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REVIEW

Naloxegol in opioid-induced constipation: a new paradigm in the treatment of a common problem

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Abstract: Opioid-induced constipation (OIC) imposes a significant burden for patients taking pain medications, often resulting in decreased quality of life. Treatment of OIC with traditional medications for functional constipation can be incompletely effective, leading to nonadherence with opioid treatment and undertreated pain. An emerging class of medications that counteract the adverse effects of opioids in the gastrointestinal tract while preserving central nervous system-based pain relief may represent a paradigm shift in the prevention and treatment of OIC. One of these medications, naloxegol, is a once-daily, oral opioid antagonist that is effective, well-tolerated, and approved for treatment of OIC in patients with noncancer pain. More studies are needed to demonstrate this same utility in patients with cancer-related pain.

Keywords: opioid-induced constipation, chronic pain, bowel care, peripherally acting mu-opioid-receptor antagonist, OIBD

Introduction: opioid-induced constipation (OIC) and its burden

Opioids, the most frequently prescribed class of drugs in the US, are an essential tool in the treatment of pain. They function through their agonistic effects on mu receptors in the central nervous system (CNS). Agonism of mu receptors outside of the CNS can lead to undesired adverse effects. In the gastrointestinal (GI) system, it decreases peristalsis and muscular contractions, decreases secretion of water and electrolytes, and increases rectal sphincter tone. This collection of effects is known as opioid-induced bowel dysfunction (OIBD). Symptoms of OIBD include abdominal pain, gastroesophageal reflux, anorexia, bloating, xerostomia, hard feces, incomplete evacuation, and constipation. Unfortunately, patients do not typically develop tolerance to these GI side effects, leading to patient dissatisfaction with opioid therapy.[1,2]

Reported prevalence of OIC varies widely between studies, as 60%–94% and 40%–60% of patients take opioids for malignant and nonmalignant pain, respectively.[3,4] This makes OIC the most common symptom of OIBD. Interestingly, until recently, there has been no consensus definition for OIC, which perhaps contributed to some of the variation in reported OIC prevalence.[5] Most trials of anticonstipation agents do not define OIC in the study and often rely on a history of opioid use along with the following traditional measures of functional constipation:

- Defecation frequency of <3 complete spontaneous bowel movements per week
- Hard lumpy stools
- Incomplete evacuation
- Infrequent spontaneous bowel movements without the use of a laxative within 24 hours of defecation.[6]

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A working group of gastroenterologists, palliative care specialists, and neurologists proposed the following consensus definition in their 2014 *Neurogastroenterology and Motility* review article:

> A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, harder stool consistency.[4]

More recent consensus recommendations from the American Academy of Pain Management in 2015 proposed the 3-item Bowel Function Index (BFI) as a validated assessment tool to detect OIC and provide a threshold for pharmacologic intervention. The BFI asks patients to consider, over the preceding 7 days on a scale of 0–100, the following three parameters:

- Ease of defecation
- Feeling of incomplete defecation
- Personal judgment of constipation.

The panel further suggests that patients on chronic opioids using typical first-line therapies for OIC with scores ≥30 on the BFI be considered for prescription medication intervention.[7]

Despite the lack of consensus definition until recently, multiple studies suggest that OIC is perhaps the most debilitating side effect of opioid therapy and a significant burden for patients. Nearly 1/3 of individuals on opioids state that constipation is their most bothersome symptom,[6] suggesting that OIC may be even more distressing than the underlying chronic pain.[2] OIC impairs patients' ability to carry out their activities of daily living and results in decreased productivity at work, quality of life, sense of well-being, and level of health in general.[2,8–10] Compared to patients without OIC, patients suffering from chronic OIC are more likely to miss work or feel impaired in their performance.[2] Even among patients who also take traditional laxatives, 81% of patients still reported OIC as their most bothersome side effect.[10]

As a result of the prevalence and severity of OIC, many chronic pain patients are often forced to choose between adequate pain relief and comfortable bowel function. Multiple studies illustrate this dilemma.[4,8,11] Studies have found 8%–33% of patients report altering or stopping their opioid use due to OIC, thereby severely limiting the clinical benefit of opioids.[8,11] In the PROBE study,[4] 92% of patients who altered their opioid regimen due to OIC subsequently experienced increased pain, and 86% of those experiencing increased pain reported that it moderately to greatly reduced their quality of life and activities of daily living.

