

## Nausea and Vomiting Side Effects with Opioid Analgesics during Treatment of Chronic Pain: Mechanisms, Implications, and Management Options

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### ABSTRACT

*Objectives.* Gastrointestinal (GI) side effects such as nausea and vomiting are common following opioid analgesia and represent a significant cause of patient discomfort and treatment dissatisfaction. This review examines the mechanisms that produce these side effects, their impact on treatment outcomes in chronic pain patients, and counteractive strategies.

*Results.* A number of mechanisms by which opioids produce nausea and vomiting have been identified. These involve both central and peripheral sites including the vomiting center, chemoreceptor trigger zones, cerebral cortex, and the vestibular apparatus of the brain, as well as the GI tract itself. Nausea and vomiting have a negative impact on treatment efficacy and successful patient management because they limit the effective analgesic dosage that can be achieved and are frequently reported as the reason for discontinuation of opioid pain medication or missed doses. While various strategies such as antiemetic agents or opioid switching can be employed to control these side effects, neither option is ideal because they are not always effective and incur additional costs and inconvenience. Opioid-sparing analgesic agents may provide a further alternative to avoid nausea and vomiting due to their reduced reliance on mu-opioid signalling pathways to induce analgesia.

*Conclusions.* Nausea and vomiting side effects limit the analgesic efficiency of current opioid therapies. There is a clear need for the development of improved opioid-based analgesics that mitigate these intolerable effects.

*Key Words.* Chronic Pain; Opioids; Adverse Events; Nausea; Vomiting; Gastrointestinal

### Introduction

Chronic pain is a debilitating condition affecting a significant proportion of the population. In Europe, one in five adults experiences chronic pain (as reported in the Pain in Europe survey of 46,394 respondents) [1] and similar prevalence figures are reported in other populations [2–5]. Yet, for a substantial number of patients, treatment appears to be unsatisfactory [1,6–8]. In accordance with the growing health problem represented by the management of chronic pain conditions, the use of opioid analgesic

treatment is expanding to include both malignant and nonmalignant chronic pain [9].

Although some patients can achieve sustained partial pain relief with opioid therapy without intolerable side effects [10], many patients are not being treated adequately, for reasons that include concerns over tolerability, as well as with addiction issues [11] (although the risk of addiction in chronic pain is, at present, not well understood). An important reason for the discontinuation of opioid therapy is due to concerns over the tolerability profile of this drug, particularly with strong opioids such as morphine. The major reasons for discontinuation of opioid analgesic treatment are gastrointestinal (GI) side effects (i.e., nausea, vomiting, and constipation) along with central nervous system side effects [12]. The

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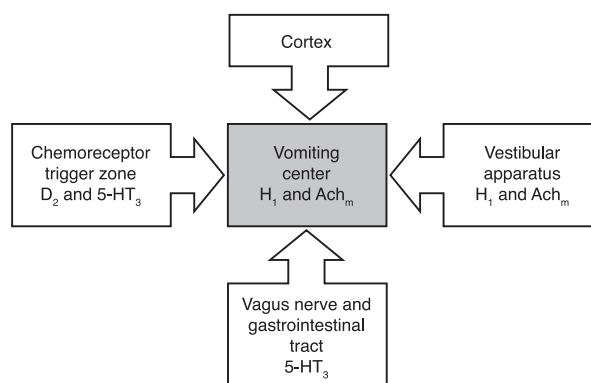
incidence of nausea and vomiting reported in patients treated with opioids for chronic pain in a clinical trial setting ranges from 10% to 50% [13–16]. While other GI side effects of opioids such as constipation can be prevented and controlled to some degree by various measures such as laxatives, increased fiber consumption and stool softeners [11], nausea and vomiting effects are more difficult to control fully in the majority of patients [17]. Indeed, in some patients, pain alone may cause nausea and vomiting. There is, therefore, a need for development of new analgesic drugs with improved benefit–risk profiles for chronic pain management.

