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The use of naloxone for the treatment of opioid-induced constipation (OIC)

Curtis Cole
Pacific University

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The use of naloxone for the treatment of opioid-induced constipation (OIC)

Abstract
Background: Opioid-induced constipation (OIC) is a major problem that can have a significant impact on a patient’s quality of life (QoL). The use of opioids for both long and short term analgesia has been the standard treatment for many years. All opioids, like oxycodone, can be connected with the development of bowel dysfunction, with constipation being one of the more frequently reported adverse effects. Many of the standard methods and protocols that hospitals use seem to have little effect on this continuing problem.

Hypothesis: That the use of oral naloxone Prolonged Release (PR), in conjunction with oxycodone PR, will improve patient bowel function, without effecting analgesia or creating additional side effects that decrease patients’ QoL.

Study Design: Exhaustive search of available medical literature.

Methods: The intent of this study was to seek out and review the most current literature available on this problem utilizing a minimum of three search engines. The review of literature was limited to Randomized Control Trials (RCT) published since 2008.

Results: five studies were found that met the criteria for inclusion in this review. Two of the five were based upon the same data although with separate clinical questions.

Conclusion: The studies showed that naloxone PR, when given to a patient who is established on a stable dose of oxycodone PR, significantly improved the patients’ bowel function, without adding additional adverse events, causing opioid withdrawal or decreasing analgesic properties, and that the optimum ratio which produced the leased number of adverse events was 2:1.

Degree Type
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Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Rob Rosenow PharmD, OD

Second Advisor
Annjanette Sommers MS, PAC

Keywords
constipation, naloxone

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The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
The use of naloxone for the treatment of opioid-induced constipation (OIC)

Curtis Cole

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 15th, 2009

Faculty Advisor: Rob Rosenow PharmD, OD
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Curtis Cole grew up in Corvallis, Oregon; the same town where he later received his undergraduate degree in Exercise and Sports Science from Oregon State University. He and his wife were married in 1980, and raised three children. Curtis was in the National Guard, ROTC at Oregon State, and after graduation, returned to active duty in the U.S. Army as a commissioned officer. He spent the next six years as a helicopter pilot until his discharge in 1991. During his time in the military, he was trained as a combat field medic and was able to do extensive humanitarian aid and medical missions work while stationed in Central America. He also ran an outpatient rehabilitation clinic for the Physical Therapy department at Blanchfield Army Hospital just prior to his discharge. Before returning to school to pursue a Masters Degree in Physician Assistant Studies, Curtis was a volunteer firefighter/EMT for his local fire department. He continues to stay active in his community and volunteers with Salem Free Medical Clinic. After graduation from PA school, he plans to remain in the area where he has his same lovely wife, same 3 children, and 3 wonderful grandchildren.
Abstract

**Background:** Opioid-induced constipation (OIC) is a major problem that can have a significant impact on a patient’s quality of life (QoL). The use of opioids for both long and short term analgesia has been the standard treatment for many years. All opioids, like oxycodone, can be connected with the development of bowel dysfunction, with constipation being one of the more frequently reported adverse effects. Many of the standard methods and protocols that hospitals use seem to have little effect on this continuing problem. **Hypothesis:** That the use of oral naloxone Prolonged Release (PR), in conjunction with oxycodone PR, will improve patient bowel function, without effecting analgesia or creating additional side effects that decrease patients’ QoL. **Study Design:** Exhaustive search of available medical literature. **Methods:** The intent of this study was to seek out and review the most current literature available on this problem utilizing a minimum of three search engines. The review of literature was limited to Randomized Control Trials (RCT) published since 2008. **Results:** five studies were found that met the criteria for inclusion in this review. Two of the five were based upon the same data although with separate clinical questions. **Conclusion:** The studies showed that naloxone PR, when given to a patient who is established on a stable dose of oxycodone PR, significantly improved the patients’ bowel function, without adding additional adverse events, causing opioid withdrawal or decreasing analgesic properties, and that the optimum ratio which produced the leasted number of adverse events was 2:1. **Keywords:** constipation, naloxone, humans only, RCTs only, recent studies 2008 to current.
Acknowledgements

To Peyton Cole, thank you for always being there for me, being the best mother any children could ask for, for being the “spear” when I needed it, and for being a strong woman who is able to take on any task. You are my inspiration.