Not only does OIC impact patients' quality of life, it also results in increased health care costs. Compared to patients who did not alter their opioid therapy, those who modified their regimen due to OIC had greater health care resource use as evidenced by increased number of surgeries, ER visits, and hospitalizations in the previous 6 months due to pain (odds ratio [OR] of 3.72 for having surgery, OR of 1.88 for ER visits, and OR of 2.47 for hospitalization). They also had more pain-related and OIC-related drug and health care provider out-of-pocket costs.[12] Another cost analysis in Sweden showed an increased burden of cost for patients with severe OIC. Severe OIC was associated with increased direct and indirect costs when compared to patients with no or mild constipation. Sick leave was found to be the largest cost. Use of outpatient facilities and total medication costs were also increased. Depending on the patient's work status, the difference in monthly total cost could be as much as EUR 1,525 for those with severe OIC versus EUR 1,034 for those without OIC.[13] These quality of life and health care cost data suggest a significant unmet need in the diagnosis and treatment of OIC.

OIC treatment: historical and peripherally acting mu-opioid-receptor antagonists (PAMORAs)

Until recently, there has been little differentiation between treatment of functional constipation and that for OIC. Traditionally, treatment includes lifestyle modifications such as increased fiber intake, liquid intake, and physical activity.[2] As these nonpharmacologic measures often do not adequately relieve OIC, treatment then turns toward the use of laxatives. Laxatives function as stimulants, which increase smooth muscle contraction, and as stool softeners, which act as surfactants, lubricants, and osmotics. Stimulants include senna and bisacodyl. Stool softeners include docusate, mineral oil, lactulose, and polyethylene glycol.[2]

Interestingly, some of these traditional remedies have been proven ineffective or harmful in recent years. Docusate has not demonstrated efficacy in randomized controlled studies for OIC compared to placebo,[14] and the use of bulk-forming laxatives (psyllium or fiber) was found to worsen constipation or even cause bowel obstruction the setting of opioid use.[2] No laxative has been found to be superior to any other.[15] Currently, no GI society has published treatment guidelines specifically for managing OIC,[6] although the need for such guidelines has been outlined recently by Camilleri et al.[4]

Numerous professional societies including the European Association of Palliative Care and the National Comprehensive Cancer Network recommend prophylactic laxatives at the onset of opioid therapy despite a lack of randomized trials to validate such a practice.[6] Even with such prophylaxis, studies suggest that the majority of patients do not achieve adequate relief from OIC. Coyne et al[8] found that among patients who took recommended doses of laxatives, 94% failed to have adequate response. Kumar et al[2] found that 54% of patients prescribed concurrent laxatives with their opioids did not achieve the desired level of symptomatic (constipation) improvement more than half the time. The relative lack of efficacy of traditional approaches to constipation for OIC may be due at least in part to the distinct pathophysiology of OIC.[6]

More recently, medications aimed specifically at the GI tract's opioid receptors have been employed to combat OIC. These include a combined, prolonged-release, oral naloxone/oxycodone product that has been shown in a randomized, double-blind study to provide a statistically significant improvement in BFI scores with no significant difference in pain control in patients with both cancer-related and noncancer-related chronic pain. Naloxone, typically utilized for its ability to cross the blood–brain barrier to reverse life-threatening opioid overdoses, has low systemic bioavailability (<3%) in a prolonged-release formulation.[16]

PAMORAs are a newer class of medications that are unable to cross the blood–brain barrier allowing them to counteract opioids' GI side effects while preserving CNS-mediated analgesia. PAMORAs include methylnaltrexone, alvimopan, and naloxegol.

Methylnatrexone has been shown to be superior to placebo for treatment of OIC in patients who failed traditional management.[15,17] Its limitations include subcutaneous administration and restricted indication, ie, use only in patients with advanced disease.[1] Alvimopan is available in oral formulation, but is restricted to short-term use for post-operative ileus as clinical trials showed increased incidence of myocardial infarction with long-term use.[1,18] Naloxegol, (Movantik™, AstraZeneca, Cambridge, England) is an oral, once-daily PAMORA currently approved by the US Food and Drug Administration (FDA) for treatment of OIC in noncancer pain.

