

For naloxegol the RR was 1.5 (95% CI 1.21 to 1.86; n=481), resulting in an NNT of ~6.7. For PR OXN the change in BFI was less pronounced compared with the total popula-

tion (MD -8.93 95%CI -16.26 to -1.59; n=75). Within the naloxegol and PR OXN studies no heterogeneity was detected. However, a difference between both studies was the definition with respect to laxative refractory patients and laxative inadequate responder patients. For the PR OXN study a patient was considered laxative refractory if the patients still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl). For naloxegol a patient was considered a laxative inadequate responder when the patient took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire.

For PR OXN also prospective observational studies were available in this population. In the observational studies the definition for laxative refractory patients was comparable to the laxative regimens used in daily practice, a patient that was considered laxative refractory had failed on the standard of care laxative regimens used in daily practice. The analysis showed a significant and clinically relevant improvement of the BFI in this population (ΔBFI -49.0 95%CI -53.6 to -44.4; n=110), suggesting that despite failing normal laxative regimens patients can still benefit from using opioid antagonist treatment.

Although no direct comparisons between PAMORA's and/or PR OXN are available, we did not observe differences in efficacy between PAMORA's and PR OXN in the meta-analyses. As no differences are observed in efficacy and side effects, treatment choice should be made on pharmaceutical properties of the products, patient preferences, costs and product availability. For instance, MNTX is only available as subcutaneous injection which might be perceived a burden to patients, whereas first results of treatment can occur already within 4 hours of the first injection. PR OXN is an oral combination product limiting the choice of opioid to oxycodone. The oral combination however might be a benefit to therapy adherence in comparison to single oral products, but this remains to be elucidated. Furthermore, between countries differences exist between products with regard to availability to patients due to differences in registered indication (e.g. between EU versus US) and local reimbursement decisions which can differ per country.

Limitations

There are some limitations to our analyses. Firstly, there is heterogeneity in the analyses of the bowel function outcomes, this heterogeneity might be caused by differences in the trial populations. Detected differences identified were differences with respect to OIC at baseline due to differences in definitions for OIC as well as differences is the underlying pain conditions (e.g. malignant pain and non-malignant pain). Other differences that could affect bowel function might have been: use of chemotherapeutics and other drugs[90], level of physical activity and co-morbidities[11]. To reduce heterogeneity due to trial populations when studying OIC and the efficacy/effect with respect to OIC,

Poulsen et al. have developed a model for OIC in healthy volunteers, in which these population differences can be ruled out and it will be interesting to see results of comparing opioid antagonists in healthy volunteers with laxative-refractory OIC with at least 4 weeks treatment duration[91].

Another limitation was the fact that we could not rule out publication bias for all studies as not all protocols were published online. For this we acknowledge a positive trend that the more recent studies protocols were freely available. Finally, although the observational study data support the data from clinical trials (at least for PR OXN and in patients with OIC at study entry), it is not possible to use these data for definite conclusions as there is a strong heterogeneity in the data and publication bias could not be ruled out.

Another limitation of the study is related to increasing concerns in the US and Europe with respect to opioid therapy, especially in non-malignant pain patients. In this systematic review also studies were included in which patients with non-malignant pain were treated. For the patients in these studies physicians decided that opioid therapy was required and could not be stopped. In daily practice an alternative option in especially non-malignant pain patients might be strictly evaluating the need for opioid therapy, as cessation of opioid therapy will also improve OIC.

CONCLUSION

Opioid antagonists, have been approved for the treatment of opioid induced constipation for a decade (first approval in EU dating from 2008 for PR OXN and MNTX). Despite approval and growing consensus with regard to using these agents in clinical practice the uptake in formal guidelines is still minimal. Together with the study by Nee et al. 2018 (describing the safety and efficacy with regard to non-responders on opioid antagonists) this study provides further evidence on the efficacy with respect to bowel function and pain of opioid antagonists, like naloxegol, alvimopan, naldemedine, PR OXN and MNTX, in the treatment of OIC in patients with opioid treatment for chronic pain.