This article will review data on the reasons for nausea and vomiting associated with opioid use, why these side effects present a problem for clinicians and patients, and options to improve the efficiency of opioid analgesics for use in chronic pain conditions. Medline literature searches were performed using a combination of the following keywords: nausea/vomiting and opioid and pain. Articles included in this review were manually selected based on their relevance to nausea and vomiting side effects experienced during opioid treatment of chronic pain. Other references were selected on an ad hoc basis to provide additional support.

### Mechanism of Emetogenic Effects

Various stimuli that lead to nausea and vomiting act on the “vomiting center” in the medulla oblongata of the brain. This “center” is not a discrete locus but rather consists of groups of loosely organized neurones (sensory and motor control nuclei located mainly in the medulla but also in the spinal cord), which can be activated in a co-ordinated sequence [18]. Nausea and vomiting can be stimulated or repressed via chemoreceptors present in the vomiting center [19], receiving inputs from different locations [20]. Nausea and vomiting are usually initiated by peripheral irritant stimuli acting on the gastrointestinal tract, which are transduced into sensory signals transmitted centrally to the vomiting center by vagal and sympathetic afferent nerves. However, the same sensations can be induced by direct stimulation of particular brain regions [21].

The vomiting center receives input from four major areas: the chemoreceptor trigger zone (CTZ) for vomiting, the GI tract, the vestibular apparatus in the temporal lobe, and the cerebral cortex (Figure 1) [20]. Opioids exert emetogenic effects through multiple mechanisms, principally



**Figure 1** Sensory input into the “vomiting center” of the brain. D2 = D2 dopaminergic; 5-HT3 = serotonin type 3; H1 = histamine type 1; Ach<sub>m</sub> = muscarinic acetylcholine. Adapted with permission from Herndon et al. [20].

involving three of these areas, namely: direct stimulation of the CTZ, inhibition of gut motility, and stimulation of the vestibular apparatus. The role of the cortex in opioid-induced nausea is unclear, but may be related to a patient recalling previous episodes of nausea and/or vomiting after opioid therapy [20]. The effects are mediated via interaction with specific opioid receptors (mu, delta, and kappa subtypes) in the brain and spinal cord and, in some circumstances, at peripheral sites [22,23].

### Opioid Stimulation of the CTZ

The neurons that make up the CTZ are found within the area postrema at the floor of the fourth ventricle. The permeability of the blood-brain barrier at the CTZ means that these neurons may be directly stimulated by many toxins, metabolites or drugs, including opioids, that are present in the systemic circulation [20]. The mechanism of opioid-induced stimulation of the CTZ occurs via the activation of opioid mu and delta receptors [24], and signaling to the vomiting center occurs primarily via dopamine D<sub>2</sub> receptors as well as via serotonin (5-HT<sub>3</sub>) receptors present in the CTZ [20]. Opioid-evoked emesis mediated via the CTZ decreases with repetitive opioid administration, with the development of tolerance to emesis possibly dependent on the type of opioid administered [25–27].

### Opioid Inhibition of Gut Motility

Central, as well as peripheral, opioid receptors are involved in inhibiting gut motility, but the predominant mechanism appears to be via activation of mu receptors in the GI tract [28], leading to

decreased GI transit via effects on the circular and longitudinal muscles of the intestine involved in peristalsis. However, kappa receptor agonists have also been shown to inhibit gut motility [29], and so may also play a role in this phenomenon. Signaling to the vomiting center from the GI tract occurs via a serotonergic signaling pathway [20]. Opioid inhibition of gut motility can lead to distension of the gut, increased GI emptying time and constipation, resulting in stimulation of visceral mechanoreceptors and chemoreceptors. This, in turn, is often responsible for nausea and vomiting in terminally ill patients receiving opioid drugs [20].

#### *Opioid Stimulation of the Vestibular Apparatus*

The vestibular apparatus is located in the bony labyrinth of the temporal lobe, and is responsible for detecting changes in equilibrium. The vestibular apparatus is stimulated directly by most opioids, although the mechanism by which this occurs remains to be determined [20]. It has been postulated that mu receptors on the vestibular epithelium are responsible for opioid-induced stimulation of the vestibular apparatus [30], but kappa and delta receptors are also localized within the inner ear [31]. Sensory input to the vomiting center occurs via the histamine H<sub>1</sub> and cholinergic ACh<sub>m</sub> pathways [19,20]. Emesis may be more common if patients are ambulatory, with nausea stimulated by rapid movement and dehydration [19].

