The efficacy of standard laxative use for the prevention and treatment of opioid induced constipation during oxycodone use: a Dutch small observational pilot study.

Gineke Koopmans-Klein
Michel F.M. Wagemans
Hans C.H. Wartenberg
Yvonne J.B. van Megen
Frank J.P.M. Huygen

Published in: Expert Review of Gastroenterology & Hepatology 10(4):4547-553
DOI: 10.1586/17474124.2016.1129275
ABSTRACT

Objective
Dutch clinical guidelines recommend that a standard laxative treatment (SLT) should be prescribed concomitantly when starting opioid treatment to prevent opioid-induced constipation (OIC).

Clinical evidence for SLT in the treatment of OIC is lacking, therefore an observational pilot study was performed to explore the efficacy and tolerability of SLT on OIC in patients treated with the opioid oxycodone.

Results
Twenty-four patients (58% female, median (range) age 65 (39-92)) were included in this pilot study. The analysis showed that 9 out of 21 patients (43%) were non-responders to SLT. When also taking into consideration patients tending to develop diarrhea 75% of patients are non-responsive to SLT.

Conclusion
This pilot study indicates that optimal laxative therapy (SLT) might not be effective and feasible for the prevention and treatment of OIC.
INTRODUCTION

Opioids are an option for the pharmacological treatment of moderate to severe pain and are generally used when non-opioid treatments are ineffective or contra-indicated [1-3]. A significant disadvantage of all opioid use is opioid induced constipation (OIC). Although there might be variation in occurrence of OIC depending on the type of opioid used, OIC is a side effect of all opioids and has a negative impact on pain treatment, quality of life and daily activities [4-12].

Opioid induced constipation (OIC)

To date OIC is defined as: ‘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, or harder stool consistency’[12]. OIC is characterized by three major symptoms: hard and dry stools, impeded and painful defecation and significantly less frequent stools than normal for the patient (in general defined as less than 3 bowel movements per week). Other associated symptoms are flatulence, colic pain and pelvic pressure pain [4, 13-16]. OIC can lead to an increased morbidity and even mortality of patients. It can result in bleeding, pain, gastro-intestinal reflux, nausea, vomiting and rectal pain as well as hemorrhoids, diverticular disease and fecal impaction [4, 13-16]. Severe OIC can result in complications like fecal impaction with paradoxical diarrhea and incontinence, bowel obstruction, bowel rupture, pseudo-obstruction with anorexia, urine retention with overflow incontinence and delirium[6, 14]. Surveys in patients suffering from OIC have shown that OIC also has an impact on the treatment of pain. Almost 2/3 of patients change their opioid dosage; patients change to a lower dose (10.2%), skip dosages and/or are using opioids irregularly (7.5%) or stop using opioids for their pain management (5.4%) [6, 11]. Moreover, OIC can in itself also be a cause for pain; the majority of patients with OIC report pain caused by OIC. Pain caused by OIC results in more discomfort than pain caused by the underlying condition [6, 11, 17].

Current management of OIC in Dutch clinical practice

Management of OIC usually consists of non-pharmacological and pharmacological approaches. The international consensus is that treatment of OIC should be focused on the prevention of OIC rather than treatment of already manifest OIC [12, 18-22]. Pharmacological treatments include osmotically acting laxatives (e.g. magnesium oxide, lactulose and polyethylene glycol), stimulant laxatives (e.g. bisacodyl and sennosides), stool softener (e.g. liquid paraffin and sodium docusate), bulk forming laxatives (e.g. isphagula and methylcellululose) or enema’s (e.g. sodium laureysulfate and sodium phosphate). When these laxatives fail opioid antagonists like oxycodone/naloxone combina-

Erasmus University Rotterdam
tion, methylnaltrexone or naloxegol can be considered. These treatment possibilities for OIC have already been reviewed in several recent publications by Nelson et al., Argoff et al. and Camilleri et al.[12, 21, 22]

In the Netherlands pharmacological treatment for constipation due to opioid therapy is described in Dutch clinical guidelines regarding treatment of cancer pain and for the treatment of constipation[23, 24]. These guidelines recommend that laxatives should be concomitantly prescribed when starting opioid treatment [23, 24]. As literature on treatment of OIC at time of guideline development was sparse and non-conclusive, the recommendations were predominantly based on expert opinion taking in consideration the high incidence of OIC in patients treated with opioids, the harm it can cause for patients and practical experience [23, 24].

