



# Pain Management in Cancer Care: Overcoming Barriers to Improve the Management of Chronic Pain

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## Introduction

Overcoming barriers to pain management in cancer care is critical to improving quality of life in patients living with cancer. The European Pain in Cancer (EPIC) survey was conducted in more than 5,000 cancer patients from 12 countries and is the largest study to date on the prevalence, treatment and impact of cancer-related pain.<sup>1</sup> Results of the EPIC survey indicate that pain is widespread, frequent, and long-lasting, is often inadequately controlled, and is a significant factor in reducing quality of life in patients with cancer. The study showed that a significant proportion of patients with cancer-related pain do not receive any prescription pain medication at all to manage their pain. Among those who do receive treatment, many find that their prescription does not adequately control pain and breakthrough pain remains a significant problem. Furthermore, the study revealed widespread concern about the side-effects of pain medications. While effective medications are available, appropriate treatments are not always prescribed and side-effects of treatment are often overlooked. It is thought that barriers to the identification and reporting of pain may contribute to its suboptimal management.

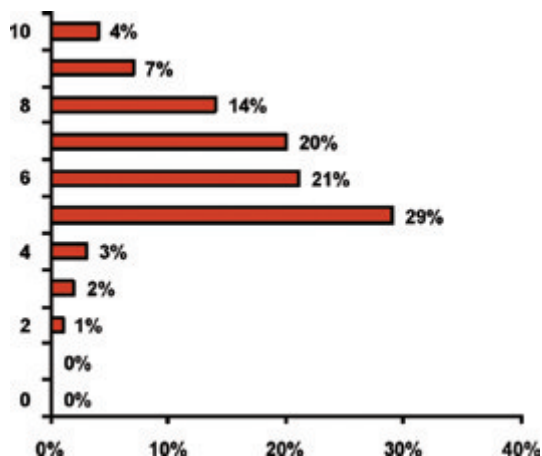
To overcome barriers and improve the management of chronic pain in cancer, treatment options must be balanced against a series of limiting factors pertaining to pain medications, including their side-effects, which are frequently highlighted as a key concern for patients living with cancer. In light of the forth coming joint European Cancer Organisation (ECCO) and European Society for Medical Oncology (ESMO) Multidisciplinary Congress in Berlin, Germany on 20–24 September 2009, this editorial will provide insights into the management of pain in cancer for all individuals involved in the delivery of patient care.

### Pain is a central but often overlooked feature of patients' lives

Pain is the key symptom leading to a diagnosis for cancer, with 31% of patients reporting pain as their reason for visiting the doctor prior to their cancer diagnosis. Results of the EPIC survey indicate that more than half of patients with cancer (57%) experience pain on a daily basis and that the majority of patients (88%) have experienced pain within the past month.

All patients consider themselves to be in some level of pain, with an overwhelming 94% of survey respondents reporting moderate to severe pain, as indicated by a score of 5 or more on a 10-point pain scale (figure 1). Despite the availability of effective pain medications, approximately one in four patients with moderate to severe pain do not receive any treatment.

Figure 1: The majority of patients with cancer report experiencing moderate to severe pain

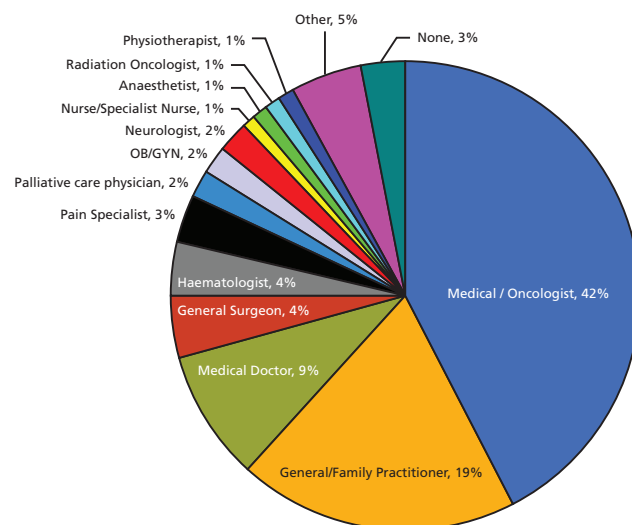


**EPIC Survey Question:** Thinking about the last time you experienced pain, please give me a number from 0 to 10 indicating the intensity of your pain where a "0" means "no pain at all" and a "10" means "the worst pain imaginable".