To my children, for putting up with my failures as a father, bad dad humor, and for staying in school so you don’t end up like me.
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List of Abbreviations

BFI…………………………………………………………………………………………….Bowel Function Index
CSBM……………………………………………………………………Complete Spontaneous Bowel Movement
ECG…………………………………………………………………………………………….Electrocardiogram
ED………………………………………………………………………………………………Emergency Department
EMT……………………………………………………………………………Emergency Medical Technician
EtOH…………………………………………………………………………………………….Alcohol
GI………………………………………………………………………………………………Gastrointestinal
IV………………………………………………………………………………………………Intravenous
NAS…………………………………………………………………………………………….Numerical Analog Scale
OIC………………………………………………………………………………………………Opioid Induced Constipation
PAC-SYM……………………………………………………………………………………Patient Assessment of Constipation Symptoms
PR………………………………………………………………………………………………Prolonged Release
QoL…………………………………………………………………………………………….Quality of Life
RCT…………………………………………………………………………………………….Randomized Controlled Trials
SAEs……………………………………………………………………………………………Serious Adverse Events
The use of naloxone for the treatment of opioid-induced constipation (OIC)

Introduction:

Oxycodone is a semi-synthetic strong opioid analgesic that has become one of the most widely used since it was first used clinically in 1917. Opioid-induced constipation (OIC) is a major problem that can have a significant impact on a patient’s quality of life (QoL). The use of opioids for both long and short term analgesia has been the standard treatment for many years. The opioid-mediated side effects of opioid therapy are well documented and include but are not limited to respiratory depression, nausea, sedation, bowel dysfunction, and itching. OIC is the most frequently reported adverse event associated with opioid therapy. Although most of the symptoms of bowel dysfunction experienced by patients receiving short or long-term opioid therapy subside with chronic use, constipation often persists, requiring additional intervention. The physical discomfort and pain caused by constipation can force patients either to discontinue their opioid therapy to reduce the opioid dose, resulting in inadequate pain control. Many of the current treatment strategies and protocols for OIC are nonspecific and therefore, are often ineffective. Prophylactic laxative use improves symptoms in some patients, however, laxatives do not address the opioid receptor-mediated mechanism of bowel dysfunction, and a substantial number of patients do not achieve management of their problem. OIC can become so severe that some patients opt to discontinue analgesic therapy altogether, resulting in issues of patient compliance, under treatment of pain, and an impairment of QoL. The adverse effects of opioids on bowel function result largely from binding to opioid receptors in the plexus myentericus and plexus submucosus on the gut, while the analgesic effects are largely due to opioid receptors binding in the central nervous system. Prevention of OIC and bowel dysfunction in general, is considered to be a more effective strategy than trying to then treat it as it occurs. Once these two separate principals are understood, it should then be possible to provide adequate pain control, while reducing OIC and improving bowel function.
Naloxone is a pure competitive opioid receptor antagonist, which is used intravenously (IV) for the blockade and reversal of exogenously administered opioids. The drug in its IV form has long been used by emergency services (EMS) personnel on the ambulance and in the emergency department (ED), as an opioid overdose antidote. Because of extensive first-pass hepatic metabolism, orally administered naloxone has negligible systemic bioavailability of approximately 2%.\textsuperscript{12, 13} The systemic and central availability after oral administration is, therefore, negligible and it acts, almost exclusively, on opioid receptors in the gastrointestinal tract. Naloxone should, therefore, be able to block the effects of opioids in the gut, while allowing the centrally mediated analgesic effect of opioids to remain.\textsuperscript{9}
Methods:

An exhaustive literature search using the following search engines: OVID, MEDLINE, CINAHL. The search was performed utilizing the following search terms: constipation and naloxone. Inclusion criteria used to limit the number of articles included adult humans only, randomized controlled trials (RCT) only, and articles published from 2008 to the present. Exclusion criteria were as follows, trials addressing methylnaltrexone use, and articles published before 2008. Methylnaltrexone, although from the same class of medications as naloxone, is administered through subcutaneous injection. The difference in methods of delivery was used as an exclusion criterion to focus the review on naloxone, which is administered orally. Using only studies that were published in 2008 and 2009 allowed only the most current information to be considered for review. Five randomized control trials were located which met the entire inclusion and exclusion criteria.

