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# The Efficacy of Peripheral Opioid Antagonists in Opioid-Induced Constipation and Postoperative Ileus: A Systematic Review of the Literature.

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# **The Efficacy of Peripheral Opioid Antagonists in Opioid-Induced Constipation and Postoperative Ileus: a Systematic Review of the Literature**

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Eric Schwenk, Alexander Grant, Marc Torjman, Stephen McNulty, and Jaime Baratta have no conflicts of interest to declare.

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been a paid lecturer for AcelRx, Merck, Salix, and Mallinkrodt. None of these companies were involved in any aspect of the development of this manuscript.

**Running Title:**

Opioid antagonists for constipation and ileus

1 **Abstract (149 words)**

2           Opioid-induced constipation has a negative impact on quality of life for patients  
3 with chronic pain and can affect more than a third of patients. A related but separate  
4 entity is postoperative ileus, which is an abnormal pattern of gastrointestinal motility  
5 after surgery. Non-selective  $\mu$ -opioid receptor antagonists reverse constipation and  
6 opioid-induced ileus but cross the blood-brain barrier and may reverse analgesia.  
7 Peripherally acting  $\mu$ -opioid receptor antagonists target the  $\mu$ -opioid receptor without  
8 reversing analgesia. Three such agents are FDA-approved. We reviewed the literature for  
9 randomized, controlled trials that studied the efficacy of alvimopan, methylnaltrexone,  
10 and naloxegol in treating either opioid-induced constipation or postoperative ileus.  
11 Peripherally acting  $\mu$ -opioid receptor antagonists **may be** effective in treating both opioid-  
12 induced bowel dysfunction and postoperative ileus **but definitive conclusions are not**  
13 **possible due to study inconsistency and the relatively low quality of evidence.**  
14 Comparisons of agents are difficult due to heterogeneous endpoints and no head-to-head  
15 studies.

## 16 **Introduction**

17           Despite recent focus on the opioid epidemic millions of patients rely on opioids to  
18 treat their chronic pain.<sup>1</sup> Opioid-related adverse drug effects are common, especially  
19 opioid-induced bowel dysfunction (OIBD), which is a spectrum of symptoms including  
20 dry mouth, nausea, vomiting, gastric stasis, bloating, abdominal pain, and opioid-induced  
21 constipation (OIC).<sup>2</sup> OIC is especially prevalent, affecting up to 41% of patients taking  
22 long-term opioids.<sup>3</sup> A working group of experts recently proposed that OIC be defined as  
23 a change when initiating opioid therapy from baseline bowel habits that is characterized  
24 by any of the following: reduced bowel movement frequency; development or worsening  
25 of straining to pass bowel movements; a sense of incomplete rectal evacuation; or harder  
26 stool consistency.<sup>4</sup>

27           Postoperative ileus (POI) is a related but distinct entity from OIC that also  
28 involves loss of forward propulsive motion of the gut but in the perioperative setting. A  
29 standard POI definition does not exist in the literature, but the authors of one review  
30 suggest that it is “an abnormal pattern of gastrointestinal motility, most frequently  
31 occurring after abdominal surgery” and encompasses the “interval from surgery until  
32 passage of flatus/stool and tolerance of an oral diet.”<sup>5</sup> POI has a multifactorial etiology  
33 that is shared with OIC, including the surgical stress response,<sup>6,7</sup> the inflammatory  
34 response that accompanies bowel manipulation,<sup>6,7,8</sup> and opioids that are both  
35 endogenously released by the GI tract<sup>7</sup> and given by **clinicians** for intra- and  
36 postoperative analgesia.<sup>9</sup> Most importantly, POI can be a driver of poor patient  
37 satisfaction, increase hospital length of stay, and increase overall hospital costs.<sup>10</sup>

38 Throughout the hospital **physicians** will likely encounter patients with one or both  
39 of these conditions and **need a good working knowledge of the basic mechanisms and**  
40 **therapeutic options that are available to treat these relatively common pathophysiologic**  
41 **states.**

