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Point/counterpoint: Should full agonist opioid medications be offered to hospitalized patients for management of opioid withdrawal?

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POINT/COUNTERPOINT

Should full agonist opioid medications be offered to hospitalized patients for management of opioid withdrawal?

POINT

Opioid Agonist Therapy for Hospitalized Patients with Opioid Use Disorder: An Alternate Treatment Pathway

Drs. Stern, D'Orazio, and Work

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

In the setting of the ongoing national overdose crisis,[1] there is an urgent need for novel approaches to quality and compassionate patient care. People with opioid use disorder (OUD) are frequently hospitalized, often with complications of substance use, and experience disproportionately worse health outcomes than those without OUD.[2,3] Such hospitalizations are often marked by uncontrolled pain and withdrawal symptoms, as well as patient-directed discharge.[4] The standard of care treatment for people with OUD is one of three Food and Drug Administration-approved medications for opioid use disorder (MOUD), including methadone, buprenorphine, or naltrexone, and the hospital setting has been identified as a "reachable moment" for initiation of MOUD.[5] There has been recent interest in the use of short-acting opioid agonist therapy for hospitalized patients with opioid withdrawal.[6–8] We argue that the current armamentarium of treatment options are inadequate for effective care of all hospitalized patients with OUD, and that additional opioid agonist therapies such as oxycodone and hydromorphone, including both long-acting and short-acting formulations, should be included as a vital component of in-hospital management of opioid withdrawal.

Buprenorphine and methadone are highly effective medications for people with OUD, improving treatment retention, decreasing illicit opioid use, and improving mortality.[9] But what reasonable options exist for patients who are not interested in MOUD during periods of hospitalization? In the setting of prior personal experience, concerns about withdrawal, or ongoing uncontrolled pain, patients with severe opioid dependence do not uniformly choose to initiate buprenorphine or methadone upon admission to the hospital. While novel methods of buprenorphine initiation that bypass the need for a pretreatment withdrawal period are becoming commonplace,[10] fear of precipitated opioid withdrawal, and concerns over effective analgesia, lead many patients to decline treatment with buprenorphine when hospitalized. Methadone is a full opioid agonist and a natural choice for pain management and withdrawal relief, however, efficacious dosing for management of pain and withdrawal symptoms often requires several days of subtherapeutic treatment dosing. Delays in achieving therapeutic dosing are especially noteworthy in light of the presence of highly potent fentanyl in the contaminated and unregulated US drug supply. Even if adequate dosing can be achieved during a period of hospitalization, continuation of newly started methadone following hospitalization is fraught with prohibitive region-specific logistical and legal hurdles, in particular for patients who require extended stays in postacute care facilities.[11]

Opioid agonist therapy can be considered a bridge to several potential treatment pathways for hospitalized patients with OUD. For a patient who is initially reluctant to initiate MOUD, an alternate opioid agonist such as oxycodone or hydromorphone can be utilized to effectively manage pain and opioid withdrawal during the initial phase of hospitalization, buying time to revisit interest in MOUD when initial symptoms are better controlled. Regarding transition to buprenorphine, prescription oxycodone has a more predictable half-life than illicitly manufactured fentanyl, and when timed properly, the risk of precipitated opioid withdrawal during transitions from oxycodone to buprenorphine can be all but eliminated. For a patient interested in methadone treatment, oxycodone can be utilized to control pain and withdrawal symptoms until methadone can be titrated to effective dosing. What about the patient who is uninterested in MOUD? A patient with OUD and significant

opioid dependence should not be required to accept MOUD to receive medical care, and treatment with opioid agonist therapies during a period of hospitalization can be considered a safe bridge to continued opioid use after discharge, protecting a patient's opioid tolerance as a form of harm reduction, and ultimately mitigating the risk of fatal overdose following hospitalization.