First choice treatments in the Dutch guidelines were defined based on available studies at time of guideline development; treatments of first choice are the osmotically acting laxative lactulose and polyethylene glycol plus electrolytes (which is also considered to be bulk forming) of which PEG plus electrolytes is the most prescribed laxative. If these are not effective enough addition of a stimulant laxative like bisacodyl (orally or rectally) can be considered[23, 24].

Next to the recognition of OIC in the Dutch guidelines a quality indicator was set up within the Dutch Health Care Transparency Program ensuring that all patients with an opioid prescription also had a prescription of a laxative, in order to improve outpatient drug safety [25, 26]. The Institute for Rational Use of Medicines (IVM) published the 2013 results of this quality indicator in the Monitor Prescribing Behavior Practitioners. The calculation of the quality indicator was based on reimbursement data of community pharmacists and dispensing general practitioners collected by Vektis, a national data-center for healthcare insurers. These data showed that on average 49% (median 48%, range 33-64%) of patients on opioids were prescribed a laxative together with their opioid prescription[27]. Also data from the Dutch Foundation for Pharmaceutical statistic, gathering data from more than 95% of the community pharmacies in the Netherlands, show that in 90% of participating community pharmacies less than 60% of patients were prescribed a laxative together with their opioid prescription in 2013 [28]. These results show that, despite implementation of the quality indicator, physicians do not always follow guidelines. Moreover, the Dutch laxative guidelines can be interpreted in different ways.

However, to date two main interpretations of the Dutch laxative guidelines are used with respect to laxative treatment schedules: 1. Provide a laxative prescription together with the opioid prescription and use laxative on an as needed basis and 2. Standard laxative treatment (SLT) consisting of intake of laxative together with the opioid on a daily basis, starting at day one. Laxative use is reduced in case of development of diarrhea and increased when not effective or on increase of opioid dose. The effect of “as
needed” intake of laxatives was already clearly visible in clinical trials investigating the efficacy of prolonged-release oxycodone/naloxone where laxative use in the control arm was “as needed” [29-35]. Interestingly, the impact of the SLT for laxative intake has not been investigated yet. Moreover, there are no unambiguous incidence- and/or prevalence rates for failure of laxatives in OIC. In this report a descriptive analysis of an observational pilot study is described investigating the efficacy of laxative treatment according to SLT in the Netherlands with respect to bowel function and tolerability as well as patient handling of laxatives.

PATIENTS AND METHODS

A prospective observational study was performed investigating a standard laxative treatment regime (SLT) consisting of prophylactic daily intake of polyethylene glycol (PEG) with electrolytes and bisacodyl as needed. This SLT was started together with opioid-intake at day 1. Nine centers in the Netherlands, in which the laxative regimen PEG with electrolytes and bisacodyl was standard of care, participated. Since patients were treated as they would have been treated in daily practice and were not subject to additional procedures the study did not fall under the scope of the Medical Research Involving Human Subjects Act. The Agreement on Medical Treatment Act and the Personal Data Protection act did apply. All patients who were prescribed at least 2x10 mg oxycodone Slow Release (SR) and the SLT regime were followed for 28 days by their physician. No other in- and exclusion criteria were applied.

Bowel function was measured with the Bowel Function Index (BFI), a measure which is specific and validated for OIC (BFI[36]; Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is subject of European Patent Application Publication No. EP 1 860 988 and corresponding patents and applications in other countries). A BFI below 28.8 is considered normal (not constipated) in opioid-treated patients and a decrease of at least 12 points in BFI is considered clinically relevant [36-39].

In addition, the Bristol Stool Form Scale (BSFS) was used to assess bowel function. BSFS gives an indication of the type of stool from watery stools (diarrhea) to dry and hard lumps (constipation). Type 1 and 2 indicate constipation, type 3 and 4 represent normal stools, type 5 represents a stool tending towards diarrhea and type 6 and 7 represent diarrhea [40]. Analgesia was measured with a numerical pain score (Numerical Rating Scale (NRS), 0-100). Laxative use (daily dosage and treatment duration) as well as adverse events were also registered.

Descriptive analyses of the results are presented. To evaluate the efficacy of the SLT regime a responder analysis was performed.
Responder analysis: A responder to laxative treatment was defined as:
1. a patient with a clinically relevant improvement of already present constipation (decrease of BFI with 12 points or more) or as a patient who did not develop constipation as measured with the BFI (BFI remains below 30 points throughout the observation) **AND**
2. a patient without development of diarrhea (type 6 or 7 of the Bristol Stool Form Scale) **AND**
3. a patient without early discontinuation due to adverse events of laxative treatment.