Naloxegol: brief pharmacology

Naloxegol reduces OIC by functioning as a PAMORA. Chemically, it is a PEGylated form of naloxone.[19,20] It does not reverse pain relief primarily due to its inability to cross the blood–brain barrier.[3]

Pharmacokinetic summary

Naloxegol reaches two peaks in concentration following oral administration. The first peak occurs in less than two hours, and the second peak occurs at anywhere from 24 minutes to 3 hours later due to enterohepatic recycling. Fatty meals and grapefruit juice can increase naloxegol plasma concentrations; therefore, it is recommended to take it on an empty stomach and avoid grapefruit juice.[19]

Because metabolism is primarily through the CYP3A4 enzyme, naloxegol is contraindicated if there is concurrent use of strong CYP3A4 inhibitors or inducers. A dose reduction of 50% is recommended with concurrent use of moderate CYP3A4 inhibitors.[19]

The half-life of naloxegol is between 6 and 11 hours. Excretion is primarily in the feces.[19] No dose adjustment is recommended for mild-to-moderate hepatic impairment. Naloxegol use is not recommended for patients with severe hepatic impairment due to lack of investigation in this population.[19]

Renal clearance is only a minor route of elimination for naloxegol. It is not removed with standard hemodialysis.[21] For patients with creatinine clearance less than 60 mL/min, the recommended starting dose is 12.5 mg daily, with an increase of 25 mg daily if tolerated and if OIC persists.[21]

Clinical studies of naloxegol: efficacy, safety, and patients' perspectives

Efficacy

Key Phase I, II, and III trials evaluating pharmacokinetics, efficacy, and safety of naloxegol are summarized in Table 1. Two of the Phase III trials compared response rates between placebo and naloxegol doses of 12.5 mg daily and 25 mg daily. Response was defined as at least three spontaneous bowel movements per week that was at least 1 greater than baseline. These changes needed to be seen in at least 9 of the 12 trial weeks and at least 3 of the last 4 weeks of the trial. The KODIAC 04 trial found significant response at both doses, while the KODIAC 05 trial found significant response at the 25 mg dose.

Secondary end points evaluated in these trials included time to first spontaneous bowel movement, mean number of spontaneous bowel movements per week, mean number of days per week with at least one spontaneous bowel movement, severity of straining, hardness of stool, and need for rescue laxative use.[22] Although results were variable for the 12.5 mg dose, all of the secondary end points had positive responses at the 25 mg dose. In an analysis of the subgroup of patients with moderate-to-very-severe OIBD who failed prior use of laxatives, significant response to both doses

