**Opioid-related bowel dysfunction: prevalence and identification of predictive factors in a large sample of Italian patients on chronic treatment**

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**Abstract.** – Background and Objectives: Opioid-bowel dysfunction (OBD) is a broad range of symptoms potentially associated with opioid therapy. This prospective, multicentric study assesses the prevalence of OBD in patients on analgesic therapy for the treatment of pain from any cause and identifies the factors associated with the onset of this side effect.

**Materials and Methods:** Consecutive patients aged >18 years, on analgesic treatment with opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or other therapies for chronic pain of any aetiology were included in the study. The association of OBD with gender, age, pain aetiology and analgesic treatment was analyzed by multivariate analysis and logistic analysis.

**Results:** In total, 2324 patients were included in the study. The prevalence of OBD symptoms was 63.5%, despite that the wide majority of patients (89.5%) were receiving laxatives. OBD symptoms were judged as directly correlated with analgesic therapy in 85.1% of cases. The highest prevalence of constipation was reported with morphine, whereas the lowest was observed in patients on oxycodone CR and buprenorphine TTS. Statistical analysis showed that patients on opioids have a higher likelihood of experiencing OBD symptoms than those on NSAIDs or other treatments (66.2% vs 37.0%), and this probability is even higher in those with cancer-related pain (69.3%). Female gender and age >70 years also appeared as risk factors. The logistic analysis indicated that cancer-related pain, increased age and the use of fentanyl are positive predictors of the presence of OBD, whereas the administration of oxycodone CR was associated with a decreased incidence of these symptoms.

**Discussion:** Even with the limitation of any observational experience, this study suggests, for the first time, the existence of some factors predictive of the onset of OBD symptoms in patients on analgesic treatment. Moreover, different opioids seem to be associated with a different risk of experiencing these symptoms.

**Key Words:**
Constipation, Laxatives, OBD, Opioid.

**Introduction**

Opioids represent the elective treatment for chronic cancer- and non cancer-related pain of moderate-severe intensity1,2. However, it is widely accepted that opioid therapy may be associated with the onset of some adverse events, such as nausea/vomiting, dizziness, itching and opioid-induced bowel dysfunction (OBD)3,4.

The frequency and severity of side effects determined by central interactions with opioid receptors constantly decreases over time. In contrast, the symptoms of OBD, which are mediated by peripheral µ receptors, persist for the entire duration of opioid treatment5-7. The symptoms of OBD include constipation, decreased gastric emptying, abdominal cramping, spasm, bloating, delayed GI transit and the formation of hard dry stools5,6. The association between OBD and chronic fatigue and/or insomnia has also been documented8. Of note, the onset of OBD may result in the interruption of opioid treatment or in the reduction of analgesic efficacy in up to 30% of patients5,8. A recent study highlighted the marked reduction of quality of life experienced by patients with OBD9. Laxatives are often prescribed to provide relief from OBD symptoms, but their efficacy, on the basis of available evidence, appears overall limited8,10.

Despite the severe impact of OBD on the effectiveness of opioid therapy and quality of life,
only few reports have investigated the prevalence of this condition in patients on opioids for cancer- and non cancer-related pain. Moreover, the differential effect of the various opioids in the induction of OBD has been only poorly documented. This multicentric study, with a prospective design, aims to assess the prevalence of OBD in patients on analgesic therapy for the treatment of pain from any cause, and to identify the factors associated with the onset of this side effect. Moreover, the efficacy of prescribed laxatives for the treatment of OBD symptoms was also evaluated.

Patients and Methods

Study Setting and Design

This observational, prospective, non-interventional study was conducted in 20 Italian Centers specialized in the treatment of pain, located all throughout the Country, from 1st January 2010 to 31th March 2010. The study was conducted in accordance with the Helsinki Declaration; the study protocol was approved by the Local Ethical Committees of each Center, as appropriate, and all patients gave an informed and educated consent before the inclusion in the study.

Patients

Consecutive patients aged >18 years, on analgesic treatment with opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or other therapies for chronic pain of any aetiology were included in the study.

Data Analysis and Statistical Methods

For every single patient, a trained investigator (always the same for each participating Center) was asked to fill a questionnaire composed of 15 items, which included demographic characteristics, analgesic therapy, information on pain control, presence of OBD symptoms and possible correlation with analgesic treatment, and laxative treatment. Moreover, this questionnaire included the Bowel Function Index (BFI), which was recently validated at a European level, to assess the severity of OBD as perceived by patients.

