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On-Demand Clinical News

Management of Hepatic Encephalopathy in Hospice and Palliative Care

By: Brett Gillis, PharmD, RPh

Liver damage that progresses over time results in a terminal condition known as end-stage liver disease or chronic liver failure. Cirrhosis, or scarring of liver tissue, is a common end point in patients with advanced liver disease from which serious complications stem in end-of-life care. One of these complications, hepatic encephalopathy, is particularly burdensome for patients and families

Hepatic encephalopathy is a brain dysfunction that occurs as a result of hepatic dysfunction. It is a complex neuropsychiatric syndrome marked by personality and mental status changes, intellectual impairment, and/or physical dysfunction that varies greatly in occurrence and intensity. Some patients present with only mild forgetfulness, while others may experience severe movement dysfunction and coma. Asterixis, or shaking of the hands or arms, is the hallmark sign of overt hepatic encephalopathy (see Figure 1).

Figure 1: Common Signs and Symptoms of Hepatic Encephalopathy

Common Signs and Symptoms of HE

Mental	**Physical**
Confusion	Changes in sleep pattern
Shortened attention span	Difficulty with hand movements
Forgetfulness	Musty breath
Mood swings	Sweet breath
Personality changes	Slurred speech
Inappropriate behavior	Jumbled speech
Difficulty with basic arithmetic	Slowed movement
Fearfulness	Asterixis (Shaking or flapping of hands or arms)
Disorientation	Coma

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Tapering Off Opioids In the Hospice and Palliative Care Population

By: Kristin Speer BCPS, RPh, Pharm.D.

On occasion, in hospice and palliative care, you may encounter a patient who is not responding well to opioids. Maybe they are having intolerable adverse effects or are suffering from opioid induced toxicities from high doses. Unfortunately, some patients, family members, or caregivers abuse and divert opioids. There can be several different reasons for withdrawing or tapering off opioids.

How should the clinician generally approach tapering?

We will review several concepts and methods here, but the short answer is: many methods and protocols exist, but high-quality evidence for tapering opioids is lacking. Every case must be individualized.

The first step in approaching an opioid taper is to consider the reason for discontinuation, and the amount of opioid being taken. These factors will influence the rate of the taper. For example, if taking very high doses, a too-rapid taper may cause withdrawal or drug seeking (however, we will discuss below how relatively fast tapers from high opioid doses are still possible without causing significant withdrawal symptoms). Another example: if diversion is the reason for going off opioids, the opioids should be discontinued immediately.

Before constructing the taper, be sure to check for pharmacy benefit coverage limitations, availability of specific opioid products, and strengths at the local pharmacy.

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Flexibility may be needed. Hospice clinical pharmacists can help significantly with determining an appropriate and cost-effective opioid formulation, route, and tapering schedule.

If the patient is using several opioids, consider consolidating them into a single long-acting formulation to make the taper easier to manage. Try to choose a product that offers small dosing increments to facilitate a slow taper. Fentanyl patches can be tricky, but they can be tapered in decrements of 12 mcg/hr or switched to a long-acting oral formulation of another opioid such as methadone or morphine ER. Once initiated, adjust the taper based on response, such as appearance of withdrawal symptoms. A short-acting formulation can be used once the lowest dose of the long-acting formulation is reached.

Some patients may be a higher risk of failure for tapering off. These might include patients on very high doses, those who have a substance use disorder, active psychiatric disorder, previous outpatient taper failure, or benzodiazepine use. Consider specialist referral for these patients at a higher risk of failure. Consider also consulting a hospice, palliative care, or pain-certified pharmacist; they are experts who can help manage complex pain and opioid patients. Please note that if benzodiazepine discontinuation is also indicated, opioids should be discontinued first.

How fast and by how much should we reduce the opioid?

As mentioned previously, it usually depends on the reason you are tapering your patient off, and how much they are taking. Typically, in cases of severe adverse effects, overdose, or substance abuse disorders, the taper should be quicker, over about two to three weeks. In most other cases, consider tapering every week by up to 10% of the original total daily dose. An even slower taper (such as 10% every two to four weeks) may be needed for patients who have been taking opioids for years and/or at very high doses.

However, the clinician should know that rapid tapers are possible without causing significant withdrawal symptoms, when it's indicated and necessary – even at higher opioid doses. High opioid doses may be able to be tapered rapidly (such as 25% to 50% every few days) until reaching about 60 mg to 80 mg of morphine or its equivalent per day. Then the rate can and should be slowed - reducing by about 10% of the original dose, per week, to prevent withdrawal. Based on some evidence, the minimum dose to prevent withdrawal may be only 25% of the previous day's dose.