MEDLINE and CINAHL each had a few of the articles that met the criteria, but OVID was able to locate all of the five articles that were eventually used in this review. There were two of the articles which utilized the same data, Meissner, W. 2009 and Nadstawek, J. 2008. The original paper published in 2008 contained all of the same data, but was not organized in a manner that was easily understood nor did it follow standard formatting. This article was looking to find the optimum ratio for the two drug combination most effective in improving bowel function while maintaining adequate pain control. The more recent article, published in 2009 in the European Journal of Pain, looked more at overall pain control and bowel function rather than optimum ratios. This article was the focus of study being more precise in its interpretation of the data, thereby painting a much clearer picture for the reader. Although this later article did not make any new assumptions or provide additional insight it was presented in the standard format that did contain all of the usual figures and tables normally included in this type of study. Additionally, a search was performed to locate any review articles which may have already existed that covered the same information or question. Once again all three of the
above search engines and terms were utilized. The articles selected for this review had been published in the last twelve to eighteen months, so no current review articles were located.

All five studies were randomized, double blinded, and placebo-controlled (see table I for a comparison and amount in the study populations). In addition, four of the five studies included a 3rd phase which was open-label. In both the Lowenstein, O 2009 study and the Simpson, K 2008 study, patients who completed the double-blind phase were eligible to enter an additional 52-week open-label extension designed to assess the long-term safety of the oxycodone PR/naloxone PR combination. This phase III had not been completed at the time of this review and is scheduled to be reported in a separate study in the future.3, 5 The Meissner, W. 2009 and Nadstawek, J. 2008 studies also had a phase III portion which consisted of only the time between visits 5 and 6 which were open-label visits.1, 2

For all of the studies phase I was the screening phase in which participants were qualified for participation, a run-in period designed to titrate patients to a stable and effective analgesic dose of Oxycodone PR of 40, 60, or 80mg. During this phase patients on other pre-study opioid therapy were converted to an equivalent study medication dose. Participants were also qualified to participate in the next phase of the study based upon the inclusion/exclusion criteria. Male and female patients aged 18 years old and currently using opioid therapies to control pain on an around-the-clock basis were eligible. They also had to have constipation caused or aggravated by an opioid and were likely to benefit from opioid therapy for the duration of the study. Exclusion criteria included history of hypersensitivity to oxycodone, naloxone or related products, current EtOH or drug abuse, severe cardiovascular or respiratory disease, severe liver or renal insufficiency, or acute pancreatitis. Patients were also excluded if they had a history of paralytic ileus, psychoses, Parkinson’s disease, females who were pregnant or lactating, or did not have adequate contraception, and any other condition which may effect GI motility. Care was taken in all of the studies to insure the two groups of patients utilized were as similar in demographics and distribution as possible.
Phase II was the double blinded placebo phase which utilized oxycodone PR and placebo or oxycodone PR and naloxone PR were used. In the Meissner, W. 2009 and Nadstawek, J 2008 studies an additional 2 control groups were included in an attempt to identify the optimum dosage ratio between oxycodone PR and the naloxone PR. In those two studies patients were randomised to four study groups. The randomization program balanced the relation between four naloxone dose groups (10, 20, 40mg, or placebo) in block sizes of four (1:1:1:1 randomization). The dosing groups and ratios are shown in Table 2.1.2

The means used to asses overall patient improvement and/or positive outcomes, were conducted utilized several different parameters, usage of laxatives, BFI (bowel function index figure 1), CSBM (complete spontaneous bowel movement), increase or decrease in adverse events, the use of rescue medication, sleep disturbance, and pain assessment.