42 Conventional therapies, including fiber, opioid rotation, stool softeners, and  
43 laxatives, have limited data to support their use in OIC.<sup>11</sup> They may be used initially with  
44 relatively low risk and minimal cost but are unlikely to effectively treat the symptoms  
45 alone. Non-specific opioid antagonists can reverse OIC and POI but may reverse  
46 analgesia as well.<sup>12</sup> Drugs that specifically block the  $\mu$ -opioid receptor outside of the  
47 central nervous system, collectively known as peripherally acting  $\mu$ -opioid receptor  
48 (PAM-OR) antagonists, have been developed as a possible solution to this problem.  
49 PAM-OR antagonists specifically target the  $\mu$ -opioid receptor in the peripheral nervous  
50 system and treat one of the major underlying mechanisms of both OIC and POI. In the  
51 United States three such drugs are approved for one of these two indications: alvimopan,  
52 methylnaltrexone, and naloxegol.

53 Currently, alvimopan has approval from the Food and Drug Administration (FDA  
54 as a “peripherally acting  $\mu$ -opioid receptor antagonist indicated to accelerate the time to  
55 upper and lower gastrointestinal recovery following partial large or small bowel resection  
56 surgery with primary anastomosis.”<sup>13</sup> Methylnaltrexone was first approved as a  
57 subcutaneous injection “for the treatment of opioid-induced constipation in patients with  
58 advanced illness who are receiving palliative care, when response to laxative therapy has  
59 not been sufficient”<sup>14</sup> and very recently was approved in the oral formulation for patients  
60 with chronic non-cancer pain and OIC.<sup>15</sup> The most recent addition to the PAM-OR

61 antagonists, naloxegol, has been in clinical use since its approval in 2014 as “an opioid  
62 antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult  
63 patients with chronic non-cancer pain.”<sup>16</sup> Several randomized trials involving PAM-OR  
64 antagonists have recently been published<sup>17,18</sup>; in addition, previous reviews have focused  
65 solely on a single agent<sup>19,20</sup> or either OIC<sup>21</sup> or POI<sup>22</sup> but not both. Therefore, an update  
66 that discusses strengths and limitations of the evidence is warranted. We conducted a  
67 systematic review for randomized, placebo-controlled trials that compared alvimopan,  
68 methylnaltrexone, and naloxegol to placebo and had efficacy as the primary endpoint.  
69 The subsequent discussion will focus on the evidence for these PAM-OR antagonists in  
70 treating OIC and POI.

71

72

73 **Methods**

74 We conducted the review protocol using the Preferred Reporting Items for  
 75 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>23</sup> During the months of  
 76 April and May 2016 and again in February 2017, we conducted searches using PubMed  
 77 and Scopus databases looking for randomized, placebo-controlled trials that studied the  
 78 efficacy of alvimopan, methylnaltrexone, or naloxegol in patients with OIC or  
 79 postoperative ileus. The last date searched was February 3, 2017. There were no date  
 80 limitations placed on the searches in either database. We used the following search  
 81 protocol in PubMed: (((“alvimopan”[Supplementary Concept] OR “alvimopan”[All  
 82 Fields]) OR (“methylnaltrexone”[Supplementary Concept] OR “methylnaltrexone”[All  
 83 Fields]) OR (“naloxegol”[Supplementary Concept] OR “naloxegol”[All Fields])) OR  
 84 “peripheral opioid antagonist”[All Fields] OR “peripherally acting opioid antagonist”[All  
 85 Fields] OR (peripheral[All Fields] AND mu[All Fields] AND antagonist[All Fields]) OR  
 86 (peripheral[All Fields] AND mu[All Fields] AND (“narcotic  
 87 antagonists”[Pharmacological Action] OR “narcotic antagonists”[MeSH Terms] OR  
 88 (“narcotic”[All Fields] AND “antagonists”[All Fields]) OR “narcotic antagonists”[All  
 89 Fields] OR (“opioid”[All Fields] AND “antagonist”[All Fields]) OR “opioid  
 90 antagonist”[All Fields])) OR “opioid antagonist”[All Fields] AND (“postoperative ileus”  
 91 OR “opioid-induced bowel dysfunction”[All Fields] OR “opioid-induced  
 92 constipation”[All Fields]).