Early treatment with opioid agonist therapy, including long-acting and short-acting formulations, is a reasonable and important alternative clinical pathway for hospitalized patients with OUD. Up-front mitigation of pain and control of withdrawal symptoms is an essential component of hospital-based care. Management of these symptoms is patient-centered, facilitates provider-patient alliance, and buys time to initiate medical treatment and offer evidence-based MOUD. Although often requiring high doses to achieve symptom control, a basal-bolus opioid agonist treatment strategy is a logical clinical approach, and in our experience utilizing an addiction medicine consult service, safe in the monitored setting of the hospital. While morphine equivalent calculations for a given quantity of heroin or fentanyl analog are not straightforward, there is a clear advantage to the ability to use an easily titratable medication in response to a rapidly changing and highly potent drug supply. This approach is most successful when used as part of a protocolized treatment pathway, with a clear dose titration and monitoring plan, ideally based on knowledge of the potency of the local drug supply, and with buy-in from multidisciplinary team members including administration, pharmacists, clinicians, and nurses. Some potential challenges to this approach include concerns about high opioid dosing, provider and nurse discomfort, questions about legality and safety, and off-label medication use. These are legitimate questions that deserve attention and institutional review. However, the current treatment paradigm is insufficient to facilitate effective medical care, and our inability to effectively manage pain and withdrawal symptoms often leaves patients no choice but to leave the hospital early.

To be clear, the hospital should be considered a "reachable moment" for provision of MOUD, and ideally all patients who are amenable should be administered buprenorphine or methadone in the hospital setting, with a clear plan for treatment continuation after hospital discharge. But for the sizable population of patients who do not want to initiate MOUD immediately upon arrival to the hospital, use of the full range of opioid agonist therapies represents a patient-centered option that should be included as an inpatient OUD care pathway to prevent early termination of treatment.

COUNTERPOINT

Short-acting opioids should supplement, not replace, evidence-based opioid withdrawal management with methadone or buprenorphine

Drs. Calcaterra and Thakrar

> A great part of the tragedy of this opioid crisis is that, unlike in previous such crises America has seen, we now possess effective treatment strategies that could address it and save many lives, yet tens of thousands of people die each year because they have not received these treatments. Ending the crisis will require changing

> policies to make these medications more accessible and educating primary care and emergency providers, among others, that opioid addiction is a medical illness that must be treated aggressively with the effective tools that are available.
>
> -Dr. Nora Volkow, Director of the National Institute on Drug Abuse

We appreciate the Point authors' advocacy for hospitalized patients with OUD in the accompanying perspective piece. We *strongly agree* that hospitalized patients with OUD might benefit from supplemental full-agonist opioids, especially during early methadone titration, as part of low-dose buprenorphine initiation, and to manage acute pain.[6]

We disagree, however, with the Point authors' recommendation for hospitalists to use opioids like oxycodone or hydromorphone as monotherapy for opioid withdrawal for patients who decline long-term treatment for OUD. This approach neglects the established efficacy of methadone and buprenorphine for opioid withdrawal, risks introducing new dosing challenges that could make hospitalizations less patient-centered, and could have the unintended effect of excusing hospitalists from learning how to use methadone and buprenorphine at a time when these medications are already vastly underutilized.[12]

The term "medications for OUD" can be ambiguous in the context of this discussion. MOUD is often used to describe long-term, maintenance OUD treatment with methadone, buprenorphine, or extended-release naltrexone.[13] The term can also be used to refer to methadone or buprenorphine for opioid withdrawal management in the hospital.

As the Point authors argue, hospitalized patients who decline MOUD for long-term OUD treatment still deserve effective opioid withdrawal management. However, based on existing evidence, the safest and most effective management of opioid withdrawal involves methadone or buprenorphine (or, in regions where it is available, i.e., Canada, slow-release oral morphine).[14,15] We urgently need to update this evidence in the era of high-potency synthetic opioids, like fentanyl.[16] While this evidence develops, we believe hospitalists should adapt established best practices for hospital-based opioid withdrawal management rather than starting anew. Thus, we recommend short-acting full agonist opioids for opioid withdrawal, when necessary, to augment methadone or buprenorphine as long as there is no medical contraindication to these medications.

