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"I have such a hard time hitting myself, I thought it'd be easier": perspectives of hospitalized patients on injecting drugs into vascular access devices

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Abstract

Background: Hospital patients who use drugs may require prolonged parenteral antimicrobial therapy administered through a vascular access device (VAD). Clinicians' concerns that patients may inject drugs into these devices are well documented. However, the perspectives of patients on VAD injecting are not well described, hindering the development of informed clinical guidance. This study was conducted to elicit inpatient perspectives on the practice of injecting drugs into VADs and to propose strategies to reduce associated harms.

Methods: Researchers conducted a focused ethnography and completed semi-structured interviews with 25 inpatients at a large tertiary hospital in Western Canada that experiences a high rate of drug-related presentations annually.

Results: A few participants reported injecting into their VAD at least once, and nearly all had heard of the practice. The primary reason for injecting into a VAD was easier venous access since many participants had experienced significant vein damage from injection drug use. Several participants recognized the risks associated with injecting into VADs, and either refrained from the practice or took steps to maintain their devices while using them to inject drugs. Others were uncertain how the devices functioned and were unaware of potential harms.

Conclusions: VADs are important for facilitating completion of parenteral antimicrobial therapy and for other medically necessary care. Prematurely discharging patients who inject into their VAD from hospital, or discontinuing or modifying therapy, results in inequitable access to health care for a structurally vulnerable patient population. Our findings demonstrate a need for healthcare provider education and non-stigmatizing clinical interventions to reduce potential harms associated with VAD injecting. Those interventions could include providing access to specialized pain and withdrawal management, opioid agonist treatment, and harm reduction services, including safer drug use education to reduce or prevent complications from injecting drugs into VADs.

Keywords: Vascular access devices, Substance-related disorders, Hospitalization, Harm reduction, Patient-centered care

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Background

Hospitalization rates due to infections associated with injection drug use (e.g., infective endocarditis, osteomyelitis, and skin, soft tissue, and pulmonary infections) are

increasing in the USA and Canada [1–4]. These infections are caused by unsafe injection practices (e.g., injecting with non-sterile syringes) [1, 5], drug excipients in certain pharmaceutical drugs [6, 7], and/or fillers and other particulates in street-sourced drugs [8]. Treatment of these infections includes prolonged parenteral antimicrobial therapy administered through vascular access devices (VADs). VADs comprise various types of catheters inserted to access peripheral or central vessels (e.g., peripherally inserted central catheter (PICC), intravenous (IV) line) [9].

Due to the extended length of parenteral antimicrobial therapy, patients who do not use drugs are frequently discharged to home and treated as outpatients [10]. Conversely, people who inject drugs (PWID) often remain hospitalized for the duration of their treatment due to concerns that unstable housing or ongoing drug use may inhibit treatment adherence and that patients will inject drugs and/or diverted medications into these devices [9–11]. However, there is a lack of empirical evidence on the prevalence and health risks associated with injecting drugs into VADs among either outpatient or hospitalized PWID [12–15]. Nevertheless, clinical guidance in many jurisdictions advises inpatient hospitalization and close monitoring as the primary strategy to prevent VAD complications for this patient population [9–11].

Yet drug use can occur in hospital settings [16–20]. Cohort and structured surveys with PWID in Canada [16–18] and the USA [19, 20] report that between 30 and 50% of participants continued to use drugs while hospitalized. Injection drug use in hospital can occur for many reasons including uncontrolled pain and withdrawal symptoms or to manage symptoms of stress or anxiety [21, 22]. To circumvent discovery by hospital staff and avert negative repercussions, patients have described using drugs in their hospital rooms and patient washrooms, in other areas of the hospital, and in other nearby public locations [21, 22]. Patients often consume drugs in non-sterile locations, reuse syringes, and rush their injection. These actions only compound the risk of developing infections and other health complications [17, 21, 22]. Patients who continue to use drugs while hospitalized are also at increased risk of experiencing stigma [23, 24] and initiating discharge prior to treatment completion, and experiencing unplanned readmission and mortality [19, 25–27].

Extant research that explores VAD injection primarily describes the prospective and retrospective experiences of outpatients participating in this practice and suggests that the practice is uncommon. For example, of 33 PWID eligible to receive outpatient parenteral antimicrobial therapy within a residential addiction treatment facility, over 90% reported that their PICC line did not precipitate a desire to inject into the device or increase their motivation to use drugs [20]. In a cohort study of 67 PWID receiving outpatient therapy, only 2% of those who failed treatment did so because of VAD injection [12]. Three case studies have similarly described non-hospitalized people injecting into VADs, including a cannula self-inserted into a femoral vein [28], a central venous catheter [29], and a port-a-cath [30]. A recent Canadian qualitative study [31] examined the practice of injecting into PICC lines, a common type of vascular access device. Through retrospective interviews with 24 people who use drugs living with HIV/HCV who had been hospitalized at least once in the past 5 years and 26 healthcare providers, the authors found that even though few participants reported engaging in this practice, healthcare providers reported that fears of PICC line tampering influenced clinical care decision-making. Our study extends this work by exploring in depth the perspectives and experiences of VAD injection among a sample of PWID hospitalized on medical or surgical units of a large tertiary care facility.

Objectives

The objectives of this analysis were to (1) describe inpatient experiences and motivations to inject drugs and/or diverted medications into VADs, and (2) propose clinically relevant and patient-centered recommendations to reduce the harms associated with this practice.

Methods

Setting

The study was completed at a large, urban acute care hospital in Western Canada that treats many structurally vulnerable patients with complex health and social needs and high rates of drug and alcohol use disorders. The hospital has an addiction medicine consultation team. At the time of this study, the consultation team offered patients with drug and alcohol use disorders expert pain and withdrawal management, opioid agonist and other medication treatment, harm reduction supplies, addiction counselling, and wraparound health and social supports (e.g., brokered access to housing and income supports, and health promotion interventions such as screening for sexually transmitted infections and immunizations) [24]. This study was conducted by a University-based researchers affiliated and colocated on site with the addiction medicine consultation team (KD is also medical director of the team).

Methodology

Our findings are part of a broader mixed-method evaluation examining the provision of sterile injection supplies by the consultation team to hospital inpatients. The

results described in this study organically emerged as the study progressed and were analyzed as an independent theme. We used a focused ethnography as a research approach, which is a time-limited method of eliciting detailed answers to delineated research questions within a distinct group or context, and semi-structured interviews as our sole data collection tool, which comprise predetermined open-ended questions. In line with previous applied health research studies, our focused ethnography did not include participant observation [32, 33]. The interview questions explored hospitalized participants' experiences receiving clinical care, using drugs while hospitalized (including their perspectives of receiving sterile supplies), and their thoughts on how care for hospitalized PWID can be improved. A trained qualitative researcher (HB) obtained informed consent, audio-recorded, and conducted all interviews in a location within the hospital of the participants' choosing. Participants received $20 CAD honoraria.

Participant recruitment and data collection

Between April 20, 2017, and March 7, 2018, we approached inpatients from general medical and surgery units who had reported recent injection drug use to the consultation team and offered participation in a one-hour interview. We completed interviews with 25 patients (Table 1); theoretical saturation was reached after interview 21, meaning that no new concepts or themes emerge in subsequent interviews [32]. We asked almost all the participants ($n=24$) about their perspectives of injecting drugs and/or diverted medications into VADs; one interview was terminated early by participant request.

Data analysis

Interview recordings were transcribed and deidentified, and participants assigned pseudonyms. The average interview length was 51 min. The software ATLAS.ti 8 was used to organize the data iteratively. We employed latent content analysis, which entails examining, highlighting, and labeling groups of words and sorting the labeled text using codes that reflect similar meanings. This form of analysis is inductive allowing classifications to flow from the text [34]. We then explored latent aspects of the text by collating codes, collapsing and

Table 1 Participant information

Variable	Descriptive statistics *n* (%)
Demographics	***N*=25**
Gender	
Female	12 (48)
Male	12 (48)
Transgender	1 (4)
Ethnicity	
First Nations, Inuit, or Metis	20 (80)
White	5 (20)
Age	
30–39	7 (28)
40–49	10 (40)
50–59	7 (28)
60+	1 (4)
Drug use characteristics	***N*=25**
Length of drug use (years)	
1–10	13 (52)
11–20	4 (16)
21–30	3 (12)
31–40	5 (2)
Utilization of drug consumption supplies	
Accepted and used supplies	19 (76)
Did not accept supplies	4 (16)
Accepted but did not use supplies	2 (8)

reconsidering categories, and then abstracting at a higher level of interpretation [34].

Rigor

Rigor in qualitative research is a set of strategies used to strengthen study quality [32]. To ensure rigor, we employed a second experienced qualitative researcher who was also a member of the research team to randomly and separately analyze 20% of the transcripts to ensure concordance of interpretation [35]. Additionally, we regularly consulted members of an advisory group to elicit feedback on the appropriateness of study procedures and validity of the analysis. The advisory group comprised people with lived experience of drug use and hospitalization; over half also self-identified as Indigenous [35].

Results

Nearly all participants had heard of patients injecting into their VADs (specifically PICC and IV lines). Participants implied that hospitalized PWID with VAD would have at least contemplated participating in the practice. Some participants had unsuccessfully attempted to inject into their VADs, but a few had successfully injected into their VADs at least once during their current hospitalization, or during previous hospitalizations.

"You just connect her and…dial in direct": reasons for injecting into a VAD

The primary motivation reported for this practice was easier venous access, because many participants and their peers had vein damage associated with long-term injection drug use or improper injection techniques. Injecting into their VADs was seen as "quicker," "easy," and "convenient" for people whose "veins [were] …all done." Participants perceived injecting into a VAD as less harmful than prolonged attempts to secure venous access because it reduced the frequency of injection site injury and associated infection risks. Participants also described that acute withdrawal could complicate injection drug use and challenge venous access, further increasing the appeal of injecting into a VAD. As "Allison" told us:

> *'Oh my god, some mornings, when it's my first fix and I can't do it and I just want to cry or just want to scream. It sometimes, it actually brings me to the point of tears because I can't get it…It's frustrating… It's easier to [inject in your VAD] than having to find a vein and chance missing it. If you miss it then there goes the first shot you know. The strongest shot. The shot that counts.*

For some participants, the frustration associated with finding venous access was so severe that they described wanting a dedicated VAD for drug use while in hospital and even to be discharged from hospital care with their VAD intact.

> *Well, they're always going to use [their VAD] because you know, they don't have to dig in their skin or anything, it's a perfect little port. And you know, when a person is leaving [hospital] they're all like, no you can't leave with that. Let them, you're only helping so that they're not going to go digging around in their skin and stuff. - 'Carl'*

A few participants described how the psychoactive effects of drugs were stronger when using a VAD compared to injecting intravenously and believed some people may prefer injecting via this route.

> *I've done it. Yeah…It's just an easy port...you don't have to mark yourself up, you don't have to look for nothing, you just connect her and...dial in direct...I think it just hits you a little bit harder and faster... somebody that wants to get high, yeah, it's probably the more enticing route to go. - 'Kenneth'*

"One awful, fuckin' big chance": awareness of potential risks

Participants who actively injected into VADs, or those who supported the practice, either described no associated risks or implied that the benefits of injecting outweighed the risks. Yet most refrained entirely from the practice or reported stopping when they learned of potential risks or experienced related harm. These participants perceived the practice as "scary," "risky," "dangerous," and "one awful, fuckin' big chance" and people who participate in it as "nuts."

In terms of potential risks, participants worried that injecting into a VAD with non-sterile syringes or contaminated drugs could lead to circulatory issues or additional infection risks.

> *Oh yeah for sure. Right in the PICC line, for sure. It's easy. It's a mainline right to your veins. But that's dangerous man, infection. Oh my god, lot of things, not good, I wouldn't do it. I wouldn't do it. I'm too scared. - 'Leah'*
> *In the process of diluting your substance...you might not even be able to see it but any particle...can be built right into that line, can get in your bloodstream and cause a clot, cause any kind of numerous problems, it's very dangerous. - 'Kenneth'*

Many participants were also aware that some types of VADs provide more direct access to central veins and, as such, believed that injecting into these devices (i.e., PICC lines) may increase their risk of overdose. For example, "Silvia" described contemplating injecting into her

PICC line but ultimately refrained. According to her, "I was actually thinking of it too, but then I thought… no, that's a little bit too close to my heart." "Silvia" did, however, describe a desire to inject into a VAD that was not a PICC line because of her struggles to inject herself. "Silvia's" first experience with injecting drugs was when she was thirteen years old and after thirty years of use, she had developed severe venous damage. According to "Silvia":

> *Like we could put it in there and then you flush it and then you lock it...Make it safer...I'm not saying PICC line site either. But like where it won't fall out...people are not getting their shot, because they're wasting it, because they can't get a line.*

One participant described overdosing after injecting into her VAD. When we asked "Elsa" if she had ever injected into a VAD, "Elsa" reported doing so a few times in the past. According to "Elsa," "I'll never do that again, because it goes directly to your heart and I like, I almost died." "Elsa" described recent engagements with local harm reduction organizations where she received safer drug use education, and she had also been prescribed methadone. These supports, along with a personal desire to reduce physical harms to herself, helped "Elsa" refrain drug use during her current hospitalization.

Most participants, nevertheless, used general and vague terms when describing VADs and displayed limited knowledge of how the devices functioned. Several participants were not aware of how to inject properly into their VADs, despite the exigency some felt to use their devices.

> *I've heard people say they've done it but I don't know how they could do the PICC line because it's so long right. It goes all the way to…I don't know, I would have to ask somebody to show me how they do it. - 'Linda'*
>
> *But I actually tried, that wouldn't work as far as here, so I maybe take this thing off and put it back on after. When you do the flush it's massive, then I, lose a lot of water, probably work too. I did almost try it but not really. Because I have such a hard time hitting myself. I thought it'd be easier, you know what I mean. - 'Owen'*

In addition, some participants reported unsubstantiated beliefs regarding VADs and safety. One participant implied that the risk of developing an infection after injecting into an IV line was less than the risk associated with injecting into a PICC line. According to "Andria," "Obviously, going into the PICC line isn't safe…but if they had like something in their foot…a foot you can lose, your heart…" Participants also described witnessing specific unsafe practices related to VADs. "Thomas" recounted witnessing a fellow patient "take a needle out of their leg" to utilize it for injecting drugs through other means. "Oliver" described patients injecting into their VAD to "flush syringes," meaning to retract blood into a used syringe and then reinject, to ensure any leftover drug residue in the syringe was consumed. "Washing" of syringes, filters, and other injection drug equipment in this manner is a strategy used by PWID to stretch limited personal drug supplies [36], which may be more difficult to maintain while hospitalized and unable to participate in work to generate income.

"Show them the process…to be as clean as possible": reducing harms

Some participants we spoke with reported attempts to lower potential risks associated with injecting in their VADs by titrating their dose (using a small amount of drug to start) and keeping their VAD as sterile as possible. According to "Dean":

> *Mm-hmm. I've done it… It gets better, you don't miss or nothing, it's already there….And it's safe to do it as long you're not doing a whole lot, you keep it clean like the nurses do, you clean it with swabs and that.*

One participant felt most patients passively relied on nurses to keep their VAD clean. "Rhonda" explained that patients who inject in their VADs think to themselves, "I've got an IV, I don't even have to try and find a vein now…the nurses come and flush them out before they do everything, so it stays clean." However, "Andria" felt that staff should proactively educate patients with VADs on the risks associated with injecting drugs into their devices but also provide sterile injection supplies and knowledge on how to clean and maintain these devices if they choose to inject.

> *Maybe show them properly. Say show them how to use the flush. Show them to, say if you're going to do it and you're going to do it here, then you're going to do it properly… have to set your own standards too, to what you feel is safe…you could educate them… and then show them the process…to be as clean as possible. - 'Andria'*

Yet only one participant described hospital staff discussing the practice of injecting into VADs. According to "Candice," "the IV team, or the infectious disease team told me if I use my PICC line to get high they will shoot antibiotics into my [arm], muscular injection, the whole time I'm here." She interpreted this admonition as benevolent concern on the part of her care team, and it successfully deterred her from using her device.