TRANSPARENCY

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Disclosures

F.J.P.M. Huygen has nothing to disclose. As employers of Mundipharma Pharmaceuticals B.V. Y.J.B. van Megen and G. Koopmans-Klein report personal fees from Mundipharma Pharmaceuticals BV, during the conduct of the study and personal fees from Mundipharma Pharmaceuticals BV, outside the submitted work.

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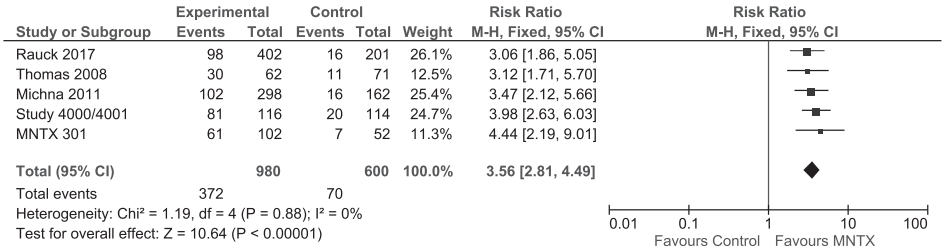
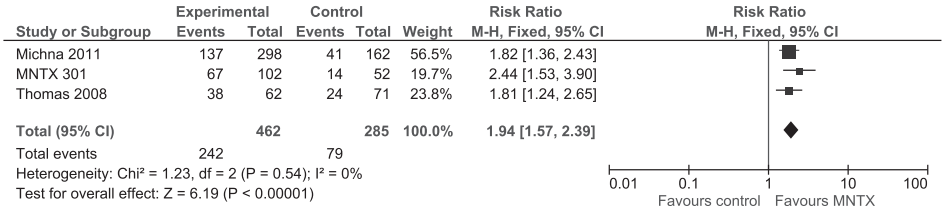
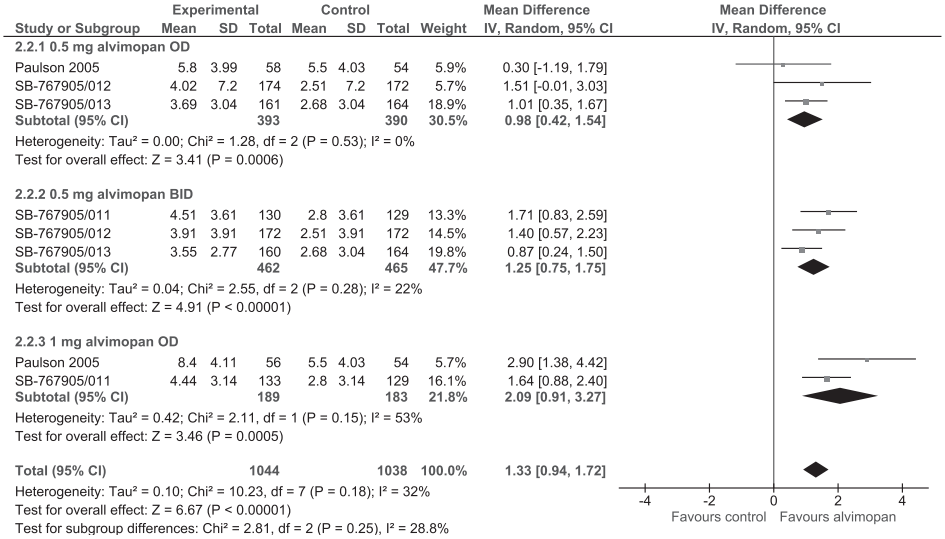
SUPPLEMENTARY FIGURES



