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## Things We Do for No Reason™: Avoiding methadone for opioid withdrawal

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The “Things We Do for No Reason” series reviews practices, which have become common parts of hospital care, may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent “black and white” conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

### CLINICAL SCENARIO

A 37-year-old woman with opioid use disorder (OUD) hospitalized for cellulitis shares that she injects 1 g of fentanyl daily. She fears starting buprenorphine due to precipitated withdrawal and asks for methadone. Instead, the hospitalist starts her on 10 mg of oxycodone every 4 h. On hospital Day 2, she self-discharges.

### WHY HOSPITALISTS AVOID OFFERING METHADONE FOR OPIOID WITHDRAWAL

Methadone, buprenorphine, and extended-release naltrexone are the three Food and Drug Administration (FDA) approved medications for OUD. Methadone is a schedule II-controlled substance and in US ambulatory settings, only Opioid Treatment Programs (OTPs) can dispense methadone—with few exceptions.<sup>1</sup> Strict ambulatory regulations

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#### CONFLICT OF INTEREST STATEMENT

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contribute to misconceptions about methadone's legality for opioid withdrawal treatment during hospitalization.

Methadone's pharmacology leads to concerns about patient safety. It is a long-acting opioid agonist, peaks at 3–4 h, has a half-life of 24 h, and reaches a steady state at 3–7 days.<sup>1</sup> It requires a specific titration so that dose-stacking, oversedation, and overdose do not occur.<sup>1</sup> Since the cytochrome P450 3A4 (CYP3A4) pathway primarily metabolizes methadone, its levels can increase or decrease in the setting of CYP3A4 inhibitors and inducers.<sup>1</sup> Methadone can also cause QTc prolongation at higher doses (>100 mg/day) or in combination with other QTc prolonging medications.<sup>1</sup>

Hospitalists also avoid methadone due to lack of addiction training and stigma toward patients with addiction.<sup>2,3</sup> These reasons for avoiding methadone compound and result in hospitalists ignoring addiction, viewing it as outside the scope of hospital medicine, or leaving it to specialists to address resulting in low overall rates of treatment during hospitalization.<sup>3–7</sup>

## **WHY HOSPITALISTS SHOULD OFFER METHADONE FOR OPIOID WITHDRAWAL**

More than 50 years of data demonstrate that methadone is safe and effective when titrated appropriately.<sup>1</sup> Hospitalists can legally provide methadone for opioid withdrawal per 1306.07 Code of Federal Regulations.<sup>8</sup> This code states that hospitalized patients can be “administered or dispensed opioids for maintenance or detoxification as an adjunct to a condition other than addiction.”<sup>8</sup> In other words, hospitalists can start, continue, and titrate methadone and other opioids for opioid withdrawal when patients are hospitalized for a primary condition other than a substance use disorder (e.g., cellulitis, heart failure, high-risk pregnancy).

Methadone is a life-saving medication that reduces overdose and all-cause mortality.<sup>9,10</sup> It is associated with decreased acute care utilization and, by treating opioid withdrawal, a lower risk of self-discharges.<sup>7,10</sup> Methadone should be offered for withdrawal management regardless of a patient's desire or ability to continue it after hospitalization.<sup>11</sup> In addition to treating and preventing withdrawal, prescribing methadone during hospitalization offers an opportunity to initiate OUD treatment. Patients started on methadone for OUD are more than twice as likely to present to an OTP after discharge.<sup>12</sup> Even when patients are ambivalent about continuing methadone after discharge, their readiness to engage in outpatient treatment likely increases as they achieve relief of withdrawal. However, only 15% of people with OUD receive OUD treatment during admission.<sup>5</sup>

Without treatment, patients may use unprescribed opioids to manage withdrawal symptoms and self-discharge before completing medical treatment, increasing mortality and risk for rehospitalization. In one study, more than 40% of individuals who used drugs reported unprescribed substance use during hospitalization.<sup>6</sup> Opioid agonists, like methadone, treat opioid withdrawal and may decrease in-hospital substance use while improving trust.<sup>2</sup>