Data from each questionnaire were collected and analyzed at a central level. All data were analyzed by descriptive statistics. The association of OBD with gender, age, pain aetiology and analgesic treatment (strong opioids, weak opioids, NSAIDs and other; association therapies were not considered to avoid confounding factors) was analyzed by multivariate analysis (e.g., classification and regression trees) and logistic analysis, as appropriate, considering all drugs and only the two most prescribed strong opioids and the most prescribed weak opioid. A specific analysis was also performed on the results collected on the BFI questionnaire for patients on the two most prescribed strong opioids and the most prescribed weak opioid. A p value <0.05 was considered statistically significant. Statistical analysis was performed with SAS software 9.1 (SAS Institute Inc, Chicago, US).

Results

Study Population and Prevalence of Constipation

In total, 2324 patients (1053 males; mean age 66.6±13.1 years) were included in the study. Their baseline characteristics are summarized in Table I. Two thirds of them (66.7%) were affected by cancer pain. Seven hundred and five patients were on combination therapy, while 1619 were on monotherapy. Most patients on monotherapy (74.1%) were on strong opioids (in most cases oxycodone CR [n=931 doses administered; 27.5% of total doses administered], fentanyl tss [n=357; 10.5%] and morphine [n=335: 9.9%]).

Table I. Baseline characteristics of patients (n=2324). All values are represented as number (%) if not otherwise stated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1053 (45.3)</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.6 ± 13.1; 20-97</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>1552 (66.7)</td>
</tr>
<tr>
<td>Analgesic therapy</td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>705 (30.3)</td>
</tr>
<tr>
<td>Strong opioids</td>
<td>1207 (74.6)*</td>
</tr>
<tr>
<td>Weak opioids</td>
<td>293 (18.1)*</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>91 (5.6)*</td>
</tr>
<tr>
<td>Other</td>
<td>27 (1.7)*</td>
</tr>
<tr>
<td>OBD symptoms</td>
<td>1476 (63.5)</td>
</tr>
<tr>
<td>Treated with laxatives</td>
<td>1321 (89.5)</td>
</tr>
<tr>
<td>Unsatisfactorily pain control</td>
<td>1009 (43.4)</td>
</tr>
</tbody>
</table>

*Percentage calculated on the total number of patients on monotherapy (n=1619).
The prevalence of OBD symptoms was 63.5%; the wide majority of patients (89.5%) was on laxatives, in most cases of osmotic nature (n=295; 37.2%), followed by emollients (n=192; 24.2%). About one out of five patients without constipation (22.4%) were in treatment with laxatives (30.1% of which of osmotic nature). Pain was not satisfactorily controlled in 43.4% of patients, with an insufficient control of pain being most common in patients with pain of non-cancer aetiology than in those with cancer pain (54.7% vs 37.6%, p<0.0001).

**Association of Constipation with Gender, Age and Pain Aetiology**

Statistical analysis showed that gender was not associated with the presence of constipation (males: 64.4%; women: 63.2%; p=0.5757, chi-square test), whereas a trend towards a higher frequency of these symptoms in patients >50 years was observed (Table II). Moreover, patients with cancer-related pain had a higher frequency of constipation, with respect to those with non-cancer pain (69.1% vs 53.1%; p<0.0001, chi-square test).

**Association of Constipation with Analgesic Therapy**

OBD symptoms were judged as directly correlated with analgesic therapy in 85.1% of cases. Although a statistical analysis was not feasible due to different sample sizes, a trend towards a different prevalence of OBD symptoms with each opioid was observed (Figure 1). In particular, the highest prevalence of constipation was reported with morphine, whereas the lowest was observed in patients on oxycodone CR and buprenorphine TTS.

The likelihood of experiencing OBD in association with different analgesic therapies and other factors, as assessed by statistical analysis, is reported in Table III. Overall, patients on opioids have a higher likelihood of OBD symptoms than those on NSAIDs or other treatments (66.2% vs 37.0%), and this probability is even higher in those with cancer-related pain (69.3%). Female

**Table II.** Prevalence of OBD symptoms in different age groups. All values are expressed as number (%).

<table>
<thead>
<tr>
<th>OBD symptoms</th>
<th>0-20 years (n = 1)</th>
<th>21-30 years (n = 18)</th>
<th>31-40 years (n = 61)</th>
<th>41-50 years (n = 173)</th>
<th>51-60 years (n = 387)</th>
<th>61-70 years (n = 599)</th>
<th>71-80 years (n = 708)</th>
<th>&gt; 70 years (n = 366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>36 (59.0)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Tramadol/paracetamol</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Codein</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Codein/paracetamol</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Morphine</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Oxycodone CR</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Oxycodone/paracetamol</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
<td>42 (55.5)</td>
<td>82 (47.3)</td>
<td>249 (64.3)</td>
<td>383 (63.9)</td>
<td>453 (63.9)</td>
<td>262 (71.5)</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence of OBD symptoms with each single opioid or NSAIDs.
gender and age >70 years also appeared as important risk factors.