93 Our search protocol for Scopus included the following: ( ALL ( alvimopan ) OR  
 94 ALL ( methylnaltrexone ) OR ALL ( naloxegol ) OR ALL ( peripheral opioid  
 95 antagonist ) OR ALL ( peripherally acting opioid antagonist ) OR ALL ( opioid

96 antagonist ) AND ALL ( opioid-induced bowel dysfunction ) OR ALL ( opioid-induced  
97 constipation ) OR ALL ( postoperative ileus ) ) AND DOCTYPE ( ar ) AND ( LIMIT-  
98 TO(LANGUAGE,"English" ) ).

99

#### 100 *Inclusion Criteria*

101 Studies that were written in English involving clinical patients who had OIC and  
102 were being given either a PAM-OR antagonist or placebo or were given a PAM-OR  
103 antagonist or placebo for the purpose of treating or preventing POI were included.

104

#### 105 *Exclusion Criteria*

106 Studies that examined a PAM-OR antagonist in the setting of experimentally  
107 induced OIC (giving healthy volunteers codeine followed by a PAM-OR antagonist, for  
108 example) were extracted but included in a separate table and not included in the formal  
109 review. Studies that were prospective but did not include a placebo group were excluded,  
110 as were studies in which patients were not randomized. Also excluded were post-hoc or  
111 subset analyses of clinical trials that had been previously published. When applicable,  
112 only the blinded portion of a study was reviewed and analyzed.

113

#### 114 *Review Protocol and Evidence Grading*

115 Evidence quality was assessed using the Grades of Recommendation, Assessment,  
116 Development, and Evaluation (GRADE) approach (see Tables 1 and 2).<sup>24</sup> Using this  
117 approach, studies are classified as high, moderate, low, or very low quality of evidence.

118 All articles were first reviewed independently by ES and AG and assessed for  
119 inclusion in the review. If the determination could not be made from reading the article  
120 title, the abstract was reviewed, and if ambiguity remained after that, the full article was  
121 subsequently downloaded and reviewed. Reference lists from screened articles were  
122 searched as well. Discrepancies were resolved by discussion between ES and AG.  
123 Articles that met all inclusion criteria but studied OIC treatment in healthy volunteers  
124 were not included in the formal review but are shown separately in Table 1.  
125  
126

## 127 **Results**

### 128 *Study Selection*

129 Initial search of the literature yielded 1,314 articles (Figure 1). Screening of  
130 reference lists yielded two additional studies.<sup>25,26</sup> One additional study that was initially  
131 excluded because it referred to alvimopan as ADL 8-2698, its investigational name, was  
132 later included in the review after confirming that it did in fact study alvimopan (Figure  
133 1).<sup>27</sup> Because of the overlap between PubMed and Scopus databases, there were 158  
134 duplicates. Reasons for exclusion are shown in Figure 1. The two most common reasons  
135 for exclusion were that PAM-OR antagonists were not studied (n=588), which primarily  
136 applied to Scopus articles, and that the studies were not randomized, controlled trials  
137 (RCTs; n=459). A total of 23 studies were included in the final review. The four RCTs  
138 that enrolled healthy volunteers were grouped separately and are shown in Table 1.<sup>28-31</sup>

139

### 140 *Opioid-Induced Bowel Dysfunction Studies in Healthy Volunteers*

141 Four Phase 1 studies enrolled healthy volunteers and administered a  $\mu$ -opioid  
142 agonist to induce delay in gut transit and then administered a PAM-OR antagonist to  
143 evaluate its effects on gut transit time compared to placebo (Table 1).<sup>28-31</sup> In the single  
144 study on alvimopan,<sup>30</sup> 12 mg was given along with codeine 30 mg four times a day and  
145 alvimopan reversed the codeine-induced delay in gut transit and improved gut transit in  
146 patients not given codeine as well.

