Published in final edited form as:

J Addict Behav Ther Rehabil. 2015 ; 4(2): . doi:10.4172/2324-9005.1000138.

Managing Opioid Use Disorder During and After Acute Hospitalization: A Case-Based Review Clarifying Methadone Regulation for Acute Care Settings

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Abstract

Objective—Treatment with an opioid agonist such as methadone or buprenorphine is the standard of care for opioid use disorder. Persons with opioid use disorder are frequently hospitalized, and may be undertreated due to provider misinformation regarding the legality of prescribing methadone for inpatients. Using a case-based review, this article aims to describe effective management of active opioid withdrawal and ongoing opioid use disorder using methadone or buprenorphine among acutely ill, hospitalized patients.

Methods—We reviewed pertinent medical and legal literature and consulted with national legal experts regarding methadone for opioid withdrawal and opioid maintenance therapy in hospitalized, general medical and surgical patients, and describe a real-life example of successful implementation of inpatient methadone for these purposes.

Results—Patients with opioid use disorders can be effectively and legally initiated on methadone maintenance therapy or buprenorphine during an inpatient hospitalization by clinical providers and successfully transitioned to an outpatient methadone maintenance or buprenorphine clinic after discharge for ongoing treatment.

Conclusions—Inpatient methadone or buprenorphine prescribing is safe and evidence-based, and can be used to effectively treat opioid withdrawal and also serves as a bridge to outpatient treatment of opioid use disorders.

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Financial Disclosures: The authors have no relevant financial interests to disclose.

Why is it Important that Providers Understand the Use of Methadone in Acute Care Settings?

In 2013, 681,000 Americans used heroin and 1.5 million adults used prescription opiates for nonmedical purposes [1]. Many of these individuals present to the emergency room (ER) with opioid-related and unrelated issues, and are oftentimes hospitalized. In the hospital setting, patients with an opioid use disorder fear stigma and poor care. They are more likely to leave against medical advice (AMA), and face a high risk of death following discharge [2–7]. Providers often face challenges when caring for patients with an opioid use disorder who are hospitalized for an acute medical illness. Treatment with an opioid agonist medication, such as methadone or buprenorphine, is the most evidence-based approach to manage opioid use disorders [8–11] and opioid withdrawal symptoms. Providers' lack of familiarity with the regulations regarding inpatient prescription of methadone to treat opioid withdrawal and manage opioid use disorder represents sub-standard inpatient care for this high-risk population and drives a culture of avoidance in addressing highly prevalent opioid use disorders among patients in hospitals across the nation.

Establishing the diagnosis of an opioid use disorder is an important first step in management, although providers should be careful not to allow this step to be prohibitive to the provision of safe and humane patient care. Differentiating an opioid use disorder from physiologic dependence, as in the case of prescribed opioids for chronic pain, can be done readily using DSM-5 criteria for opioid use disorder as a guide. The following case illustrates the clinical utility of inpatient methadone use and is followed by a discussion of the principles of methadone prescribing in the inpatient setting.

Ms. Smith is a 40 year-old woman with Acquired Immunodeficiency Syndrome (AIDS), hepatitis C, and current injection drug use (IDU), who had multiple recent admissions for cellulitis and fever. During each of the patient's prior several admissions she required 2 mg of oral hydromorphone every three to four hours to adequately control her pain. She left several previous admissions against medical advice, often in the setting of potentially life-threatening illness, due to uncontrolled pain and opioid withdrawal. She re-presented to the emergency department with low back pain, fever, chills and left upper extremity redness, swelling and pain for three days.

On admission, the patient was found lying in the fetal position, ill-appearing and emaciated. Her temperature was 37.9°Celsius, pulse 82, blood pressure 97/54, and respiratory rate 17 with 100% oxygen saturation on room air. The patient's lungs were clear to auscultation, and no murmurs were detected on cardiac exam. She had an erythematous, swollen, 1.5 centimeter by 1.5 centimeter indurated area located in the right antecubital fossa with surrounding erythema extending to the distal half of the forearm, tender to palpation and slightly warmer than the rest of her arm. The patient had scattered track marks extending up and down both arms. The patient was diagnosed with cellulitis with probable evolving abscess in the antecubital fossa and was admitted to the medicine service for treatment with intravenous antibiotics.