#### *The Complexity of Opioid Effects*

The emetogenic mechanisms involved for a specific opioid depend on the specificity of an opioid for mu, delta, or kappa receptors. Thus, for example, mu opioid receptor agonists have been associated with nausea and vomiting, but kappa opioid receptor agonists may not be [32]. The clinical situation is often complicated by the variety of different opioid-related emetogenic mechanisms. These can vary from patient to patient, more than one may be active in any one patient at the same time, and the mechanisms may change from acute- to long-term opioid use. For example, emetogenic effects caused by medullary CTZ stimulation often decrease very rapidly [22,27]. In some patients, however, nausea and vomiting side effects are known to persist during long-term treatment [33]. Furthermore, analgesic tolerance (a reduction in the pain-relieving effect of opioids) usually manifests over time as multiple cellular and molecular adaptations take place, including neuroplastic changes [22,27,34–36]. As a consequence, dose escalation is

common in order to maintain the same level of pain relief, but this is likely to enhance the risk of recurring nausea and vomiting as well as other side effects. Dose escalation must therefore be controlled in order to maintain opioid efficacy while limiting the risk of adverse events [37].

Conversely, higher doses of some opioids (such as morphine) may actually reduce nausea and vomiting by interacting with mu opioid receptors in the vomiting center rather than the CTZ [38,39]. Thus, the relationship between opioid use and the incidence of nausea and vomiting is complex. Other potential complicating factors include the choice of opioid. Although the incidence of nausea and vomiting appears to vary little with the type of opioid analgesic used, some opioids have been reported to induce less nausea and vomiting than others [40], even at carefully controlled equianalgesic doses [41]. For example, oral morphine was associated with a significantly greater incidence of nausea than any other opioid or treatment modality studied [41].

### **Implications for Clinicians and Patients**

#### *The Clinician's Perspective*

From the clinician's perspective, it is important to identify the underlying cause of nausea and vomiting from among the multiple causative mechanisms for each patient so that effective treatment can be chosen (Table 1). Opioid stimulation of the CTZ leading to nausea and vomiting can be treated with dopamine receptor antagonists such as phenothiazines (e.g., prochlorperazine) or butyrophenones (e.g., haloperidol and droperidol), though dopamine antagonism with these agents can cause a range of side effects such as drowsiness, constipation, dystonia, parkinsonism, tardive dyskinesia, torsades de pointes, and neuroleptic malignant syndrome [20,42,43]. Serotonin receptor antagonists (e.g., dolasetron, granisetron, and ondansetron) are also effective for the prevention of nausea and vomiting caused by opioid stimulation of the CTZ, and are associated with a good tolerability profile [17,20]. It is worth noting that although these drugs have been approved by the Food and Drug Administration (FDA) for the treatment of nausea and vomiting, they have not been specifically approved for opioid-induced nausea and vomiting.

Metoclopramide acts directly on the GI tract and is thus effective against nausea caused by gastric stasis [39] and is often considered to be the

**Table 1** Drugs for treating nausea (used in a palliative care setting)

Drug Class	Mechanism of Action	Nausea Response
Butyrophenones (haloperidol, droperidol)	D <sub>2</sub> blockade in CTZ	Chemical irritation, visceral Vestibular
Phenothiazines and derivatives (chlorpromazine, prochlorperazine, thiethylperazine)	D <sub>2</sub> blockade in CTZ and GI tract	Vestibular
Antihistamines (cyclizine, diphenhydramine, hydroxyzine, meclizine, promethazine)	H <sub>1</sub> blockade in vomiting center and vestibular apparatus	Vestibular
Anticholinergic agents (hyoscine, scopolamine)	Muscarinic blockade in vomiting center and GI tract	Vestibular
Serotonin antagonists (dolasetron, granisetron, ondansetron)	5-HT <sub>3</sub> blockade in GI tract and CTZ	Gastric stasis
Prokinetic agents (metoclopramide)	D <sub>2</sub> blockade in GI tract and CTZ; 5-HT <sub>4</sub> stimulation in GI tract; 5-HT <sub>3</sub> blockade in CTZ and GI tract (high dosages)	Gastric stasis
Benzodiazepines (lorazepam)	GABA agonist	Anticipatory nausea