The safety and assessments, in all studies, consisted of recording and monitoring all adverse events and serious adverse events (SAEs), screening of patient’s diaries and monitoring hematology, blood chemistry, urine values, vital signs, electrocardiogram (ECG), and physical examinations. All patients had the ability to discontinue the study at any time during any phase.
Results:

The Lowenstein O, Leyendecker P, Hopp M, et al study used BFI (figure I), along with average pain over the last 24 hours utilizing the pain intensity numerical rating scale (NRS 1-10). Constipation was assessed using the PAC-SYM questionnaire which measures the severity of 12 symptoms of constipation over the prior seven days using a five point scale (0= absent, 1= mild, 2= moderate, 3= severe, 4= very severe), and finally a CSBM a week. The analysis in this study revealed the in just the first four weeks of the double-blinded phase, the difference in mean BFI scores between the two groups was statistically significant in favor of the oxycodone PR/naloxone PR group, see Table 2. The study effectively demonstrated that oxycodone PR when used in combination with naloxone PR is superior to oxycodone PR (with regards to improving opioid-induced bowel dysfunction), and particularly with respect to reducing opioid-induced constipation. The treatment with oxycodone PR plus naloxone PR produced statistically and clinically significant improvement in BFI scores without sacrificing the analgesic efficacy of the oxycodone component, as evidenced by pain intensity scales that were comparable between the two groups and remained constant throughout the study (see figure III).

The Meissner W, Leyendecker P, Mueller-Lissner S, et al study used the Nadstawek J, Leyendecker P, Hopp M, et al data to examine additional areas of interest. The studies primary outcomes of interest were mean pain and mean bowel function rather than finding the ratio which provided the best overall outcome. Pain was assessed subjectively using a numerical analog scale (NAS) where 0= no pain and 100 = worst imaginable pain. The NAS was completed twice daily by each patient (in their diary. Mean bowel function was based on patients’ subjective assessment utilizing the standard BFI, see Figure 1. This study showed that improvement in the patients BFI with almost no statistical change in pain control can be achieved with the drug combination. This study
echoes the benefits of an oxycodone PR and naloxone PR combination, adding that the 2:1 dosing ratio provided the least severe and fewest side effects.

The Nadstawek J, Leyendecker P, Hopp M, et al studies primary focus was to find the optimum ratio between oxycodone PR and naloxone PR that produce the least number of adverse side effects, while still providing improved bowel function. This study used additional groups that allowed for the variety of ratios needed to properly assess outcomes (table II). The 2:1 ratio was shown to have the best result in reducing OIC with the least number and severity of adverse events. This study indicates that the addition of naloxone PR to oxycodone PR improves patient assessment of their analgesic therapy. Patients noted no additional side effects and no impact on the analgesic efficacy of the oxycodone PR, with improvements in bowel function and reduction in laxative intake. There was a dose-dependent increase in stool frequency and dose-dependent decrease in laxative use. This study showed that the combination of the two drugs was able to benefit a significant number of patients suffering from chronic pain, allowing them to receive analgesia on a long-term basis and consequently to improve their quality of life.

Simpson K, Leyendecker P, Hopp M, et al, had the primary goal of assessing whether patients had improvements in constipation by utilizing a fixed 2:1 ratio of oxycodone PR and naloxone PR by evaluating changes in the reported BFI. Secondary concerns of this study were improvements in symptoms of constipation and the patients’ average pain over the last 24 hours at each double-blinded visit utilizing a NAS of 0-10. The numbers provided in table III clearly show a 26.9 point improvement in BFI scores just three weeks into the study. Along with the BFI, this study also utilized the PAC-SYM questionnaire to assess changes in constipation. The number of CSBM’s improved by 66% after just four weeks. All this was achieved while still maintaining stable pain control.

