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# There is relief for constipated patients taking opioids.

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# There is relief for constipated patients taking opioids

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**ABSTRACT** A critical appraisal and clinical application of Tack J, Lappalainen J, Diva U, Tummala R, Sostek M. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. *United European Gastroenterol J.* 2015 Oct;3(5):471-80. doi: [10.1177/2050640615604543](https://doi.org/10.1177/2050640615604543)

**Keywords:** opioid induced constipation, naloxegol

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## Clinical Context

The patient is an 89 year old female with chronic musculoskeletal pain and constipation. She has severe degenerative joint disease manifested by deformities in the distal and proximal interphalangeal joints, arthropathy of bilateral knees and hips, and thoracic kyphosis resulting in her head and cervical spine completely anterior to her center of gravity which presents as neck pain. The pain management clinic performed joint and spinal injections, but that did not provide relief of pain. She also has chronic constipation at baseline. She can maintain a regular bowel movement only with combination of maintenance Miralax, stool softeners, and lactulose solution. Opioids provide pain relief, but cause incapacitating constipation not relieved with additional therapy in addition to her baseline medications for management of constipation. She has tried milk of magnesia, magnesium citrate, Fleets® enema, fiber products, or Dulcolax® stimulant without relief. She gave up on opioid medicines despite the pain relief they offered because she could not tolerate the discomfort and risks of constipation. Her daughter attends clinic with her and asked, "I've seen commercials on television advertising a new medicine for 'opioid induced constipation.' Can my mother take that medicine?"

## Clinical Question

What is most appropriate treatment modality available for opioid induced constipation in our patient?

## Research Article

Tack J, Lappalainen J, Diva U, Tummala R, Sostek M. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. *United European Gastroenterol J.* 2015 Oct;3(5):471-80. doi: [10.1177/2050640615604543](https://doi.org/10.1177/2050640615604543)

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## Literature Review

Because the patient's daughter mentioned an advertisement specifically for opioid induced constipation, we started searching the literature in PubMed using the search term opioid induced constipation (OIP). Those search terms showed results with many review articles and opinion papers<sup>1-6</sup> which were not thought to be appropriate for review because of poor validity. There was one paper with descriptive content analysis of social media posts related to OIC.<sup>7</sup> There was also a retrospective study which also was considered a weaker study design.<sup>8</sup> There was a Consensus Recommendation on Initiating Treatment for OIP that summarized multiple Patient Reported Outcome (PRO) measures, including the Patient Assessment of Constipation—Symptoms (PAC-SYM) and Patient Assessment of Constipation-Quality of Life (PAC-QOL) scores. The PAC-SYM measure included abdominal symptoms (abdominal discomfort, pain, bloating, and cramping) and rectal symptoms (pain, burning, bleeding/tearing) as well as stool completeness, consistency, and straining.<sup>9</sup> Although heavily sponsored by pharmaceutical corporations, this paper describes peripherally acting  $\mu$ -opioid receptor antagonists (PAMORAs), methylnaltraxone and naloxegol, as well as a chloride channel activator, lubipristone, which are approved for treatment of OIC in the United States. Using the "Similar Articles" feature in PubMed did not reveal any papers related to the clinical question. We then searched each of the PAMORAs sequentially in PubMed.

Using the search terms "lubipristone and opioid induced constipation" revealed two randomized controlled trials. The first by Jamal, Adam, Jansen, et. al. reported "No significant differences were observed in quality-of- life measures or the use of rescue medication."<sup>10</sup> The second study had a high dropout rate (68%) and significant medication side effects, including 11% absolute increase in nausea, 7% increase in diarrhea, and 6% increase in abdominal distention.<sup>11</sup> Therefore, we looked at alternative PAMORAs.

Methylnaltraxone is administered subcutaneously and therefore was deemed inappropriate for this patient. We next searched "naloxegol, opioid induced constipation, randomized controlled trial" in PubMed, which revealed three relevant papers. The paper by Webster, Chey, and Tack was an open label trial, making it a weaker study methodology.<sup>12</sup>

Disease oriented outcomes, including time to first bowel movement or number of bowel movements per week, were used as primary outcome measures for both the remaining trials. Both of these papers used the same patient cohort. The study design, authorship, and data analysis were sponsored by AstraZeneca. The paper by Chey, Webster, Sostek, et. al. had a very poor description of results reporting "pain" such that we felt it wouldn't be useful for our patient.<sup>13</sup> Therefore, we chose the paper by Tack, Lappalainen, Diva, et. al, to review for this critical appraisal and clinical application.<sup>14</sup> The Level of Evidence is B according to the SORT Criteria.

## Critical Appraisal

Seven hundred twenty cases were analyzed from a subset of two previously reported randomized controlled trials. The study population used laxatives for a minimum of 4 days out of 2 weeks or patients taking greater than or equal to 2 laxative classes.<sup>13</sup> The authors provide Table 1 verifying that baseline characteristics between those studied receiving placebo, 12.5 mg and 25 mg of naloxegol were similar, indicating that the original randomization worked. In addition to increased frequency of spontaneous bowel movements, secondary outcomes of PAC-SYM score and PAC-QOL score provided patient oriented evidence.

Patients meeting inclusion criteria were between the ages of 18-84 years receiving opioid medication of 30-1000mg per day of morphine-equivalent dose. Given the broadness of the inclusion criteria, these patients are similar to those seen in our clinic; however the specific patient used in our clinical context is slightly older than those included in the study, as she is 89 years old.

The 25 mg dose of naloxegol was more effective than the 12.5 mg dose. Median time to first post dose spontaneous bowel movement was 7.6 hours for 25 mg of naloxegol, 19.2 hours for the 12.5 mg dose of naloxegol, compared to 41.1 hours for placebo. The baseline dose of opioid medication and pain scores did not change, but PAC-SYM scores (straining, stool consistency, and completeness of bowel movements) and PAC-QOL favored active therapy, providing some evidence of symptom relief. Although this is a relatively new medication, it is able to be prescribed for patients at our clinic. There were only eight patients lost to follow up for the time to spontaneous bowel movement, making the intention to treat analysis valid. Although there is a graph indicating improvement in PAC-SYM scores for naloxegol 12.5 mg (the dose prescribed to our patient) compared to placebo, details were not adequate to calculate a number needed to treat.



Serious adverse events were similar between groups (3.3-5.5%) and the common adverse events were abdominal pain, diarrhea, and nausea.

## Clinical Application

Because the patient was elderly, we initiated the 12.5 mg dose schedule. After prescribing naloxegol, the medical assistant informed us, "The script for naloxegol was denied by the insurance company. The insurance company says they will pay for lubiprostone tabs 24 mcgm or 8 mcgm. Can she have that one instead?" We reviewed research papers during the literature review and rejected this medication as not having patient oriented outcomes.<sup>10,11</sup> We asked to speak with the insurance company pharmacy manager. The medical assistant later said, "Thirty minutes of yelling and screaming with her insurance company and I finally got her medication approved. My ear is numb and I feel like I need an anxiety pill." After receiving the naloxegol, the patient reported good symptomatic relief of both constipation and pain control with opioids.

Lessons learned:

- 1.) Direct to Consumer advertised medications should be reviewed by the doctor.
- 2.) There are many patients suffering from constipation, which in elderly patients can be dangerous.
- 3.) There are treatment options available for opioid induced constipation.
- 4.) Doctors need to advocate for their patients against inappropriate therapeutic substitution suggested by insurance companies.

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