Table 1 Details of relevant naloxegol studies

Study	Phase	N and population studied in	Study design and dosing	Toxicities	Efficacy measures and outcomes
Bui et al,[27] 2014	I	N=28 with renal impairment and eight with normal renal function	Dual-center, open-label, nonrandomized, parallel-group study; renal function defined by MDRD equation for eGFR: normal >80 mL/min/1.73 m^2, moderate renal impairment 30–59 mL/min/1.73 m^2, severe renal impairment <30 mL/min/1.73 m^2; naloxegol 25 mg PO ×1 for all participants; patients with ESRD 2 doses: 2 h before dialysis and 2 h after dialysis, 7-d washout period	No related serious AEs were reported	AUC was 1.7× greater in moderate and 2.2× greater in severe compared to normal; C_{max} was 1.8× greater in severe compared to normal No good correlation between renal clearance and total clearance as renal is a minor route of elimination; 1.2% removed during IHD
Bui et al,[21] 2014	I	N=8 with normal hepatic function and eight with mild hepatic impairment	Single-dose, nonrandomized, open-label, parallel-group study conducted at a single center Hepatic function defined by Child–Pugh class: Class A considered mild and class B moderate Naloxegol 25 mg PO ×1 for all participants	No related serious AEs were reported	AUC in mild hepatic impairment 82.9% and 82.3% in moderate hepatic impairment
Webster et al,[25] 2013	II	N=207; ≥18 y, receiving 30–1,000 mg of oral morphine equivalent per day for nonmalignant or cancer-related pain on stable regimen with documented OIC; exclusions: renal, hepatic, or cardiovascular disease, prognosis <6 mo, history of GI bleeding, or GI disorder making bowel movements hard to quantify	Multicenter, randomized, DB, placebo-controlled, dose-escalation study; 5 mg, 25 mg, 50 mg orally in sequential cohorts with placebo control	Abdominal pain, diarrhea, and nausea with increased frequency and severity in 50 mg group; no evidence of opioid withdrawal or worsening pain	Primary end point: change in spontaneous BMs/wk over baseline at the end of wk 1 statistically significantly improved compared to placebo at 25 mg and 50 mg doses; secondary end points: change over baseline across wks 2, 3, and 4; change over baseline at the end of wk 4; time after first dose of naloxegol to first laxation; improvement over baseline compared to placebo maintained in 25 mg and 50 mg cohort over 4 wk
Chey et al,[22] 2014	III	KODIAC 04: n=652; KODIAC 05: n=700; outpatients 18–84 y on stable dose of 30–1,000 mg of oral morphine equivalents for >4 wk with good pain control and no cancer diagnosis, GI obstruction, or increased risk for bowel perforation who had confirmed, active OIC	Multicenter, randomized, DB, parallel-group, placebo-controlled study; received naloxegol 12.5 mg or 25 mg, or placebo for 12 wk	More common in 25 mg group; diarrhea, abdominal pain, nausea, and vomiting; no evidence of opioid withdrawal or worsening pain	Primary end point: 12 wk response rate (≥3 spontaneous BMs/wk and inclusive of ≥1 spontaneous BM over baseline for ≥9/12 wk and ≥3/4 of the final wk); higher response for 25 mg group over placebo for both trials and for 12.5 mg group over placebo in KODIAC 04 trial
Webster et al,[23] 2014	III	KODIAC 08: n=804; outpatients 18–84 y on stable dose of 30–1,000 mg of oral morphine equivalents for >4 wk with good pain control and no cancer diagnosis, GI obstruction, or increased risk for bowel perforation who had confirmed, active OIC; some were rolled over from prior KODIAC studies	Multicenter, open-label, randomized, parallel-group study; received naloxegol 25 mg or placebo	Abdominal pain, diarrhea, nausea, headache, and flatulence; no evidence of opioid withdrawal or worsening pain	Eleven patients stopped due to diarrhea and nine due to abdominal pain; no incidences of bowel perforation or cardiovascular events considered drug-related; no evidence of opioid withdrawal or worsening pain; minimal use of bisacodyl rescue doses in treatment group

Abbreviations: AE, adverse event; AUC, area under the plasma concentration curve; BM, bowel movement; C_{max}, maximum plasma concentration; d, days; DB, double-blind; eGFR, estimate glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; IHD, intermittent hemodialysis; MDRD, Modification of Diet in Renal Disease; mo, months; OIC, opioid-induced constipation; PO, by mouth; y, years.

was found in KODIAC 04 and to the 25 mg dose in the KODIAC 05 trial.[22]

Safety and tolerability

Recorded adverse events were mostly GI in nature and occurred more commonly at the 25 mg dose of naloxegol.[22,23] Approximately 10% of participants taking the 25 mg dose discontinued use due to adverse events, with diarrhea the most common reason in KODIAC 04 and abdominal pain being the most common reason in KODIAC 05.[22] Overall pain scores and mean daily opioid doses remained unchanged. Possible symptoms of withdrawal were rare and felt to be artifacts caused by the symptom scoring system.[22]

A third Phase III trial followed patients taking naloxegol over 1 year. As in KODIAC 04 and 05, an approximately 10% discontinuation rate was found due to GI adverse effects.[23] Most participants reported an unwanted adverse effect from naloxegol; however, in general, they were considered as being mild to moderate in severity. No change in reported pain, opioid use, or symptoms of withdrawal was observed.[23]

No major events or bowel perforation was reported. However, the studies excluded participants in whom there was evidence of bowel obstruction or conditions that increased risk of bowel perforation.[22,23] An additional study in healthy men showed that QT/QTc intervals did not increase more than 30 ms with doses up to 150 mg.[24]

Patients' perspectives

Unfortunately, clinical trials of naloxegol have included relatively little patient-oriented outcomes data. Webster et al's Phase II trial,[25] however, did assess patients' perceptions of their OIC symptoms and quality of life on naloxegol. Webster et al[25] used three common, validated questionnaires to assess patients' perspectives: the Patient Assessment of Constipation-Symptom Questionnaire (PAC-SYM), qualifying abdominal, rectal, and stool symptoms; the Patient-Assessment of Constipation Quality of Life Questionnaire (PAC-QoL), assessing physical discomfort, worries/concerns, psychosocial discomfort, and satisfaction; and the Short Form Health Survey (SF-36), which yields an 8-scale profile of functional health and well-being scores.

