Use of Buprenorphine/Naloxone in an Adult with Cystic Fibrosis

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INTRODUCTION

Pain is a common comorbidity experienced by people with cystic fibrosis (pwCF), with a pooled prevalence among adults of 77% reported in the literature.[1] Potential sources of pain in pwCF include sinusitis, pleurisy, pancreatitis, arthropathy, and rib fractures.[1] Pain in pwCF can interfere with necessary treatments to maintain lung health (e.g., airway clearance, physiotherapy, exercise) and has been associated with lower mood, physical functioning, and health-related quality of life.[1] General approaches to managing pain in pwCF include nonpharmacological alternatives (e.g., rest, application of heat or cold, massage, acupuncture), non-opioid analgesics (e.g., acetaminophen, nonsteroidal anti-inflammatory agents, antispasmodic treatments, neuropathic pain agents, thoracic epidural analgesia), and opioid analgesics.[2] In a survey of 274 adults with CF in the United States, 101 (37.2%) reported receiving a prescription for analgesics, with opioids prescribed for 48 (17.5%).[3]

Despite the high prevalence of pain in pwCF, there is a paucity of knowledge about pain management and the use of prescription opioids in this population, including the potential benefits and harms of these medications. Here, we describe the successful transition of an adult with CF from hydromorphone to buprenorphine/naloxone for management of chronic pain, including the minimization of adverse effects and symptoms of withdrawal during reduction of the opioid dose.

CASE REPORT

A 41-year-old man with CF, who was receiving hydromorphone for pain, was admitted to hospital for management of acute nausea and vomiting.* The Opioid Stewardship Program (OSP), delivered by a hospital-based team that aims to optimize prescribing of opioids in the acute care setting, was consulted to assist with opioid management.

*The patient provided written consent for publication; nonetheless, potentially identifying demographic characteristics have been minimized.

Hydromorphone was first prescribed for this patient about 1 year before the hospital admission for pain related to right-sided rib fractures sustained from a fall. Before this injury, he had pre-existing right-sided chest pain related to insertion of a chest tube and pleurodesis for the management of recurrent pneumothorax; this pain was controlled with gabapentin. The hydromorphone was initially helpful for the acute pain related to the rib fractures and facilitated an increase in his physical functioning, but over time it stopped providing as much pain relief. The patient also began to feel dependent on the hydromorphone, and the majority of his time was focused on when he could take his next dose. In this context, the patient was motivated to taper off the hydromorphone.

During a previous hospitalization 8 months before the current admission, he attempted to taper the hydromorphone with support of the hospital's Complex Pain Team. At that time, he was able to decrease the dose from 8 mg orally every 4 hours to 4.5 mg orally every 4 hours; however, the dose was subsequently increased back to 8 mg every 4 hours following insertion of a jejunostomy tube. Under the care of an outpatient pain clinic, he again attempted to taper his hydromorphone, but was unable to reduce the dose below 7 mg orally every 4 hours. The primary barrier to tapering hydromorphone further, as reported by the patient, was the discomfort associated with withdrawal symptoms of sweats, myalgia, nausea, and malaise. He also noted that the hydromorphone had an erratic analgesic effect, resulting in intermittent and unpredictable withdrawal symptoms between doses. The patient's dependence on hydromorphone and his desire to avoid withdrawal symptoms began to interfere with his social relationships and limited his time and engagement with his family. He denied taking more or higher doses of hydromorphone than prescribed, taking additional prescribed or nonprescribed opioids, or using any non-oral routes of administration.

The patient's medical conditions and medications before admission and in hospital (upon initial assessment by the OSP team) are outlined in Table 1. Upon admission, due to

nausea and vomiting, hydromorphone 3 mg subcutaneously (SC) every 4 hours was prescribed. Following their assessment, the OSP team suggested a transition from hydromorphone to sublingual (SL) buprenorphine/naloxone for management of chronic pain, with a subsequent slow taper to achieve the patient's goal of eventually discontinuing opioid therapy. The rationale for this recommendation included the fact that SL absorption of buprenorphine could bypass potentially erratic absorption in the gut and, hopefully, decrease the occurrence of withdrawal symptoms between doses. Furthermore, once-daily dosing offers more convenience, and the long half-life would allow for a more gradual taper with the possibility of minimizing withdrawal symptoms. It was noted that the patient might need a higher dose of buprenorphine/naloxone due to known interaction with lumacaftor.

The patient agreed to the initiation of buprenorphine/naloxone according to the following microdosing regimen (dose indicating buprenorphine component): 1 mg SL once (day 1), 1 mg SL twice daily (day 2), 2 mg SL twice daily (day 3), 2 mg SL 3 times daily (day 4), 4 mg SL twice daily (day 5), 12 mg SL once daily (day 6), 16 mg SL daily (day 7 onward). Hydromorphone was continued at 3 mg SC q4h and discontinued on day 7 of the buprenorphine/naloxone titration.