On admission, the inpatient infectious disease service was consulted to assist with further management. The patient was well-known to the attending on the infectious disease consult service as he had been her primary care provider and HIV doctor for over twenty years. She was known to have a fifteen year history of intravenous (IV) heroin use, but had not revealed this to the admitting providers as she did not feel comfortable doing so. She was also smoking 1 pack per day, with a 25 pack-year history, but had no other history of illicit drug or alcohol use. On the patient's second day of admission, the patient's primary care HIV physician compassionately but directly questioned the patient in a non-judgmental manner about ongoing heroin use. The patient hesitantly disclosed the fact that she had been using heroin multiple times daily, felt out of control, and would like to get help with her opioid use disorder (despite having denied use to multiple previous providers). She revealed that she did not disclose this initially out of fear that her hospital care would be compromised, her pain undertreated, and medical professionals would behave differently towards her. She reported that she had "had enough" and expressed interest in initiating methadone to treat her heroin dependence, with which she had had a successful 6 months of sobriety within the recent past.

The patient's primary HIV provider recommended to the medicine and psychiatry consult team that methadone be initiated to treat acute opioid withdrawal. All providers were in agreement that heroin was the driving issue behind most of this patient's underlying comorbidities. Despite advanced illness, ongoing injection drug use contributed to this patient's difficulty taking anti-retrovirals on a daily basis and was the precipitating factor behind several prior hospitalizations and discharges against medical advice. The physician's recommendation to initiate methadone was immediately challenged, citing concerns for legality of newly prescribing methadone while a patient is hospitalized. Other providers involved in Ms. Smith's care expressed fear that such action was illegal unless prescribed at low doses (10 to 30 milligrams) three times daily for the diagnosis of pain rather than acute opioid withdrawal. The infectious disease attending directly addressed these concerns and clarified the issue by referencing key legal documents, including Title 21 of the Code of Federal Regulations (CFR) section 1306.07C [12], after discussing the case with representatives from both the Center for Substance Abuse and Treatment (CSAT) as well as the Drug Enforcement Administration (DEA).

What is the Magnitude of the Opioid Problem on a National Level?

Nationally, both opioid sales and deaths from opioid overdose have been steadily rising since the start of the 21st Century [13,14]. Prescription opioids were involved in 16,651 overdose deaths nationally in 2010 alone [14]. Rates of death due to overdose from prescription opioids have more than quadrupled over the past decade [14]. The Department of Health and Human Services (HHS) has declared prescription-opioid-overdose deaths an epidemic prompting action at the federal, state and local level [15]. HHS has defined four major objectives in order to address the opioid overdose epidemic, including to: 1) provide prescribers with the knowledge to improve prescribing decisions and to identify patients' problems related to opioid use, 2) reduce inappropriate access to opioids, 3) increase access to effective overdose treatment, and 4) provide substance use disorder treatment to persons addicted to opioids [15]. The rising increase in prescription opioid use among non-medical

users has consequently led to a startling increase in heroin use and overdose deaths due to heroin over the past decade [16].

Why is it Important for Providers to Recognize and Treat Hospitalized Patients with Opioid Use Disorders?

Patients with substance use disorders are a particularly vulnerable population. These patients have higher hospitalization rates, more co-morbidities, greater insurance costs, and increased use of medical services than those without substance use disorders (SUD) [17,18]. The risk of drug-related death is increased nearly ten-fold for patients with a SUD in the first month after hospital discharge [19]. Maintenance treatment with an opioid agonist reduces the risk of death from overdose by 50% [20]. In addition, with institution of the affordable care act (ACA) and increasing insurance coverage, the enrollment of opioid dependent patients in treatment programs to address opioid use disorders will likely increase [21,22].