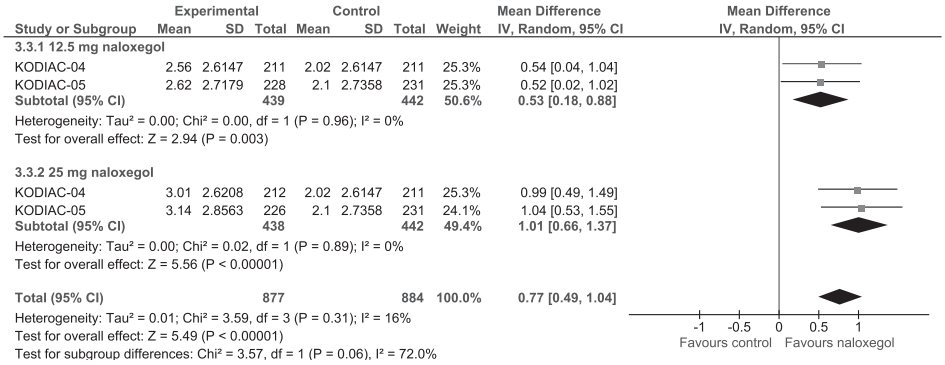
Supplementary Figure 1: Forest plot of comparison: Effect of methylnaltrexone on bowel function efficacy (RCTs) with respect to Rescue Free Bowel movements (within 4 hours after first dose).



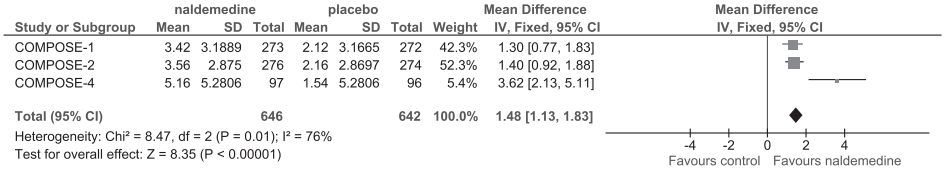
Supplementary figure 2: Forest plot of comparison: Effect of methylnaltrexone on bowel function efficacy (RCTs), with respect to Rescue Free Bowel movements (within 24 hours).



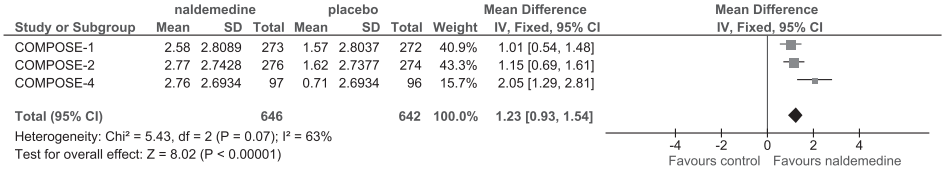
Supplementary figure 3: Forest plot of comparison: Effect of alvimopan on bowel function efficacy (RCTs), with respect to Number of bowel movements per week.



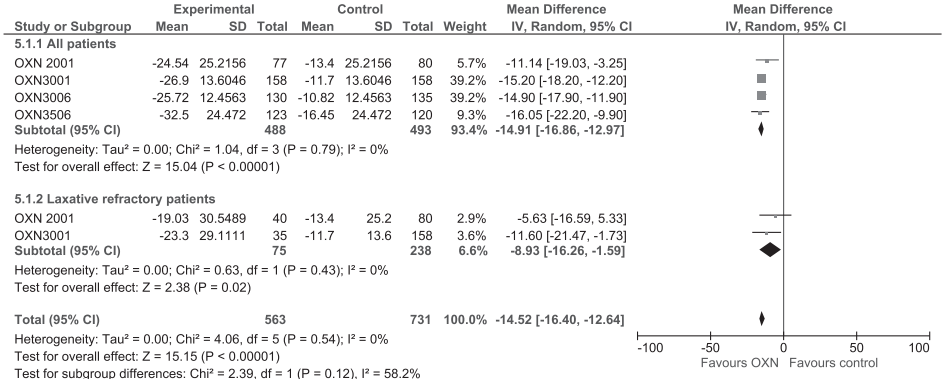
Supplementary figure 4: Forest plot of comparison: Effect of naloxegol treatment on bowel function efficacy (RCTs), with respect to Change from baseline number of SBMs per week.