However, for most participants, the anticipation of severe repercussions, such as changes to their pain or withdrawal management medication regimes, resulted in them being mistrustful of hospital staff. They therefore concealed their drug use, including use that involved injecting into their VADs. "Curtis" considered injecting into his VAD, but according to him, "I didn't, I didn't, no I didn't want to make it that noticeable that I was using when I left so to speak. When I had come back in, you can pretty much, [the nurses] know, you can just tell they know." According to "Lydia," nursing staff had suspected that she was actively consuming drugs after finding a powder in her purse and as a result, her pain medication regime was changed from tablet to liquid, which caused her distress. When "Lydia" was asked how to make sure patients were safe when injecting into their VAD, she responded that attempts by hospital staff to prevent drug use fostered mistrust and impeded patients from using safer injection techniques. According to "Lydia":

> *Well, that's when you explain to them about [using sterile needles]. But then when you have your nurses screwing that up for you guys, good luck. Of course they're going to go back to hiding, right?...People would care about having [sterile needles] and doing it cleanly and dadadada if, you know, you weren't gonna get in trouble, right?*

Discussion

In this study, nearly all participants were aware of the practice of injecting drugs into VAD. However, most participants chose not to regularly inject into their VAD because they perceived the practice as risky. Of those who participated in the practice, most described easier venous access as the primary motivation for themselves and others to inject into their VADs. This practice was often seen as pragmatic and less deleterious than direct intravenous injection, particularly for people who had difficulty finding a vein and injecting themselves. Despite these reported advantages, many participants described a lack of knowledge regarding how VADs functioned. Several participants, including some who had injected into their VADs, appeared unaware of the potential negative health outcomes or strategies to reduce associated risks and implied a need for nonjudgmental education to ensure their safety while injecting into their VADs.

Injecting drugs into VADs is a concern for clinicians administering parenteral antimicrobial therapy to PWID and is often the primary reason PWID are deemed ineligible for outpatient treatment [9–11]. Inpatient supervision by hospital staff is advised to prevent this practice [9–11], but our findings suggest that this advice may not be effective at either informing patients of the risks of, or preventing, VAD injecting. Moreover, extant literature indicates that other common interventions designed to deter in-hospital drug use (e.g., confiscation of injection supplies, enhanced surveillance, and monitoring) may in fact increase risks for patients (e.g., rushed injection, using alone and in unsafe circumstances, premature discharge) [21, 22]. Our study did not systematically explore whether staff took measures to deter non-medical VAD nor whether participants experienced harms because of these deterrence measures. However, participant accounts demonstrated a need for hospital staff to be aware of the motivations and experiences of PWID injecting in their VADs. This may aid in providers anticipating and addressing patient needs through non-stigmatizing care, which could include staff adopting trauma-informed approaches to patient care, being mindful of words and body language when interacting with PWID, and prioritizing patient autonomy and choice [37, 38].

A key strategy for addressing VAD injecting is to reduce hospitalized patients' need to inject drugs in the first place. It is imperative that patients have expeditious access to effective, tailored pain and withdrawal management [39, 40], injectable and oral opioid agonist therapy [41, 42], counselling [39, 42], and social supports, including peer support and social workers [24, 43] during their hospitalization. These interventions should be provided with the active consent and collaboration of patients.

There is also some evidence to suggest positive treatment outcomes in PWID receiving parenteral antimicrobial therapy outside of acute care hospitals [13, 14, 44, 45]. Patients with current or previous injection drug use have successfully completed parenteral therapy and participated in minimal, or at least comparable to average, drug use while residing in medical respite facilities (i.e., temporary shelters that provide medical services to people experiencing homelessness) [13, 46], and from within their private homes [44]. With sufficient support (i.e., access to stable housing, substance use disorder discharge planning, regular check-ins with clinical staff, access to agonist medication or other substance use treatment), PWID may be able to successfully complete parenteral antimicrobial therapy in the community and have low rates of substance use and VAD injection [13, 14, 17, 44, 45].

It is also important to recognize that even with maximal medical and social support, some PWID will continue to inject while hospitalized. For example, empirical evidence suggests that prolonged drug use may result in impaired volitional control [47]. Additionally, there are currently no evidence-based pharmaceutical treatments for those with stimulant use disorders [48] and many acute care facilities still do not provide patients with

opioid use disorders evidence-based medication treatment or harm reduction interventions [49]. Clinicians therefore should be educated and encouraged to engage patients with previous or active injection drug use in non-stigmatizing and factual conversations about reducing harms associated with drug use, including the potential risks of injecting into VADs [15, 50]. Research to quantify VAD injecting risks is urgently needed to facilitate such factual discussions. Meanwhile, staff may consider periodic laboratory monitoring to identify and treat incipient infections due to drug use [17]. Several outpatient clinics have established patient care plans, which have included verbal or written agreements from patients to refrain from injecting into their VADs [13, 14, 51, 52]. Clinics have also utilized specialized dressing or security seals on patients' VADs to more easily detect drug use [13, 14, 51, 52]. However, these technologies were not employed in our study setting, and patients' perspectives of these preventive measures are currently unknown, as is their effectiveness for preventing harm to patients.

If injection drug use into VADs is suspected or confirmed, discharging patients or abruptly discontinuing or modifying antimicrobial therapy to a less appropriate regimen is not recommended [9, 22, 53, 54]. These actions may preclude patients from completing vital treatment, compound the burden on hospital staff by increasing the likelihood of patients experiencing unplanned readmissions [54], and increase patients' risk of mortality [27, 55]. Instead, hospital policies should address how patients who continue to use drugs will be supported to complete their medical treatment [38]. Staff should be trained and encouraged to have non-stigmatizing and transparent conversations with patients and offer patients sterile injection supplies, safe syringe disposal instructions, and a naloxone kit [53]. To obviate patients' perceived need to inject into their VADs, clinical staff or a peer support worker could also educate patients on vein finding and maintenance to encourage safe injection practices [56, 57].

A hospital-based supervised consumption service, if available [58, 59], could further reduce health risks of VAD injecting. Supervised consumption services are well described in the literature [60, 61] and aim to provide a safer and cleaner environment where people can consume pre-obtained drugs in hospital under the supervision of trained staff without the need to rush or fear of criminal prosecution [59]. Supports available within these services, such as nursing assistance to locate a vein, may result in fewer patients needing to use their VAD due to inability to find other venous access. Early experience suggests that when patients are given access to supervised consumption services in hospital settings, the incidence of injecting into VAD is quite low (i.e., occurring in only 5% of visits) [58]. Patients with refractory opioid use disorders could also be prescribed injectable opioid agonist therapy (i.e., hydromorphone, diacetylmorphine) and receive their doses (via self-injection or nurse-administered intramuscular injection) within the supervised consumption service. Injectable opioid agonist therapy is well established in community settings and has been shown to reduce drug use and improve treatment retention [62, 63].

In cases where education and available supports have not deterred VAD injecting, staff might consider supervising patients injecting into their VADs from within their hospital room (in jurisdictions where this is permissible) [64], or demonstrating how to more safely and sterilely inject into VADs, requesting patients avoid certain VADs, and establishing a non-punitive system for patients to report to hospital staff after use [15, 57]. However, more research is needed to evaluate the effectiveness of these harm reduction strategies for reducing health harms of VAD injecting for hospitalized PWID.

Strengths and limitations

This study supports recent research that suggests hospital policies regarding the use of PICC lines in hospitalized PWID are inadequate and that the integration of harm reduction strategies into clinical care is needed [31]. However, this study used a subset of data from a broader mixed-method evaluation that elicited the perspectives of inpatients who reported recent or active injection drug use to a harm reduction addiction medicine consultation team and who were offered sterile injection supplies at the bedside (most participants accepted those supplies). As such, awareness of and experience with VAD injection may have been higher than other hospitalized patients with a history of drug use. Also, use of VADs for injection emerged as an independent theme as the study progressed, limiting a more in-depth a priori exploration of this topic. Finally, this study was conducted in a large city in Western Canada and may not be generalizable to other dissimilar contexts.

Conclusions

Given the imperative to ensure PWID receive high-quality hospital care and are able to complete their antimicrobial treatments, we have outlined several potential strategies that could help to address the issue of VAD injecting in hospitals. However, further research is needed to identify and quantify the actual health risks and prevalence of this practice. Quantitative and qualitative studies that elicit the perspectives of both clinical staff and PWID could determine the acceptability and optimal mix of interventions for

preventing potentially deleterious patient outcomes associated with injecting into VADs.

Abbreviations
IV: Intravenous line; PICC: Peripherally inserted central catheter; PWID: People who inject drugs; VAD: Vascular access device.

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Author contributions
EH and HB conceptualized the study with input from co-investigators. EH, KD, GS, TB, MT, and BP acquired funding to support the project leading to this publication. HB and EH collected the data, and HB led the analysis with support from EH. HB wrote the initial draft of the study, and all authors provided critical review, commentary, or revisions prior to its submission for peer review. EH provided oversight and leadership for all aspects of the research reported herein. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article because it is a qualitative study.

Declarations

Ethics approval and consent to participate
The study received human research ethics approval from the University of Alberta's Health Research Ethics Board.

Consent for publication
Not applicable.

Competing interests
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Publisher's Note

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MAJOR ARTICLE

In-Hospital Illicit Drug Use and Patient-Directed Discharge: Barriers to Care for Patients With Injection-Related Infections

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Background. Hospitalized persons who inject drugs are at a greater risk of adverse hospital outcomes including discharge against medical advice, inpatient illicit drug use, overdose, and death. However, there are limited data on the frequency and outcomes of these events in the United States.

Methods. This retrospective analysis included patients with injection-related infections receiving a protocol for injection drug use (IDU) at University of Alabama at Birmingham Hospital from 2016 to 2017. In-hospital IDU was suspected or reported drug usage plus confirmatory drug screen, and documented discharges "against medical advice" were deemed patient-directed discharges (PDD). We analyzed the frequency of and associations between in-hospital IDU, PDD, 30-day readmission, and deaths (between 2016 and 2019) using McNemar's tests. Logistic regression models evaluated the association between PDD, in-hospital IDU, readmission, and death.

Results. Overall, 83 patients met inclusion criteria: 28 (34%) with in-hospital IDU, 12 (14%) PDD, 9 (11%) died, and 12 (14%) 30-day readmission. In-hospital IDU was significantly associated with PDD ($P = .003$), 30-day readmission ($P = .005$), and death ($P = .0003$). Patient-directed discharges and 30-day readmission were not significantly associated with death nor with each other.

Conclusions. In a cohort of patients receiving inpatient care for injection-related infections, illicit drug use, PDD, 30-day readmissions, and death were common. Furthermore, patients who use illicit drugs while hospitalized are significantly more likely to leave early, be readmitted, and/or die. We must design models of care that prevent adverse outcomes, including drug use and PDD, to reduce barriers to evidence-based treatment of infections.

Keywords. AMA; hepatitis C; in-hospital drug use; IVDU; OUD.

For persons who inject drugs (PWID), hospitalization is described as a "reachable" moment, a time when they have access to medical care and addiction services [1]. However, as many as 30% of PWID leave the hospital prematurely, against medical advice (AMA) [2]. Because "AMA discharge" is not a patient-centered term and can further stigmatize PWID, we prefer "patient-directed discharge" (PDD). Most persons who leave in this context have incomplete documentation, incomplete referrals including outpatient parenteral antibiotic therapy (OPAT), and incomplete or no prescriptions sent to a pharmacy. Not only does this abbreviate inpatient care, such as antibiotics, but PDD precludes linkage to outpatient services for substance use disorder and is associated with hospital readmissions and mortality [3, 4]. In one Canadian study of all hospitalized persons with PDD, there was a 3-fold higher risk of death in the following year relative to patients who did not leave early but were matched by age, gender, and hospital admission diagnoses [3]. There was a statistically larger percentage of PWID in the cohort leaving PDD (54%) relative to those who did not (23%, $P < .001$). In addition to PDD, hospitalized PWID are at greater risk of inpatient illicit drug use, overdose, and death [5]. Although drug use and PDD may be amenable to hospital-based interventions, there are limited data on the frequency and relationship between these events in the United States in the context of the opioid epidemic.

For many PWID, the hospital serves as a "risk environment" [6]. Factors outside of a patient's control (ie, stigma, management of withdrawal) interact to exacerbate or improve care [7]. In a study of patients with substance use disorder, Simon et al [8] explored reasons for PDD from the patient perspective. Negative interactions with staff, untreated withdrawal and

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pain, and restrictive hospital policies were commonly cited reasons that participants leave the hospital setting prematurely. However, for PWID with serious infections, Addiction Medicine (AM) consultation may be protective. One study demonstrated that AM consultation was associated with a lower likelihood of PDD and a greater likelihood of completing antimicrobial therapy [9].

We previously reported on the University of Alabama at Birmingham (UAB) Hospital protocol for PWID with acute bacterial infections, which included a 9-item risk score to identify those at greatest risk for continued injection drug usage (Supplemental Table). In 2016, the UAB Hospital developed the Intravenous Antibiotic and Addiction Team (IVAT) team, a hospital-based protocol for PWID with acute bacterial infections [10]. The IVAT is an interdisciplinary team including AM and Infectious Diseases (ID) clinicians that was initially designed to provide guidance on the safety of OPAT in PWID for infections such as endocarditis and osteomyelitis, which require intravenous antibiotics for weeks or more [10]. Patients receive IVAT when they have a documented or a suspected history of injection drug use (IDU) and an injection-related infection. Physicians request IVAT consultation for patients who disclose IDU, have documentation of IDU, or display visible signs or symptoms of injection-related infection. In this scenario, the physician orders an electronic IVAT consultation, which triggers both AM and ID consultations. Substance use disorders are diagnosed by the AM consultation team based on patient self-report and history. In cases of opioid use disorders (OUD), our AM providers prescribe medications for OUD (MOUD), which is associated with reduction in illicit opioid use, overdose, death, and retention in treatment [11, 12]. Furthermore, MOUD reduces hepatitis C virus (HCV) and human immunodeficiency virus (HIV) acquisition, improves adherence to treatment for viral infections, and supports HIV suppression [13, 14]. Addiction Medicine consultants may request consultation from the pain management team when indicated. All patients admitted to UAB receive universal HIV and HCV screening.

Patients who are receiving community-based MOUD are continued on this treatment. Because the standard of care at UAB hospital is for ID physicians to write intravenous antibiotic prescriptions at discharge, it is unlikely for patients to be discharged to OPAT without seeing an ID consultant.

The IVAT interdisciplinary team relies on a 9-item risk assessment [10], conducted by AM staff, to classify risk for continued IDU and inform discharge planning. Only those deemed "low risk" as defined by a score of 0–3 are discharged on OPAT. Others are treated in the hospital for the duration of their antibiotic therapy. This scoring system was developed using the expert opinion of our AM faculty to identify "low risk" patients: those unlikely to experience continued drug use on discharge (Supplemental Table). The 9-item risk assessment has not been validated. We have previously described our findings that the IVAT intervention, including the risk score, reduced length of stay by approximately 20 days and hospital costs by 33% [10].

The objective of this study is to evaluate the frequency of and associations between PDD, drug use, readmissions, and death among PWID at UAB. Based on our observations caring for PWID, we hypothesized that in-hospital drug use and PDD would be frequent and contribute to readmissions and mortality. In the secondary analysis, we hypothesized that the 9-item risk score would be associated with adverse hospital outcomes.

METHODS

In this retrospective analysis, we included persons receiving the IVAT intervention at UAB from October 2016 to December 2017. Because the IVAT intervention must be initiated by providers, it is possible that patients with undiagnosed injection drug usage were excluded. Only the first hospitalization during the study period was included in this analysis. Psychiatric diagnoses were defined as a Diagnostic and Statistical Manual of Mental Disorders (*DSM-5)*-specified psychiatric disorder documented by *International Classification of Diseases, Tenth Revision* (ICD-10) code during the hospital period. Hepatitis C virus was identified as patients with a positive HCV antibody on universal screening followed by a confirmatory test, the presence of HCV ribonucleic acid. Patient-directed discharge was defined as a patient leaving the hospital before completion of discharge orders and was obtained from discharge documentation. In-hospital drug use was defined as suspected or reported illicit drug usage (syringes found at bedside, altered mental status, overdose) plus a urine drug screen (UDS) with presence of substances other than what was prescribed including opioid and nonopioid drugs of abuse. For example, if patients were prescribed oxycodone, and the opiate test and oxycodone tests were positive, this was not considered in-hospital illicit drug use due to potential cross-reactivity. The UDS was performed with a qualitative point-of-care immunoassay test, which was ordered in cases of clinical suspicion for substance use. Medications for OUD use was defined as prescription for a US Food and Drug Administration-approved treatment for OUD including buprenorphine, methadone, or extended-release naltrexone at any point during the hospitalization (not for pain control). Readmissions included any readmission within 30-days to a UAB hospital for any reason. Patient-directed discharge, illicit drug use, readmissions, and death were obtained via chart review.