Methadone, in addition to being OUD treatment, offers important advantages to other full-agonist opioids in withdrawal treatment. This includes methadone's analgesic and long-acting properties, which we can leverage by splitting dosing to treat both acute pain and withdrawal. In addition, compared with a partial opioid agonist like buprenorphine, situations when patients may prefer methadone over buprenorphine include: (1) previous buprenorphine-induced precipitated withdrawal; (2) regular fentanyl use, which may increase the risk of precipitated withdrawal with buprenorphine initiation; (3) methadone's full opioid agonism; and (4) acute pain.<sup>13</sup>

## WHEN HOSPITALISTS SHOULD AVOID OFFERING METHADONE FOR OPIOID WITHDRAWAL

Patient preference should guide opioid withdrawal treatment. Some patients may prefer buprenorphine for withdrawal when they want to continue OUD treatment after discharge given variable geographical availability of methadone and strict methadone regulations requiring frequent OTP visits which makes methadone adherence challenging.<sup>14</sup> Weighing the risks and benefits through shared decision-making can help patients determine the best treatment option.

When the QTc (>500 ms) is prolonged, hospitalists should replete electrolytes, limit nonessential QTc prolonging medications, reassess the QTc, and discuss the risks, benefits, and alternatives to methadone, including buprenorphine and other opioid agonists (e.g., oxycodone, hydromorphone) for opioid withdrawal.<sup>15</sup> Hospitalized patients may have metabolic derangements or require medications that prolong the QTc and these should be addressed and discussed with the patient when selecting opioid withdrawal treatment. In one study, the methadone dose was only weakly associated with QTc prolongation and not associated with cardiac events.<sup>16</sup>

When optimized, methadone should not sedate patients. However, individuals with conditions affecting respiratory drive (e.g., advanced chronic obstructive pulmonary disease) or methadone metabolism (e.g., end stage renal disease, end stage liver disease) may not tolerate methadone due to sedation. In these instances, hospitalists should also discuss risks, benefits, and alternatives with patients.

## WHAT WE SHOULD DO

We should assess patients for risk of opioid withdrawal and offer and initiate evidence-based treatment, including methadone, in patients who select it.<sup>11</sup> For patients without a formal OUD diagnosis who want to continue methadone after discharge, confirm the diagnosis using the *Diagnostic Statistical Manual of Mental Disorders, 5th edition*. Start and titrate methadone (Table 1) when patients endorse early opioid withdrawal symptoms after confirming they have opioid tolerance and are not actively sedated.<sup>1</sup> Because methadone is a full opioid agonist and can be initiated before withdrawal develops it is unnecessary to obtain a Clinical Opioid Withdrawal Scale (COWS) score when starting it. We should also offer adjunctive medications (e.g., clonidine, loperamide, and ondansetron) for withdrawal, though these do not address the underlying pathophysiology of opioid withdrawal and

insufficiently mitigate symptoms.<sup>17</sup> Clinicians should recognize that patients using fentanyl or other potent synthetic opioids may have high tolerance and need higher doses of opioid agonists, including methadone, to alleviate withdrawal.<sup>18</sup> When patients decline methadone or buprenorphine for opioid withdrawal, their opioid withdrawal symptoms or pain are not controlled on methadone or buprenorphine alone, or they are undergoing low-dose buprenorphine initiation, hospitalists can offer alternative opioid agonists (e.g., oxycodone, hydromorphone) during hospitalization though we cannot prescribe these medications for withdrawal at discharge.<sup>15</sup>

When a patient already receives methadone for OUD at an OTP, confirm their dosing information with the methadone clinic and continue it. If a patient missed doses, the OTP can guide methadone dosing, unless an addiction consultation team can provide recommendations.

In cases where patients prefer methadone and the QTc remains prolonged after addressing intervenable causes, hospitalists should communicate with outpatient clinicians and the OTP, document the risk-benefit conversation, and consider more slowly titrating methadone while monitoring the QTc if the patient is stable.

