Critique author	Ed Whitney

Bibliographic Data	
Authors	Chey WD, Webster L et al.
Title	Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain
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Citation	N Engl J Med 2014;370:2387-96.
Other information if relevant	

Methods	
Aim of study	To investigate the efficacy and safety of naloxegol for the treatment of opioid-induced constipation
Design	Two identical and simultaneous multicenter randomized double-blind studies (study 04 and study 05)

Participants	
Population from which participants are drawn	Outpatients taking a stable total daily dose of 30-1000 mg of morphine equivalent for 4 weeks or longer
Setting (location and type of facility)	115 centers in the US and Europe for study 04 142 centers in the US and Europe for study 05
Age	52
Sex	834 women, 503 men
Total number of participants for whom outcome data were reported	1337

Inclusion criteria	- Age 18 to 84 - Reporting symptoms of opioid induced constipation defined as <3 spontaneous bowel movements (BM) per week with one or more of these symptoms: hard or lumpy stools, straining, or a sensation of incomplete evacuation in at least 25% of BM during the 4 weeks prior to screening - If these symptoms were reported at screening, they were confirmed by means of a 2-week period of data from an electronic daily diary recording stool frequency and characteristics - Receiving a stable maintenance opioid regimen for pain with no anticipated change for the duration of the study
Exclusion criteria	- Uncontrolled pain despite opioid analgesic therapy - Cancer within five years of enrollment - Use of medications associated with diarrhea or constipation other than opioids - Evidence of bowel obstruction or conditions that increase the risk of bowel perforation
Other information if relevant	- Most common reason for opioid use was back pain in 56% of participants - Mean duration of opioid use was 3.6 years - More than 50% of participants were classified as having an "inadequate laxative response," meaning that the participant took laxatives for at least 4 days within 2 weeks but continued to have constipation symptoms

Intervention Groups

Group 1	
Group name	Placebo
Number in group	446 (214 in study 04 and 232 in study 05)
Description of intervention	Placebo once daily
Duration of treatment period	12 weeks
Co-interventions if reported	- During the trial, laxatives and products such as prune juice and herbal laxatives were not permitted - If a BM had not occurred within 72 hours after the last recorded BM, the use of up to 3 doses of 10-15 mg of bisacodyl as a rescue treatment was permitted, with a one-time use of an enema

Additional information if relevant	

Group 2	
Group name	Naloxegol 12.5 mg
Number in group	445 (213 in study 04 and 232 in study 05)
Description of intervention	Naloxegol 12.5 mg once daily
Duration of treatment period	12 weeks
Co-interventions if reported	- -During the trial, laxatives and products such as prune juice and herbal laxatives were not permitted - If a BM had not occurred within 72 hours after the last recorded BM, the use of up to 3 doses of 10-15 mg of bisacodyl as a rescue treatment was permitted, with a one-time use of an enema
Additional information if relevant	

Group 3	
Group name	Naloxegol 25 mg
Number in group	446 (214 in study 04 and 232 in study 05)
Description of intervention	Naloxegol 25 mg once daily
Duration of treatment period	12 weeks
Co-interventions if reported	- During the trial, laxatives and products such as prune juice and herbal laxatives were not permitted - If a BM had not occurred within 72 hours after the last recorded BM, the use of up to 3 doses of 10-15 mg of bisacodyl as a rescue treatment was permitted, with a one-time use of an enema
Additional information if relevant	-

Primary outcome	

Outcome name and criteria for definition	Response rate, defined as 3 or more spontaneous BM per week (without the use of rescue laxative in the previous 24 hours) *and* an increase of at least one spontaneous BM per week above baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 weeks
Time points measured and/or reported	End of 12 weeks
Differences between groups	- Trials 04 and 05 had similar but not identical results and were reported separately - In trial 04, both dosage levels of naloxegol performed better than placebo, where the response rate was 29.4% - The response rate in the 12.5 mg group was 40.8% and in the 25 mg group was 44.4% - In trial 05, only the 25 mg group had a higher response rate than placebo, where the response rate was 29.3% - The response rate in the 12.5 mg group was 34.9% and in the 25 mg group was 39.7%
Additional information if relevant	

Secondary outcomes	
Outcome name and criteria for definition	- Response rate in the subpopulation of participants who had an inadequate response to laxatives before enrollment - Time to first postdose spontaneous BM - Mean number of days per week with one or more spontaneous BM - Rescue laxative use - Changes in opioid daily use - Changes in pain score - Discontinuation due to adverse events
Time points measured	12 weeks
Differences between groups	- The constipation-related secondary outcomes tended to be better with naloxegol than placebo - The 25 mg naloxegol group had a higher rate of discontinuation due to adverse events than the 12.5 mg or the placebo group, chiefly diarrhea (2.8-3.4 % of patients) and abdominal pain (1.9-3.9% of patients) - In all three groups, the daily opioid doses and pain scores were stable throughout the 12 weeks of the trial - The response rate in the subgroup with an inadequate response to pre-enrollment laxatives was similar to that in the entire patient population

Additional information if relevant	

Conclusions	
Key conclusions of study authors	- These two large phase 3 trials of naloxegol both showed superiority of 25 mg/d of the drug over placebo, and one of the trials also showed superiority of the 12.5 mg dose - The stability of the opioid dosage and pain scores supports the peripheral site of action of naloxegol with the preservation of centrally-mediated analgesia - It was unclear why the 12.5 mg dose was superior to placebo in trial 04 but not in trial 05, since the methods were the same in both trials

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	Some of the details of randomization are presented in a 585-page protocol which is available online as an appendix
Allocation concealment *(selection bias)*	Low	
Blinding of participants and personnel *(performance bias)*	Low	
Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Low	

Selective outcome reporting? *(reporting bias)*	Low	
Other bias		

Sponsorship if reported		
Study funding sources if reported	AstraZeneca	
Possible conflicts of interest for study authors	Disclosure forms were online at the Journal website, and relevant conflicts of interest include grants, consulting fees, nonfinancial support, and stock options, but not dollar amounts	
Notes:		

- **Comments by DOWC staff**

- The reasons for the superiority of 12.5 mg of naloxegol over placebo were not clear to the authors
- This makes it uncertain which dose should be recommended as a starting dose
- Due to the fairly rigid structure of the protocol, dose increases from 12.5 to 25 mg were not permitted during the study period
- Even though there were two trials detailed in the protocol, and both were of the same high quality, for purposes of rating evidence, they should be regarded as a single large trial due to having the same population base, methods, and investigators
- Some practical issues remain unaddressed in an efficacy trial of this nature: how many and how long a trial of standard laxatives should be done before consideration is given to the use of a drug which acts as a peripheral mu receptor antagonist
- One relevant issue not addressed by the study is that it is assumed that patients will be maintained on opioids indefinitely for noncancer pain, joint pain, and fibromyalgia, which affects its external validity but not its internal validity

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline x☐ High quality ☐ Adequate ☐ Inadequate	High quality for good evidence that naloxegol can alleviate opioid-related constipation, and that a 12.5 mg dose may be an acceptable starting dose with an acceptable side effect profile
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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