A similar statistical analysis was conducted only in patients on oxycodone CR, fentanyl tss (the two most prescribed strong opioids) or codein/paracetamol (the most/prescribed weak opioid, in fixed combination with paracetamol) (Table IV). Overall, the likelihood of OBD is higher in oncologic patients >50 years on fentanyl tss (77.4%) than in subjects on oxycodone CR or codein/paracetamol (66.8%). In non-oncologic patients >50 years, the likelihood of developing OBD is lower with oxycodone CR (47.1%) than with the other drugs (69.2%).

The logistic analysis indicated that cancer-related pain, increased age and the use of fentanyl are positive predictors of the presence of OBD, whereas the administration of oxycodone CR was associated with a decreased incidence of these symptoms (Figure 2).

**BFI Questionnaire**

The analysis of the BFI questionnaire suggested that patients on codein/paracetamol and oxycodone CR had improved results when compared to subjects treated with fentanyl TTS ($p<0.05$) (Figure 3).

**Discussion**

The results of this observational study, conducted in a large population of patients, suggest that the prevalence of OBD in patients on analgesic treatment is quite high. To our knowledge, this is the largest analysis on this topic conducted to date. In particular, statistical analysis suggested that the likelihood to experience OBD symptoms is higher in patients undergoing opioid treatment. Noteworthy, the prevalence of OBD is high despite that most patients took laxatives to improve these symptoms.

These findings are in agreement with some previous reports. In the PROBE-1 study, which evaluated 322 patients on opioid treatment, the incidence of OBD was 45% despite laxative therapy, and patients reported an at least moderate impact of OBD symptoms on quality of life. The overall modest efficacy of laxatives in the relief from OBD symptoms was also suggested by a Cochrane meta-analysis on 280 patients included in four randomized trials.

The above-cited study, however, did not investigate the factors associated with the onset of OBD; our analysis was, to our knowledge, the first to address this important issue. In particular, the presence of cancer-related pain, increased age and the use of fentanyl TTS appeared to be associated with an increased prevalence of OBD, whereas the use of codein/paracetamol and oxycodone CR was associated with a lower incidence of this event. Moreover, the present study suggests that single opioids could be associated with a different risk to develop OBD. Despite that a proper statistical comparison was not com-
pletely feasible due to the different number of patients taking each drug, oxycodone (CR and in combination with paracetamol) and buprenorphine were associated with the lowest percentage of patients experiencing OBD. This finding could have a great relevance to clinical practice, as the onset of OBD often results in treatment interruption and/or reduction of analgesic efficacy, partly due to an impairment in drug absorption\(^5,8\). Moreover, a recent pharmacoeconomic analysis, based on Swedish data, suggested that the total cost per patient-month for patients with severe constipation is higher than that for patients with mild, moderate, or no constipation.

\(1049\)

**Figure 2.** Profile of different predictors associated with OBD symptoms.

**Figure 3.** Results of the BFI questionnaire in patients on oxycodone CR, fentanyl tss (the two most prescribed strong opioids) or codein/paracetamol (the most – prescribed weak opioid).
On these bases, some improvements in the current management of OBD appear necessary. The overall incidence of these symptoms can be limited by prescribing opioids, when necessary, associated with a lower risk of developing OBD. Moreover, the specific management of OBD symptoms is based on three different therapeutic strategies: oral alvimopan, subcutaneous methylaltrexone, and a fixed combination of oral prolonged-release naloxone with prolonged-release oxycodone. These drug entities reduce motor stasis in the gut with a favorable adverse effect profile, while the analgesic effect of opioids remains stable.

Moreover, even if not explicitly included in the study objectives, the results of our analysis could represent a further validation of the BFI questionnaire, which was previously advocated, and a confirmation of the low rate of pain control in cancer and non-cancer patients on analgesic therapy.

It must be acknowledged that this study has a number of limitations, which include the short period of enrolment, the different number of patients on each drug, and the fact that results were limited to the Italian scenario. However, in addition to the large sample size and the robust statistical analysis, it provides a “real life” picture of the prevalence of OBD symptoms in patients on analgesic treatment. Well-designed observational studies do represent in fact a valuable source of information, as they may identify clinically important differences among different therapeutic options.

In conclusion, this large study suggests the existence of some factors predictive of the onset of OBD symptoms in patients on analgesic treatment. Moreover, different opioids seem to be associated with a different risk of experiencing these symptoms.

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References