Vondrackova D, Leyendecker P, Meissner W, et al had the primary goal of demonstrating the analgesic superiority of oxycodone PR when used with naloxone PR over placebo
measured as the time from initial dose of study medication to recurrent pain events (inadequate analgesia) during the double-blinded phase. Secondary objectives of this study were to assess the average daily pain during treatment based upon a pain intensity scale over a 24 hour period, comparing sleep quality during treatment, and the finally the amount of rescue medication used per day. This study easily showed the difference in the time to recurrent pain events between the two groups. The mean time to pain events was 19.3 days in the placebo group and 32.2 days in the oxycodone PR naloxone PR group. Throughout the study the placebo group had statistically significant increases in incidents of risk of experiencing a pain event, increased “average pain over the last 24 hours” scores, increased “interference with sleep” scores, and an increase in the use of the intake of rescue medication.

All of the studies showed that the treatment of OIC with the combination of oxycodone PR and naloxone PR had a significant effect on improving patients’ bowel function, utilizing the standard Bowel Function Index (figure I). Additional findings included; no significant decrease in the analgesic effect of the oxycodone (figure II), that the best ratio for combining the oxycodone PR and naloxone PR medications was 2:1, and that the incidence of additional adverse events also did not significantly increase.
Discussion:

Because the Bowel Function Index (BFI) was commonly referred to in all the studies it is important to understand how the numbers are arrived at and to put them into context. The BFI is the mean score of three distinct components which are assessed at each visit. Each of the three areas have a numerical analog scale (NAS 0= easy/no difficulty/not at all, 100= very strong/very difficult). The three areas assessed are; ease of defecation, feeling of incomplete bowel evacuation, and a personal judgment of constipation (for complete BFI forms see figure I). Higher scores, therefore, indicate worse bowel function. Each of these questions referred to the patients’ experience over the past 7 days. Based upon the data, a change in BFI > 12 points is regarded as clinically significant. The BFI scores from the studies reviewed were consistently improved by > 23 points, an amount almost double of what is considered clinically significant (see table III).

One of the main stays of treatment for moderate to severe pain, in patients who suffer pain due to illness or injury, is opioids. As is with most medications, there are side effects. With opioid use there can be bloating, abdominal pain, nausea, constipation, headache, and others. Opioid-induced constipation is the one side effect that does not improve given long term use, is a major problem effecting QoL, may cause the patient to increase their opioid dosage, or in some cases, they stop taking their medication all together.

Treating a side effect with another medication carries additional risks of its own. The new drug’s side effects may become worse than the drug originally taken, and can many times just muddy the water. Once the pharmacology of the study medications is understood the ability to effectively treat patients with the drug combination becomes self evident.

The review of all five of these articles shows that the addition of an opioid antagonist like oral naloxone PR, when administered in conjunction with oxycodone PR, not only improves bowel function with minimal side effects, but does so with little or no change in the analgesic effects of the
original medication. These studies also provided the optimum dosage ratio (2:1) which produced the least number and severity of adverse events. This all serves to improve patient QoL and overall satisfaction with providers and institutions.
Recommendations:

Of the five studies included for review, three were conducted in Germany, one was conducted in England, and one was conducted at clinics in four European countries. Additional studies performed in the United States for additional validation should be considered.

Finally, the opioid antagonist methylnaltrexone, which has been studied for the reduction of OIC, should be studied with oral naloxone to compare the effectiveness of the two different methods of delivery (one orally and the other by subcutaneous injection).
Conclusion:

All five of these studies have demonstrated an overall statistically significant improvement in bowel function, a decrease in the incidence of OIC, and no negative impact on the analgesic efficacy of opioid treatment. This combination of medications has the potential to improve the acceptance of long-term opioid usage in the treatment of chronic pain. The ability to control the side effect of OIC while having no negative effect on analgesia represents a positive alternative for this patient population. The drug combination will also be of great benefit to healthcare professionals who are responsible for the care of patients with severe chronic pain. With the reduced incidence of OIC and subsequent need for laxatives, enemas, and manual evacuations, the management of patients can be greatly improved.
References:


7. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005;29(Suppl. 5); 547-56.