D<sub>2</sub> = D<sub>2</sub> dopaminergic; CTZ = chemoreceptor trigger zone; GI = gastrointestinal; H<sub>1</sub> = histamine type 1; 5-HT = serotonin; GABA =  $\gamma$ -aminobutyric acid. Adapted with permission from Herndon et al. [20].

first-line therapy for opioid-induced nausea due to its side-effect profile and mechanisms of action [20]. Thus, if nausea is associated with early satiety, bloating or postprandial vomiting, all of which are signs of delayed gastric emptying, metoclopramide is a reasonable initial treatment [13]. Metoclopramide reduces gut transit times through enhancement of the acetylcholine response in the GI tract, and is thus beneficial to patients with nausea associated with constipation [20,44]. Metoclopramide also inhibits peripheral dopamine and serotonin receptors and, additionally, appears to provide D<sub>2</sub>-receptor inhibition in the CTZ at high doses [20].

Several classes of agents are effective against vestibular vertigo-like symptoms. Histamine antagonists (e.g., cyclizine) are active at the vomiting center as well as the vestibular apparatus, which make them valuable in the treatment of nausea associated with movement or vertigo. In contrast, anticholinergic drugs (e.g., scopolamine) exert an antiemetic effect via their inhibition of acetylcholine signaling directly within the vomiting center [13,20,45,46]. Side effects associated with antihistamines and anticholinergic agents may be bothersome (e.g., xerostomia, constipation, blurred vision, and confusion), but at low dosages the drugs are generally well tolerated.

In some cases, a single antiemetic agent may be sufficient to relieve nausea and vomiting, but this is not always the case, and sometimes the combination of more than one antiemetic may be necessary [43]. For example, the combined blockade of dopamine and serotonin receptors by haloperidol and ondansetron, respectively, may sometimes be required to relieve intractable nausea and vomiting [43,47]. Alternative options include switching to another antiemetic or an alternative opioid

[13,48], use of low doses of an opioid receptor antagonist such as naloxone [49], as well as nonpharmacological interventions. Nonpharmacological interventions include increased access to fresh air, limiting dietary intake (e.g., avoiding sweet, salt, fatty, and spicy foods), providing distractions (e.g., talking, music, reading, etc.), and relaxation techniques such as rhythmical breathing and positive visual imagery [19].

Unfortunately, there is a lack of clinical trial data concerning the use of antiemetics in patients with opioid-induced nausea and vomiting, and even these limited data are equivocal. A systematic review of chronic pain therapy in 67 trials involving 3,991 patients (with cancer pain or noncancer pain), identified seven studies and three case studies of antiemetic agents, and showed a wide variation in antiemetic efficacy, with many studies of a very small size (four of the seven trials consisted of less than 20 patients) [43]. Moreover, a randomized, double-blind, placebo-controlled trial of ondansetron and metoclopramide in 92 patients failed to show a significant reduction in emesis in either treatment group compared with those given placebo [50].

In addition to tolerability issues surrounding the use of opioids, most antiemetics are associated with their own tolerability problems, as has been previously noted [43]. Moreover, before the treatment of opioid-induced nausea and vomiting can be started, other emetogenic drugs used in patients with chronic pain (e.g., digoxin, antibiotics, iron, and cytotoxics) should be tapered or discontinued if possible, which can cause further problems [43].

However, there have been recent developments in antiemetic therapy. For example, risperidone, an atypical antipsychotic that blocks dopaminergic D<sub>2</sub> and serotonergic 5-HT<sub>2</sub> receptors, has recently

been shown to be an effective antiemetic in the treatment of refractory opioid-induced nausea and vomiting in advanced cancer patients ( $N = 20$ ) [51]. Furthermore, a randomized, double-blind, placebo-controlled trial showed that the use of low doses of the opioid receptor antagonist naloxone proved to be effective in reducing morphine-induced nausea in children and adolescents ( $N = 46$ ) without significantly affecting analgesia [49].