Oxycodone or hydromorphone as monotherapy for opioid withdrawal is likely to be less effective and could lead to adverse events, including overdose. The Point authors suggest that hospitalists should ideally use "knowledge of the potency of the local drug supply" to guide initial dosing for oxycodone or hydromorphone. However, even addiction specialists have difficulty predicting response to an initial dose of oxycodone or hydromorphone since, as the Point authors acknowledge, "morphine equivalent calculations for a given quantity of heroin or fentanyl are not straightforward." We believe it is unrealistic to expect a hospitalist with little or no addiction training and high patient volumes to initiate and titrate these medications alone for opioid withdrawal. The Point authors do suggest that this approach would ideally be implemented in a hospital setting with an addiction consultation, however, most nonacademic hospitals in the United States do not have an

addiction consultation service or regular access to an addiction specialist,[17,18] making the Point authors' recommendations inaccessible to many readers of the *Journal of Hospital Medicine*. Without up-to-date knowledge of the potency of unregulated opioid supplies or expert advice to inform dosing, patients are at high risk of iatrogenic under- or overdosing of opioids with this approach.

In contrast, standard protocols for methadone and buprenorphine initiation and dose titration can be easily followed by most hospitalists. If a patient reports ongoing withdrawal symptoms, pain, or cravings with methadone or buprenorphine dose titration, the hospitalist can augment therapy with additional doses of methadone or buprenorphine or with short-acting opioids.[15] We believe this approach is better supported by evidence. It is also more likely to be implemented, since it makes fewer demands on nursing staff compared to oxycodone or hydromorphone monotherapy, where patients are more likely to face peaks and troughs in opioid withdrawal relief. Thus, we believe this approach would be more effective for opioid withdrawal management and could thereby decrease the risk of unprescribed substance use in the hospital, contentious interactions between hospital staff and patients, and self-directed discharges.[4,19]

Some patients may decline methadone and buprenorphine even for opioid withdrawal. In these circumstances, hospitalists should explore this reluctance and debunk misconceptions. For example, hospitalists should ensure that patients understand that methadone does not precipitate withdrawal and that it does not block the effects of other full-agonist opioids at doses used for opioid withdrawal; methadone can only help relieve opioid withdrawal symptoms and will not make these symptoms worse. For some high-risk patients who continue to decline methadone and buprenorphine for withdrawal, clinicians might need to reach for alternative long-acting opioids, as the Point authors suggest. This will depend on the clinical circumstances. Patients certainly have autonomy to decline treatments or to choose between equally effective medications. However, there are situations where this might not be appropriate—for OUD, as with other conditions, there are clinical circumstances where we would not order less effective treatments based solely on patient preference (e.g., we would not let patient preference alone determine which antibiotics to use for sepsis). With all that said, in our experience, it is exceedingly rare for patients to continue to decline both methadone and buprenorphine for opioid withdrawal once we clarify the distinction between using these medications for opioid withdrawal management in the hospital and using them as long-term maintenance treatment after discharge.

Methadone and buprenorphine for opioid withdrawal can also facilitate smoother discharges, even for patients who initially decline long-term OUD treatment. Some patients change their minds about outpatient treatment once they experience the stability of adequately dosed, once or twice-daily opioid agonist treatment with methadone or buprenorphine. Hospitalizations are unique opportunities to initiate and titrate these medications while minimizing opioid withdrawal. We agree with the Point authors that "continuation of newly started methadone treatment following hospitalization is fraught with prohibitive region-specific logistical and legal hurdles," however, methadone and buprenorphine continuation after discharge is at least a possibility. Federal regulations currently bar the use of

oxycodone and hydromorphone for maintenance treatment of OUD in skilled nursing facilities and outpatient settings.[20]

Last, and perhaps most importantly, the Point authors do not acknowledge that the vast majority of hospitalized patients with OUD are never prescribed methadone or buprenorphine—the standard of care—as long-term OUD treatment. Use of these specific medications is associated with increased days of antibiotic therapy,[21] decreased risk of recurrent infection,[22] and reduced overdose mortality[23] among hospitalized patients with infections and OUD, however, hospital clinicians are reluctant to initiate these medications due to a lack of experience and training.[24] In one study of Veterans Affairs hospitals, fewer than 15% of hospitalized patients with OUD were ever treated with these medications.[12] Proposing the use of oxycodone or hydromorphone as monotherapy for opioid withdrawal management in a generalist journal could encourage hospitalists to use these medications as a first-line approach instead of methadone or buprenorphine. While it is certainly possible that a basal-bolus dosing of oxycodone or hydromorphone might have similar or superior outcomes, until this evidence emerges, we are reluctant to recommend an approach to opioid withdrawal for hospitalists that minimizes methadone and buprenorphine.