Data on deaths from any cause were obtained from the electronic medical record and death records from the Jefferson County Coroner Medical Examiner's Office, the county in which most of the Birmingham metro area resides, from October 2016 to December 2019. This includes inpatient deaths captured in the electronic medical record and deaths in the community evaluated by the Medical Examiner's office. This

date was selected to include any deaths that occurred from the study start until December 2019.

In the primary analysis, we analyzed the frequency and associations between PDD, in-hospital IDU, 30-day readmission, and death using McNemar's tests. In the secondary analysis, we used univariate and multivariate logistic regression models to explore association with these outcomes. We focused on only 5 factors in the multivariate models due to the overall small sample size, and the specific factors were selected based on univariate results and our clinical observations as members of the IVAT team. Odds ratios (ORs) and associated 95% confidence intervals (CIs) are reported. All analyses were completed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). The study was approved by UAB Institutional Review Board.

RESULTS

Primary Analysis

Overall, 83 hospitalized patients were referred for the IVAT intervention over the study period (Table 1). The median age was 36 years, 47 (57%) were male, 78 (94%) were white, 46 (55%) were uninsured, 68 (82%) reported illicit opioid use before admission, and 33 (48%) of these 68 were prescribed MOUD during admission, 28 (34%) reported methamphetamine use, and 27 (33%) reported polysubstance use (Table 1). There were 28 (34%) with in-hospital IDU, 12 (14%) had PDD, 9 (11%) died, and 12 (14%) experienced a 30-day readmission.

Of those receiving MOUD, most (76%) received buprenorphine and naloxone, 17% received methadone, and 7% received naltrexone. The most common indication for admission in IVAT recipients is infective endocarditis (38%), vertebral osteomyelitis/epidural abscess (13%), osteomyelitis/septic arthritis (21%), bloodstream infection (4%), and skin and soft-tissue infection (12%) [10]. Comorbidities included 61 (73%) had hepatitis C, 3 (4%) had HIV, 40 (48%) had a psychiatric diagnosis, and 10 (12%) had a history of endocarditis (data not shown). Of the 28 with in-hospital IDU, UDS results were as follows: 21 with opioids (75%), 14 with stimulants (50%), 4 with cannabis (14%), 9 with benzodiazepines (32%), and 18 with multiple illicit drugs present (64%). Of these patients, 11 (39%) had evidence of buprenorphine on UDS and 2 (7%) had methadone.

Of the 9 deaths that occurred over the study period, 6 occurred in a hospital: 4 at UAB and 2 at community hospitals. Of the 4 UAB hospital deaths, 2 were during the sentinel admission and 2 were during readmissions. A total of 5 were referred for autopsy, none of whom had detectable levels of buprenorphine on autopsy testing, meaning they were either not prescribed or not taking it. Of those referred for autopsy, the causes of death included the following: 4 opioid toxicity (3 of 4 with fentanyl, occurring after discharge) and 1 trauma (pedestrian hit by motor vehicle).

Using McNemar's test, we found that in-hospital IDU was significantly associated with PDD ($P = .003$), 30-day

Table 1. Summary of Hospitalized Persons Who Inject Drugs Receiving Care for Injection-Related Infections at an Academic Teaching Hospital, 2016–2017

	Overall N (%)	In-Hospital Illicit Drug Use N (%)		PDD Discharge N (%)		30-Day Readmission N (%)		Death N (%)	
Characteristics		No	Yes	No	Yes	No	Yes	No	Yes
Age (median, years)	36.3	37.1	34.7	36.3	33.6	36.3	37.7	36.2	37.3
Gender									
Male	47 (57)	33 (60)	14 (50)	44 (62)	3 (25)	41 (58)	6 (50)	40 (54)	7 (78)
Female	36 (43)	22 (40)	14 (50)	27 (38)	9 (75)	30 (42)	6 (50)	34 (46)	2 (22)
Race									
White	78 (94)	50 (91)	28 (100)	67 (94)	11 (92)	67 (94)	11 (92)	69 (93)	9 (100)
Black	3 (4)	3 (5)	0 (0)	2 (3)	1 (8)	2 (3)	1 (8)	3 (4)	0 (0)
Other	2 (2)	2 (4)	0 (0)	2 (3)	0 (0)	2 (3)	0 (0)	2 (3)	0 (0)
Insurance									
Public	26 (31)	20 (36)	6 (21)	23 (32)	3 (25)	22 (31)	4 (33)	22 (30)	4 (44)
Private	11 (13)	9 (16)	2 (7)	10 (14)	1 (8)	10 (14)	1 (8)	9 (12)	2 (22)
Uninsured	46 (55)	26 (47)	20 (71)	38 (54)	8 (67)	39 (55)	7 (58)	43 (58)	3 (33)
Opioid Use	68 (82)	43 (78)	25 (89)	58 (82)	10 (83)	58 (82)	10 (83)	60 (81)	8 (89)
Methamphetamine use	28 (34)	18 (33)	10 (36)	21 (30)	7 (59)	26 (37)	2 (17)	26 (35)	2 (22)
Polysubstance	27 (33)	16 (29)	11 (39)	20 (28)	7 (58)	25 (35)	2 (17)	25 (34)	2 (22)
Psychiatric Diagnosis	40 (48)	30 (55)	10 (36)	31 (44)	9 (75)	34 (48)	6 (50)	39 (53)	1 (11)
Inpatient MOUD	33 (40)	15 (27)	18 (64)	27 (38)	6 (50)	29 (41)	4 (33)	31 (42)	2 (22)
9-Item Risk Assessment									
High	40 (48)	21 (38)	19 (68)	30 (42)	10 (83)	36 (51)	4 (33)	35 (47)	5(56)
Low	43 (52)	34 (62)	9 (32)	41 (58)	2 (17)	35 (49)	8 (67)	39 (53)	4 (44)

Abbreviations: MOUD, medications for opioid use disorder; PDD, patient-directed discharge.

Table 2. Odds of Adverse Hospital Events for Persons Who Inject Drugs

Characteristics	Univariate Model Odds Ratio (95% CI)	*P* Value	Multivariable Model Odds Ratio (95% CI)	*P* Value
In-Hospital Illicit Drug Use				
Gender				
Female	1.50 (0.60–3.75)	.39	1.84 (0.53–6.32)	.33
Male[a]	–		–	
Opioid Use				
Yes	2.33 (0.60–9.04)	.22	0.81 (0.15–4.28)	.81
No[a]	–		–	
MOUD				
Yes	4.80 (1.81–12.72)	**<.01**	**3.50 (1.11–11.07)**	**.03**
No[a]	–		–	
Psychiatric Diagnosis				
Yes	0.46 (0.18–1.18)	.11	**0.26 (0.07–0.97)**	**.04**
No[a]	–		–	
9-Item Risk Assessment				
High (5–9)	**3.42 (1.31–8.94)**	**.01**	**3.23 (1.01–10.35)**	**.04**
Low (1–4)[a]	–		–	
Length of stay[b]	1.10 (0.93–1.29)	.27	1.05 (0.87–1.27)	.58
Patient-Directed Discharge				
Gender				
Female	**4.89 (1.22–19.65)**	**.03**	3.31 (0.64–17.19)	.15
Male[a]	–		–	
Opioid Use				
Yes	1.12 (0.22–5.74)	.89	1.51 (0.17–13.13)	.71
No[a]	–		–	
MOUD				
Yes	1.63 (0.48–5.57)	.44	0.83 (0.16–4.31)	.82
No	–		–	
Psychiatric Diagnosis				
Yes	3.87 (0.97–15.51)	.06	2.88 (0.53–15.69)	.22
No[a]	–		–	
9-Item Risk Assessment				
High (5–9)	**6.83 (1.39–33.49)**	**.02**	**7.56 (1.20–47.49)**	**.03**
Low (1–4)[a]	–		–	
Length of stay[b]	0.84 (0.63–1.12)	.23	0.71 (0.47–1.05)	.09

Bold text denotes statistical significance for a *P* value < .05.

Abbreviations: CI, confidence interval; MOUD, medications for opioid use disorder.

[a]Reference.

[b]Odds ratio for length of stay represents outcome associated with each week of inpatient care. Multivariable models include gender, opioid use, psychiatric diagnosis, and 9-item risk assessment.

readmission ($P = .005$), and death ($P = .0003$). Patient-directed discharge and 30-day readmission were not significantly associated with death nor with each other (data not shown). In univariate analysis, we found that receiving MOUD at any point during the admission was significantly associated with in-hospital illicit drug use (OR = 4.8, $P < .01$) (Table 2). Cravings are a part of the 9-item risk assessment (Supplemental Table) and were present in 28 of 83 (34%) of patients. Cravings were significantly associated with in-hospital drug use (OR = 4.99; 95% CI, 1.87–13.32; $P = .0013$) (data not shown). Also in univariate models, female gender was significantly associated with PDD (OR = 4.89, $P = .03$).

Secondary Analysis

Finally, we explored the association of the 9-item risk score and found that a score of 5 or greater was significantly associated with both in-hospital illicit drug use and PDD with an OR of 3.4 and 6.8, respectively. For this reason, we categorized those with a score of 5 or more as "high risk" for the purpose of this secondary analysis evaluating the association of the risk score with adverse hospital outcomes. [Note: This is in contrast to our prior analysis using the 9-item risk score to determine discharge disposition in which a score of less than or equal to 3 was used to determine which patients could be discharged with OPAT based on AM physician expert opinion [10].]

In multivariable models, we found that the 9-item risk is significantly associated with both IDU and PDD when controlling for gender, opioid use, MOUD, psychiatric diagnosis, 9-item risk, and length of stay (Table 2). Furthermore, presence of a comorbid psychiatric diagnosis was associated with in-hospital illicit drug use. Receiving MOUD at any time during the hospital period was associated with in-hospital illicit drug use (adjusted aOR [aOR] = 3.50, $P = .03$) but was not associated with PDD (aOR = 0.83, $P = .82$). Using the same variables to model 30-day readmissions, only length of stay was significant: there was a significant reduction in 30-day readmissions for every 7 days increase in length of stay (OR = 0.58, $P = .03$; data not shown). Because there were only 9 deaths, we did not fit models for this outcome.

DISCUSSION

As ID physicians, we have an essential role in identifying and mitigating hospital risks for PWID [6]. Our findings confirm that hospitalized PWID are highly vulnerable due to a lack of insurance, psychiatric disorders, use of multiple substances, including methamphetamines, and high mortality. Our results support our hypothesis: understudied hospital outcomes for PWID including drug use while hospitalized, PDD, readmissions, and death are surprisingly frequent. Furthermore, these adverse outcomes are strongly linked: illicit drug use in the hospital is associated with PDD, hospital readmission, and death. The implications of suboptimal hospital care due to substance use and PDD are greater in states like Alabama where hospitals are the only safety net for uninsured residents without Medicaid expansion. Because 55% of patients in our study were uninsured, a majority have limited access to primary care, ID, and AM services. Thus, preventing adverse hospital outcomes that truncate hospital care delivery may be lifesaving in PWID with bacterial infections in these regions.

More than one third of our patients were identified as using illicit drugs during admission. This is similar to results by Fanucchi et al [5] who report that approximately 40% of hospitalized PWID (requiring intravenous antibiotics) use drugs during admission. We are unaware of additional literature in the United States describing in-hospital illicit drug use perhaps due to the difficulties in identifying this behavior, which is concealed due to stigma and criminalization [15]. A Canadian study suggests that more than 40% of persons who use drugs reporting ever using drugs while hospitalized [16]. Our findings suggest that in-hospital drug use is strongly associated with PDD, readmissions, and death; however, this topic needs further study in the context of the US drug use epidemic. Nonetheless, because of the harm associated with illicit drug use, it is imperative that health systems begin to implement patient-centered ways to prevent illicit drug usage including the use of MOUD, management of withdrawal, pain, and other triggers for substance use [17]. We recommend that ID providers inquire about illicit drug use in a nonjudgmental manner and ensure rapid AM consultation, MOUD, and supportive services (eg, peer recovery support) to promote retention in infection treatment [9]. Due to the painful nature and surgeries indicated for injection-related injections, pain should be anticipated and managed aggressively. Uncontrolled pain is a trigger for drug use and potentially leads to PDD [2, 18]. It is worth noting that hospitalized patients report using illicit drugs to manage pain and withdrawal because these symptoms, when untreated, interfere with their medical treatment [6].

The number of patients leaving via PDD (14%) in our population of hospitalized PWID was lower than expected. This is lower than the 20% rate of PDD observed in the overall population of PWID receiving care at UAB through 2018 [19]. Patient-directed discharge in other cohorts of PWID with acute infections varies from 12% to more than 30% [5, 9]. For uninsured PWID, there may be little or no community-based ID and/or primary care access. When a PWID leaves via PDD with a partially treated bacterial infection in a rural state like Alabama, they often face insurmountable barriers to healthcare. In this context, we anticipated that PDD would be associated with readmissions and death, which was not the case. However, it is possible that our small sample size and short follow-up time did not allow us to detect this association. Regardless, leaving via PDD has been associated with poor health outcomes, including as much as a 12-fold increase in 30-day readmissions and a 2-fold increase in deaths [3, 20, 21].

Recent data from Simon et al [8] describe common reasons that PWID leave hospitals via PDD: poorly managed withdrawal, cravings, and/or pain, stigma, and discrimination, and restrictive hospital policies. Hospitals must develop patient-centered interventions to respond to these obstacles and retain patients with severe life-threatening bacterial infections. Creating a safe and healing environment will require prompt evidence-based treatment of withdrawal, pain, mental health comorbidities, and eradication of stigma, especially stigma directed to PWID from providers and staff [15]. Although there are limited data on in-hospital illicit drug use, there are data that AM consultation reduces PDD in PWID. To prevent withdrawal and cravings that may trigger PDD, patients with OUD should receive MOUD. Many patients in our cohort report using multiple drugs, including methamphetamine, for which there is no effective pharmacotherapy. Thus, physicians and staff should work with patients to identify an approach that reduces cravings, withdrawal, and other triggers for substance use. Finally, eradication of stigma from hospital staff is essential to promote healing and reduce PDD [6, 18].

Our findings suggest that this 9-item risk may identify patients at greatest risk for specific adverse hospital outcomes, but the limited study size and single Southeastern site limit the generalizability of results. Because the study inclusion required

documented or suspected IDU, we likely did not capture all patients with a history of drug usage. Thus, results may represent patients with more severe substance use disorder and/or infections. Furthermore, because MOUD was not received by all patients with OUD in this real-world study, it is possible that MOUD was prescribed preferentially for those with the most severe OUD. The results may not be applicable to other hospitals where access to AM and/or ID providers is limited [22]. Our results likely minimize the magnitude of adverse events because readmissions occurring outside of our health system and deaths in the community not reported to county coroners were not captured. Likewise, the use of illicit drugs during hospitalization is difficult to detect as part of routine care given the criminal nature and stigma associated with this activity. The UDS immunoassay that our health system utilizes measures hydromorphone, codeine, hydrocodone, methadone, heroin, oxycodone, and morphine; however, it does not detect fentanyl. Therefore, this study does not capture fentanyl use in the hospital.

It is noteworthy that receiving MOUD at any time during the admission was associated with in-hospital illicit drug use, but we urge caution in interpreting this finding. Due to the observational nature, there was no standardization in time to MOUD initiation, MOUD selection (buprenorphine vs naltrexone vs methadone), or dose. The UDS tests were not collected in standard intervals but instead were often collected reflexively based on patient behaviors (eg, syringes at bedside, intoxication). It is possible that in-hospital drug use was underdiagnosed because patients may have refused UDS or left via PDD. It is also challenging to understand whether MOUD preceded in-hospital illicit drug use or whether MOUD was initiated in response to illicit drug use. We believe there are 3 explanations for the association between MOUD and illicit drug use in the hospital: (1) stimulant, benzodiazepine, and polysubstance use that is not amenable to MOUD; (2) limited MOUD uptake and adherence; and (3) MOUD as a marker of severity of OUD. As noted in the results, a large percentage used stimulants (50%), cannabis (14%), and benzodiazepines (32%) in the hospital, which are not treated by MOUD. Thus, one would not expect these behaviors to respond to MOUD. It is notable that these substance-use behaviors in the hospital are similar to findings by Fanucchi et al [5] (41% stimulants, 35% benzodiazepines). We also found that few patients had MOUD detected on UDS, which suggests that either MOUD had not been initiated, treatment was interrupted, or patients were not taking the medication as prescribed. This is consistent with our findings in a prior evaluation of MOUD uptake among IVAT recipients: patient disinterest, failure to receive AM consultation, and PDD were cited as common reasons that MOUD was not received during admission [23]. Finally, in our prior evaluation of the IVAT team [23], we found that a greater percentage of patients with high-risk scores (62%) received MOUD relative to mild risk (29%). Thus, MOUD is likely a marker for severity of OUD, which may confound results on the relationship between MOUD and illicit drug use. This relationship deserves further study to understand how to optimize MOUD uptake to reduce high-risk behaviors. Despite these limitations, because this is only the second publication of in-hospital illicit drug use in the United States and the first study of this phenomenon in the context of MOUD use, we believe the results are still informative. Furthermore, the results are consistent with reports on the complex, morbid outcomes of hospitalized PWID [3, 4, 6].