Overall, the evidence indicates that the side effects of opioid therapy in chronic pain patients—such as nausea and vomiting—represent a significant barrier to achieving effective pain control and patient compliance. In a survey of 569 general practitioners in the United Kingdom, 74% cited pain medication side effects as a major barrier to effective pain control in patients with chronic non-cancer pain. In addition, 58% cited poor patient compliance (also linked to tolerability), and 96% believed treatment could be improved [52].

#### *The Patient's Perspective*

From the patient's perspective, nausea and vomiting are among the most disturbing and distressing side effects that they experience [53]. Several studies have demonstrated the negative impact of opioid-induced nausea and vomiting on patient functionality and quality of life outcomes [54–56]. Moreover, nausea and vomiting are particularly common side effects in patients with chronic non-cancer pain taking opioid analgesics. The meta-analysis by Moore and McQuay, which included 34 trials of opioid use in chronic noncancer pain involving 5,546 patients, showed that dry mouth (25%), nausea (21%), and constipation (15%) were the most common adverse events, with 22% of patients discontinuing treatment as a result of these side effects [16]. A systematic review of randomized, placebo-controlled trials of opioids for the treatment of chronic noncancer pain showed that nausea was reported in 32% and vomiting in 15% of patients (vs 12% and 3%, respectively, in those given placebo) [57]. Thus, the relative risk (95% confidence interval [CI]) was 2.7 (2.1–3.6) for nausea and 6.1 (3.3–11.0) for vomiting in these patients. The rate of discontinuation due to adverse events among patients receiving opioid was 24% (relative risk 1.4 [95% CI 1.1–1.9] vs placebo), and just 44% were still on treatment at the end of study follow-up [57]. Furthermore, nausea and vomiting are not necessarily short-term effects, as shown by a 3-year U.S. registry study in which 219 patients received long-term oxycodone (mean duration 541.5 days; mean dose  $52.5 \pm 38.5$  mg/day) [33].

In this study, nausea and vomiting were reported by 12% and 7% of patients, respectively [33]. In most patients, the reporting of side effects decreased with the duration of therapy, but in minority of cases, nausea and vomiting were still occurring after 3 years [33].

The side effects of medication for chronic pain are of great concern to patients, as shown by a European survey of patients with chronic pain [1]. Two-thirds of survey respondents were concerned about the side effects of their pain medication [1]. Similar concerns were expressed in the Roadblocks to Relief survey conducted by the American Pain Society [58]. Furthermore, patients often cite nausea and vomiting as reasons for discontinuing their analgesic medication. In two comparative studies of immediate-release and controlled-release oxycodone given to patients with chronic noncancer or cancer pain, the most frequently cited reasons for treatment discontinuation among those with noncancer pain were nausea and vomiting [59].

#### *Cost Implications*

Economic issues surrounding the cost implications of poor tolerability to opioid therapy for chronic pain are beginning to receive attention [56,60–62]. Drug costs form a small proportion of the total economic burden, as the cost of medical personnel time typically forms more than 70% of total health care spent [60]. Nevertheless, the cost of managing nausea and vomiting associated with opioid treatment will incur additional drug acquisition costs for antiemetics, as well as health care staff time to diagnose, prescribe and administer these agents, in addition to the cost of switching to another opioid if side effects become unmanageable [56,61,62]. Other costs associated with poor tolerability of opioids are those for additional pain relief (e.g., with non-opioid analgesics), as the tolerable dose of opioid may be limited by its side effects such as nausea and vomiting [56,61,62]. Furthermore, these side effects can lead to poor treatment compliance and patients' attitudes that their pain is not being treated effectively by their doctor (28% of patients in a European survey reported that their doctor did not know how to control their pain, and 40% with chronic pain that their pain was not well managed) [1], resulting in patients consulting one physician after another in an attempt to seek improved pain management. The costs incurred by noncompliant behavior in chronic pain patients have also been calculated [62,63].