The *Journal of Hospital Medicine* recently published a consensus statement outlining recommendations for hospital-based OUD treatment using methadone and buprenorphine.[15] We hope these recommendations are disseminated and implemented widely and that hospitalists consider using short-acting opioids to supplement, rather than replace, this approach when necessary.

REBUTTAL

All opioid medications should be available to hospitalized patients with opioid withdrawal

Drs. Stern, D'Orazio, and Work

We appreciate the Counterpoint authors' acknowledgment of a potential benefit from use of short-acting opioids to supplement evidence-based opioid withdrawal management. We believe this to be an important point of agreement. If the outcome of this perspective piece is momentum toward acceptance of such an approach, our patients will be better served.

We believe that the Counterpoint authors mischaracterize our argument by focusing on opioid monotherapy as a replacement for methadone or buprenorphine. The crux of our argument is that the full range of legal opioid therapies should be made available to hospitalized patients with opioid withdrawal. These medications should not replace buprenorphine or methadone, which should continue to be considered first-line therapies for management of opioid withdrawal. Rather, opioids such as oxycodone and hydromorphone can serve as short-term supplementary tools, either to mitigate in-hospital discomfort, or to assist with transitions to methadone or buprenorphine.

We disagree with the Counterpoint authors that it is "exceedingly rare" for patients to decline methadone or buprenorphine. In our experience, even in response to extensive

discussion, patients are often not prepared to start these medications early in presentations to the hospital.

We advocate for improved access to methadone in hospitals. For largely nonclinical reasons, use of methadone is often restricted in the hospital setting, and hospitalists may be reluctant to start treatment due to concerns about discharge planning[11] or misconceptions about legality and safety.[25] To that point, we agree that urgent efforts to reduce barriers to in-hospital utilization of methadone are needed. We need to advocate for the removal of restrictions on continuation of hospital-initiated methadone in postacute care settings, and we need to develop effective, patient-centered processes for outpatient treatment continuation after periods of hospitalization. But this will take time.

We appreciate that the Counterpoint authors highlight use of supplemental short-acting opioids for management of opioid withdrawal. We believe that the distinction between short-acting and long-acting opioids may be exaggerated. In our experience, extended-release oxycodone is an attractive medication in the hospital setting for the management of opioid dependence for many reasons, including the ability to rapidly titrate dosing without concern for a stacking effect, the lack of peaks and troughs compared to short-acting opioids alone, and the absence of significant QTc prolongation. The Counterpoint authors are correct to highlight the limited number of addiction specialists in the United States, but with unprecedented morbidity and mortality for patients with OUD, we cannot afford to wait for a specialty workforce to develop. Hospitalists are experienced with the use and safety profile of opioid agonist therapy for the management of pain, familiar with concepts of dose titration, and perhaps most importantly, uniquely situated to interact with people experiencing withdrawal when presenting for medical care. Why not add a tool to more rapidly mitigate withdrawal symptoms, ease the physical burden of hospitalization, and facilitate transition to lifesaving MOUD?

Our nation is in the midst of a historic public health crisis, and in the past year an unprecedented number of people died from overdose. We have a limited number of effective tools at our disposal to contend with an ever-changing, highly potent, unregulated drug supply. All patients should be offered evidence-based, guideline-driven MOUD. The medical community should take concrete steps to minimize legislative, educational, and logistical barriers to this treatment, and the hospital setting should truly be considered a “reachable moment” for the initiation of buprenorphine and methadone. But we also need to acknowledge spaces where current options may fall short, and identify additional tools such as full agonist opioids, to help patients complete hospital care and facilitate transitions to evidence-based treatment and safe discharge.

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