CONCLUSIONS

In closing, we hope to inspire ID physicians, staff, and researchers to take an active role in responding to the drug use epidemic. It is impossible to provide evidence based prevention and/or treatment for infections in substance using populations without adequate treatment of the underlying addiction. This is true for severe bacterial infections and bloodborne infections such as HIV. Moreover, it is not sufficient to evaluate hospital care for PWID using the same benchmarks as the general population (eg, length of stay, readmissions). Additional outcomes require investigation including PDD, MOUD uptake, illicit drug use, and overdose while hospitalized. To effectively deliver ID care in the hospital setting and support linkage to community-based care, we must identify patient-centered ways to intervene on the unique health outcomes that contribute to the devastating morbidity and mortality of injection-related infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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A Proposal for Addiction and Infectious Diseases Specialist Collaboration to Improve Care for Patients With Opioid Use Disorder and Injection Drug Use Associated Infective Endocarditis

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Patients with injection drug use-associated infective endocarditis and opioid use disorder often receive treatment for the infection that fails to address its underlying cause. People who inject drugs (PWID) and develop serious infections also face disparities in antibiotic management, particularly with regards to use of outpatient parenteral antimicrobial therapy (OPAT). We highlight literature on OPAT in PWID challenging the notion that PWID cannot be managed with OPAT. Given that OPAT use amongst PWID and non-PWID yields similar outcomes, we argue that a bias against OPAT use in PWID is unwarranted and may reflect stigma rather than data. We further note the proven value of comprehensive OUD treatment on endocarditis treatment outcomes, which also addresses the potential safety concerns of OPAT in PWID, and propose a treatment model in which Addiction and Infectious Disease specialists collaborate to integrate opioid use disorder treatment into injection drug use-associated infective endocarditis care.

Key Words: infective endocarditis, injection drug use, opioid use disorder, outpatient parenteral antimicrobial therapy, PICC

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Injection drug use (IDU) is a risk factor for severe infections including infective endocarditis (IE) and hospitalizations for IDU-associated IE are rising. Unfortunately, patients with IDU-IE and OUD frequently receive care focused on OUD sequela (ie, endocarditis) while failing to address the underlying cause. In 1 study of patients with OUD and *Staphylococcus aureus* bacteremia (43% with IDU-IE), 98% received an infectious diseases consultation, 100% received an echocardiogram, and 100% received an appropriate duration of antibiotic therapy; in contrast, 74% received treatment for their substance use disorder beyond recommendation of abstinence, 29% received a psychiatry consult, and only 2% discharged with a clear plan for ongoing outpatient addiction care.[1] Among a sample of patients hospitalized for IDU related infections, Jicha et al found that less than one-fifth of patients had any form of outpatient SUD treatment recommended by primary teams on discharge despite frequent recommendation of "cessation" of substance use.[2]

People who inject drugs (PWID) and develop serious injection-related infections (SIRIs) face disparities in antibiotic management. Standard treatment for IE consists of prolonged (2–6 week) courses of intravenous (IV) antibiotics via a long-term catheter, often completed at home in a practice termed outpatient parenteral antimicrobial therapy (OPAT). PWID have traditionally been excluded from this model of treatment due to concern for misuse of the IV catheter to inject drugs, precipitating venous thrombosis, catheter-associated bloodstream infection, or other complications.[3] As an alternative approach, prolonged hospitalization for IV antibiotic therapy is limited by cost and patient nonadherence, particularly when the underlying substance use disorder is not addressed. Here, we highlight the literature supporting OPAT in PWID and propose a treatment workflow in which Infectious Disease and Addiction specialists collaborate to integrate OUD treatment into IDU-IE care.

WHAT ARE THE OUTCOMES OF OPAT IN PATIENTS WHO INJECT OPIOIDS?

Recent data challenge the notion that PWID cannot be treated with OPAT. Suzuki et al identified 10 studies (2 prospective, 8 retrospective) examining OPAT outcomes in PWID, most of which enrolled patients with active or recent (ie, within the past year) IDU.[3] Specific substance use disorder interventions were offered infrequently in these studies, including drug counseling (n = 3), group treatment (n = 2), urine toxicology screening (n = 2), opioid therapy (n = 1), and a comprehensive harm reduction framework including sterile

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injection equipment, training, and rescue naloxone (n = 1). Despite this, rates of OPAT treatment completion ranged from 72% to 100%, comparable to or better than OPAT completion rates reported among non-PWID.[4] Mortality during OPAT was 0% in 7 studies and 2%–10% in the remaining 3; of note, in the study reporting a 10% mortality rate, mortality was no better in a comparator population of non-PWID receiving OPAT.[3] The 3 studies reporting documented catheter manipulation noted rates of 0%–2% and no difference in line infection between PWID and non-PWID receiving OPAT. Data of OPAT in PWID receiving concurrent addiction treatment is even more encouraging; Price et al, reporting a cohort of 68 such patients, noted 100% antibiotic completion without a single episode of overdose, death, or catheter-related complication.[5]

Finally, while other evidence suggests that OPAT for PWID may be more labor-intensive compared to non-PWID, patient-centered outcomes remain similar. Comparing 159 PWID to 6493 non-PWID treated with OPAT for serious infections, Dobson et al reported PWID had higher incidences of after-hours calls for telephone consultation to troubleshoot catheter complications and accidental dislodgements, but no difference versus non-PWID in all-cause catheter removal for thromboses, bloodstream infections, or other complications. In addition, 98% of PWID completed their treatment, and only a single patient was readmitted to the hospital.[6]

We conclude that robust data suggests OPAT, the current standard of care for serious infections like IE in non-PWID, achieves similar outcomes with similarly low rates of adverse events in PWID. Thus, a preference for alternative antimicrobial approaches in PWID versus non-PWID is not justified. Moreover, rates of discharge against medical advice among patients with OUD admitted for IE have been reported as high as 34%–48%; hence, shortened hospitalizations facilitated by OPAT may improve overall quality of care in this population even where rates of OPAT noncompletion, catheter misuse, and other complications are high.[7]

WHAT CAN BE DONE TO IMPROVE OUTCOMES OF OPAT IN PATIENTS WHO INJECT OPIOIDS?

Efforts to optimize OPAT outcomes in PWID largely consist optimizing patient selection for OPAT and comprehensively managing the underlying OUD. A review of 679 patients treated for IDU-IE found that initiation of pharmacotherapy for OUD within 30 days of discharge was associated with substantial reduction in all-cause mortality at 1 year after discharge (adjusted hazard ratio 0.30; 95% confidence interval 0.1–0.89).[8] Inpatient pharmacotherapy for OUD in patients with SIRI has also been associated with significant reductions in against medical advice discharge.[7] Fanucchi et al report a model of integrated OUD and IDU-IE care with opioid agonist treatment and OPAT achieved infection cure and substance use outcomes similar to or better than usual care while also achieving a >3 week mean reduction in length of stay.[9] Importantly, Suzuki et al showed that the majority of inpatients with OUD and IE are receptive to medication for opioid use disorder (MOUD) when offered by addiction specialists.[10]

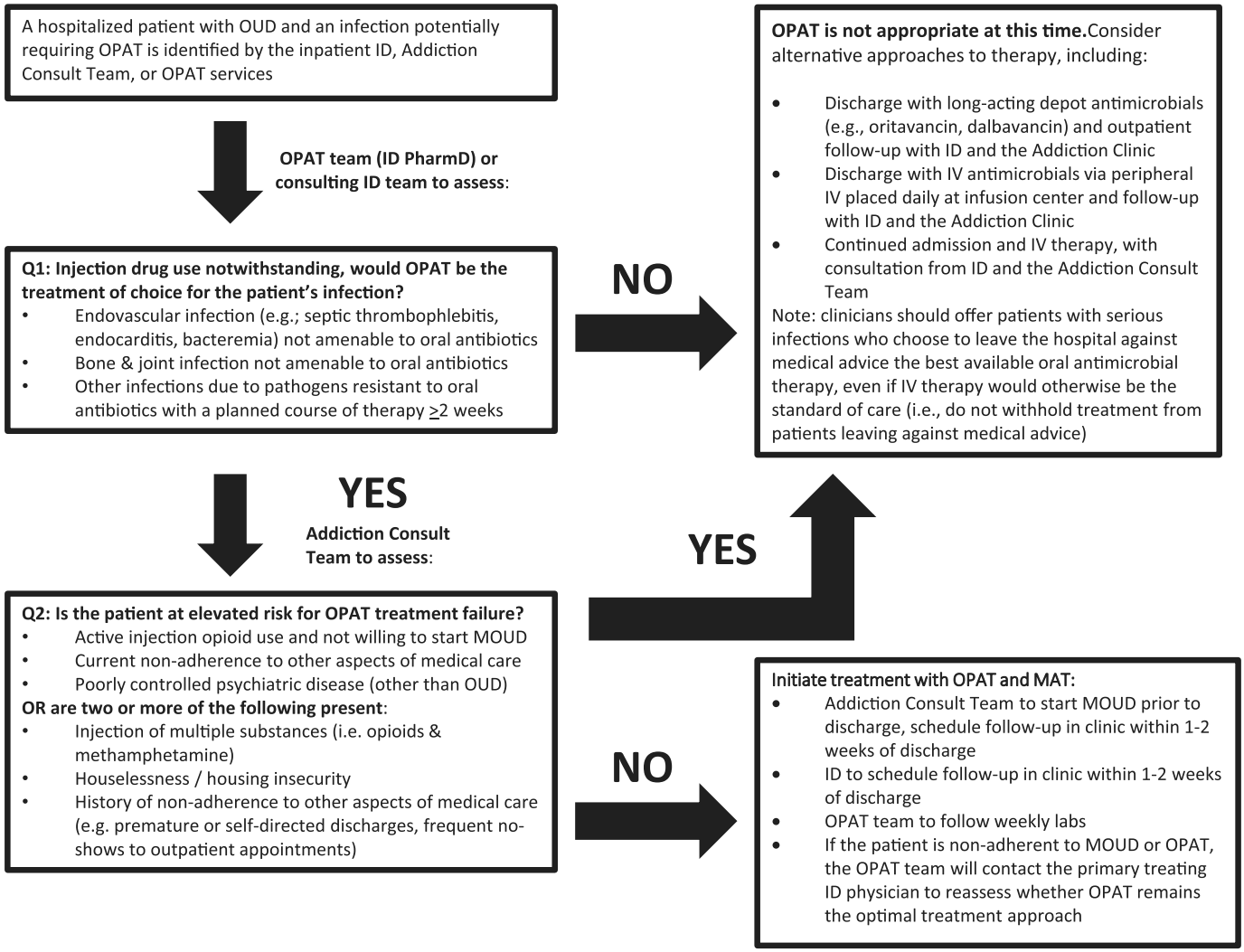
Evidence-based identification of patients at highest risk of complications and treatment noncompletion may improve OPAT outcomes. PWID with housing instability are more likely to have evidence of line tampering, develop secondary bloodstream infection, and have a 30-day readmission related to OPAT versus their non-PWID and housed PWID peers.[11] Eaton et al validated a 9-point risk assessment tool for OPAT treatment failure in PWID, which included active cravings, unstable home environment, co-occurring psychiatric diagnosis, history of drug overdose or multiple relapses, polysubstance use, family history of addiction, history of trauma, and limited willingness to change.[12] The authors offered OPAT to PWID defined as "low-risk" (≤3 points on their assessment tool), reporting significant reductions in mean LOS and cost savings with no increased rate of readmission with this intervention.

Improving outcomes in patients with IDU-IE will require multidisciplinary efforts to actively treat OUD, mitigate potential clinician bias with evidence-based screening tools that assess likelihood of OPAT success, and engage social work and public health services to address social determinants of health. Early engagement of patients in addiction treatment via inpatient addiction consultation services is likely a key strategy to reducing recurrent hospitalizations for OUD-associated endocarditis.[13]

FUTURE DIRECTIONS AND MODELS OF CARE

We propose a collaborative care model incorporating physician and pharmacist specialists in Addiction and Infectious Diseases into a comprehensive approach to MOUD and OPAT in patients with IDU-IE and other SIRIs requiring prolonged IV antibiotic therapy. This model should emphasize short-term follow-up and planning for outpatient continuation of MOUD to improve adherence to both MOUD and OPAT. We have adopted such a workflow at the University of Nebraska Medical Center, which could be adapted to fit other institutions based on local patient populations and their needs (Fig. 1).

In implementing this workflow, we encountered obstacles that clinicians at other institutions should anticipate. First, many of our patients with OUD have concurrent injection methamphetamine use, a disorder for which both treatment options and data on OPAT success and safety are far more limited. A contingency management approach, in which patients receive financial or other incentives to abstain from injection methamphetamine use, has been described but not reported in the context of infection; we believe applying this approach for patients who inject methamphetamine and are receiving OPAT merits further study.[14] Second, resistance to a collaborative model of care from hospital leadership, home infusion services, or both may arise out of concern for medicolegal risk if a catheter is misused. To address these concerns, we recommend adopting a formal institutional protocol congruent with scientific evidence (such as those cited here), and endorsed by key stakeholders including Infectious Diseases, Addiction Medicine and/or Addiction Psychiatry, and OPAT team leaders, and the institutional legal team.



Legend:
OUD= Opioid Use Disorder; IV= intravenous; ID = Infectious Diseases; OPAT= Outpatient Parenteral Antimicrobial Therapy; MOUD = Medication for Opioid Use Disorder

FIGURE 1. The University of Nebraska Medical Center Collaborative Model.

Such a workflow is likely to require continuous reevaluation and revision as standards of care for OUD and IE treatment (in all patients, not just PWID) continue to evolve. For instance, new data support early transition to oral antibiotics for IE, which may obviate the need for OPAT in at least some of these cases.[15] Novel long-acting IV antibiotics (eg, dalbavancin) may allow effective SIRI treatment without a long-term catheter, and present an opportunity for psychiatrists to share their experiences with infectious disease colleagues, as the former have managed patients with depot antipsychotics in the ambulatory and home settings for many years. Finally, formal multidisciplinary endocarditis teams including cardiothoracic, infectious disease, and addiction specialists, and patient-centered treatment planning conferences, may improve IE outcomes.

CONCLUSIONS

OUD and IDU-IE are concurrent public health crises that require effective, multidisciplinary care focused on treating both diagnoses. Given that OPAT use amongst PWID and non-PWID yields similar outcomes and is likely superior to attempting prolonged hospitalization for PWID with IE, general preference against OPAT in PWID is unwarranted. Clinicians should address bias against PWID by embracing evidence-based protocols for OPAT and comprehensive OUD treatment in this setting- and ultimately, by advocating for public policy facilitating harm reduction to limit the complications of IDU.

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Harm Reduction Journal

CASE STUDY

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Self-injecting non-prescribed substances into vascular access devices: a case study of one health system's ongoing journey from clinical concern to practice and policy response

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Abstract

Background: Overdose-associated deaths and morbidity related to substance use is a global public health emergency with devastating social and economic costs. Complications of substance use are most pronounced among people who inject drugs (PWID), particularly infections, resulting in increased risk of hospitalization. PWID often require intravenous access for medical treatments such as antibiotics; however, vascular access may be limited due to the impacts of long-term self-venipuncture. While vascular access devices including peripherally inserted central catheters (PICCs) allow reliable and sustained routes of administration for indicated therapies, the use of PICCs among PWID presents unique challenges. The incidence and risks associated with self-injecting non-prescribed substances into vascular access devices (SIVAD) is one such concern for which there is limited evidence and absence of formal practice guidance.