**RESULTS**

Of the nine centers asked to participate six included a total of 24 patients in the period July 2012 until October 2013. The majority of patients were female (58%), which is consistent with the patient population with chronic pain, median (range) age of patients was 65 (39-92) years, and all but one patient had non-malignant pain. At the start of the study 22 of 24 patients had severe pain (pain NRS score ≥60). Table 1 describes the demographics of the included patient population. The average (sd) pain score decreased from 74.2 (14.5) (median(range) 80 (30-90)) to 53.0 (26.2) (median(range) 53 (5-90)) after 4 weeks of treatment.

**Table 1**: Demographics of included patients

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>male, n (%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>female, n (%)</td>
<td>14 (58%)</td>
</tr>
</tbody>
</table>

| Median (range) age (yrs) | 65 (39-92) |

<table>
<thead>
<tr>
<th>Previous medication, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-step I</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>WHO-step II</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>WHO-step III</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>adjuvantia</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Painscore (NRS) at start of observation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>average (sd)</td>
<td>74 (14)</td>
</tr>
<tr>
<td>median (range)</td>
<td>80 (30-90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Origin of pain, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>malignant</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>non-malignant</td>
<td>23 (96%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BFI at start of observation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>average (sd)</td>
<td>26.6 (27.3)</td>
</tr>
<tr>
<td>median (range)</td>
<td>21.8 (0-77)</td>
</tr>
</tbody>
</table>

| Patients with BFI>28.8 at start of observation, n (%) | 9 (37.5%) |
Table 2 lists the BFI at study start, at the final visit and the delta BFI, as well as the highest value of the Bristol Stool Form Scale and the three criteria of the responder analysis. For three patients data were insufficient to perform a responder analysis.

Table 2: Patient-level data of constipation at start of study (based on BFI≥28.8), BFI at start of study, BFI at study completion, highest BSFS value during the study, individual responder parameters and responder analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Constipated at start (Y/N)</th>
<th>BFI start</th>
<th>BFI end</th>
<th>ΔBFI</th>
<th>BSFS: Highest type during study</th>
<th>patient achieved a decrease in BFI ≥12 or had a BFI&lt;28.8 during observation (Y/N)</th>
<th>patient did not experience diarrhea (type 6 or 7) during the observation (Y/N)</th>
<th>patient did not experience adverse events due to laxative use (Y/N)</th>
<th>Responder analysis (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>7</td>
<td>6.7</td>
<td>-0.3</td>
<td>6</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>6.7</td>
<td>3.3</td>
<td>-3.4</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>1.7</td>
<td>3.3</td>
<td>1.6</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>4</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>23.6</td>
<td>20</td>
<td>-3.6</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>16</td>
<td>12</td>
<td>-4</td>
<td>4</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>77</td>
<td>43</td>
<td>-34</td>
<td>7</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>Y</td>
<td>60</td>
<td>4</td>
<td></td>
<td></td>
<td>Y</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>50</td>
<td>43</td>
<td>-7</td>
<td>6</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>Y</td>
<td>50</td>
<td>23</td>
<td>-27</td>
<td>6</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>Y</td>
<td>56</td>
<td>30</td>
<td>-26</td>
<td>4</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>13</td>
<td>N</td>
<td>0</td>
<td>23</td>
<td>23</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>14</td>
<td>N</td>
<td>16.6</td>
<td>46.7</td>
<td>30.1</td>
<td>5</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>Y</td>
<td>50</td>
<td>43.3</td>
<td>-6.7</td>
<td>5</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>N</td>
<td>0</td>
<td>13.3</td>
<td>13.3</td>
<td>6</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>Y</td>
<td>53</td>
<td>50</td>
<td>-3</td>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>N</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>19</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>20</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>21</td>
<td>N</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>Y</td>
<td>53</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>N</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Y</td>
<td>77</td>
<td>50</td>
<td>-27</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
At the start of the observational study 38% (9/24) of patients already suffered from constipation (BFI>30), constipation could even be rated as severe OIC (BFI>50). Five of these 9 patients were using WHO-step 3 medication, 3 were using WHO-step 2 medication and one patient was using WHO-step 1 medication only (diclofenac+paracetamol). Despite the observed constipation (based on BFI) none of the patients were using laxatives on a regular (daily) basis as recommended in the Dutch guidelines. At study start all patients (constipated and non-constipated) were switched to standard laxative treatment regime with daily intake of PEG+electrolytes and as needed bisacodyl (orally).

