

[ CASE REPORT ]

## Naldemedine-induced Opioid Withdrawal Syndrome in a Patient with Breast Cancer without Brain Metastasis

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### Abstract:

Opioid-induced-constipation (OIC) can be treated by naldemedine and other peripherally acting mu-opioid receptor antagonists (PAMORA) via a novel mechanism. We describe the case of a 52-year-old female outpatient who developed OIC while receiving oxycodone for pain due to cancer with multiple bone metastases. Although she did not have brain metastasis, opioid withdrawal syndrome (OWS) developed after taking naldemedine orally. Her Clinical Opiate-Withdrawal Score (COWS) was 19 (moderate symptoms). However, she recovered from OWS on intravenous fentanyl and a continuous infusion of oxycodone. She did not develop OWS thereafter and was discharged two days after recovery.

**Key words:** naldemedine, opioid-induced-constipation (OIC), opioid withdrawal syndrome (OWS)

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### Introduction

All opioids exert analgesic effects by binding to mu-opioid receptors (MORs) in the brain and spinal cord. However, opioids also bind to intestinal MORs and cause opioid-induced constipation (OIC) by decreasing gastrointestinal transit and fluid secretion from organs, as well as the intestines and colon. Patients who are physiologically dependent upon opioids develop opioid withdrawal syndrome (OWS) if they abruptly reduce or stop taking opioids or start taking opioid antagonists. Most patients who continuously use opioids for relief from cancer pain develop OIC, which has historically been treated with magnesium oxide, lactulose, picosulfate and rubiprostone. Naldemedine is a new, structurally modified naloxone in which a side chain has been added to increase the molecular weight and avoid infiltrating the blood-brain barrier (BBB). Its mechanism of action against OIC differs from that of any other medication for OIC. Naldemedine-induced OWS should be considered

when the BBB breaks down due to conditions such as brain metastasis. This report describes naldemedine-induced OWS in a breast cancer patient who did not have brain metastasis.

### Case Report

The patient was a 52-year-old woman with estrogen-receptor and progesterone-receptor positive, human epidermal growth receptor 2-negative breast cancer with multiple bone metastases, who was being treated as an outpatient. She had undergone chemotherapy and hormone therapy and had been controlling her pain with celecoxib (200 mg/day) and oxycodone (80 mg/day) for three years. The oxycodone caused OIC, which she tried to treat with magnesium oxide (2,000 mg/day), sennoside (36 mg/day) and sodium picosulfate. However, she defecated only once every few days and desired a different type of medication.

We added naldemedine (0.2 mg/day) to treat the OIC. One hour after her first intake, she developed frequent diarrhea and vomiting with upper abdominal pain and presented

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**Table. The Clinical Opiate Withdrawal Score (COWS).**

Resting Pulse Rate: _____ beat/minute <i>Measured after patients or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	GI Upset: <i>over last 1/2 hour</i> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 4 multiple episode of diarrhea or vomiting
Sweating: <i>Over past 1/2 hour not accounted for by room temperature or patient activity.</i> 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	Tremor <i>observation of outstretched hands</i> 0 no tremor 1 tremor can felt, but not observed 2 slight tremor observed 4 gross tremor or muscle twitching
Restlessness <i>Observation during assessment</i> 0 able to sit still 1 reports difficulty sitting still, but is to do so 3 frequent shifting or extraneous movement of legs/arms 5 unable to sit still for more than a few seconds	Yawning <i>Observation during assessment</i> 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches <i>If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored</i> 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing <i>Not account for by cold symptoms or allergies</i> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initial of person completing assessment: _____

Score: 5-12=mild; 13-24=moderate; 25-36=moderately severe; more than 36=severe withdrawal

at the emergency room with restlessness, tremor, irritability, watery diarrhea, multiple joint aches, vomiting, upper abdominal pain, frequent yawning, runny nose, gooseflesh skin and prominent piloerection on her arms. She was diagnosed with OWS induced by naldemedine based on her medical history and physical findings. Her Clinical Opiate Withdrawal Score (COWS) was 19, indicating moderate symptoms (Table) (1). Her COW subset scores were as follows: GI upset, 4; sweating, 1; tremor, 2; restlessness, 1; yawning, 4; anxiety or irritability, 1; bone or joint aches, 2; gooseflesh skin, 3; runny nose or tearing, 1. We treated her with intravenous fentanyl (25 µg) until recovery from OWS, which was achieved with 75 µg of fentanyl. Enteritis was suspected based on the emergency CT findings (Figure).