Case presentation: We report the experience of a multidisciplinary team at a health organization in Vancouver, Canada, working to characterize the incidence, patient and healthcare provider perspectives, and overall impact of SIVAD. The case study of SIVAD begins with a patient's perspective, including patient rationale for SIVAD, understanding of risks and the varying responses given by healthcare providers following disclosure of SIVAD. Using the limited literature available on the subject, we summarize the intersection of SIVAD and substance use and outline known and anticipated health risks. The case study is further contextualized by experience from a Vancouver in-hospital Overdose Prevention Site (OPS), where 37% of all individual visits involve SIVAD. The case study concludes by describing the systematic process by which local clinical guidance for SIVAD harm reduction was developed with stakeholder engagement, medical ethics consultation, expert consensus guideline development and implementation with staff education and planned research evaluation.

Conclusion: SIVAD is encountered with enough frequency in an urban healthcare setting in Vancouver, Canada, to warrant an organizational approach. This case study aims to enhance appreciation of SIVAD as a common and complex clinical issue with anticipated health risks. The authors conclude that using a harm reduction lens for SIVAD policy and research can provide benefit to clinicians and patients by offering a clear and a consistent healthcare response to this common issue.

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Background

Vancouver, British Columbia, Canada, with a metropolitan population of 2.5 million in a province of 4.7 million people, is facing a public health emergency of drug overdose and associated death [1]. In 2021 alone, 535 Vancouver municipal and 2267 provincial illicit drug toxicity deaths were reported, representing the leading cause of unnatural death with an average 6 deaths per day [2]. It is well known that persons who inject drugs (PWID) are at increased risk of overdose and invasive bacterial infections such as infective endocarditis or osteomyelitis, with associated increases in hospitalization rates, morbidity and mortality compared to those who do not inject drugs [3–6].

Many of these bacterial infections require ongoing intravenous (IV) medications and vascular access devices (VADs). Peripheral intravenous catheters and peripherally inserted central catheters (PICCs) are clinically indicated in these circumstances. A PICC is often used when vascular access is limited or IV medications such as antibiotics are required for several weeks. Traditional peripheral VAD options may be limited in some PWID as a result of chronic venous disease induced by years of self-venipuncture, making PICCs an important (and sometimes necessary) consideration when protracted IV therapy is required [7].

Clinicians caring for patients who use substances in hospital and community settings, including Overdose Prevention Sites (OPS) and Supervised Consumption Sites (SCS) [8], may encounter patients self-injecting non-prescribed substances into their vascular access devices (SIVAD) rather than performing self-venipuncture. To date, the incidence of SIVAD and related complications has not been well studied, nor is it known if harm reduction measures reduce risks associated with SIVAD. No formal guidance has been issued regarding an optimal approach to this complex clinical issue from healthcare institutions, professional colleges, or harm reduction research and policy development bodies.

This paper describes a case study at Providence Health Care (PHC), an organization in Vancouver, British Columbia, where SIVAD is encountered with relative frequency. It begins with an exploration of SIVAD from the perspective of an individual patient, followed by data collected from a local Vancouver OPS and a review of the available literature in an attempt to characterize the clinical context, incidence and anticipated risks of SIVAD. The case study concludes by describing the systematic efforts of a multidisciplinary team in Vancouver to create and implement a local nursing clinical practice guideline and associated education and research plan around harm reduction approaches to SIVAD.

The authors also discuss current knowledge gaps and controversies around the medical, ethical and legal legitimacy of harm reduction for SIVAD and applicability of the Vancouver approach to other national and international contexts. This paper's aim is to enhance the clinical understanding of SIVAD and through transparent shared experience, encourage other healthcare teams to develop and research SIVAD-related practices that are appropriate for their local context.

Methods

This descriptive case study is comprised of multiple related research efforts sharing a common research objective: understanding SIVAD practice and impact at our health organization to inform development and implementation of related policy and practice. Rather than having a prespecified overarching research plan and methodology, this case study integrates mixed methods of multiple related projects identified and purposefully brought together through organization-wide efforts—risk management and ethics consultations—triggered in part by incident cases of SIVAD. The methodology of individual projects is further outlined in relevant sections.

SIVAD patient perspective and clinical features

Patient perspective of SIVAD

Patient-centered care begins with exploring patient perspectives. As outlined in "Robin's" case (see Table 1), hospitalization can be challenging for people with substance use disorders (SUD) as they may experience withdrawal symptoms and cravings following interruption of their usual substance use patterns [9]. Unmanaged pain, withdrawal and cravings may lead individuals to use non-prescribed substances while admitted to hospital [10]. Self-venipuncture options may be limited in some PWID because of venous thrombosis, sclerosis and occlusion of preferred injection sites in the upper and lower extremities [7]. A minority of PWID will inject into the internal jugular vein in the neck, the femoral vein in the groin, or smaller veins in the forehead or penis, which are often perceived as "higher risk" for complications, such as infection and excessive blood loss [11, 12].

As described by "Robin", patients may perceive benefits arising from SIVAD such as avoiding self-venipuncture in

Table 1 Patient experience and perspective of SIVAD

Robin is 38 years old and lives in Vancouver's Downtown Eastside. She describes herself as a vibrant, active community member who has been injecting drugs for the last 14 years. She lost both of her parents in a tragic accident in her young adulthood, creating complex and strained family relationships. In her early 20's, she started using stimulants and at age 25 began taking oxycodone for her osteoarthritis. At age 27, she began injecting drugs intravenously (IV). She receives injectable opioid agonist therapy (iOAT)[1] at an outpatient clinic, but iOAT alone has not been sufficient to treat her pain and opioid tolerance, and she continues to use additional non-prescribed IV drugs
Five years ago, Robin was admitted to hospital with a skin infection. It was around this time that she had run out of veins in her arm that she could easily inject into. Thus, she started injecting substances into her abdomen, legs, upper arms and jugular vein. Frequent vein misses ("missed hits") resulted in many areas of skin breakdown and abscesses. A peripherally inserted central catheter (PICC) was inserted for her to receive IV antibiotics
She remembers being in a lot of pain and watching the nurses clean and flush the line, attach syringes loaded with opioids, and administer the medication so easily. She thought "I could do that." She started collecting pre-packaged saline flushes accessible around the hospital unit and was relieved not to have to inject into her neck, and to have a way to avoid severe "dope-sickness" (withdrawal)
During subsequent admissions to hospital, she disclosed her PICC use to nurses and physicians and asked for sterile supplies. Sometimes the IV team inserting the PICC informed her about the risks of using it, and sometimes she was given supplies and education on how to use/access the PICC using sterile technique. One healthcare provider told her "You're going to kill yourself" by using the PICC, but she was not told how or why this may be true
On a recent hospital admission for another infection, her desired discharge plan was to receive IV antibiotics as an outpatient. Unfortunately, this was declined because she disclosed PICC use to healthcare providers. Instead, her IV antibiotics were switched to oral and her PICC removed. This came as a surprise to Robin, who felt as though she was being punished for her honesty. She does not recall anyone talking to her about this change in discharge plans. Because of this situation and based on variability in provider responses to her PICC line use, she no longer discloses her PICC use because she fears it will compromise relationships with healthcare providers, and ultimately, her healthcare
Robin says that she frequently sees patients at community OPSs injecting into vascular access devices using unsterile technique. Often, she will intervene and offer advice when she sees unsafe practices but worries about the lack of education among people who inject drugs
A review of Robin's medical record reveals that she has received care from addiction medicine, infectious disease, internal medicine and wound care specialists during several recent admissions. Notes indicate that clinicians were aware of Robin's PICC use, with some notes referring to "tampering" or "abuse" of the line. One provider noted that the patient was instructed by community workers on how to use her PICC to inject. There were no notes regarding patient-provider discussions around the risks of PICC use or teaching about sterile technique. She was given general education on overdose prevention. On several occasions, notes indicate that Robin left hospital with her PICC in place, despite the team's plans to remove it prior to discharge

Patient perspective refle ts a synthesis of medical records and multiple voluntary interviews with 'Robin' conducted by an addiction nurse educator during hospital admissions and community follow-ups between 2017 and 2020 as part of an ongoing patient experience exploratory study. Demographic details have been anonymized. Permission for publication was obtained and consent signed by the individual providing the above perspective

[1] *SIVAD* self-injection into vascular access device, [2]*iOAT* injectable opioid agonist therapy. [3]*PICC* peripherally inserted central catheter

less desirable or challenging sites, or maintaining venous access to avoid or alleviate drug withdrawal. Patients may or may not be aware of SIVAD related health risks and may receive a variety of responses from healthcare providers ranging from PICC removal and discharge to education on risks and provision of harm reduction supplies.

Just as "Robin" experienced, the majority of PWID with a history of hospital PICC insertion interviewed by Guta and colleagues for a recent qualitative study reported that they had been subjected to "threats of discharge". Stigmatizing experiences were common. And similar to "Robin's" observations about awareness of risk, many PWID may be unaware of the possible risks of SIVAD [13].

Potential infectious and non-infectious risks of SIVAD

As exemplified by "Robin's" recurrent hospitalizations, PWID, independent of IV access or its use, are at increased risk of overdose and invasive bacterial infections [3, 4]. Additionally, VADs themselves have inherent risks. These risks are modified by device, patient, and care environment related factors. For context, among non-PWID with central venous catheters or PICCs, the estimated incidence of associated bloodstream infections (BSI) is between 0.5 to 5.8% and deep venous thrombosis 3%, over the time period that a catheter remains in place [14, 15]. VAD malposition is estimated to occur in up to 9.3% of patients, while device dysfunction occurs at rates up to 78 per 10,000 indwelling days [16]. VAD complications often require device interventions, such as occlusion management, repair, removal, and replacement [17, 18].

Mirroring "Robin's" experiences in hospital, clinicians report concern about risks of using PICCs in PWID, especially in non-clinical environments, with some opting to remove PICCs and pursue second line oral antibiotic treatment for infections due to fears of liability and censure from colleagues [13]. While increased risk of VAD complication among PWID is often cited, empirical evidence demonstrating this is absent. Risk may be inferred and influenced by general conceptions about the risks of IV drug use (IDU) [19]. Where evidence exists, objective and perceived risk discordance becomes apparent.

Among a cohort of 159 PWID receiving extended courses of outpatient antibiotics via VAD, no significant differences in incidence of BSI, thrombosis, or complications warranting device removal were seen when compared with non-PWID in the same program [20]. A recent review of published studies evaluating the safety of outpatient parenteral (IV) antibiotics for PWID also

found no difference in rates of IV access-related adverse events when compared with non-PWID [21]. There are limitations of the available data including lack of standardized assessment for and documentation of SIVAD incidence among study populations. Furthermore, selection bias for more medically and socially stable PWID to include in studies and non-standardized application of SIVAD prevention policies and harm reduction measures may limit generalizability of existing studies.

In summary, although the rates and types of complications associated with SIVAD have not been clearly defined, it could be anticipated that patients who engaged in SIVAD may experience serious harms, with some resembling the risks of traditional self-venipuncture (e.g. blood stream infection, overdose) and others unique to SIVAD (e.g. air embolism, thrombosis, loss of device functionality). Harms may be more likely if patients are unaware of best practices around VAD care including the need for sterile technique and proper routine flushing following injection of substances [22, 23]. The potential impact of SIVAD harm reduction measures, including education on risks, sterile technique, or provision of single-use, sterile supplies is unknown.

Experience from Vancouver overdose prevention sites and supervised consumption sites

In the absence of formal practice guidelines, Overdose Prevention Sites (OPS) and Safe Consumption Sites (SCS) in Vancouver have developed informal harm reduction approaches to SIVAD. OPSs, like SCSs, are spaces where people can inject their own non-prescribed substances using single-use, sterile equipment. While SCSs are federally funded and have nursing staff on site, OPSs are typically staffed by peers (people with lived/living experience of substance use) and are provincially sanctioned as a temporary response to British Columbia's drug overdose and death public health emergency [8, 24].

At Insite, an SCS in Vancouver's Downtown Eastside neighborhood, staff report engaging in harm reduction activities around SIVAD since 2006 and have developed an internal nursing resource covering risk education (e.g. overdose, VAD dysfunction) and sterile self-injection procedures [25, 26]. Staff at Insite encourage clients to access veins via self-venipuncture or to inject into a muscle rather than use their VAD if present. Nurses also assess VAD function and for localized signs of infection. If a client elects to use their VAD despite education regarding risks, staff provide education on the safest possible SIVAD technique and sterile injection supplies. This informal nursing guideline is currently for internal use only and is not published or publicly accessible at this time.

In 2018, the St. Paul's Hospital Overdose Prevention Site (SPH OPS) was opened [27, 28]. This OPS was located in a small trailer adjacent to the hospital, staffed by peer workers and was accessible to both hospital inpatients and community members. Between its opening in May 2018 and February 2021, there were 34,229 visits to this OPS of which 4931 (14%) were hospital inpatients and 1318 (27%) of patient visits involved SIVAD. A visit is defined by one individual encounter with a client, with some clients visiting multiple times per day to inject substances. Clients used identification "handles" instead of names so it is not possible to attribute the number of SIVAD visits to specific individuals (i.e. if an individual visits frequently to use their VAD, each visit is counted towards the total visits involving SIVAD). SIVAD was recorded whenever a peer noted a patient accessing their VAD to inject drugs.

When the OPS initially opened, peers reported witnessing a variety of approaches to SIVAD including, but not limited to, using water from a water bottle to flush VADs, not cleaning the PICC hub prior to injection and inserting needles into the IV tubing itself as opposed to the access port [29]. At the same time, clinical staff inside the hospital reported to Clinical Nurse Educators that hospitalized patients were engaging in SIVAD on inpatient units, often in unsupervised settings.

Due to these observed safety concerns, quality improvement measures were instituted at the SPH hospital-adjacent OPS and other Vancouver OPSs. Since 2019, peers receive standardized education on how to provide harm reduction interventions for SIVAD through a "street degree" program and OPSs stock supplies specific to SIVAD (e.g. pre-filled syringes with sterile flush solution, needleless syringes) [30]. Hospital and community patients known to be engaging in SIVAD are directed to OPSs for supervision and supplies.

Systematic approach to create standardized clinical guidance for SIVAD and address knowledge gaps

In response to observed SIVAD in Vancouver acute and community care settings, as well as growing SCS/OPS experience offering SIVAD harm reduction education and supplies, a multidisciplinary healthcare team at Providence Health Care (PHC) took steps in 2018 to examine SIVAD more formally. PHC is a health organization in Vancouver that administers care to approximately 600,000 patients annually via two acute care hospitals with approximately 500 acute beds in total. The goal of this work was to develop consistency in the response to SIVAD through a practice guideline based on available evidence and expert consensus, as well as to identify SIVAD as an issue worthy of formal clinical response, education and research.

Incident cases and risk management engagement

Instigated by a series of distressing SIVAD incidents noted by healthcare providers (e.g. patients performing SIVAD in unsupervised and unsafe environments such as medical ward shower stalls), the organization's Risk Management and Patient Safety program commissioned a SIVAD risk analysis review. A group of Infectious Diseases, Urban Health and Addiction Medicine specialist physicians, nurses, clinical ethicists and the organization's lawyer, was assembled to discuss potential patient, healthcare provider, institutional and wider community implications of SIVAD and potential harm reduction policy interventions [31]. A failure modes effect analysis (FMEA) was conducted to systematically identify and evaluate the anticipated risks of SIVAD and the impacts of potential adverse outcomes following a policy change ('failure modes'), in this case harm reduction interventions for SIVAD [32].

The FMEA ranked priorities to be anticipated and addressed when considering policy development and monitoring. The most concerning risk anticipated to arise following harm reduction implementation was increased SIVAD rates amongst the larger community of PWID (not just in those specifically educated) should it be misperceived that "clinicians now condone the use of VADs for self-injection". VAD access dysfunction was the next most concerning risk. Somewhat surprisingly, participants articulated less concerns about risk of infectious complications and overdose. This may reflect acknowledgement of baseline risks associated with IDU independent of SIVAD and an understanding that a SIVAD policy or guideline would intentionally aim to mitigate such harms.

Formal organizational SIVAD ethics consultation

Building from the FMEA, a more in-depth investigation was required to explore the implications of possible practice changes around SIVAD. In November 2019, the organization's Ethics Services program was consulted by the Urban Health program to review the following questions:

1. Will the organization support the development of a policy/guideline that permits clinicians' discretion to deliver SIVAD harm reduction education and supplies to patients with substance use disorders upon request, while also allowing for conscientious objection should clinicians wish to opt out of the practice?
2. What ethical, medical and organizational considerations ought to be considered with this approach?