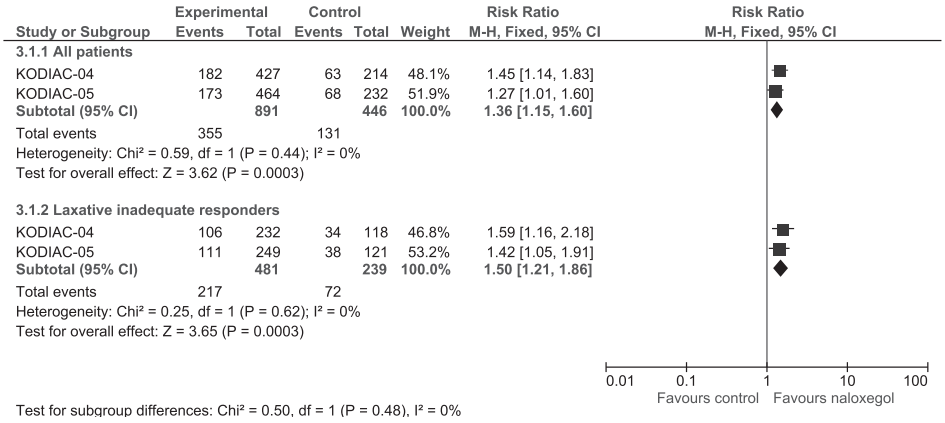
Supplementary figure 5: Forest plot of comparison: Effect of naldemedine treatment on bowel function efficacy (RCTs), with respect to Change in number of SBMs per week.



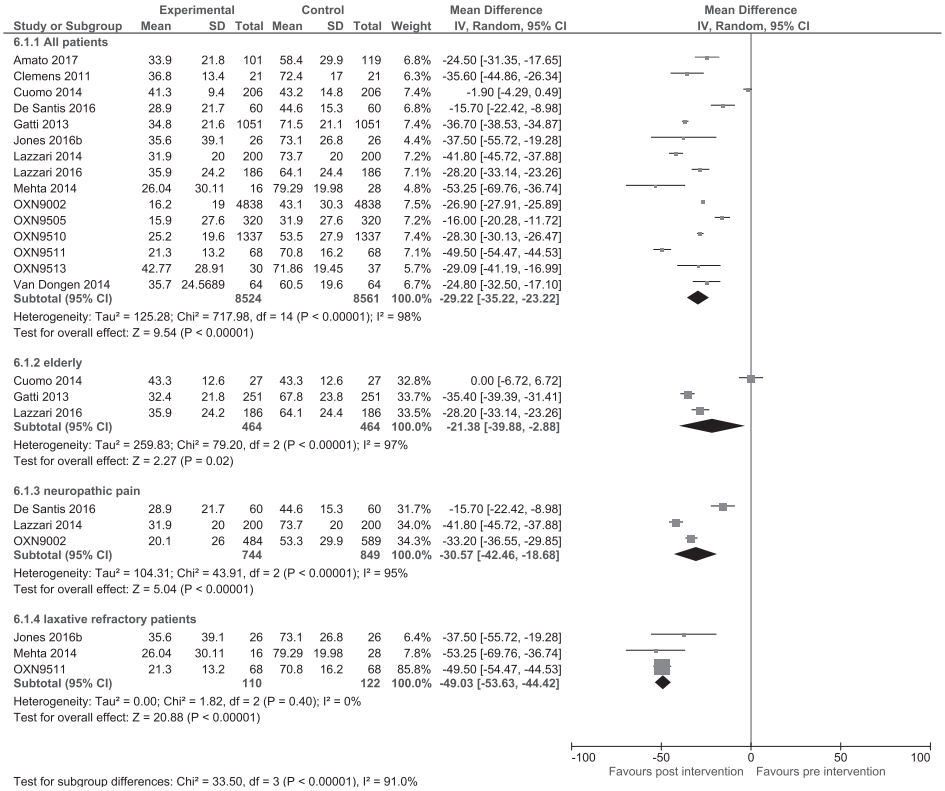
Supplementary figure 6: Forest plot of comparison: Effect of naldemedine treatment on bowel function efficacy (RCTs), with respect to Change in number of CSBMs per week.