147 In one of the studies that enrolled healthy volunteers who were given morphine  
148 and then randomly assigned to one of two doses of subcutaneous methylnaltrexone or  
149 placebo,<sup>29</sup> both the 0.1 and 0.3 mg/kg doses reversed morphine-induced delay in gut

150 transit time. Wong et al, however, did not find any difference between subcutaneous  
151 methylnaltrexone 0.3 mg/kg and placebo in reducing the codeine-induced delay in gut  
152 transit.<sup>31</sup> Yuan et al gave healthy volunteers intravenous methylnaltrexone 0.45 mg/kg  
153 after giving them morphine and found that methylnaltrexone prevented 97% of  
154 morphine-induced delay in gut transit time.<sup>28</sup>

155

### 156 *Opioid-Induced Constipation Studies*

157 A total of 14 RCTs that studied PAM-OR antagonists in the setting of OIC were  
158 included in the review (Table 2). All alvimopan studies included patients with non-cancer  
159 pain who were given oral alvimopan in either a 0.5- or 1-mg dose. The primary outcome  
160 for two studies was the percentage of patients with at least three spontaneous bowel  
161 movements (SBMs) per week.<sup>32,33</sup> One study's primary outcome was the mean frequency  
162 of weekly SBMs<sup>34</sup> and in another it was the percentage of patients that had a BM within  
163 eight hours.<sup>35</sup> When analyzing the primary outcome of the four studies on alvimopan,  
164 three showed a positive result for the alvimopan group<sup>32,34,35</sup> and one showed no  
165 difference.<sup>33</sup> Study quality was low for all four studies.

166 The effects of alvimopan on  $\mu$ -opioid receptors in the central nervous system  
167 were minimal. Three alvimopan studies reported no differences in pain scores or opioid  
168 consumption between study groups,<sup>32,33,34</sup> while one study described two patients in the  
169 1-mg alvimopan group who had increases in pain but no difference between groups  
170 receiving the 0.5-mg dose.<sup>35</sup>

171 There were seven studies on methylnaltrexone for OIC.<sup>17,18,36-40</sup> Four studies  
172 included patients with non-cancer pain only,<sup>18,36,39,40</sup> while the other three enrolled

173 patients with both cancer and non-cancer pain.<sup>17,37,38</sup> The selected dose for studies with  
174 subcutaneous methylnaltrexone was 12 mg in two studies,<sup>39,40</sup> 8 or 12 mg in one study,<sup>17</sup>  
175 0.15 mg/kg in one study, 0.15 or 0.3 mg/kg in one study,<sup>38</sup> and up to 0.365 mg/kg in the  
176 study that used intravenous methylnaltrexone.<sup>36</sup> The single study of oral  
177 methylnaltrexone included doses of 150, 300, and 450 mg.<sup>18</sup> The primary outcome was  
178 positive in all seven studies. In five studies, the primary outcome was achievement of a  
179 spontaneous bowel movement (SBM) within 4 hours of receiving the study drug<sup>17,37-38,39,40</sup>  
180 Another study had no primary endpoint but reported that laxation occurred within one  
181 minute of initiating methylnaltrexone intravenous infusion in 10 of 11 patients.<sup>36</sup> In the  
182 single study of the oral formulation, the primary endpoint was the percentage of patients  
183 with a mean number of dosing days resulting in a SBM within four hours of dosing.  
184 Although this endpoint was greater in both 300- and 450-mg groups, it was lower than  
185 the response rate for the subcutaneous formulation.<sup>18</sup> The 450-mg dose had highest  
186 efficacy without increasing adverse events. Study quality was moderate for two  
187 studies,<sup>17,18</sup> low for three studies,<sup>37-38,39</sup> and very low for two studies.<sup>36,40</sup>

188 In five of the studies, analgesia was preserved based on no differences in pain  
189 scores, opioid consumption, or both between treatment groups.<sup>17,37-38,39,40</sup> For oral  
190 methylnaltrexone, pain scores did not change from baseline.<sup>18</sup> In the remaining study,  
191 pain and opioid use were not assessed but patients reported no change in subjective  
192 withdrawal symptoms.<sup>36</sup> **In the largest study by Michna et al,<sup>39</sup> rescue laxatives were used  
193 by 61.7% of the placebo group versus 38.7% in the daily dosing group and 41.7% in the  
194 every-other-day dosing group.**