Following approval from the Senior Leadership Team in February 2020, Ethics Services conducted an organizational ethics consultation that took 6 months to complete. Organizational ethics is the discipline concerned with the principles and standards by which an organization operates. It focuses on finding the "right" way to respond to complex challenges and opportunities within the communities that the organization serves [33]. Because providing SIVAD harm reduction was recognized to be a response that could significantly impact the lives of patients, clinicians and the organization's reputation, formal ethical reflection was requested given limited medical evidence on the subject and a general absence of practice standards.

A total of 50 stakeholders were interviewed, including patients with lived/living experience of drug use/SIVAD, program leaders, physicians and nurses working in acute care or community in Vancouver, as well as clinicians at other Canadian sites. An interview question guide was developed by Ethics Services in consultation with a Clinical Nurse Educator in Substance Use. Interviews were one hour long, semi-structured, non-remunerated and occurred in person or over videoconferencing, either individually, or in small groups of up to 4 participants per participants preference. Several individuals provided information only over email. We identified stakeholders by contacting program leaders in Infectious Disease, Internal Medicine, Urban Health, Addiction Medicine, Psychiatry, IV Therapy, Risk Management, and Nursing Professional Practice. Additional stakeholders were identified during the interviews themselves (i.e. "who else should we speak to about this question?"). Stakeholder responses were organized into themes (see Table 2). No other local or national center was found to have formal organizational guidelines or policies on SIVAD harm reduction.

Following a detailed ethical analysis, the Ethics Services team determined that it would be ethically permissible to create an organizational harm reduction guideline around SIVAD. In light of the risks of harm—that is, the degree of severity and relative certainty of harms related to overdose and drug-poisoning deaths when SIVAD occurs covertly and without supervision, sterile supplies or education—the ethics team identified proportionate rationale and clear ethical justification to move forward with supervised SIVAD harm reduction, particularly within a monitored setting such as an OPS, with organizational oversight including research and dedicated staff education. With an overarching goal to save lives and engage patients in care, harm reduction strategies were believed to be appropriate as part of the comprehensive program of services PHC provides for people who use substances.

Importantly, given the general lack of directive evidence in this area, providers who do not feel comfortable

Table 2 Stakeholder Perspectives from the Organizational Ethics Consult. *Source* Providence Health Care Ethics Services Organizational ethics consult: Harm reduction, an approach for patients who self-inject non-prescribed substances into their vascular access devices, December 2020

Patient Stakeholders
• Identify personal experience with self-injection of non-prescribed substances into vascular access devices (SIVAD), but an incomplete awareness of risks, and interest in more education
• Endorse benefits of SIVAD that may not be valued by healthcare providers (e.g. avoiding "high risk" venipuncture, better management of drug withdrawal, and stabilizing substance use disorder enabling completion of medical treatment)
Nursing Stakeholders
• Indicate SIVAD harm reduction appears "common sense" and patient-centered
• Some already engage in SIVAD harm reduction, while others are uncertain and desire more education and organizational guidance and support
• No nurses interviewed expressed objection to SIVAD harm reduction but noted that some nurses will object based on moral or philosophical grounds, or because of lack of experience or evidence
Physician Stakeholders
• Desire organizational support should a legal challenge arise following an adverse event
• Infectious Diseases physicians endorse experience with infectious complications of SIVAD
• Some believe that SIVAD should prompt vascular access device removal and switch to oral antibiotics
• Some believe that shared informed decision making would be helpful in patients who SIVAD
Risk Management and Professional Practice
• Documenting a discussion on anticipated risks of SIVAD would satisfy the need for informed consent, and could mitigate legal risk to individuals and the organization
• Legal liability coverage for nurses is provided by the organization
• Harm reduction interventions are within nursing scope to provide

Table 3 Recommendations from the organizational ethics consult. *Source* Providence Health Care Ethics Services Organizational ethics consult: Harm reduction, an approach for patients who self-inject non-prescribed substances into their vascular access devices, December 2020

1. At a minimum, develop a patient education intervention around the risks of self-injection of non-prescribed substances into vascular access devices (SIVAD)
2. Consider an interim SIVAD harm reduction guideline for use in the organization, with expert stakeholder input, and an opt-out option for providers who disagree
3. Continue to develop and promote wraparound care for patients with substance use disorders (Addiction Medicine consultation, social work, and overdose prevention site (OPS) models of care)
4. Study the incidence and outcomes of SIVAD harm reduction within the organization
5. Use a standardized SIVAD chart document to demonstrate patient informed consent
6. Position SIVAD harm reduction in an OPS environment initially to ensure consistency, quality, and research opportunities
7. Develop an education program for clinicians around harm reduction generally, and practices and patient counselling techniques specific to SIVAD
8. Consider additional legal/risk evaluation regarding SIVAD harm reduction
9. Involve partner organizations in the development of guidelines, given the possible impacts to the community

with SIVAD harm reduction could opt out. See Table 3 for specific consult recommendations, which were reviewed and approved by the institution's Risk Management department and Senior Leadership Team in February 2021.

SIVAD nursing harm reduction guideline development

The Senior Leadership Team's endorsement of the Ethics Consultation recommendations was instrumental to support the development of a harm reduction guideline for SIVAD. Although intended as guidance for all healthcare providers, the document was created primarily as a nursing guideline, as it was acknowledged that nurses are the frontline providers of harm reduction education and supplies. Given that SIVAD and the impact of potential harm reduction is an emerging area of study, the guideline was positioned as an internal interim document, subject to future review and amendments as new information becomes available.

To create the guideline, a nurse educator with experience in substance use convened a working group of stakeholders that included nurses, patient care managers,

physicians, educators and social workers representing disciplines of Addiction Medicine, Infectious Diseases, and Urban Health. The group utilized the limited research evidence available (including sources referenced in the FMEA and Ethics Consult), existing organizational guidelines related to general VAD care and maintenance and information regarding strategies employed by other sites (including community run OPSs/SCSs as described above and a community OPS in Ottawa, Ontario) [34, 35].

A common concern raised by frontline nurses was potential legal liability if a nurse inadvertently flushed an IV line containing substances previously injected by a patient, resulting in patient overdose. Risk Management indicated that nurses are not liable for autonomous decisions made by capable patients, including use of substances and/or if patients experience an adverse event attributed to SIVAD. The importance of documenting an informed discussion with patients regarding risks of SIVAD was emphasized. As the organization takes a more formal harm reduction approach to SIVAD, liability coverage is in place provided nurses are practicing at the expected standard and this has been indicated within the guideline itself.

The group also consulted PHC's Nursing Professional Practice consultants and the British Columbia College of Nurses and Midwives about nursing scope of practice pertaining to harm reduction and SIVAD specifically. These bodies endorsed that harm reduction practices, including providing education and sterile supplies, are within the scope of nursing practice [36]. Importantly, they indicated that nurses can act independently of physician oversight when assessing patients and implementing harm reduction measures within scope, however, conferral with the multidisciplinary care team is encouraged to problem solve around addiction management and medical care (see Table 4).

The guideline also emphasizes that nurses have the ability to exercise discretion as to whether they will provide SIVAD education and sterile supplies to patients. If nurses choose to opt-out of this practice (e.g. concerns over the absence of evidence for SIVAD, moral objections, or clinical concerns related to patient factors), they are advised to transfer patient care to another clinician who can assess the patient. Nurses can also consult addiction medicine or more experienced colleagues and/or direct patients to the in-hospital OPS where this care is routinely offered.

The revised version of the guideline was approved and posted within the organization. The guideline is clear that providing supplies and education does not equate to condoning SIVAD or substance use in hospital and patients are directed to the in-hospital OPS. The guideline also formalizes clinical practices around SIVAD that were already being *informally* provided to patients by nurses on a case-by-case basis in hospital as well as at community SCS/OPSs over the last several years.

SIVAD nursing harm reduction guideline implementation at the SPH OPS

At the end of 2020, the hospital-adjacent OPS moved to a new location which created a gap in service for hospital inpatients. In response, SPH opened an in-hospital OPS in February 2021 [37]. It is staffed by nurses who receive specialized training on providing harm reduction education and sterile supplies. The opening of the in-hospital OPS roughly coincided with the release of the interim SIVAD nursing harm reduction guideline, as outlined above. As such, SIVAD harm reduction training is provided to nurses based on the guideline and supplemented by education from an IV Therapy nurse specialist (e.g. assisting clients with alternate vein identification and vein care) [34].

Between its opening on February 1st to October 23, 2021, the site has had 1,655 visits, 611 (37%) of which involved SIVAD, which is recorded whenever a nurse notes a patient accessing their VAD to inject substances. Staff anecdotally report that SIVAD harm reduction education is the most common education requested by

Table 4 Clinical practices around SIVAD that can be provided to patients by nurses as outlined in the clinical nursing practice guideline

1. Engage in standardized and comprehensive discussion on the risks of self-injection of non-prescribed substances into vascular access devices (SIVAD)
2. Primarily discourage SIVAD and encourage use of alternate injection techniques (e.g. venipuncture, muscular injection)
3. Complete a standardized documentation template (located in the hospital electronic medical record) that an informed discussion took place
4. If the patient decides to engage in SIVAD despite risks and alternate route suggestions, offer education on safer sterile injection techniques and provide sterile supplies, including saline flushes and alcohol swabs
5. Facilitate nursing communication about SIVAD activities to other providers, including Addiction Medicine and Infectious Disease clinicians, so that ongoing medical indication for the VAD can be assessed, and substance use disorder, withdrawal and cravings can be assessed and treatment optimized

patients, many of whom already express existing knowledge about harm reduction practices for self-venipuncture [38].

Staff education on harm reduction and SIVAD

Nurse educators specialized in the care of patients with substance use disorders presented the new guideline at in-service sessions across acute care settings. The sessions equip nurses with skills to engage in harm reduction counselling with patients (e.g. language to use, trauma-informed care, information on medical risks) and to ensure that nurses understand the purpose and limitations of harm reduction. The guideline was also presented to nursing leadership at frontline nursing meetings across the organization so that nurses could bring this information back to their colleagues.

To enhance the reach of SIVAD-specific guidance, presentations at departmental rounds have been an important avenue for ongoing discussion and education. The British Columbia Centre on Substance Use hosts a monthly "What's New in Addiction Medicine?" lecture series that is attended by a diverse range of healthcare professionals provincially. A rounds presentation reviewing SIVAD literature and approaches to VADs in PWID was delivered in May of 2021. This presentation had 65 live attendees and 102 registrants with access to online material [39].

SIVAD research in progress at providence health care, Vancouver

In line with the organizational ethics consult recommendations, research has been prioritized. Ethics approval has been obtained for a mixed-methods study of the attitudes, beliefs and practices of patients who engage in SIVAD and is currently in recruitment and data collection phases. Investigators are exploring patients' understanding of SIVAD-associated risks (e.g. infection, air embolism), personal beliefs (e.g. why patients are using VADs to inject) and influencing factors (e.g. how the practice is being learned). Investigators will also conduct chart reviews to evaluate patient outcomes, including incidence of blood stream infections, thrombosis, occlusion, VAD malposition or accidental removal. Research to determine prevalence of SIVAD in an existing community study cohort of PWID is also underway.

Discussion

There is evidence that a patient-centered, harm reduction approach to care helps PWID engage in healthcare and reduces overall harms of IDU [27, 40–42]. Harm reduction does not condone, endorse, or condemn substance use. Rather, it recognizes substance use as a reality for some individuals and focuses on reducing its harmful consequences [43]. PWID often inject in non-sterile, unsupervised settings due to stigma and criminalization, but when supported in safe environments, rates of IDU-related infections and fatal overdose decrease [44–46]. Harm reduction strategies ideally exist within a continuum of care, giving patients the option of accessing various social and medical supports that may improve their overall health [47, 48].

For patients who are informed of the anticipated risks associated with SIVAD but continue to endorse a plan to use their VAD, harm reduction interventions, including counselling about sterile technique and flushing and provision of sterile supplies is philosophically, ethically and medically analogous to sterile needle exchange/availability programs. If patients fear judgement from healthcare providers about SIVAD, they may engage in SIVAD covertly to avoid consequences such as VAD removal and premature discharge from hospital. Loss of patient engagement and concerns about overdose and adverse events up to and including death must be acknowledged. Harm reduction interventions, including safer injection techniques for non-prescribed substances helps support safer drug use patterns, access to primary care and reduced overdose frequency [49]. It is therefore plausible that supporting SIVAD harm reduction will lead to improved patient outcomes. Acknowledging that some providers may have moral distress in relation to SIVAD associated care—as highlighted in our case study—ongoing and targeted education about the purpose of SIVAD harm reduction and the existence of care pathways linking both patients and providers to skilled providers of such services must be central to any implementation plan.

There may be concern among healthcare providers that inserting PICCs or providing education on SIVAD to PWID may lead to increased IV drug use or SIVAD. Data is currently being collected and analyzed with respect to the incidence of SIVAD at the in-hospital SPH OPS following the introduction of the nursing guideline, to ascertain trends in SIVAD over time. It should be noted that the percentage of visits involving SIVAD rose from 27% in the hospital-adjacent OPS (May 2018–January 2021) to 37% at the in-hospital SPH OPS (February–October 2021). The significance of this observation requires more detailed analysis accounting for confounders and clinical outcomes. Populations accessing community and hospital-adjacent OPSs and those visiting in-hospital OPS are dissimilar and difficult to compare.

In order to mitigate the risk of increased SIVAD among populations of PWID following the introduction of harm reduction measures, it is important that any policies or guidelines developed are clear that the main goal of SIVAD harm reduction counselling is to provide

education regarding potential risks and to discourage the patient from using their VAD to inject substances. Guidelines should be clear that providing supplies and education does not mean substance use or SIVAD is condoned.

Ongoing data collection to establish baseline incidence of SIVAD among PWID in inpatient and outpatient settings and documenting the type and rate of complications are needed to understand incidence and impact of SIVAD. Furthermore, qualitative assessment of patient experiences and perspectives regarding SIVAD are needed to contextualize this data and understand how it intersects with overall health and substance use. While a study in Vancouver is underway to begin to delineate these aspects of SIVAD, larger more inclusive multicenter collaborative research evaluating SIVAD is needed to appropriately account for heterogeneity of substance use behaviors, health system resources, policies and practices. Studies relating to PICC use and complications in PWID should include consideration of SIVAD, including creating standard means of identifying and documenting SIVAD in research protocols.

Assessment of the impacts of possible SIVAD harm reduction interventions (e.g. education on risks and sterile technique, provision of sterile supplies) are also needed. Such harm reduction-oriented studies should include evaluation of the rates and types of complications, while also exploring impact on patient quality of life, engagement in healthcare and substance use trajectories. Concurrent guidance and research, rather than a typical sequential approach of research followed by policy development should be considered, reflecting urgency arising from the ongoing overdose crisis in BC and elsewhere [50, 51].

Vancouver represents a unique intersection of patient population and practice landscape, where addiction medicine services and harm reduction interventions are widely accepted and available, including SCS/OPSs. The generalizability of the work described herein may be limited or of low priority in settings without such resources and research opportunities may be scarce in settings where SIVAD incidence is believed to be low.

Conclusion

SIVAD poses complex clinical and ethical challenges that require efforts to close knowledge gaps towards the creation of guidelines and policies that support patients, clinicians and organizations in reducing harms and improving health outcomes for PWID. Although healthcare providers and organizations may prefer that patients avoid SIVAD, clinicians must be willing to engage with patients within the reality that currently exists. Much work remains ahead to establish a foundation of evidence and organizations should actively seek opportunities within their own institutions and multidisciplinary teams to study and formalize guidelines and policies around this important area of practice, reviewing and amending them as new evidence becomes available. As organizations gain experience, the publication of guidelines and collaborative efforts between institutions will be essential.

Abbreviations

BSI: Bloodstream infections; FMEA: Failure modes effect analysis; IV: Intravenous; IDU: IV drug use; OPS: Overdose prevention site; PHC: Providence health care; PICC: Peripherally inserted central catheter; PWID: Persons who inject drugs; SCS: Supervised consumption site; SPH: St. Paul's hospital; SPH OPS: St. Paul's hospital overdose prevention site; SUD: Substance use disorder; SIVAD: Self-injection of non-prescribed substances into vascular access devices; VAD: Vascular access device.