The responder analysis showed that 9 out of 21 patients (43%) were non-responders to SLT. Of the 7 patients with severe OIC at start of the study (BFI>50) completing the observation, 5 were non-responders (71%).

Non-responsiveness was primarily due to constipation (BFI) and the development of diarrhea. Only one patient experienced adverse events that were clearly related to the laxative use according to the investigator. Based on BFI-results laxative use was not effective in 4 patients, i.e. 1 non-constipated patient developed constipation despite the use of laxatives and 3 constipated patients did not reach a clinically relevant improvement of BFI. Another problem of laxative use appeared to be the development of diarrhea (a BSFS type 6 or 7) in 6 patients.

Further investigation of laxative use could be performed for 20 out of 24 patients (83%); these patients returned patient diaries with information on laxative use (data missing for patient 7, 9, 22 and 23). From the returned patient diaries it could be derived that less than half of the patients took daily laxative intake as defined in SLT, 9 out of 20 patients (45%) switched to laxative intake on an “as needed basis” (patient 6, 8, 11, 12, 16, 17, 18, 21 and 24). In 5 out of 9 cases this switch from “intake on a daily basis starting at day 1 with the opioid” to “as needed” laxative intake was due to problems with daily laxative intake, like the development of diarrhea (4 out of 9) or adverse events caused by laxatives (1 out of 9). For the other 4 patients no reason for the switch to “as needed” laxative intake could be identified from the patient diaries. The switch to an “as needed” laxative intake by the patients resulted in a daily dose of PEG+electrolytes which varied per patient and even within patients between 0-3 sachets per day (according to the SmPC of PEG+electrolytes daily dose is 1-2 sachets). For the 5 patients using additional biacodyl the daily dose of bisacodyl varied between 5-20 mg.

**DISCUSSION**

OIC is a common opioid-related side effect, which may vary between opioids, and it is known to have a major impact on opioid treatment, pain and quality of life, justifying a strong need for clear guidance. Unfortunately, the current Dutch guidelines on
prophylactic laxative treatment are not helpful in this respect. The two main interpreta-
tions of the recommendations in the guidelines are: 1. Prophylactic daily intake of a
concomitant standard laxative regime (SLT) starting together with first opioid-intake at
day 1 and 2. Intake of laxatives together with the opioid on an “as needed basis”.

This pilot study was designed to explore the impact of SLT on OIC during treatment
with the opioid oxycodone. Only patients on oxycodone were enrolled, to avoid variation
in results due to differences within opioids, moreover oxycodone is the most prescribed
opioid in the Netherlands.

This pilot study shows that the efficacy of laxatives is highly variable. 43% of patients
did not respond to the treatment with laxatives in a defined SLT regime. The percentage
of non-responders was much higher for patients who had severe OIC (BFI>50) at study entry; 71%
of these patients did not respond to SLT. These results are reflected in the
literature in which 40-70% of all opioid treated patients eventually develop OIC [19, 41]. This suggests that SLT might not be effective for the prevention and treatment of
OIC, however the results need to be confirmed in a clinical study with a larger number
of patients.

It is well-known that laxatives do not address the actual cause of OIC [37]. Laxatives
stimulate bowel-motility in the colon, while OIC is predominantly caused by inhibition
of the motility of the small intestine[42, 43]. This might be an explanation why, in daily
practice, laxatives are not always effective in the prevention and treatment of OIC [18, 41, 44, 45].

Another more common problem with laxative use is the development of laxative-
related side effects[46]. Diarrhea, one of the common side effects of laxative use, was
also noted in this pilot study. 6 patients developed diarrhea (type 6 and 7 of the BSFS).
When looking more closely at patients with type 5 of the BSFS, we found that 11 patients
tended to develop diarrhea and only 6 patients had an ideal stool consistency (type 3
and 4 of the BSFS). Using a BSFS of 5 as cut-off value for diarrhea would result in 18 out
of 24 patients (75%) being classified as non-responders to laxative treatment.

Moreover, in this pilot study 45% of patients switched from daily laxative intake in the
SLT to ”as needed” laxative intake. In half of the patients switching from “daily intake”
to an “as needed intake” the development of diarrhea and other adverse events were
responsible for this switch. Interestingly, the development of diarrhea was already
anticipated in the guidelines; laxative treatment could potentially result in the develop-
ment of diarrhea resulting in lowering or skipping of laxative dosages[19].