195           There were two published articles for naloxegol, one of which described a study  
196 involving patients with cancer and non-cancer pain<sup>41</sup> while the other studied only non-  
197 cancer pain and consisted of two smaller trials.<sup>42</sup> Both studies had positive outcomes for  
198 the primary outcome which was a greater number of SBMs per week for both 25- and 50-  
199 mg doses in the article by Webster et al<sup>41</sup> and accelerated time to first rescue-free bowel  
200 movement (RFBM) for 25 mg in both trials for Chey et al and 12.5 mg in one of two  
201 trials.<sup>42</sup> Study quality was moderate for one study<sup>42</sup> and low for the other.<sup>41</sup>

202           In both naloxegol studies, analgesia was preserved with no differences in pain  
203 scores or opioid consumption existing between study groups. **The use of rescue laxatives**  
204 **was high in placebo and treatment groups for the study by Chey et al (72.0, 63.4, and**  
205 **54.7% in study 04 and 70.7, 57.3, and 57.3% in study 05).**<sup>42</sup> When comparing naloxegol  
206 to oral methylnaltrexone, 50% of patients who received 25 mg of naloxegol had a RFBM  
207 within six hours of the first dose, compared to approximately 30% of patients who  
208 received 450 mg of oral methylnaltrexone.<sup>18,41</sup> **However, the incidence of GI adverse**  
209 **events was greater for naloxegol than for oral methylnaltrexone.**

210

### 211 *Postoperative Ileus Studies*

212           A total of 10 studies on POI were included in the review (Table 3). Primary  
213 endpoints of the studies varied but most used the achievement of either GI-2 recovery  
214 (toleration of solid food and first bowel movement) or GI-3 recovery (toleration of solid  
215 food and flatus or first bowel movement). Of the eight studies that examined alvimopan,  
216 five enrolled patients who underwent major abdominal surgery,<sup>43-47</sup> one included bowel  
217 resection,<sup>48</sup> one included patients undergoing total abdominal hysterectomy,<sup>49</sup> and one

218 included radical cystectomy.<sup>50</sup> Aside from the study by Taguchi et al,<sup>43</sup> which was a  
219 Phase I study, four of the other alvimopan studies examined both 6- and 12-mg doses,<sup>44-47</sup>  
220 while the remaining three only used 12 mg.<sup>48-50</sup> These doses were three- to six-fold  
221 greater than the doses used for OIC. Of note, six alvimopan studies excluded chronic  
222 opioid users.<sup>43,45,46,47,48,49</sup> Six studies reported positive results for the primary outcome of  
223 accelerated GI recovery (flatus, GI-2, or GI-3),<sup>43,44,45,48,49,50</sup> while two alvimopan studies  
224 found no difference between groups,<sup>46,47</sup> although Viscusi et al did report an accelerated  
225 time to GI-2 recovery (secondary endpoint) in the alvimopan group for both 6- and 12-  
226 mg doses. Study quality was moderate for four studies,<sup>45-48</sup> low for two,<sup>49,50</sup> and very low  
227 for one.<sup>43</sup>

228         Analgesia was preserved in seven of the studies for all groups,<sup>43-50</sup> with the  
229 exception of the 6-mg group in one study which demonstrated greater opioid  
230 consumption than placebo.<sup>44</sup>

231         Yu et al<sup>51</sup> studied methylnaltrexone intravenously (IV) for POI at both 12- and  
232 24-mg doses in two identical, parallel-group studies for patients who underwent  
233 segmental colectomy. For the primary endpoint of time until first SBM, they found no  
234 difference between groups. They also found no difference among any secondary  
235 endpoints. Study quality was moderate. Preservation of analgesia was unclear because the  
236 authors did not report pain scores nor opioid consumption, although they stated that  
237 “there was no evidence that methylnaltrexone increased the requirement for opioids to  
238 relieve postsurgical pain.” Viscusi et al,<sup>26</sup> in contrast, studied IV methylnaltrexone in the  
239 setting of POI and found that it accelerated time to first SBM; however, this study was

240 exploratory with a small sample size ( $n=65$ ) that was not determined prior to patient  
241 enrollment.