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Author contributions

All authors contributed to development of the manuscript. JC lead the institutional ethics consultation process and provided related content; WC and VW served as content experts on infectious complications and medical risks of SIVAD; EG, ED, MN have worked in and provide educational support the SPH OPS and provided statistics and guideline development related content; RB served as the addiction medicine content expert contributing related information on harm reduction and substance use disorders; JH was the vascular access and skilled nursing content expert providing related information about vascular access. All authors read and approved the final manuscript.

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Availability of data and materials

The St Paul's Hospital Overdose Prevention Side datasets presented are not publicly available as they include internal organizational documentation and program statistics but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was not obtained for this case summary, but ongoing unpublished research studies referred to in the manuscript have received ethics approval from the University of British Columbia Research Ethics Board.

Consent for publication

Permission was obtained and consent signed by the individual providing details for the patient perspective case description.

Competing interests

The authors declare no competing interests with respect to the research, authorship and publication of this article.

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Publisher's Note

Placing a Central Vascular Access Device in a Patient With Substance Use Disorder

The Ethical Position of the Infusion Nurse

Helen Stanton Chapple, PhD, MA, MSN, RN

ABSTRACT

When infusion nurses place central vascular access devices in patients with substance use disorder (SUD), they are both enabling treatment and making the patient more vulnerable to his or her addictive illness. Using the lens of rescue enables an exploration of the ethical position of the infusion nurse regarding these patients, even though rescue, per se, is inadequate to the complexity of the situation. Suggestions are offered to both the infusion nurse and the health care team for improving their ethical stance, as well as their care of patients with SUD.

Key words: addictive disease, beneficence, CVAD, infusion, nonmaleficence, rescue, substance use disorder

It is routine for infusion nurses to place central vascular access devices (CVADs) in patients for long-term antibiotics or chemotherapy. The practice becomes more ethically complicated when the patient has a known substance use disorder (SUD), either present or past, and outpatient therapy is expected. In placing the CVAD, the nurse has made a change to the patient's body enabling safe and ready access to its most robust areas of circulation. If the CVAD renders the patient more vulnerable to the addictive illness, does the nurse (or the health care team) bear any ethical responsibility for amplifying the patient's jeopardy? This discussion uses the lens of rescue to examine the legal and ethical position of the infusion nurse and suggests a shift in the moral relationship between the clinician and the patient. The adjustment is necessary to account for the increased risk posed by the CVAD to the patient with SUD. The article offers practical suggestions to assist the nurse and the health care team in enacting this change. A review of several concepts follows, beginning with the difficulties of SUD itself.

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SUBSTANCE USE DISORDER

A 5-year study and meta-analysis by The National Center on Addiction and Substance Abuse at Columbia University reported that addiction is a widespread, relapsing, and chronic disease, particularly of the brain.[1] The normal operations of risk and reward that most people exhibit are profoundly disrupted in persons with SUD. Active addiction alters brain chemistry, specifically its reward circuitry. Cognitive changes result that alter behavior. These modifications are dangerous, especially to the person with the disorder, because "fundamental natural drives and associated behaviors lose their value in comparison [to the substance]."[1(p21)]

Macy's[2] research regarding opioid addiction in Appalachia cites several discouraging facts about recovery from SUD. Even when a patient is able to access medically assisted therapy (MAT), getting out from under the illness of addiction is difficult, and relapse is extremely likely. Persons with SUD may also experience mental illness, low self-esteem, and suicidal ideation.[3] Active addiction can obviate "choice," partly because the fear of experiencing withdrawal symptoms (ie, being "dopesick") is overwhelming. This fear can take over, too often with fatal consequences;[2] "...the most important thing for the morphine-hijacked brain is, always, not to experience the crushing physical and psychological pain of withdrawal: to avoid 'dopesickness' at any cost."[2(p9)] Once addiction is established, the body responds to the absence of the substance, with symptoms ranging from restlessness to flu-like symptoms to seizures.[4] Onset can be rapid—within hours of the last dose. In the absence of another hit, symptoms may last from days to

weeks, depending on the substance and the length of use.[4] The intense desire to ward off this experience can bring dire consequences, including overdose. In 2018 the death toll from substance abuse overdose was 67 367 in the United States.[5]

THE PATIENT'S PRECARIOUS POSITION

If a patient with SUD is now also confronting a serious, life-threatening illness that calls for a CVAD to deliver necessary medications, the patient may be in significant peril. Perhaps the illness has come about as a direct result of the SUD, because compromise to the immune system is a common comorbidity to addictive illness.[6]

Health care facilities struggle with how to balance the need for CVAD placement with the likelihood that such patients' history of SUD has degraded their judgment and impulse control.[7,8] Clinical policy may require patient-provider contracts to enhance patient awareness that tampering is not allowed. A device may be added that will indicate to clinicians that unauthorized use has occurred. These interventions place the responsibility for the consequences of the bodily change that the nurse has enacted with the patient alone. Many would argue that such decisions are entirely appropriate. It is the patient's obligation to refrain from misusing this new access. Any ill effects for failing to exercise self-restraint, up to and including dismissal from therapy, properly belong with the patient, in this view. Yet, it does not take into account the implausibility that the "morphine-hijacked brain" will operate as if it were opioid-naïve, regardless of the addictive substance. Now that the health care team and the infusion nurse have encountered this patient and placed this device, it is possible that their ethical position in terms of the patient's welfare has shifted. Their efforts to rescue the patient from serious illness with an intervention that temporarily increases the danger of overdose is an interesting moral dilemma.

The patient's endangerment is multifaceted. Besides the possibility of tampering or even overdose by the patient, other potential problems exist. Even with the best efforts of the infusion nurse, the CVAD is subject to misuse, malfunction, and being a conduit for infection. The plan to rescue the patient from life-threatening illness or infection requires the CVAD. What does rescue mean when the means to that end could put the patient in greater harm? Does the placement of the CVAD increase the nurse's moral obligation to prevent harm, that is, to rescue? To examine this possibility further, it is helpful to turn to some of the legal and ethical thinking about the role of the rescuer.

RESPONSIBILITY TO RESCUE

Ordinarily one's individual responsibility to rescue someone from jeopardy is little to none under the law—with some state exceptions, such as laws protecting Good Samaritans.[9,10] The reason is that any obligation to rescue (or legal requirement to do so) could interfere with the would-be rescuer's individual liberty to choose to act or not.[10] If someone nearby were drowning and we could throw a rope or call for help, doing either might be a minimally expected action for an individual to take in terms of rescue. We might assume an attitude of benevolence from that person, motivating their intervention.[10] However, no legal statute compels such action.

Perhaps this juridical perspective seems incomplete. Are human beings to be held to no standard when it is so simple to make a critical difference for another person? Moving from law to ethics offers somewhat more satisfaction. The obligation to throw a rope or call for help if one encounters a stranger drowning is not a moral choice, as the law characterizes it, but rather an obligation of beneficence of one human to another, according to Beauchamp and Childress.[11] Their ethics perspective enables them to assert a higher standard of behavior than does the law. In a discussion of ideal human behavior, they propose a continuum from "strict obligation" to "weak obligation" to "ideals beyond the obligatory" to "saintly/heroic acts."[11(p48)] They notice that professionals are expected to conform to a higher level of obligation than nonprofessionals, and this distinction applies to clinicians caring for patients.

In the realm of health care delivery, the responsibility to rescue is far more fully developed than calling for help to rescue someone in danger. In ethics statements such as the *American Nurses Association Code of Ethics for Nurses,*[12] the social contract between health care professionals and the public confirms a stronger obligation of beneficence from the nurse for patients than is expected from nonclinicians.[13] Furthermore, the idea of rescuing patients from collapse and death is so compelling in itself that one can argue that it has motivated the overall design of health care delivery in the United States.[14] When hospitals hold themselves accountable for "failure to rescue" as a quality assurance concern,[15] the key role of rescue is palpable.

Beauchamp and Childress[11] also state that rescuing from harm involves aspects of 2 basic principles in ethics, nonmaleficence (the prevention of harm) and beneficence (intending good). It is ironic that, in placing a CVAD, the infusion nurse is both attempting to rescue the patient from the harm of serious illness but also expanding the risk of endangerment due to the individual's history of SUD. Beauchamp and Childress[11] discuss such a circumstance but not in a way that is useful to the infusion nurse's position. When a clinician may be taking action that is increasing the risk of harm to the patient, Beauchamp and Childress suggest a standard of "due care."[11(p160)] Taking due care as a standard assumes that the specific harm involves negligence, a "breach of duty" on the clinician's part. However, interpretations of the duty, the breach, and the harm are unclear when the problem is *not* one of negligence, as it is not in the case of CVAD placement. Certainly, the infusion

nurse never intends to diminish a patient's well-being by placing the CVAD. The nurse exercises due care as a matter of course, deploying meticulous skill in placement and teaching, which enables the treatment plan to go forward. Even though we acknowledge that rescue involves both intending good and avoiding harm, the lack of clarity regarding the nurse's ethical responsibility persists, as does the question: How can the infusion nurse be rescuing the patient if the means of rescue carries the potential for such harm?

A MORAL SHIFT AND CHANGE IN RELATIONSHIP

The ethical principles regarding rescue and the professional obligation of beneficence assume that the would-be rescuer had no role in placing the person in jeopardy. If the rescuer did play a part in placing the person in danger, then an important moral shift occurs. Nonmaleficence (one part of rescue) involves avoidance of further known or unknown harm.[11(p158)] However, by placing the CVAD in the setting of addiction, the infusion nurse has indeed increased the risk of the patient's self-harm. The harm is due to the newly available access to a major vessel coupled with the patient's altered brain chemistry brought about by the SUD. Certainly the infusion nurse is not alone in increasing this risk of harm—the past actions of the patient have played a role. The team members also share responsibility, having ordered a treatment plan that requires the CVAD to be placed. Even as its clinicians exercise all due care, the plan itself increases the team's moral obligation to prevent harm to the patient, but as the enactor of the change to the patient's body, the infusion nurse is on the sharp edge of this moral spear. It is the nurse who will be instructing the patient in how to care for the site even as she or he cautions the patient against tampering. If a patient contract is involved, the nurse may have a role in overseeing its completion.

Before exploring what the shift in this relationship might entail, it is helpful to review what is and is not under the nurse's control. No matter how meticulous the nursing care, no nurse holds sway over ultimate patient outcomes. It is not in the nurse's power to prevent the patient's death from the primary illness that the CVAD is meant to alleviate. Likewise, the nurse cannot eliminate any secondary infection, the onset of further disease, or overdose. The nurse is unable to cure the patient's active addiction nor even advise a path that will guarantee the patient's recovery. The nurse can control only 2 factors: his or her professional behavior and attitude. Rescue, in fact, does not come into play.

Reviewing the Situation

If CVAD placement in a patient with SUD alters the moral positions of the nurse and the team, but the agency of each participant is limited, then the situation may not qualify as a rescue operation. Placing the CVAD and continuing with the treatment plan are interventions designed to limit the damaging effects of the new disease in the patient's body. Doing so with excellence is to comply with prevailing standards of care. The team has just thrown their "drowning" patient a very high quality "rope." However, it would be a mistake to think of their action as a deed of rescue. Placing the line is certainly an act of beneficence designed to facilitate the delivery of life-saving medication, but the outcome of this well-intentioned act is unknown and unknowable. Yet beneficence and nonmaleficence are still relevant, and the relationship with the patient can be a touchstone for both.

Now that the team and particularly the infusion nurse have pushed the patient out on this limb for the patient's own best interests, ethically they cannot ignore the patient's precarious position. Their interest in patient welfare needs to take an expanded form so that they may allow themselves to be noncomplicit should the limb give way. Now, neither blind trust in the patient's capacity to refrain from using the CVAD nor a complacency ready to blame the patient for doing so seem to be a good moral fit for the situation. It is helpful to notice that, in placing the CVAD, the nurse and the patient become linked in at least 2 ways: the physical act of one person placing a major foreign object in another person's body and their joint hope for a good outcome, albeit in an unsafe situation. Both are seeking the good in the setting of an uncertain future, and this commonality becomes a place for them both to stand.

Relating Through Narrative

Gadow offers guidance to nurses in such situations.[16] She has described the collaboration between the nurse and the patient as an "ethic," as they fashion a relational narrative of the good that both seek. Both the nurse and the patient can contribute to the narrative: The nurse describes the purpose of the CVAD, its placement, and care; the patient may relate the circumstances of his or her life and active or nonactive addiction. Both have hopes and fears for how things will turn out. In relating their mutual perspectives to each other, a new story is created.

> Their co-constructed ethic [sic] becomes the safe harbour from where patient and nurse can venture forth to explore together the alien world created by illness, one that is laden with obstacles to the crafting of the good and the path to attain it–the goal of any ethic.[16p138]

But of course, once the CVAD is placed, the nurse and the patient do not actually "venture forth together." Their separable contexts are unspecified and fluctuating. The infusion nurse's role may not allow for ongoing interaction once the patient is discharged. The patient's environment and illness may not encourage an ability to follow the rules, even with the best of intentions. Gadow's understanding of relational narrative is particularly relevant in this situation when so much ambiguity about the future is indisputable. In the brief time that they are together, the nurse and the patient are engaged in meaning-making. They can create

a safe harbor by manifesting mutual respect, openness to one another, and presence. An obligation to excellence in infusion practice on the nurse's part is unquestioned. Along with it, the nurse must nurture humility, hope, and a commitment to the patient's understanding of his/her best self.[16] None of these faculties may be easy to come by in the setting of SUD, yet they are critical for creating a narrative of safety between patient and nurse.

PRACTICAL SUGGESTIONS

Beyond the relational narratives that may be created with particular patients, the infusion nurse may find additional ways to fortify this safe harbor that leans toward the good. Even as their individual patients' futures remain unclear, the nurse and the health care team can open themselves to greater knowledge of what patients face when they present with a history of SUD. Suggestions for specific actions follow:

1. Applying the appropriate vocabulary regarding SUD can improve clinician sensitivities to patients and each other and build trust.[17]
2. Infusion clinicians must attend carefully to professional contexts, for example, hospital policies regarding patients with SUD and who is in charge of reviewing and revising these policies.
3. Professional development opportunities that address vascular access in patients with substance abuse disorder can expand the team's perspective. They may commit to explore current research jointly on a regular basis.
4. The nurse and the health care team may consider advocacy strategies such as team-based and hospital-wide competencies regarding SUD; exploration of hospital and community-based resources for persons with addictive disease and their families; and the possibility of partnering with local MAT or syringe programs.[18]
5. Specific competency in the treatment of accidental or intentional overdose can enable policies that address the provision of naloxone and patient/family education regarding its use.
6. Collaborative creativity can expand beyond adding devices to the CVAD that indicate tampering. Additional interventions include "nudge" technology, which allows the patient to set goals and earn rewards, or texts such as those used in appointment reminders to maintain patient contact between visits.[19]

The nurse and the health care team's responsibility for the greater vulnerability they have ushered into the patient's life suggest the actions on this list as forms of nonmaleficence, that is, taking steps not to make things worse.[9] Improving clinicians' knowledge of the context of SUD will enable them to make the most of the brief time that they spend with each patient, enabling them to engage in a relational narrative that creates greater good and carries more meaning for everyone involved.

Good news regarding the prospects for outpatient management of patients with SUD and CVAD comes from a recent literature review. Despite the general reluctance of clinicians to treat patients with SUD on an outpatient basis, the outcomes and complications for outpatients with SUD and a CVAD are comparable to those undergoing this therapy without a history of addictive disease according to Suzuki et al.[8] They also raise the possibility that patient engagement with MAT concurrently with the CVAD can improve the odds even more, but this prospect requires further study. These findings are encouraging to clinicians who wish to treat patients with SUD and CVAD on an outpatient basis. At the same time, they do not alter the ethical requirement to attend to these patients' increased risk of harm, as discussed.

CONCLUSION

Perhaps the idea of "rescuing" a person with SUD on any level—from addiction, infection, or even death—is a misnomer. A more accurate depiction of nursing practice or patient care itself is to apply useful interventions while accompanying the patient in their journey through illness. The critical ethical features of the complex situation of placing a CVAD in a patient with SUD do not depart from the professional obligations inherent in any patient encounter: fidelity to the patient relationship, excellence in technique regarding CVAD placement, comprehensive patient teaching regarding care of the site, and cautions regarding potential problems. Gadow's "alien world of illness"[16] greets clinicians in almost every patient encounter, after all. Patient education may be more elaborated if extra devices, contracts, or nudge technology is involved. The nurse demonstrates an intention for good and avoidance of harm in everyday professional practice but need not suffer guilt from somehow failing to rescue the patient. Ultimate outcomes are beyond any one person's control and responsibility.