Although evidence is limited for laxatives in the treatment and prevention of OIC,
laxatives are still considered a first-line treatment for OIC because of their accessibility,
safety and low costs[12, 21]. This pilot study adds to already present data that laxatives
might not be adequate for the prevention and treatment of OIC[47]. A more pharma-
ological treatment approach targeting the opioid receptors with opioid antagonists (e.g.
oxycodone/naloxone, methylaltrexone and naloxegol) might be a good alternative for the treatment and prevention of OIC[12, 21, 22].

A limitation of this pilot study is the exploratory nature of the study. In order to design a clinical trial investigating prevention of OIC with a defined SLT taken concomitantly with opioid intake from day 1 some information is required concerning efficacy of this SLT regime. However, existing clinical trials are sparse and inconclusive necessitating a pilot study investigating the efficacy of SLT.

Another limitation of this pilot study was the impeded recruitment of patients. This might be caused by a resistance of physicians to treat patients with SLT. For most patients an “as needed” laxative treatment was expected to be more appropriate to treat and prevent OIC. Slow patient inclusion has been described before in studies addressing laxative regimens. In 2009 de Graeff et al. started a project to assess the efficacy of two laxatives (polyethylene glycol (PEG) with electrolytes versus magnesium(hydr) oxide) on the prevention of OIC. This project was terminated early due to insufficient patient recruitment (5 patients in 1.5 years) (source: http://www.zonmw.nl/nl/projecten/project-detail/preventie-van-obstipatie-bij-gebruik-van-opiodien-magnesiumhydroxide-versus-macrogolelektrolyte/voortgang/). This illustrates that patient recruitment is a problem in studies investigating the efficacy of defined SLT for the prevention of OIC.

CONCLUSION

In conclusion, this pilot study indicates that optimal laxative therapy (SLT), as defined by intake of laxatives starting on day 1 together with the opioid, might not be effective and feasible for the prevention and treatment of OIC. The responder analysis showed that 43% of patients were non-responders to SLT and results suggested that responder rate was even lower (71%) in patients with severe OIC (BFI>50). When taking into consideration patients tending to develop diarrhea 75% of patients are non-responsive to SLT. These results show that a larger clinical study is warranted investigating the efficacy and tolerability of SLT for the prevention and treatment of OIC.

TRANSPARANCY

Declaration of funding

This study was designed by Mundipharma Pharmaceuticals BV and conducted by qualified investigators under the sponsorship of Mundipharma Pharmaceuticals BV. There is no financial interest linked to the preparation, scientific advice and authorship of the article for the authors. No grants, equipment or drugs were supplied by the sponsor. All
authors were involved in the development, writing, critical reviewing and approval of this manuscript.

Declaration of financial/other relationships
M.F.M. Wagemans, H.C.H. Wartenberg and F.J.P.M. Huygen have nothing to disclose. Y.J.B. van Megen and G. Koopmans-Klein report personal fees from Mundipharma Pharmaceuticals BV, during the conduct of the study and personal fees from Mundipharma Pharmaceuticals BV, outside the submitted work.

Acknowledgements
This study was designed by Mundipharma Pharmaceuticals BV and conducted by qualified investigators under the sponsorship of Mundipharma Pharmaceuticals BV. Data were gathered by the sponsor and evaluated jointly by the authors and the sponsor. All authors were involved in the development and writing of the manuscript.

The authors would like to thank all participating patients, hospitals, physicians and research staff for participating in the study. Next to the authors, the following physicians participated as principal investigators within the centers: E. W. van den Bosch, Department of Anesthesiology and Pain Medicine, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands, V.C.P.C. van Dongen, Department of Anesthesiology and Pain Medicine, Orbis Medisch Centrum, Sittard-Geleen, The Netherlands, G.C.H. Tjiang Department of Anesthesiology and Pain Medicine, Amphia Ziekenhuis, Breda, The Netherlands, P.H.M. Passage, General Practitioner, Kerkrade, The Netherlands, J. Huijgens, General Practitioner, Wesepe, the Netherlands. The corresponding author takes responsibility for the integrity and the accuracy of the data analysis, and also had final responsibility for the decision to submit for publication.
REFERENCES

The efficacy of standard laxatives for prevention and treatment of constipation