We admitted her to differentially diagnose OWS from enteritis. At 90 minutes after recovery, the symptoms recurred, and continuous infusion of oxycodone led to recovery once gain. She did not develop any more symptoms and was switched from intravenous oxycodone to oral oxycodone the next day. The symptoms did not recur, and the absence of enteritis was confirmed the day after the switch. She was finally diagnosed with OWS based on the clinical course.

Brain MRI showed multiple metastases to the skull, but not the brain.

## Discussion

Opioid-induced constipation is diagnosed according to the ROME definition, which states that new or worsening symptoms when initiating, changing, or increasing opioid therapy, and must fulfil two or more of the following criteria in more than 25% of defecations:

- Straining to pass a bowel movement
- Passing lumpy or hard stools
- Experiencing the sensation of incomplete evacuation, obstruction, or blockage of stool
- Requiring manual maneuvers to facilitate evacuation of stool
- Fewer than three spontaneous bowel movement per week.

In addition, a patient with OIC rarely experiences loose stools without laxative use (2).

We diagnosed OIC based on her defecation status, which included items a, b, c, and e.



**Figure.** Abdominal CT image shows edematous wall thickening of the small intestine which was filled with much fluid.

Naldemedine and other peripherally acting mu-opioid receptor antagonists (PAMORAs), such as naloxegol, alvimopan, methylnaltrexone, a peripherally-acting MOR antagonist are medications for OIC with new mechanisms of action. They recover fluid secretion from the organ and gastrointestinal transit of patients with OIC (3). However, although naldemedine is designed not to infiltrate to BBB to avoid OWS, it might infiltrate the BBB, if the BBB has broken down due to brain metastasis. Thus, patients with brain metastasis should not use naldemedine to avoid OWS.

A diagnosis of OWS is made based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria for opioid withdrawal as follows (4):

A. Presence of either of the following:

1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
2. Administration of an opioid antagonist after a period of opioid use.

B. Three (or more) of the following developing within minutes to several days after criterion A:

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

The signs and symptoms of OWS are similar to those of infectious diseases such as influenza. However, this patient required a differential diagnosis from enteritis, and infection was only suspected based on the CT findings. Furthermore, her recovery from symptoms after the administration of fentanyl and oxycodone indicated a diagnosis of OWS. We used intravenous oxycodone when OWS recurred, because we aimed to confirm the absence of the adverse effects of naldemedine before administering the same dose of oral oxycodone that she had taken before. On the following day,

this dose relieved her cancer-related pain, so she was discharged.

As far as we can ascertain, this is first report of OWS caused by an adequate dose of naldemedine. Moderate-quality evidence has indicated that adequate doses of naldemedine have no effect of OWS (5). A phase 2 trial found that naldemedine (1 mg) caused moderate OWS in one of nine patients, with COWS 16 and that hydromorphone relieved the OWS (6). Our patient weighed 52 kg, and the naldemedine dose was adequate.

The question is why this patient developed OWS in the absence of brain metastasis. Brain micrometastasis that was too small for MRI to detect is one possible explanation. Patients with breast cancer often develop brain metastasis following lung cancer (7). Another possibility is that she did not have brain metastasis, and that the BBB broke down due to other causes. Zhou et al. recently reported that extracellular vesicles (EV) delivered from breast cancer cells can contribute to BBB breakdown (8). Tominaga et al. also reported that EV containing microRNA-181c released from breast cancer cells can trigger the breakdown of the BBB in the endothelium of blood vessels in the brain (9). The breakdown of the BBB in our patient might have been caused, at least in part, by EV. Thus, naldemedine might be incorporated into the brain via the BBB even in the absence of brain metastasis. Patients with cancer but not brain metastases who develop OWS due to naldemedine should be frequently monitored.

### Conclusion

We described the case of a patient without brain metastasis who was receiving opioids for cancer-related pain and who developed OWS after the administration of naldemedine. Patients with cancer, especially breast cancer, who are likely to develop brain metastasis should be identified before prescribing PAMORA.

**The authors state that they have no Conflict of Interest (COI).**

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