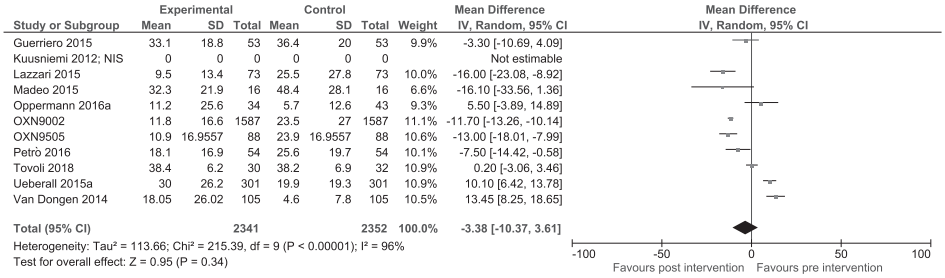
Supplementary figure 7: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy (RCTs), with respect to Bowel Function Index.



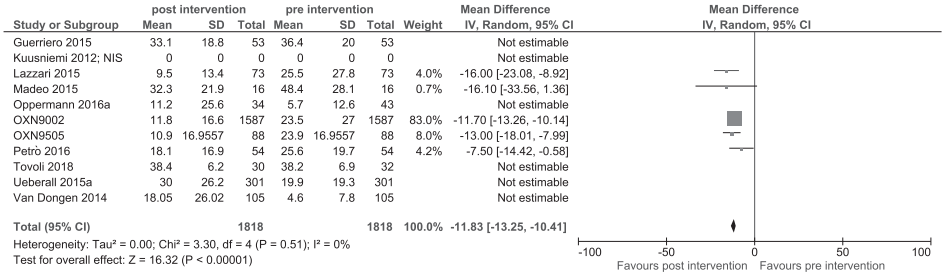
Supplementary figure 8: Forest plot of comparison: Effect of naloxegol treatment on bowel function efficacy (RCTs), with respect to Response rate (≥3 SBMs per week and increase of ≥1 SBMs for ≥9 of 12 weeks and for ≥3 of the 4 final weeks).



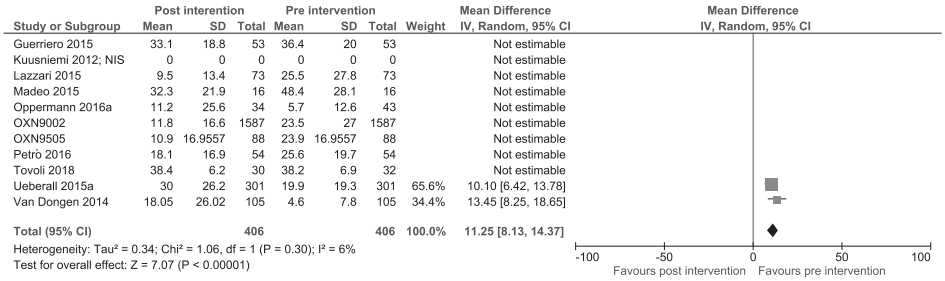
Supplementary figure 9: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients with OIC at study start (observational studies), with respect to Bowel Function Index.



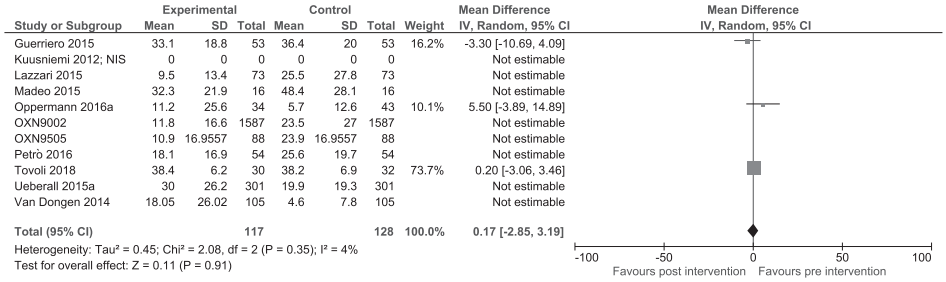
Supplementary figure 10: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies), with respect to Bowel Function Index.



Supplementary figure 11: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, improvement of BFI), with respect to Bowel Function Index.



Supplementary figure 12: Forest plot of comparison: Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, worsening BFI), with respect to Bowel Function Index.



Supplementary figure 13: Forest plot of comparison: 12 Effect of oxycodone/naloxone treatment on bowel function efficacy in patients without OIC at study start (observational studies, unchanging BFI), with respect to Bowel Function Index.