

**Lisa Edgerton,**  
PharmD, BCPS, CPP  
New Hanover Regional  
Medical Center Residency  
in Family Medicine,  
Wilmington, NC

**Bridget Loven, MLIS**  
AHEC Library, Carolinas  
Healthcare System,  
Charlotte, NC

**ASSISTANT EDITOR**

**Anne L. Mounsey, MD**  
University of North Carolina,  
Chapel Hill

## Q / What are the adverse effects of prolonged opioid use in patients with chronic pain?

### EVIDENCE-BASED ANSWER

**A / CONSTIPATION, NAUSEA, AND DYSPEPSIA** are the most common long-term adverse effects of chronic opioid use (strength of recommendation [SOR]: **B**, systematic review of low-quality studies). Men may experience depression, fatigue, and sexual dysfunction (SOR: **B**, 2 observational studies). Prolonged use of opioids also may increase sensitivity to pain (SOR: **C**, review of case reports and case series).

(This review does not address drug seeking or drug escalating.)

Patients on long-term methadone are at risk for cardiac arrhythmias caused by prolonged QT intervals and torsades de pointes (SOR: **C**, case reports).

Patients taking buprenorphine for opioid dependence may experience acute hepatitis (SOR: **C**, 1 case report).

### Evidence summary

Chronic pain is usually defined as pain persisting longer than 3 months. Evidence of the efficacy of opioids for noncancer pain has led to increased opioid prescribing over the past 20 years and with it, growing concern about adverse effects from long-term use.<sup>1</sup>

#### Nausea, constipation, dyspepsia lead side-effects parade

A Cochrane systematic review of 26 studies (25 observational studies and 1 randomized controlled trial [RCT]) of adults who had taken opioids for noncancer pain for at least 6 months assessed the adverse effects of long-term opioid therapy.<sup>2</sup> Although the authors couldn't quantify the incidence of adverse effects because of inconsistent reporting and definition of effects, they stated that the most common complications were nausea, constipation, and dyspepsia. The review found that 22.9% of patients (95% confidence interval [CI], 15.3-32.8) discontinued oral opioids because of adverse effects.

A cross-sectional observational study

evaluated self-reported adverse effects in 889 patients who received opioid therapy for noncancer pain lasting at least 3 months.<sup>3</sup> Forty percent of patients reported constipation and 18% sexual dysfunction. Patients taking opioids daily experienced more constipation than patients taking the drugs intermittently (39% vs 24%; number needed to harm [NNH]=7;  $P<.05$ ).

#### Sexual dysfunction, fatigue, depression aren't far behind

A case-control study of 20 male cancer survivors with neuropathic pain who took 200 mg of morphine-equivalent daily for a year found that 90% of patients in the opioid group experienced hypogonadism with symptoms of sexual dysfunction, fatigue, and depression, compared with 40% of the 20 controls (NNH=2; 95% CI, 1-5).<sup>4</sup>

A case-controlled observational study of 54 men with noncancer pain who took opioids for 1 year found that 39 of 45 men who had normal erectile function before opioid therapy reported severe erectile dysfunction

while taking the drugs.<sup>5</sup> Levels of testosterone and estradiol were significantly lower ( $P<.0001$ ) in the men taking opioids than the 27 opioid-free controls.

### Potentially fatal arrhythmias are a risk for some patients

From 1969 to 2002, 59 cases of QT prolongation or torsades de pointes in methadone users, 5 (8.5%) of them fatal, were reported to the US Food and Drug Administration's Medwatch Database.<sup>6</sup> The mean daily methadone dose was 410 mg (median dose 345 mg, range 29-1680 mg). Length of therapy was not reported. In 44 (75%) of reported cases, patients had other known risks for QT prolongation or torsades de pointes, including female sex, interacting medications, potassium or magnesium abnormalities, and structural heart disease.

### Buprenorphine may cause acute hepatitis

No apparent long-term hepatic adverse effects are associated with chronic opioid use. However, a 2004 case series described acute cytolytic hepatitis in 7 patients taking buprenorphine, all with hepatitis C and a history of intravenous drug abuse.<sup>7</sup> Acute symptoms resolved quickly in all cases, and only 3 patients required a reduction in buprenorphine dosage.

### Prolonged use may increase sensitivity to pain

Case reports and case series have found that prolonged use of opioids causes increased sensitivity to pain in some patients, which is difficult to differentiate from opioid tolerance.<sup>8</sup>

### Recommendations

The American Pain Society (APS) recommends anticipating, identifying, and treating opioid-related adverse effects such as constipation or nausea.<sup>1</sup> APS advises against using opioid antagonists to prevent or treat bowel dysfunction, and encourages older patients or patients with an increased risk of developing constipation to start a bowel regimen. Patients with complaints suggesting hypogonadism should be tested for hormonal deficiencies.

The Center for Substance Abuse and Treatment recommends obtaining a cardiac history and an electrocardiogram (EKG) on all patients before starting methadone and repeating the EKG at 30 days and annually thereafter to evaluate for QT prolongation.<sup>9</sup> Prescribers should also warn patients of the risk of methadone-induced arrhythmias and be aware of interacting medications that prolong the QT interval or reduce methadone elimination.

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Patients on long-term methadone are at risk for cardiac arrhythmias caused by prolonged QT intervals and torsades de pointes.

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