The patient tolerated the transition to buprenorphine/naloxone well and did not require any of the as-needed buprenorphine/naloxone doses that were available to him. He described feeling anxious during the process, particularly before discontinuation of hydromorphone, but did not experience any physical symptoms of withdrawal or change in his overall pain. He was discharged on buprenorphine/naloxone 16 mg/4 mg SL once daily. He continued to taper the buprenorphine/naloxone in the community, with initial success; however, over the subsequent 18-month period, his dose fluctuated due to new acute pain events, including dental pain, pleural effusion, and empyema. His dose peaked at 18 mg/4.5 mg per day before treatment of the empyema. After this, his dose was tapered back down to 16 mg/4 mg per day before transition to monthly

TABLE 1. Medical Conditions and Medications for a Patient with Cystic Fibrosis Prior to Admission and In Hospital

	Medications	
Medical Condition[a]	**PTA**	**In Hospital[b]**
CF	Lumacaftor/ivacaftor 400 mg/250 mg PO q12h	Same as PTA
CF-related bronchiectasis and pulmonary disease	Dornase alfa 2.5 mg nebulized bid Mometasone/formoterol 600 µg/15 µg inhaled bid Tiotropium 5 µg inhaled daily Salbutamol 200 µg inhaled qid PRN	Same as PTA Same as PTA Same as PTA Same as PTA
Chronic *Pseudomonas aeruginosa* pulmonary infection	Aztreonam 75 mg nebulized tid alternating months on/off	Held while receiving IV antibiotics
Chronic pain	Acetaminophen 975 mg PO qid Gabapentin 900 mg PO tid Hydromorphone 7 mg PO q4h	Same as PTA Same as PTA Hydromorphone 3 mg SC q4h
Opioid withdrawal	Clonidine 0.05 mg PO tid PRN	Same as PTA
Malnutrition	Feeds through GJ tube	Same as PTA
Vitamin and mineral supplementation	Vitamin D_3 4000 IU PO daily Vitamin E 200 IU PO daily Multivitamin 1 tab PO daily Ferrous fumarate 100 mg PO bid	Same as PTA Same as PTA Same as PTA Same as PTA
Pancreatic insufficiency	Pancrelipase (CREON 25): 6 caps PO tid with meals and 4 caps PO tid PRN with snacks	Same as PTA
Nausea and vomiting	Ondansetron 4 mg PO tid PRN Dimenhydrinate 50–100 mg PO tid PRN	Ondansetron 4 mg IV q8h PRN Dimenhydrinate 25–50 mg IV q6h PRN
Gastroesophageal reflux disease	Pantoprazole 40 mg PO bid	Pantoprazole 40 mg IV q12h
Mood/anxiety disorder	Venlafaxine 75 mg PO daily	Same as PTA
Low BMD with 2 prior rib fractures	Zoledronic acid 5 mg IV annually	Held; not due for dose
Insomnia	Zopiclone 5–15 mg PO qhs PRN	Same as PTA

BMD = bone mineral density, CF = cystic fibrosis, GJ = gastronomy–jejunostomy, PTA = prior to admission.
[a]Other past medical history included gastrointestinal dysmotility, chronic sinusitis, tinnitus (suspected secondary to aminoglycoside use), *Mycobacterium abscessus* pulmonary infection, reduced testosterone, and bilateral pneumothoraces.
[b]Medications the patient was taking at the time of assessment by the Opioid Stewardship Program.

SC injection of extended-release buprenorphine; the plan was to use the long half-life of the injection to help taper off buprenorphine. He received 2 monthly doses of 300 mg, followed by 2 monthly doses of 100 mg. He then began to taper by extending the dosing interval to 5 weeks before the fifth injection, 6 weeks before the sixth injection, and then discontinuing altogether. At the time this report was prepared, it had been 2 months since his last injection, and he denied any worsening pain or withdrawal symptoms.

DISCUSSION

Pain is commonly reported by pwCF and is associated with negative effects on health-related outcomes.[1] Therefore, a more comprehensive understanding of the various pain management options suitable for this population is vital to optimizing overall health and quality of life.

In addition to the established indication for treatment of opioid use disorder, buprenorphine is an effective analgesic with growing evidence for equivalent or superior efficacy relative to conventional opioids; furthermore, it is indicated, in other formulations, by the US Food and Drug Administration for chronic pain management.[4] As a partial opioid agonist, buprenorphine carries a lower risk of opioid-related adverse effects; of particular interest for pwCF is the lower risk of respiratory depression, immunosuppression, constipation, and fractures.[4,5] The partial agonist effect and inclusion of naloxone are also important in the context of potential opioid misuse; in a study involving 148 adults with CF, 10% of individuals were found to have documentation of problematic opiate use more than once in their electronic chart.[6] Furthermore, the SL formulation offers an option for those who, like this patient, experience erratic absorption from their gut. The more gradual dissociation from the mu-opioid receptors and the prolonged half-life of buprenorphine relative to other opioids reduce the risk of withdrawal symptoms between doses and in those wishing to taper.[4] Of note, the duration of analgesic effect may be shorter than the terminal half-life,[7] and patients often benefit from divided doses for pain management. In this case, the patient used both once-daily and twice-daily dosing at various times while taking buprenorphine/naloxone.

CONCLUSION

Pain and long-term opioid use are important concerns in pwCF. This case highlights that opportunities for optimizing chronic pain management exist for pwCF and that buprenorphine/naloxone presents a unique treatment option for consideration in patients requiring opiates for pain management. Given that these findings are limited to a single descriptive case, further research is required to identify optimal pain management strategies in pwCF and to evaluate clinical outcomes with buprenorphine/naloxone in this population.

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