Of 573 patients randomly selected to participate in an additional in-depth interview about cancer pain, half reported that their healthcare practitioner does not take into consideration their quality of life. While one in three patients believes that their doctor did not have enough time to discuss their pain with them, one in four patients reported that their doctor did not know how to control their pain. Less than one-quarter of patients were referred to a pain management specialist or pain clinic, with the responsibility for managing cancer-related pain typically falling to the oncologist and family practitioner (figure 2).

When prompted, only one in three patients recalled having their pain assessed on a pain scale and one in four patients reported that their healthcare provider never or rarely asked them about their pain. Of note, one in three patients reported that sometimes their pain is so bad that they feel like they want to die.

Figure 2: Health Care Practitioners with main responsibility for management of cancer pain are the Oncologist and the Family Practitioner

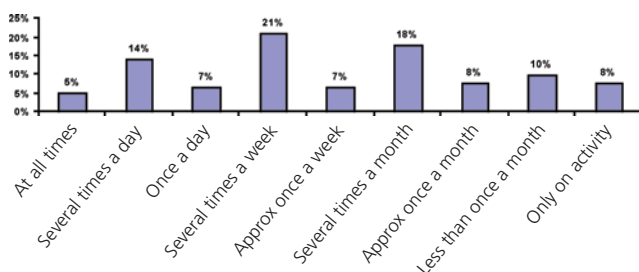


## Opioids are critical in pain management but have their own challenges

Opioids are the most widely used prescription medication among patients who receive treatment for their cancer-related pain, with 46% and 37% of patients reporting use of strong and weak opioids, respectively. Participants initially responded positively when asked how effective their prescription pain medication is, with 60% and 24% of patients reporting it to be quite effective and very effective, respectively.

However, when prompted, two of three patients reported that their prescription pain medication was not always adequate and more than half of patients (54%) experienced breakthrough pain at least once a week (figure 3). Of note, only one in three patients experiencing breakthrough pain received an additional prescription medication to treat it.

**Figure 3: More than half of patients taking prescription medication suffer from breakthrough pain at least once a week**



**Epic Survey Question:** How often do you suffer from breakthrough pain?

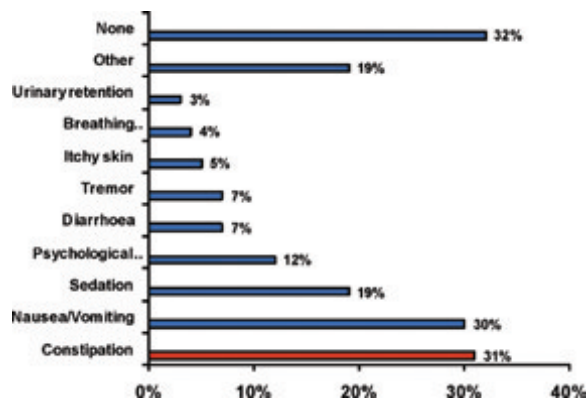
More than half of patients receiving prescription pain medication switch medications (58%) or receive treatment with more than one medication (54%). The most commonly reported reasons for switching were the requirement for a stronger medication (42%), pain becoming worse (29%), medication not working (23%), undesirable side-effects (16%), and a negative reaction to the medication (12%). The primary reasons reported for taking an additional prescription pain medication were the requirement for a stronger medication (34%), pain becoming worse (23%), duration of effect not long enough (16%), and current doctor's recommendation (10%).

### Managing cancer pain is a delicate balancing act

Side-effects of pain medications are a key concern for patients with cancer and chronic pain. Side-effects can be more distressing and difficult to manage than the pain, and the patient may feel they have acquired another problem rather than the easing of a symptom. Addressing this concern will be critical to improving the management of cancer-related pain.

The EPIC survey showed that 47% of patients worry about the side-effects of their pain medication. In fact, concern about side-effects was the third most commonly reported reason for why patients with cancer-related pain do not receive treatment (13% of non-treated patients), after managing to live with the pain (22%) and deeming medication to be no longer necessary (15%). The most common side-effect reported was constipation, followed by nausea/vomiting, sedation, and psychological effects (figure 4).

**Figure 4: Side-effects due to current prescription pain medications**



**Epic Survey Question:** What side effects have you experienced due to the current prescription medication you are taking?