What are the Signs and Symptoms of Acute Opioid Withdrawal and why is this Important to Recognize?

Management of active opioid dependence in a hospitalized, acutely-ill patient can be challenging. A patient's signs and symptoms of opioid withdrawal may overlap with signs and symptoms of other co-morbid conditions. For example, fever can be attributed to bacteremia, pneumonia, infective endocarditis, or cellulitis, but might also be a manifestation of acute opioid withdrawal or intoxication which may be missed by providers who are not considering this diagnosis as a cause for fever. Withdrawal from heroin typically begins 3 to 6 hours after last use and peaks within 36 to 72 hours, thereafter subsiding in 7 to 10 days [23]. Mild withdrawal presents as a flulike syndrome including gastrointestinal, psychological and autonomic symptoms [23]. Moderate to severe withdrawal usually involves restlessness, persistent nausea and vomiting, diarrhea, anxiety, dysphoria and intense cravings [23]. It is critical for providers to recognize withdrawal at this stage, as experiencing this level of withdrawal is frequently referenced as a reason for patients leaving prior to adequate medical therapy in order to self-medicate and abort the symptom complex. When patients are unable to inform providers of their fears of experiencing such symptoms out of fear that they will be judged, treated differentially or be perceived as "drug-seeking", a pivotal opportunity for intervention is lost and may result in an opioid-dependent patient leaving without receiving adequate treatment for potentially life-threatening illnesses.

Signs and symptoms of opioid withdrawal are therefore critical for providers to recognize early in order to provide prompt treatment. Table 1 below depicts the most common signs and symptoms of opioid withdrawal.

Is Prescribing Methadone to Treat Opioid Use Disorder and Associated Withdrawal in the Inpatient Setting Legal?

Methadone is an effective treatment for opioid use disorder and is effective for managing opioid withdrawal in order to facilitate acute inpatient care. The use of methadone for

inpatients with opioid use disorder who are interested in methadone maintenance therapy (MMT) initiation thereafter has many clinical advantages. Methadone treatment manages distressing withdrawal symptoms which can facilitate the effective treatment of acute illnesses, which can be a life-saving clinical decision in the hospital setting. In addition, initiation of methadone to treat opioid use disorders in patients hospitalized for other medical reasons should be considered as part of a comprehensive management plan. As stated previously, it is well-established that patients with active opioid use disorders are at very high risk of adverse events following a hospitalization. According to Title 21 of the Code of Federal Regulations (CFR) section 1306.07 C, "...This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief of cure is possible or none has been found after reasonable efforts," [12].

Thus, methadone can be used to treat both acute withdrawal symptoms to facilitate acute inpatient care and additionally to establish opioid replacement therapy. In the first use, methadone is tapered completely prior to discharge and in the second use the patient is directly linked and accepted by an appropriate provider in the community.

What is an Appropriate Initial Dose of Methadone?

For patients with moderate-to-severe opioid withdrawal symptoms who are not on outpatient methadone maintenance therapy, an initial dose of 20–30 mg of methadone will usually suppress withdrawal symptoms although frequent reassessment for signs of withdrawal is crucial, as overdoses can occur due to methadone's long half-life and unpredictable metabolism. Additional dosing should not occur until a peak level has been reached, around 2–4 hours after the initial dose. The total daily dose on the first day should not exceed 30 mg unless the patient is already on a stable known dose of methadone in the community, in which case the dose can be confirmed by the MMT provider [18,19]. High doses of methadone (40 mg daily or greater) can be particularly dangerous in those with underlying respiratory disease or concomitant benzodiazepine use, placing these patients at particularly high risk of overdose. For this reason, most patients should not be prescribed methadone doses of 40 mg daily at initiation, or if prescribed high doses such as this, patients should have continuous oximetry to monitor oxygenation and have frequent nurse assessments to ensure safety. Alternatively, structured tools such as the Clinical Opiate Withdrawal Scale (COWS) can provide useful guidance to clinicians regarding appropriate dose, dosing interval and frequency of monitoring required during methadone initiation.