### *Improving the Risk–Benefit Ratio of Opioid Analgesics*

Little research has been undertaken in recent years to develop opioid-sparing analgesics with improved risk–benefit profiles, despite the known need for agents such as these. In some cases, opioid-sparing adjuvant analgesics are used to allow opioid dose reduction, but this is far from an ideal solution [64]. However, nonpharmacological interventions that specifically target cognitive processes may be effective in conjunction with analgesia for patients with chronic pain. Thus, a recent study of patients' perception of chronic pain showed that treatment effects can be enhanced by interventions that specifically target cognitive processes (i.e., a multidisciplinary program including exercise, relaxation, pain education, sleep management, and cognitive restructuring exercises) [65].

Research has led to the development of several new types of opioid-based analgesic therapy, of which, some have been specifically designed to limit adverse events. Novel preparations of opioids, such as the transdermal fentanyl patches, achieve controlled transcutaneous opioid delivery by means of a fentanyl reservoir located behind a rate-controlling membrane. Constipation, nausea, and vomiting remain the most frequent adverse events with this system, although it has been associated with lower incidences of constipation when compared with systemic applications of morphine in open-label studies [66–69]. However, there were no differences found between the incidences of nausea and vomiting [66,68,70,71]. When transdermal delivery systems were evaluated against orally and intrathecally delivered opioids in a recent systematic review of long-term opioid therapy for chronic noncancer pain, intrathecal opioids achieved the lowest rates of withdrawals from clinical studies due to adverse events [72]. However, it is worth noting that intrathecal drug delivery is not practical for many patients.

One new therapeutic strategy has been to develop peripherally acting opioid receptor antagonists in order to selectively inhibit peripheral mu opioid receptors in the GI tract without reversing centrally mediated opioid-induced analgesia. Two new peripherally acting mu opioid antagonists, alvimopan and methylnaltrexone, have recently been approved by the FDA for the reduction of opioid-induced bowel dysfunction associated with opioid analgesics [73,74]. Although results of preliminary studies are promising, a recent systematic review of these agents for the relief of opioid-related constipation concluded

that there are, as yet, not enough data to determine whether or not they are effective for this purpose [75]. One concern, however, is that antiemetic agents with a restricted ability to cross the blood–brain barrier may have a reduced efficacy against nausea and vomiting mediated through central mechanisms. Also under current investigation are oral fixed combinations of opioid receptor agonists and antagonists such as prolonged-release oxycodone and naloxone, as well as oxycodone and naltrexone [76,77]. These drugs are similarly designed to reduce peripheral GI side effects by their peripheral inhibitory action on gut opioid receptors [78]. However, although these agents have a low systemic bioavailability, a negative impact on the analgesic effects of the combination products by the antagonist component cannot be excluded [79]. The combination potentially offers less dosing flexibility than the use of separate antagonists.

A novel approach is to combine more than one analgesic principle in one molecule so that both mechanisms are pharmacologically engaged. This concept was realized in tapentadol, a compound purposely designed to combine two analgesic actions, mu opioid receptor agonist activity with norepinephrine reuptake inhibition. In this case, the analgesic effect is not reliant solely on agonist activity at the mu receptor that is also responsible for side effects. Data from preclinical studies indicate that the combination of these two analgesic actions is less likely to produce opioid-mediated side effects; for example, in one of the most commonly used emesis model species, the ferret [80], tapentadol may produce fewer episodes of retching and vomiting as compared with morphine [81]. This suggests a potential therapeutic advantage over the currently available classical opioid analgesics, offering improved tolerability and equivalent analgesic efficacy.

### **Conclusions**

In conclusion, opioids cause nausea and vomiting in many patients through multiple and complex causative mechanisms. Nausea and vomiting are common side effects of opioid analgesia, and are distressing to patients, leading to a significant reduction in their quality of life. These types of side effect are often difficult to treat, can be persistent, and are major causes of noncompliance with pain relief medication. Moreover, addressing such problems is associated with a cost burden to health care services. New approaches designed to address the

clear therapeutic need may offer potential solutions to improve analgesic efficiency while diminishing the potential for adverse effects, especially nausea and vomiting, which lead to inadequate pain relief.

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