Constipation can be particularly challenging as it has the potential to discourage patients from further use of pain medications.<sup>2</sup> It is frequently reported in patients with cancer-related pain because opioids act on  $\mu$ -opioid receptors in submucosal and myenteric plexus in the gastrointestinal (GI) tract to reduce peristalsis, increase sphincter tone, impair rectal sensitivity, blockade water secretion, and increase water absorption via reduced smooth muscle tone.<sup>3</sup> However, it should be noted that multiple other constipating factors are also commonly present in patients with cancer such as physical inactivity, reduced food intake, and dehydration.<sup>4</sup>

### About OIC and its impact on patients' lives

Despite the high prevalence of constipation in patients taking medication for cancer-related pain, it is under reported by patients and under recognised by healthcare professionals. Opioid-induced constipation (OIC) may be commonly overlooked because patients do not often complain of constipation, despite the profound effect that it can have on quality of life. Constipation is not a trivial symptom; as well as causing abdominal bloating and discomfort, anorexia, nausea, and vomiting, severe constipation can lead to haemorrhoids, anal fissure, intestinal obstruction, intestinal perforation and urinary retention. It is also worth noting that constipation can occur even in patients who continue to have bowel motions, as patients may experience diarrhoea or loose stools due to faecal overflow seeping around faecal impaction.<sup>5</sup>

### Challenges in treating OIC

OIC provides many challenges in optimising pain management for patients with cancer-related pain. Compared with patients who are treated with opioids but unaffected by constipation, patients with OIC have increased visits to their doctor, more frequent absences from work, reduced ability to perform activities of daily living, and experience negative effects on their professional lives.<sup>6</sup> Furthermore, severe constipation can reduce the benefits of opioid therapy by up to 30%.<sup>7</sup> Effects of constipation may mean that the opioid dose is not appropriately applied to the pain situation,<sup>8</sup> the opioid is absorbed more slowly, or that the pain medication has to be stopped altogether.<sup>7</sup>

Challenges that clinicians face when trying to effectively treat OIC with conventional therapies includes dosing adjustments for the individual patient and a high tablet burden. When oral laxatives fail to induce a bowel movement, rectal interventions such as suppositories or enemas are used; however, these are inconvenient, disliked by the patient, often require repeat treatments for severe impactions, and have a considerable negative impact on quality of life.

In severe cases, hospital admission is required to resolve the immediate problem. Conventional laxatives used in the treatment of OIC can be ineffective, poorly tolerated, and can result in temporally unpredictable responses. It is important that healthcare practitioners educate patients in how to use conventional laxatives effectively and that their need will be ongoing for as long as the patient is taking an opioid medication.

### Management of OIC

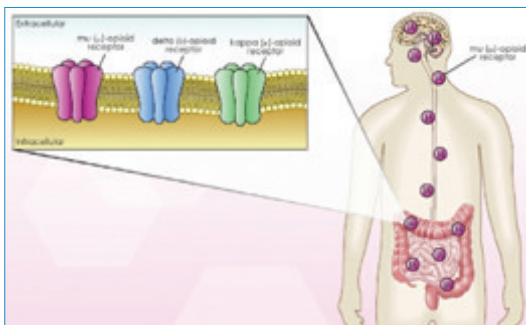
Managing OIC requires a multifaceted approach that starts with ensuring healthcare practitioners are armed with the knowledge and skills to treat OIC and can educate patients in its management. Taking an accurate history of what are normal and acceptable bowel habits for each patient is essential for the effective management of constipation.<sup>9</sup> It also involves the realisation that it requires a long-term approach involving adequate fluid and dietary fibre intake, as well as keeping physically active. It is important for patients to recognise the importance of establishing and maintaining regular elimination habits and that enough time and privacy is given for toileting.<sup>10</sup>

The fundamental aims for using laxatives can be unclear for patients but the following guidance has been suggested:<sup>9</sup>

- The aim of laxative therapy is to promote comfortable defecation rather than any particular frequency of bowel action;
- The dose should be titrated against response;
- In OIC, laxative therapy should be regular not intermittent; and
- A combination of stimulant and softener is usually required.

However, controlled studies exploring the efficacy of traditional laxatives appear lacking<sup>10</sup> and these laxatives are not specific to the underlying mechanisms of OIC. OIC is predominantly mediated by  $\mu$ -opioid receptors in the GI tract (figure 5).<sup>11,12</sup> Therefore, novel therapies which target the root cause of opioid medication-induced side effects such as constipation are needed.

Figure 5: OIC is predominantly mediated by  $\mu$ -opioid receptors in the GI tract.