Understanding of the unique pharmacology of methadone is critical for providers. The half-life of methadone is 24–36 hours and it takes four to five half-lives for steady state levels to be reached. Rapid dose escalation prior to steady-state levels has been associated with overdose, and the risk of death from overdose is increased in the first two weeks of methadone treatment [24–26].

Initiating methadone in a patient in acute withdrawal with the intention to taper that patient off methadone at discharge is less than ideal, as it is preferable to work with the patient to encourage a care plan that facilitates effective long-term opioid use disorder treatment. However, methadone may be the only option to manage acute opioid withdrawal in which case this may be the most humane option for management of acute withdrawal. If necessary, methadone can be safely tapered at a rate of decrease of 10 mg to 20 mg daily prior to discharge in select patients. In many cases, methadone should be continued as treatment for opioid use disorder after hospital discharge in interested patients, although this requires clinical providers to arrange for direct transfer to a community methadone maintenance program [12,27] after discharge.

What Other Opioid Agonists are Available to Treat Opioid Withdrawal?

Methadone is not the only medication available to providers to treat acute opioid withdrawal while hospitalized. Because methadone is metabolized by the CYP-450 enzyme system in the liver, caution must be used in severe liver disease and with many co-inducers such as antiretrovirals (efavirenz, nevirapine, ritonavir, lopinavir) and anticonvulsants (carbamazepine, phenytoin) among others (Table 2) [23]. Buprenorphine, a partial opioid agonist, is another medication that can be used to treat opioid withdrawal. Buprenorphine is available as a sublingual formulation (Subutex©) alone and in combination with naloxone, an opioid antagonist (Suboxone). This medication should only be used when the patient is in active withdrawal, to avoid precipitating an acute opioid withdrawal syndrome. Initial starting doses are typically 4 to 8 mg per day, and are then tapered over several days. The advantage to buprenorphine is that this medication can be continued as an outpatient by waived providers and has been shown to result in a shorter duration of withdrawal [28]. Waivered providers are physicians who have completed training in order to obtain a government issued waiver via special registration requirements in the Controlled Substances Act for provision of medication-assisted opioid therapy with Schedule III, IV or V narcotic medications specifically approved by the Food and Drug Administration (FDA) [29]. However, any physician can prescribe buprenorphine in the acute care setting for withdrawal. A meta-analysis comparing detoxification with methadone, buprenorphine, or clonidine determined that methadone or buprenorphine were the most effective at managing withdrawal symptoms [28].

What Should Providers Discuss with Patients Prior to Offering Opioid Agonist Treatment and Linkage to Community Based Follow-Up?

Before proceeding with methadone initiation for post-hospital maintenance, providers must discuss the appropriateness of methadone maintenance therapy with the patient. Important topics for discussion include: the diagnosis and duration of opioid use disorder, feasibility of daily outpatient follow-up at a methadone maintenance clinic, insurance coverage or method(s) of payment for methadone, transportation to and from the clinic, the benefits and risks of methadone maintenance versus alternative therapies, side effects of methadone, and any other perceived limitations or risk to methadone maintenance therapy. If a clinician and patient together decide that methadone maintenance therapy is a favorable option for treatment of opioid use disorder, then the clinician may legally decide to initiate low-dose

methadone (20–30 mg daily) while making arrangements for outpatient transfer to a methadone clinic immediately after discharge.

Back to the Case

After reviewing the federal regulations in addition to the local hospital policy, the patient's primary care HIV physician concluded that administration of methadone (but not prescription for her to take away with her after discharge) is entirely legal by federal regulation. He successfully advocated for the patient to begin methadone at a dose of 20 mg daily to treat her acute withdrawal symptoms while she remained inpatient, and arranged for her to follow-up at a community-based methadone clinic at the time of discharge for ongoing maintenance. The patient remained hospitalized for the entire treatment duration, with substantial improvement in her right arm cellulitis and resolution of fever, and antiretroviral medications were reinitiated. Her pain was well-controlled throughout the remainder of her admission after methadone initiation. She was successfully discharged with follow-up at the local methadone maintenance program. Ms. Smith was evaluated in follow-up after discharge by her primary HIV provider, and was noted to be doing well on ARV therapy and free of heroin on methadone therapy.