The study found statistically significant improvements in the aforementioned questionnaires for the group of patients taking 25 mg of naloxegol daily. These patients reported lower PAC-SYM scores for rectal symptoms, lower PAC-QoL scores for physical discomfort, and improved SF-36 scores for physical functioning, mental health, social functioning, and vitality.[25] Additionally, Webster et al[25] found that most adverse events (nausea, diarrhea, and abdominal pain) were mild or moderate and self-limiting in nature. Importantly, the results also suggested that patients did not alter their opioid use in order to relieve bowel symptoms as no statistically significant change in opioid usage was seen in patients taking naloxegol.

In their Phase III clinical trial of naloxegol, Webster et al[23] also assessed patients' use of rescue medication (bisacodyl) for those patients randomized to treatment with naloxegol at month 1, months 1–3, months 3–6, months 6–9, and months 9–12. Use of rescue medication was considered part of the usual care arm and was not tracked. Bisacodyl use for rescue among naloxegol users was low – median use was 1.1 mg per week during the first month and no use for the remainder of the 52-week study period. This suggests that naloxegol alone was sufficient for acceptable bowel function among the opioid users studied.

Clinical use and follow-up

Current recommended dosage of naloxegol is 25 mg once daily in the morning, on an empty stomach (>30 minutes before the first meal of the day or >2 hours afterward).[19,26] A lower starting dose of 12.5 mg may be indicated in patients with tolerability issues or renal impairment; naloxegol is not recommended in patients with severe liver dysfunction.[19] Clinical trials have required patients to stop other constipation treatments prior to starting naloxegol. These same trials have suggested that the need for rescue medication in addition to naloxegol is low.[23] Prescribing guidelines recommend stopping other bowel medications and restarting them only if there is an inadequate response to naloxegol after 3 days.[19]

To assess patient responses to naloxegol treatment, Camilleri et al[4] proposed two validated outcome tools specifically for OIC to determine whether particular treatments improve OIC symptoms:

- A 3-item BFI in which patients rate on a 0–100 scale their perception of:
  - Ease of defecation
  - Feeling of incomplete bowel evacuation
  - Personal judgment of constipation based on the previous 7 days.
- A bowel function diary that requires patient assessment via:
  - A 4-item module after each bowel movement
  - A 5-item module completed each evening.[4]

In the US, naloxegol is only currently approved for use in noncancer patients with OIC. In the European Union, however, it is approved for any patient with OIC and an inadequate response to treatment with more than one laxative for at least 4 days in the previous 2 weeks.[19] Additional investigation is needed to establish naloxegol's efficacy, safety, and tolerability specifically in cancer patients on chronic opioid therapy.

Conclusion

OIC is a burdensome problem for patients on chronic opioids, negatively affecting their quality of life and increasing health care costs. Traditional treatments for functional constipation often have insufficient efficacy in OIC. Naloxegol is a once-daily, oral PAMORA specifically designed to address the unique pathophysiology of OIC by inhibiting mu-opioid-receptor binding in the GI tract without reversing CNS-mediated pain relief. Clinical experience is limited, but efficacy and safety studies in patients with noncancer pain suggest a daily dose of 25 mg naloxegol is clinically effective and generally well-tolerated. Patients on naloxegol experienced improved quality of life, adherence to opioid therapy, and reduced reliance on other laxatives for regular bowel function. Naloxegol use led to statistically significant lower levels of physical discomfort as well as statistically significant improvement in physical functioning, mental health, social functioning, and vitality. There were no statistically significant changes in opioid use for patients on naloxegol, suggesting that patients did not need to alter their opioid use to relieve constipation symptoms, nor did they experience any withdrawal symptoms. Finally, studies showed a low use of rescue medication use by patients on naloxegol, suggesting that naloxegol alone was sufficient for acceptable bowel function among opioid users studied. These data, however, are currently limited to patients with nonmalignant pain, but future investigations seek to study the use of naloxegol in cancer patients with OIC.

Disclosure

The authors report no conflicts of interest in this work.

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