## Tables

### Table I

**Study comparisons**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects randomised</th>
<th>Completed Study</th>
<th>% completed study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowenstien, O 2009</td>
<td>278</td>
<td>222</td>
<td>79.8%</td>
</tr>
<tr>
<td>Meissner, W 2009</td>
<td>202</td>
<td>166</td>
<td>82.1%</td>
</tr>
<tr>
<td>Nadstawek, J 2008</td>
<td>202</td>
<td>166</td>
<td>82.1%</td>
</tr>
<tr>
<td>Simpson, K 2008</td>
<td>322</td>
<td>277</td>
<td>86.0%</td>
</tr>
<tr>
<td>Vondrackova, D 2008</td>
<td>484</td>
<td>405</td>
<td>83.7%</td>
</tr>
</tbody>
</table>

### Table II

**Oxycodone and naloxone dose groups**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone daily dose (mg)</td>
<td>Placebo</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Oxycodone daily dose (mg)</td>
<td>40, 60, 80</td>
<td>40, 60, 80</td>
<td>40, 60, 80</td>
<td>40, 60, 80</td>
</tr>
<tr>
<td>Oxycodone/naloxone dose ratio</td>
<td>40/Placebo</td>
<td>40/10 4:1</td>
<td>40/20 2:1</td>
<td>40/40 1:1</td>
</tr>
<tr>
<td></td>
<td>60/Placebo</td>
<td>60/10 6:1</td>
<td>60/20 3:1</td>
<td>60/40 1.5:1</td>
</tr>
<tr>
<td></td>
<td>80/Placebo</td>
<td>80/10 8:1</td>
<td>80/20 4:1</td>
<td>80/40 2:1</td>
</tr>
</tbody>
</table>

### Table III

**BFI comparisons Oxycodone PR/Naloxone PR groups by study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial BFI</th>
<th>Improved BFI</th>
<th>Improvement in BFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowenstien, O 2009</td>
<td>67.4</td>
<td>40.9</td>
<td>-26.5</td>
</tr>
<tr>
<td>Meissner, W 2009</td>
<td>56.5</td>
<td>26.7</td>
<td>-29.8</td>
</tr>
<tr>
<td>Nadstawek, J 2008</td>
<td>56.5</td>
<td>26.7</td>
<td>-29.8</td>
</tr>
<tr>
<td>Simpson, K 2008</td>
<td>61.8</td>
<td>34.9</td>
<td>-26.9</td>
</tr>
<tr>
<td>Vondrackova, D 2008</td>
<td>65.7</td>
<td>42.6</td>
<td>-23.1</td>
</tr>
</tbody>
</table>
### Bowel Function Index (BFI)

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

<table>
<thead>
<tr>
<th>0= easy / no difficulty</th>
<th>100= very strong</th>
</tr>
</thead>
</table>

**Ask the subject:** “During the last 7 days how would you rate your ease of defecation on a scale from 0 to 100, where 0= easy or no difficulty and 100= severe difficulty?”

**If the subject requires clarification, ask:** “During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0= easy or no difficulty and 100= severe

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

<table>
<thead>
<tr>
<th>0= not at all</th>
<th>100= very strong</th>
</tr>
</thead>
</table>

**Ask the subject:** “During the last 7 days how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0= no feeling of incomplete evacuation and 100= a very strong feeling of incomplete evacuation?”

**If the subject requires clarification, ask:** “During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale of 0 to 100 where 0= not at all and 100= very strong”

3. Personal judgment of patient (NAS) regarding constipation during the last 7 days:

<table>
<thead>
<tr>
<th>0= not at all</th>
<th>100= very strong</th>
</tr>
</thead>
</table>

**Ask the subject:** “During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0= not at all and 100= very strong”

**If the subject requires clarification, ask:** “During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0= not at all and 100= very strong”
Figure II

Mean pain intensity over the last 24 hours at each study visit during the 12 week double-blinded period.

Figure III

Mean Bowel Function Index by week: full analysis population.