American Gastroenterological Association Institute

Guidelines on Opioid-Induced Constipation

SYMPROIC® (naldemedine) is the only OIC therapy with a strong recommendation and high quality of evidence from the AGA

INDICATION

SYMPROIC® (naldemedine) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

SYMPROIC® IS AN AGA-RECOMMENDED PRESCRIPTION TREATMENT FOR OIC

The American Gastroenterological Association (AGA) Institute funded a technical review that resulted in recommendations for the management of opioid-induced constipation (OIC).

An estimated

40%-80% OF PATIENTS

on chronic opioid therapy

ARE AFFECTED BY OIC[1]

"Constipation is by far the most common and debilitating gastrointestinal effect of opioids, and some degree of constipation is near universal in patients taking opioid medications."[1]

"Because OIC results from the specific effects of opioids, it differs mechanistically from other forms of constipation, and therefore, medical management of this disorder deserves dedicated attention."[1]

Grade definitions on strength of recommendation and guide to interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends"	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests"	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
No recommendation	"The AGA makes no recommendation"		The confidence in the effect estimate is so low that any recommendation is speculative at this time.

Grade definitions of quality and certainty of the evidence

Quality grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Evidence gap	Available evidence insufficient to determine true effect.

"The overall quality of evidence supporting use of naldemedine for management of OIC was considered high. The AGA issued a strong recommendation for use of naldemedine vs no treatment in patients with OIC refractory to laxatives."[1]

Summary of recommendations

Recommendations	Strength of recommendation	Quality of evidence
1. Traditional laxatives		
a. In patients with OIC, the AGA recommends use of laxatives as first-line agents	Strong	Moderate
2. PAMORAs		
a. In patients with laxative-refractory OIC, the AGA recommends naldemedine (SYMPROIC®) over no treatment	Strong	High
b. In patients with laxative-refractory OIC, the AGA recommends naloxegol (MOVANTIK®) over no treatment	Strong	Moderate
c. In patients with laxative-refractory OIC, the AGA suggests methylnaltrexone (RELISTOR®) over no treatment	Conditional	Low
3. Intestinal secretagogues		
a. In patients with OIC, the AGA makes no recommendation for the use of lubiprostone (AMITIZA®)	No recommendation	Evidence gap
4. Selective 5-HT agonists		
a. In patients with OIC, the AGA makes no recommendation for the use of prucalopride (MOTEGRITY™)	No recommendation	Evidence gap

PAMORA=peripherally acting mu-opioid receptor antagonist.
All tables adapted from "American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation."[1]

During evaluations for these guidelines, naldemedine was the **only prescription OIC with available long-term, 52-week safety data from a double-blind, randomized, placebo-controlled safety study.**[1]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation.
- Patients with a history of a hypersensitivity reaction to naldemedine. Reactions have included bronchospasm and rash.

WARNINGS AND PRECAUTIONS

Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue if this symptom develops.

Symproic® (naldemedine) tablets 0.2 mg

GO WITH IT

INDICATION AND IMPORTANT SAFETY INFORMATION

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Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with SYMPROIC®.

Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using SYMPROIC® in such patients. Monitor for symptoms of opioid withdrawal in such patients.

DRUG INTERACTIONS

Avoid use with strong CYP3A inducers (e.g., rifampin) because they may reduce the efficacy of SYMPROIC®.

Use with moderate (e.g., fluconazole) and strong (e.g., itraconazole) CYP3A inhibitors and P-glycoprotein inhibitors (e.g., cyclosporine) may increase SYMPROIC® concentrations. Monitor for potential adverse reactions.

Avoid use of SYMPROIC® with another opioid antagonist due to the potential for additive effect and increased risk of opioid withdrawal.

USE IN SPECIFIC POPULATIONS

Naldemedine crosses the placenta and may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. SYMPROIC® should be used during pregnancy only if the potential benefit justifies the potential risk. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Avoid use in patients with severe hepatic impairment. No dose adjustment of SYMPROIC® is required in patients with mild or moderate hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions with SYMPROIC® compared to placebo in two pooled 12-week studies were: abdominal pain (8% vs 2%), diarrhea (7% vs 2%), nausea (4% vs 2%), and gastroenteritis (2% vs 1%). The incidence of adverse reactions of opioid withdrawal in two pooled 12-week studies was 1% (8/542) for SYMPROIC® and 1% (3/546) for placebo. In a 52-week study, the incidence was 3% (20/621) for SYMPROIC® and 1% (9/619) for placebo.

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information at SYMPROIC.com.

Reference: 1. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter, Hanson BJ, Sultan S, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156(1):218-226.

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