How should you monitor your patient?

Check pain control and functional status at each visit. Speaking of pain control, a common belief or expectation is that patients will experience pain when the opioid is tapered down. However, patients being tapered due to lack of efficacy may or may not experience a worsening of pain. For example, in a veterans population (n = 50) that was being tapered off opioids for reasons other than aberrant behaviors, 70% of patients had no change or less pain vs baseline, despite a 46% average dose reduction. Increased pain is an early withdrawal symptom from the opioid dose reduction, and it is not a sign that the opioid was or had been effective for the patient's pain. Pain as a withdrawal symptom should resolve after the first week, and can be managed with non-opioid analgesics and non-pharmacologic measures, which are discussed more below.

Continue to monitor for other symptoms of withdrawal; these will look like flu-like symptoms, insomnia, anxiety, abdominal cramps and other GI symptoms, goose bumps, fatigue, and/or malaise. If these occur, manage the specific symptoms, and slow your taper schedule. Do not increase the opioid dose to manage these symptoms; this is called "backpedaling", and defeats the purpose and goals of care. Pharmacotherapy for the management of these symptoms is discussed more below.

How can withdrawal symptoms be managed?

Medications can be used if there are no clinical contraindications, and should be used alongside non-pharmacologic methods, or when non-pharmacologic methods are not fully effective

For malaise and myalgias, acetaminophen or NSAIDs like ibuprofen can be given. For nausea, ondansetron, promethazine or prochlorperazine can be used. Insomnia and anxiety can be managed with trazodone or hydroxyzine. Hydroxyzine can also be used as needed for lacrimation (excessive tearing from the eyes), and for rhinorrhea (or runny nose).

When it comes to opioid tapering, the bottom line is that it is a highly individualized process that can be done relatively quickly or slowly, but successfully. Use your resources and interdisciplinary team members to help construct a successful opioid taper. Regular follow up and monitoring of the patient are also key.

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Since the liver is unable to convert ammonia to urea for excretion from the body, it results in build-up and is the primary toxin implicated in hepatic encephalopathy. Increased ammonia levels disrupt the neurochemical balance and function of the brain. Hepatic encephalopathy is generally associated with a precipitating factor. Common precipitating factors of hepatic encephalopathy include (but not limited to): dehydration/hypovolemia, electrolyte disturbance, metabolic acidosis, hypoxia, hypoglycemia, medications, infection, hepatocellular carcinoma and/or vascular occlusion.

The preferred treatment approach to managing hepatic encephalopathy includes: eliminating or managing underlying or precipitating factors, implementing non-pharmacological (lifestyle) interventions, and then pharmacotherapy and supportive care. Even though medications are a mainstay of treatment for hepatic encephalopathy, it should be noted that certain medications may cause or contribute to the condition. Isoniazid was the first medication to be attributed to precipitating hepatic encephalopathy. Since then, medications including: benzodiazepines, opioids, antidepressants, and anti-seizure medications have been implicated. While many of these medications cannot be avoided, it is recommended to give the lowest effective dose and consider alternatives whenever feasible. If the precipitating factor(s) cannot be eliminated or managed and lifestyle modifications are unsuccessful, pharmacotherapy should then be considered.

Pharmacotherapy for hepatic encephalopathy targets increasing bowel motility to increase excretion of ammonia and/or decrease the production of ammonia. Since ammonia is initially produced by GI bacteria, the medications used to treat hepatic encephalopathy are believed to mediate ammonia in the GI tract. Lactulose, an osmotic laxative, is first-line due to its record of safety and efficacy in clinical practice and low cost. It is important to note that lactulose should be titrated to achieve two to three soft bowel movements per day or an adequate dose to manage symptoms. Second-line agents, antimicrobials such as neomycin, metronidazole, and vancomycin, work to suppress bacterial load and reduce bacterial toxin production. Neomycin is generally the best tolerated and most commonly prescribed antimicrobial for the management of hepatic encephalopathy in hospice and palliative care. If lactulose and/or neomycin are ineffective or not tolerated, then rifaximin (Xifaxan) may be considered as a third-line agent in combination with lactulose (or alone if lactulose has not been tolerated). Rifaximin is generally well tolerated, but its high cost and the lack of strong clinical comparative trials continue to favor use of lactulose and neomycin.

HE is a common manifestation in end-stage liver disease. Consider safety, efficacy and cost when managing HE at end of life. With these factors in mind, lactulose is the mainstay of treatment.

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