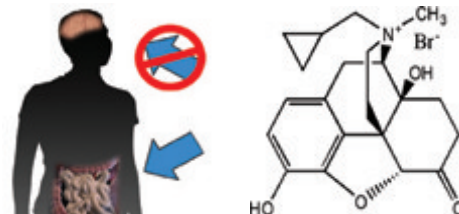
### Evolving targeted treatments for OIC

Several targeted treatments that act as opiate antagonists are currently under investigation for the treatment of OIC. Non-specific opiate antagonists that exhibit both central and peripheral effects include naloxone, naltrexone, nalmefene and naloxone-3-glucuronide. These agents have been shown to provide varying degrees of laxation efficacy.<sup>13-16</sup> However, reversal of analgesic effects is common with these compounds due to their effects on central opioid receptors.<sup>13,14</sup>

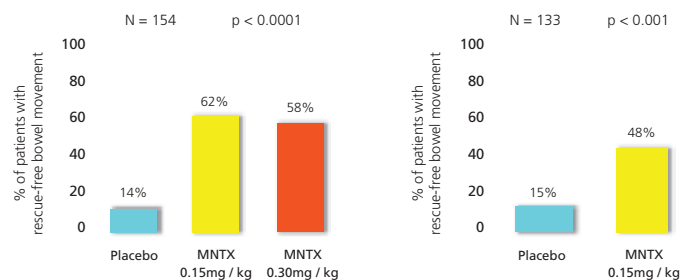
Selective blockade of peripheral  $\mu$ -opioid receptors in the GI tract is thought to relieve constipation without compromising the centrally mediated effects of opioid analgesia or precipitating withdrawal. Peripherally acting opiate antagonists include alvimopan and PEG-naloxol, which are both currently investigational compounds, and methylnaltrexone – the only peripherally acting  $\mu$ -opioid receptor

antagonist which has been licensed by the European Medicines Evaluation Agency (EMA) for use in the treatment of OIC. Methylnaltrexone is indicated in patients with advanced illness who are receiving palliative care when response to usual laxative therapy has not been sufficient

Methylnaltrexone targets the pathophysiology of OIC. N-methylation of the uncharged centrally mediated opioid receptor antagonist, naltrexone, results in a charged derivative of the compound that has restricted ability to cross the blood-brain barrier due to its polarity and low lipid solubility.<sup>17</sup> Therefore, methylnaltrexone blocks peripheral but not central opioid receptors to reverse OIC without reversing analgesia or inducing withdrawal.



Results from phase III trials in patients with advanced illness have shown that methylnaltrexone is an effective treatment for OIC that can be used every other day or with longer intervals between injections. In a study of 154 patients with advanced illness and less than three bowel movements in the preceding week, significantly more patients who received a single subcutaneous dose of methylnaltrexone 0.15 or 0.30 mg/kg achieved a rescue-free bowel movement within 4 hours, compared with placebo recipients.<sup>18</sup> In a similar study of 133 patients, significantly more patients receiving subcutaneous methylnaltrexone 0.15 mg/kg than placebo ever other day for 2 weeks achieved a rescue-free bowel movement within 4 hours of drug administration.<sup>19</sup>



Oxycodone and naloxone as an opioid agonist/antagonist prolonged release (PR) combination tablet has been used effectively in Germany since 2006 (Targin<sup>®</sup>) and has recently become available in the UK (Targinact<sup>™</sup>) and is licensed for severe pain. Oxycodone is a semi-synthetic strong opioid used in the management of cancer pain.<sup>20</sup> Naloxone is a competitive ( $\mu$ ,  $\delta$  and  $\kappa$ ) opioid receptor antagonist often used intravenously to reverse the effects of opioid overdose.<sup>21</sup> When naloxone is given orally, it has minimal systemic bioavailability of around 2%, because of extensive first-pass hepatic metabolism.<sup>22</sup> At therapeutic oral doses, naloxone exerts a local inhibitory effect on opioid action in the GI system without interfering with the CNS.<sup>23</sup>

Results from phase III trials in patients with chronic noncancer pain have shown that oral PR oxycodone/naloxone can provide improvements in bowel function in constipated patients with noncancer pain, compared with oral PR oxycodone.<sup>24,25</sup> Overall, the addition of naloxone to oxycodone in a PR combination tablet has been shown to reduce symptoms of OIC and may improve the acceptability and tolerance of opioid medications in patients with severe chronic pain without reducing the analgesic effect of oxycodone.<sup>24,25</sup>

## Overcoming the barriers: Conclusion

OIC is one of the barriers that need to be overcome to improve the quality of life for patients living with cancer. Pain management in cancer care requires healthcare professionals to constantly reassess the common side effects of pain medications and be proactive in their management. This may involve a delicate balancing act of providing adequate pain relief while ensuring side effects do not outweigh the benefits, as a negative experience of pain medication can influence patients to discontinue their use.<sup>2</sup> Laxatives used proactively rather than reactively can help and pain medications that target OIC are available with others being investigated.