242

243

244

245 **Discussion**

246 This review demonstrates that PAM-OR antagonists **may be** effective for OIC and  
247 POI without reversing opioid-mediated analgesia **but study design inconsistency and**  
248 **variable endpoints makes definitive conclusions impossible**. PAM-OR antagonists as a  
249 class prevent opioid-induced increases in gut transit time in healthy volunteers and  
250 provide specific, targeted treatment of OIC and POI that result from a loss of coordinated  
251 propulsive action in the gut due to opioids.

252 The studies reviewed ranged from very low to moderate quality according to the  
253 GRADE recommendations for rating study quality.<sup>24</sup> There is especially a need for  
254 comparative studies that directly compare two or more of the three agents studied here.  
255 Heterogeneity in endpoints as well as study protocols was a problem throughout the  
256 literature.

257 Our results agree with the meta-analysis by Ford et al,<sup>21</sup> who found that  
258 methylnaltrexone was more effective than placebo in treating OIC. While their analysis  
259 included six trials, ours included eight. They also concluded that alvimopan was superior  
260 to placebo for OIC and included four trials, as we did. They too noted considerable  
261 heterogeneity among studies, more so with methylnaltrexone. Subsequent pooled  
262 analyses confirmed the efficacy of methylnaltrexone<sup>52,53</sup> and suggested that it may be  
263 particularly effective in those patients taking large daily opioid doses. Rauck et al  
264 reported that gastrointestinal side effects with oral methylnaltrexone occurred at the same  
265 rate as in the placebo group,<sup>18</sup> which did not appear to be the case with the subcutaneous  
266 formulation.<sup>17,39</sup> This should be considered when choosing between the two formulations,  
267 although this finding needs additional confirmatory studies.

268           Although alvimopan was studied in the setting of OIC, it is approved only for the  
269 treatment of POI in hospitalized patients who have undergone partial small or large  
270 bowel resection surgery.<sup>54</sup> This is reflected by the existence of fewer studies for  
271 alvimopan in OIC and the lack of recent, late-phase studies and post-hoc analyses. As  
272 stated by Irving et al, “alvimopan was under clinical development for long-term treatment  
273 of opioid-induced constipation but this program has been discontinued.”<sup>33</sup> Concerns by  
274 the Food and Drug Administration over the “imbalance” in the number of cardiovascular  
275 events (more myocardial infarctions) in the alvimopan group versus placebo group  
276 prompted the discontinuation of the OIC program and limited its approved indication to  
277 inpatient use only.<sup>55</sup> Positive results in one of the two replicate Phase 3 studies<sup>32</sup> but not  
278 the other<sup>33</sup> speak to the lack of evidence for a specific dose and inconsistent study design  
279 between these and an earlier Phase 2 study.<sup>34</sup>

280           Naloxegol, the newest PAM-OR antagonist in the group, has demonstrated  
281 positive results in both studies in this review and agrees with the findings of other  
282 reviews.<sup>19</sup> Leppart and Woron reported that naloxegol was effective in up to 49% of  
283 patients not responsive to standard laxatives and that naloxegol has been shown to be  
284 more effective than placebo in patients with OIC and noncancer pain. No studies have  
285 been performed in cancer patients.<sup>19</sup> The approved dose is 25 mg.<sup>16</sup> Comparison of  
286 naloxegol to oral methylnaltrexone is difficult because the primary endpoints are not the  
287 same from the published studies. However, the available data suggest that while both  
288 agents are effective, adverse effects occurred at a greater frequency with naloxegol  
289 compared to placebo<sup>41,42</sup> while patients who received oral methylnaltrexone had a similar

290 rate of adverse effects as the placebo group.<sup>18</sup> Although confirmatory studies are needed,  
291 this suggests oral methylnaltrexone may have a superior side-effects profile.