CYP3A4 interactions are not contraindications to methadone, and guidance from a pharmacist can aid in a safe titration plan. We can initiate methadone even if patients are unsure about continuing it after discharge or may want to switch to buprenorphine later. When patients want to continue methadone after discharge, connect them to an OTP, if available. Hospitals can partner with OTPs to directly admit patients and support rapid treatment access. Hospitalists can also request an exception to 1306.07(b) Code of Federal Regulations to dispense methadone for up to 3 days to patients with opioid withdrawal newly started on methadone who want to continue it after discharge while they connect to an OTP.<sup>8</sup> Offer all patients naloxone and harm reduction as part of overdose prevention.<sup>19</sup>

## RECOMMENDATIONS

1. Assess patients for opioid withdrawal and offer and initiate evidence-based treatment, using shared decision making, regardless of a patient's plan to disrupt opioid use or continue treatment after discharge.
2. When patients prefer methadone titrate it appropriately (Table 1) recognizing that dosing guidelines may not reflect patient needs in the setting of potent opioids (e.g., fentanyl).
3. Offer adjunctive medications (e.g., clonidine, loperamide, and ondansetron) in addition to opioid agonist therapy to mitigate opioid withdrawal symptoms.
4. Link patients who want to continue methadone to local OTPs on discharge. If there is no accessible OTP, discuss risks, benefits, and alternatives to methadone.
5. Prescribe naloxone and discuss harm reduction as part of overdose prevention.

## CONCLUSION

With our worsening addiction epidemic and increasing overdose deaths, hospitalizations involving addiction are rising.<sup>20</sup> As hospitalists, we can do our part to address this crisis by offering and initiating evidence-based opioid withdrawal treatment.

Returning to our case, the patient presents to another hospital a week later with uncomplicated bacteremia. The hospitalist begins methadone and titrates it to alleviate withdrawal symptoms. The patient completes hospitalization and follows up at a local OTP to continue methadone after discharge.

What do you do? Do you think this is a low-value practice? Is this truly a “Thing We Do for No Reason™”? Let us know what you do in your practice and propose ideas for other “Things We Do for No Reason™” topics. Please join in the conversation online at Twitter (#TWFNDR)/Facebook and don’t forget to “Like It” on Facebook or retweet it on Twitter.

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Methadone initiation and titration guideline for hospitalized patients with opioid withdrawal.

TABLE 1

Day 1	Initiate methadone at 20–30 mg, unless there is concern for oversedation. Give up to 10 mg every 4 h as needed for opioid withdrawal or cravings. Traditionally, 40 mg has been the maximum total daily dose on Day 1; however, patients using fentanyl commonly need higher doses.
Day 2	Start with the total methadone dose you prescribed on Day 1 and give up to 10 mg every 4 h as needed for opioid withdrawal or cravings. Traditionally, 50 mg has been the maximum total daily dose on Day 2; however, patients using fentanyl commonly need higher doses.
Day 3	Start with the total methadone dose you prescribed on Day 2 and give up to 10 mg every 4 h as needed for opioid withdrawal or cravings. Traditionally, 60 mg has been the maximum total daily dose on Day 3; however, patients using fentanyl commonly need higher doses.
Day 4 and beyond	Start with the total methadone dose on Day 3. Uptitrate until patients reach 60 mg or stop at a lower dose based on relief of withdrawal, cravings, and patient preference. Traditionally, we have waited 72 h after reaching 60 mg/day to allow methadone to reach steady state. However, patients using fentanyl may need faster up-titration to effectively manage withdrawal and cravings.

*Note:* This table is adapted from OTP guidelines for OUD and opioid withdrawal management primarily developed for patients with pill- and heroin-based OUD.<sup>1</sup> Methadone titration guidelines are rapidly evolving due to increased opioid tolerance in patients who use potent opioids, including fentanyl.<sup>18</sup> Many patients may need more rapid methadone titrations and/or additional opioid agonists to relieve opioid withdrawal. In these instances, hospitalists can involve an addiction consultant if possible. When patients have acute pain, consider splitting the methadone dose to leverage methadone’s analgesic effects. However, consolidate methadone prior to discharge as most patients cannot continue split dosing at an OTP.

Abbreviations: OTP, Opioid Treatment Program; OUD, opioid use disorder.