Management of OIC can be improved. It is important for us as healthcare practitioners to take time to listen to patients' concerns and act on what they tell us, while applying therapeutic approaches that will encourage concordance with treatment.

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## Abbreviated Prescribing Information

Before prescribing Relistor® please refer to full Summary of Product Characteristics.

**Presentation:** Relistor 12 mg/0.6 ml solution for injection. Each vial of 0.6 ml contains 12mg methylaltraxone bromide. One ml of solution contains 20 mg methylaltraxone bromide. For subcutaneous injection. **Uses:** Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient. **Dosage:** For adults only. Relistor should be added to induce prompt bowel movements when response to usual laxative therapy has not been sufficient. The recommended dose is 8 mg (0.4 ml) (for patients weighing 38-61 kg) or 12 mg (0.6 ml) (for patients weighing 62-114 kg). Patients whose weight falls outside of the ranges quoted should be dosed at 0.15 mg/kg. The recommended administration schedule is one single dose every other day. Doses may also be given with longer intervals, as per clinical need. Patients may receive two consecutive doses 24 hours apart, only when there has been no response (bowel movement) to the dose on the preceding day. **Renal patients:** In patients with severe renal impairment (creatinine clearance <30 ml/min), the dose should be reduced to 8 mg (0.4 ml) for those weighing 62-114 kg, and to 0.075 mg/kg for those whose weight falls outside of the 62-114 kg range. There are no data available from patients with end-stage renal impairment on dialysis, and methylaltraxone is not recommended in these patients. **Hepatic impairment:** Mild to moderate hepatic impairment – no adjustment necessary. Severe hepatic impairment (Child-Pugh Class C) – no data available, and methylaltraxone is not recommended in these patients. **Paediatric patients:** Should not be used in children under 18 until further data is available. **Elderly patients:** No dose adjustment recommended. **Administration:** Rotate injection site. Not recommended to inject into areas where skin is tender, bruised, red or hard. Scars or stretch marks should be avoided. **Contraindications:** Hypersensitivity to the active substance or excipients. Known or suspected mechanical gastrointestinal obstruction or acute surgical abdomen. **Warnings and Precautions:** Should not be used for treatment of patients

with constipation not related to opioid use. If severe or persistent diarrhoea occurs with treatment, patients should be advised not to continue therapy and consult their doctor. Treatment can result in rapid onset (within 30-60 minutes) of a bowel movement therefore patients should be made aware and be in close proximity to toilet facilities. Methylaltraxone has not been studied in clinical trials for longer than 4 months, and should therefore only be used for a limited period. Relistor should only be used in patients who are receiving palliative care and added to usual laxative treatment. Not recommended in patients with severe hepatic impairment or with end-stage renal impairment requiring dialysis. Use in patients with colostomy, peritoneal catheter, active diverticular disease or faecal impaction has not been studied. Therefore, should only be administered with caution in these patients. **Pregnancy and Lactation:** Should not be used during pregnancy unless clearly necessary. The decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy should take in to account the benefit of breast-feeding to the child and the benefit of Relistor therapy to the woman. **Effects on ability to drive and use machines:** Dizziness may occur. Undesirable Effects: Very common (≥1/10): abdominal pain, nausea, flatulence and diarrhoea. Common (≥1/100, <1/10): dizziness, injection site reactions (e.g. stinging, burning, pain, redness, oedema). **Legal Category:** POM. **Package Quantities:** Cartons containing: 1 x 0.6 ml vial, or 7 x 0.6 ml vial kit with 7 x 1 ml injection syringes with retractable needle and 14 x alcohol swabs. **Basic NHS Cost:** £21.05 – 1 x 0.6 ml vial, £147.35 – 7 x 0.6 ml vial. **European Marketing Authorisation Number(s):** EU/1/08/463/001; EU/1/08/463/003. For full prescribing information and details of other side effects see Summary of Product Characteristics. **Full prescribing information is available on request from:** Wyeth Pharmaceuticals, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH. Tel: 0845 367 0098. **Date of Prescribing Information:** 04 July 2008 Code no. ZAPI083 Doc ID 48683