292 For POI, the only PAM-OR antagonist FDA-approved for this indication is  
293 alvimopan. Heterogeneity in endpoints was a problem throughout the literature with most  
294 studies using some composite form of return to GI function. When given preoperatively  
295 and continued postoperatively, we found that alvimopan is effective in reducing POI. An  
296 important exclusion in many of the studies was opioid use prior to surgery. This could  
297 limit the number of patients who can receive alvimopan.

298 Viscusi et al reported that both methylnaltrexone and alvimopan do not cross the  
299 blood brain barrier for different reasons: for methylnaltrexone, this is due to its polarity  
300 and low lipid solubility that results from the addition of a fourth methyl group to  
301 naltrexone, making it a quaternary structure; for alvimopan, this is due its high polarity as  
302 a zwitterion.<sup>7</sup> Our review included three additional alvimopan studies and one additional  
303 methylnaltrexone study not included in theirs. We found no evidence for reversal of  
304 opioid-mediated analgesia, although one study did not include any measurements.<sup>51</sup>

305 Methylnaltrexone studies for POI had conflicting evidence in this review. In the  
306 two studies that evaluated it in this context,<sup>26,51</sup> the IV formulation was given  
307 postoperatively. It should be noted that the study that reported positive results enrolled 65  
308 patients, while the study that found no improvement with methylnaltrexone was actually  
309 the results of two identical studies with n=515 and n=533.

310 It should be noted that three alvimopan studies<sup>45,47,50</sup> and one methylnaltrexone<sup>51</sup>  
311 POI study specified that they did not allow epidural analgesia in the protocols, which is  
312 understandable given the existing evidence for epidurals.<sup>56</sup> In the other POI studies it was

313 not stated whether epidural analgesia was excluded. In a multimodal or enhanced  
314 recovery after surgery (ERAS) pathway involving epidural analgesia, the duration of  
315 ileus in the placebo group would likely be shorter. Similarly, intravenous lidocaine has  
316 been shown to reduce duration of ileus and this was excluded from the studies as well.<sup>57</sup>  
317 Therefore, clinicians should consider this when evaluating the potential improvement in  
318 POI duration that a PAM-OR antagonist may produce.

319 Comparative-effectiveness studies in this field are clearly needed. None of the  
320 studies included in this review compared one PAM-OR antagonist to another. This makes  
321 direct comparisons difficult especially when heterogeneity in endpoints for the individual  
322 studies is taken into account. In addition, laxatives were permitted in some studies and  
323 not others, further complicating the picture. Although we did not analyze medication cost  
324 in this review, these charges as well as insurance coverage are additional considerations  
325 that may affect choice of agent.

326 This review has some limitations. We were unable to determine if there were  
327 unpublished studies that did not show positive results, and it is possible that some of  
328 these stopped prematurely. This may be particularly true with alvimopan, which was  
329 studied for OIC and subsequently abandoned for that indication. Second, there may be  
330 some studies that were not located through our search protocols. We attempted to  
331 minimize this limitation by combining two search databases, using two reviewers, and  
332 using as broad of a selection of search terms as feasible. However, studies with different  
333 key words or search terms could have been omitted.

334

335 **Conclusion**

336 In conclusion, PAM-OR antagonists may be effective in both OIC and POI but  
337 the inconsistency of study design, study endpoints, and lack of comparative studies limits  
338 the strength of our recommendations. Within the class methylnaltrexone has the most  
339 consistent evidence, and its oral formulation may be slightly less effective than the  
340 subcutaneous formulation but cause fewer gastrointestinal adverse effects. Although  
341 naloxegol is more effective than placebo for OIC, it appears to cause more adverse  
342 effects than oral methylnaltrexone. Alvimopan is the only FDA-approved and most well-  
343 studied agent for POI. Comparative studies are lacking. A multimodal treatment strategy  
344 for OIC and POI is recommended for these multifactorial disease states and evaluation of  
345 these agents combined with epidural analgesia and intravenous lidocaine is needed.  
346 Additional PAM-OR antagonists are currently under development but the potential  
347 market for these agents may become smaller as efforts to fight the opioid epidemic  
348 intensify.

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