Why Should Providers Identify and Appropriately Manage Opioid Use Disorders during an Inpatient Hospitalization?

Opioid use disorder is a treatable condition that results in tremendous cost, morbidity, and mortality when not addressed. Outpatient visits are not always a feasible avenue to reach high-risk patients with opioid use disorders. Methadone treatment is available in sixty-five countries around the world [30]. An estimated 2.1 persons per 100,000 throughout the United States are receiving methadone from a non-opioid treatment program provider [31]. A total of 660 detoxification programs and 547 hospitals throughout the US routinely prescribe methadone for the treatment of acute opioid withdrawal and/or opioid use disorder [32]. Prescribing methadone for hospitalized patients with opioid use disorders to treat acute withdrawal and for maintenance therapy is not only legal but also entirely appropriate, as opioid agonists, buprenorphine and methadone, are the most effective treatments we have to treat opioid use disorders. Not only does methadone treat potentially life-threatening conditions in this population, but it may also serve as a bridge to recovery in collaboration with the treating clinician by encouraging the establishment of a plan for long-term management of opioid use disorder after discharge. This is a humane and compassionate approach to clinical situations such as that described above, among the myriad of options. Clinicians must learn to recognize these “teachable moments” in hospitalized patients with opioid use disorders, where options for maintenance therapy can be discussed and an individualized plan for recovery established.

What are the Key Factors in Managing Opioid Use Disorders in Hospitalized Patients?

Cornerstones to effective management of active opioid withdrawal and ongoing opioid dependence among acutely ill, hospitalized patients include:

1. Establish a diagnosis of opioid use disorder (versus physiologic dependence) and discuss the implications of this diagnosis with the patient.
2. Create a trusting, open, mutually respectful doctor-patient relationship, wherein which the patient does not fear differential treatment after disclosing an opioid use disorder,
3. Recognize acute opioid withdrawal in the acutely ill, hospitalized patient, and utilize hospitalization as an opportunity to engage patients, initiate treatment, and provide linkage to ongoing care,
4. Formulate a therapeutic alliance with hospitalized patients with opioid use disorder and the entire care team about goals of management of acute withdrawal and pain control, as well as a long-term management plan for the patient's addiction,
5. Educate providers on federal, state, and hospital policies regarding available options for the management of acute opioid withdrawal symptoms in patients with opioid use disorder, so as to reduce fears about litigation and to minimize providers' avoidance in addressing this pivotal issue head-on,
6. Familiarize providers with available medications to treat acute opioid withdrawal in hospitalized patients and their common side effects (methadone, buprenorphine, among other symptoms-related medications).

Acknowledgement

This work was supported by NIH grants K24 DA022112 and P30 AI042853.

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Table 1

Common Signs and Symptoms of Opioid Withdrawal.

Signs	Symptoms
Diaphoresis	Abdominal cramps
Diarrhea	Anxiety
Fever	Arthralgia, myalgia
Hypertension	Craving
Insomnia	Irritability
Lacrimation	Nausea
Mydriasis	Restlessness
Piloerection	
Rhinorrhea	
Tachycardia	
Vomiting	
Yawning	

Source: O'Connor PG, Samet JH, Stein MD. Management of hospitalized intravenous drug users:role of the internist. Am J Med.1994;96:551–556.

Table 2

Effect of selected medications on methadone.

Decreasing methadone effect
Carbamazepine, phenytoin
Efavirenz, nevirapine
Lopinavir/ritonavir
Rifampin
Increasing methadone effect
Azoles
Macrolides
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Tricyclic antidepressants

Source: Methadone hydrochloride injection, USP [package insert]. Newport, Ky: Xanodyne Pharmaceuticals; 2006.

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