What may be somewhat different here is, that in order to "lean toward the good,"[13] the infusion nurse and the health care team may need to heighten their own self-awareness. They have an obligation to stay updated on the facts of SUD and to promote respectful policies and actions that avoid making the situation for the patient even more unstable.

For the nurse, the extra layer of vulnerability added to the patient by the CVAD obligates a more intentional level of fidelity to the patient. In their time together, the nurse must inquire about the patient's circumstances and listen actively to the responses so that teaching is targeted and problem-solving techniques make sense. Both the patient and the nurse are hopeful for a positive outcome yet acutely aware that the situation is fraught with difficulty. If they can acknowledge these realities together, they will have created a common narrative that has meaning to them both and may help to sustain them going forward.

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Emergency Department Visits Involving Opioid Overdoses, U.S., 2010–2014

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INTRODUCTION

In 2015, opioid-involved overdoses accounted for 33,091 deaths in the U.S., 12,989 of which involved heroin.[1] In addition to overdose deaths, many more individuals suffer nonfatal overdoses.[2] No recent study has examined trends in opioid overdoses treated in hospital emergency departments (ED) separately for non-heroin opioids and heroin. This study analyzes trends and the associated direct medical costs for such ED visits.

METHODS

Data from the 2010–2014 Nationwide Emergency Department Sample (NEDS), a component of the Healthcare Cost and Utilization Project, was used. NEDS is the largest all-payer ED database in the U.S., yielding national estimates of hospital-based ED visits from a sample of approximately 20% of U.S. hospital-based EDs.[3] ED visits were examined, and stratified by gender, age, and region. The ICD-9-CM was used to identify overdoses. Non-heroin opioid overdoses were identified as those with a first-listed diagnosis of 965.00, 965.02, or 965.09, or a first-listed external cause of injury code of E850.1 or E850.2. Heroin overdoses were identified using 965.01 and E850.0.[4] The first-listed diagnosis in ED data is considered to be the diagnosis or condition in the medical record chiefly responsible for the services provided.[5]

Direct medical costs associated with ED visits in 2014 were estimated by the expected primary payer. Often, charges reported in NEDS are greater than the amount reimbursed by payers. Charges were converted to costs using cost-to-charge ratios from the National Inpatient Sample.[6] Average cost-to-charge ratios from opioid overdoses in the National Inpatient Sample based on hospital region, urban/rural location, and teaching status were applied. Total direct medical costs were estimated by multiplying the number of visits by the mean cost per visit.

Average annual percent change from 2010 to 2014 was calculated using Joinpoint analysis. Multivariable logistic regression was used to assess linear trends controlling for age, sex,

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and region. Data were weighted to provide nationally representative estimates and analyzed with Stata, version 14.2 and Joinpoint, version 4.4.0.0. Data were analyzed in 2017.

RESULTS

Downward trends were observed for non-heroin opioid overdose visit rates (average annual percent change= −1.6%, $p<0.001$ for linear trend), particularly among younger populations and in the West (Table 1). The rate of heroin overdose visits increased (average annual percent change=33.3%, $p<0.001$ for linear trend), with increases observed across all demographic groups and regions.

In 2014, there were an estimated 81,631 ED visits for non-heroin opioid overdoses and 66,023 visits for heroin, with estimated direct medical costs of $95.2 million and $57.5 million, respectively (data not shown). Among non-heroin opioid overdoses, Medicare was the largest payer ($33.6 million), followed by Medicaid ($25.5 million). Meanwhile, Medicaid ($20.9 million) and uninsured patients ($18.7 million) were the largest payers of heroin overdoses.

DISCUSSION

From 2010 to 2014, ED visit rates for non-heroin opioid overdoses declined 4.0%, while visit rates for heroin overdoses increased 222.2%, consistent with increases in heroin use and overdose deaths.[5] In 2014, the 147,654 ED visits for opioid overdoses resulted in $152.8 million in direct medical costs. Over half of these costs ($83.7 million) were borne by the public sector. These findings suggest there were 5.2 ED visits for every opioid-related overdose death in 2014.[1]

This analysis has limitations. First, non-heroin opioid overdoses cannot be separated by those resulting from prescription opioids or illicit synthetic opioids. For example, overdoses attributable to prescription fentanyl cannot be distinguished from those attributable to illicitly manufactured fentanyl.[7] Second, NEDS includes hospital charges, and cost-to-charge ratios were used to estimate costs. Lastly, costs are underestimated because NEDS only captures hospital facility charges and excludes physician and professional fees.

Although the costs reported in this study only represent a portion of the economic burden of opioid overdose, abuse, and dependence, estimated at $78.5 billion,[8] these findings shed important insight on the opioid overdose epidemic and highlight the importance of continued attention and action. Given the strong association between prescription opioid misuse and heroin use,[9] a comprehensive approach to reducing opioid misuse is needed. Opioid prescribing guidelines, such as the *CDC Guideline for Prescribing Opioids for Chronic Pain*, including an increased use of non-opioid pain therapy, could help reduce the number of people exposed to opioids.[10] In addition, states can apply policies that can reduce opioid overdose, including mandated prescription drug monitoring program use and pain clinic laws.[11] Additional actions are needed, such as increasing access to and use of naloxone; increasing access to evidence-based treatment for opioid use disorder, such as medication-assisted treatment; and reducing the supply of illicit opioids.

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Table 1

Trends in the Rate[a] of Emergency Department Visits Involving Non-Heroin Opioid and Heroin Overdoses, U.S., 2010–2014

	Non-heroin opioid overdoses[b]							Heroin overdoses						
Characteristics	**2010**	**2011**	**2012**	**2013**	**2014**	**AAPC[c] (95% CI)**	***p*-value[d]**	**2010**	**2011**	**2012**	**2013**	**2014**	**AAPC[c] (95% CI)**	***p*-value[d]**
Overall	81,142 (25.5)	85,367 (26.6)	82,728 (25.5)	80,522 (24.4)	81,631 (24.5)	−1.6 (−4.3, 1.1)	<**0.001**	20,123 (6.6)	26,794 (8.7)	36,873 (12.0)	46,065 (14.9)	66,023 (21.2)	33.3 (29.0, 37.7)	<**0.001**
Age, years														
<18	4,455 (6.0)	4,707 (6.4)	4,490 (6.1)	3,955 (5.4)	4,372 (5.9)	−2.0 (−7.9, 4.9)	**0.045**	229 (0.3)	244 (0.3)	309 (0.4)	254 (0.3)	413 (0.6)	14.9 (−10.1, 46.8)	**0.02**
18–29	16,608 (32.0)	16,719 (31.9)	15,313 (29.0)	13,183 (24.8)	14,075 (26.3)	−6.2 (−11.7, −0.5)	<**0.001**	10,187 (19.6)	13,926 (26.6)	19,196 (36.4)	23,553 (44.3)	31,719 (59.3)	31.3 (26.6, 36.2)	<**0.001**
30–39	11,797 (29.4)	12,901 (32.1)	12,006 (29.7)	11,669 (28.5)	11,853 (28.6)	−1.7 (−6.1, 2.9)	**0.003**	4,389 (10.9)	5,881 (14.6)	8,233 (20.4)	11,293 (27.6)	17,637 (42.5)	39.9 (33.8, 46.3)	<**0.001**
40–49	14,819 (34.0)	14,992 (34.7)	14,475 (33.8)	13,559 (32.2)	12,665 (30.5)	−2.9 (−5.5, −0.2)	<**0.001**	2,881 (6.6)	3,629 (8.4)	4,871 (11.4)	5,743 (13.6)	8,455 (20.4)	31.5 (24.1, 39.3)	<**0.001**
50–64	22,716 (38.4)	24,488 (40.4)	24,727 (40.4)	25,247 (40.8)	25,489 (40.7)	1.3 (−0.5, 3.1)	0.10	2,250 (3.8)	2,946 (4.9)	3,988 (6.5)	4,882 (7.9)	7,146 (11.4)	30.7 (25.2, 36.4)	<**0.001**
≥65	10,386 (25.7)	11,194 (27.1)	11,713 (27.1)	12,903 (28.9)	13,167 (28.5)	2.7 (0.6, 5.0)	0.42	177 (0.4)	160 (0.4)	277 (0.6)	340 (0.8)	648 (1.4)	37.7 (16.2, 63.2)	<**0.001**
Sex														
Male	39,168 (25.2)	40,629 (25.8)	38,829 (24.5)	37,538 (23.4)	38,683 (23.9)	−2.0 (−4.5, 0.6)	<**0.001**	14,455 (9.4)	19,472 (12.6)	26,172 (16.9)	32,270 (20.7)	46,428 (29.7)	32.3 (27.3, 37.4)	<**0.001**
Female	41,969 (25.7)	44,728 (27.2)	43,899 (26.3)	42,974 (25.3)	42,934 (25.0)	−1.3 (−4.3, 1.8)	**0.001**	5,667 (3.8)	7,322 (4.8)	10,702 (7.0)	13,791 (9.0)	19,595 (12.7)	35.6 (30.5, 40.8)	<**0.001**
Region														
Northeast	12,466 (21.6)	12,898 (22.4)	13,709 (23.5)	13,779 (23.4)	14,029 (23.8)	2.4 (0.7, 4.2)	0.24	5,533 (10.2)	7,250 (13.5)	12,712 (23.6)	14,975 (27.5)	24,491 (45.4)	44.7 (30.9, 60.1)	<**0.001**
Midwest	16,357 (24.2)	16,700 (24.5)	17,412 (25.5)	16,691 (24.1)	17,942 (26.0)	1.3 (−1.9, 4.5)	0.60	7,857 (12.1)	10,073 (15.4)	11,643 (17.9)	15,657 (24.3)	19,855 (30.8)	26.2 (21.2, 31.3)	<**0.001**
South	31,830 (27.0)	35,078 (29.5)	33,309 (27.5)	32,684 (26.4)	32,104 (25.6)	−2.2 (−6.7, 2.6)	**0.002**	2,847 (2.5)	4,064 (3.6)	6,987 (6.1)	9,882 (8.5)	15,123 (12.9)	51.3 (44.1, 58.8)	<**0.001**
West	20,489 (27.7)	20,692 (27.6)	18,298 (24.0)	17,367 (22.5)	17,556 (22.2)	−6.3 (−9.9, −2.5)	<**0.001**	3,886 (5.3)	5,407 (7.3)	5,532 (7.4)	5,550 (7.4)	6,554 (8.6)	10.3 (−0.3, 22.0)	<**0.001**

Note: Boldface indicates statistical significance ($p<0.05$). Annual data are shown as *n* (rate). Visits are included regardless of disposition. Visits with a first-listed diagnosis and a first-listed external cause of injury code indicating a non-heroin opioid overdose and a heroin overdose were classified using the first-listed diagnosis.

[a] Age-adjusted rate per 100,000.

[b] Includes poisoning by opium, methadone, and other opiates and related narcotics (excluding heroin).

[c] Average annual percent change estimated from Joinpoint regression using age-adjusted rates.

[d] Significance of linear trend was tested using the F-statistic from a multivariable logistic regression controlling for age, sex, and region.

AAPC, average annual percent change.

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How Increasing Medical Access to Opioids Contributes to the Opioid Epidemic: Evidence from Medicare Part D

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Abstract

Drug overdoses involving opioid analgesics have increased dramatically since 1999, representing one of the United States' top public health crises. Opioids have legitimate medical functions, but they are often diverted, suggesting a tradeoff between improving medical access and nonmedical abuse. We provide causal estimates of the relationship between the medical opioid supply and drug overdoses using Medicare Part D as a differential shock to the geographic distribution of opioids. Our estimates imply that a 10% increase in opioid medical supply leads to a 7.1% increase in opioid-related deaths among the Medicare-ineligible population, suggesting substantial diversion from medical markets.

JEL codes:

I11; I12; I13

1. Introduction

Drug overdose deaths have risen steadily for the past two decades and are the leading cause of death from injuries in the United States. Overdoses involving opioids have been the dominant driver of this epidemic. In 2017, opioids were involved in 47,600 overdose deaths (Scholl et al., 2019), six times the number of opioid overdoses in 1999. The current level of opioid misuse is a "public health crisis" and the Centers for Disease Control and Prevention (CDC) label it the "fastest growing drug problem in the United States" (CDC, 2012).

A growing economics literature evaluates mechanisms to curb the rising overdose rate such as adoption of "must access" prescription drug monitoring programs (PDMPs) (e.g., Buchmueller and Carey, 2018), the introduction of abuse-deterrent opioids (e.g., Alpert et al., 2018), and improving access to substance abuse treatment (Swensen, 2015). Less

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research is dedicated to understanding the underlying causes of the opioid epidemic, which is critical information when designing policies to address this crisis. In this paper, we focus on the striking rise in opioid supply as a driving force of the sharp growth in overdoses, especially for the "first wave" of the opioid crisis, preceding the transition to heroin and fentanyl. There are three main motivations for this focus on supply and diversion. First, the role of large increases in the medical opioid supply is generally unknown. While additional access to opioids is often implicated as a potential reason for the opioid crisis (e.g., Ruhm, 2019), others have hypothesized that abuse is driving the rise in supply.[1] This latter hypothesis is more consistent with the "deaths of despair" argument (Case and Deaton 2015, 2017), suggesting that opioid supply plays a role but that the primary causes of the rise in overdoses and corresponding reductions in life expectancy are due to changes in underlying cultural and economic conditions.

Second, the United States is unique in its level of access to opioids. The United States is the largest consumer of opioid pain relievers, consuming twice as much per capita as the second largest consumer (International Narcotics Control Board, 2011). The CDC estimates that there were 82.5 opioid prescriptions per 100 people in the U.S. in 2012 and 12 states had more opioid prescriptions than people (Paulozzi et al., 2014).

Third, reduced opioid supply is not necessarily a policy goal, which differentiates opioids from drugs typically studied in the substance use literature. Unlike most drugs associated with overdose deaths and other harms, opioids remain an important medical tool which, in certain cases, are even believed to be underprescribed.[2] Opioid therapy is an effective instrument for acute pain management, although the efficacy of opioids for chronic non-cancer pain is limited (Dowell et al., 2016). While these drugs have legitimate medical functions, they are also highly-addictive, prone to abuse, and frequently diverted from their intended medical use. Despite clear concurrent national trends in overdoses and medical distribution of opioids since 1999 (Bohnert et al., 2011) as well as geospatial correlations (Paulozzi and Ryan, 2006), there is little empirical evidence of the causal relationship between the increasing supply of medically-intended opioids and spillovers to the nonmedical market. Understanding the nature of this connection is critical for considering appropriate policies to address this epidemic. This paper helps fill that void.

Despite the United States' unprecedented opioid supply, little is known about the broader non-medical spillovers caused by increasing access to opioids for medical use or the role of these spillovers in explaining the high rate of drug overdoses. What is known is that *two-thirds* of people who report nonmedical use of prescription pain relievers get them from a friend or relative (SAMHSA, 2015), suggesting significant scope for increases in medical opioid supply to explain proportional rises in overdoses. Khan et al. (2019) find that overdose rates increased for people without an opioid prescription when a family member received an opioid prescription. In this paper, we focus on the role of diversion in explaining national overdose trends. We study the spillovers of increasing opioid supply on a population

[1]For example, the Florida "pill mills" likely causally increased the state supply of opioids by attracting individuals intending to acquire opioids for nonmedical use to purchase more opioids.

[2]Greco et al. (2014) provides evidence that undertreatment of pain through opioid therapy is frequent for patients with cancer. Chaparro et al. (2014) finds systematic evidence in the literature of the efficacy of short-term opioid therapy.

that did not gain additional medical access to opioids. Diversion itself is difficult to measure, but we provide indirect evidence of its importance.

The economics literature has studied the abuse of illegal drugs (Becker, Grossman and Murphy, 1991; Grossman and Chaloupka, 1998; Jacobson, 2004), shocks to the supply of illegal drugs (Dobkin and Nicosia, 2009; Galenianos, Pacula, and Persico, 2012), and misuse of legal drugs (Carpenter and Dobkin, 2009; Chaloupka, 1991; Manning et al., 1989). There is surprisingly little work on negative spillovers associated with increasing medical access to prescription drugs. Despite the public health and economic importance of the opioid crisis, there is little quasi-experimental research dedicated to understanding its underlying causal mechanisms. While the crisis has recently transitioned such that illicit opioids (heroin and fentanyl) have more prominent roles, deaths involving prescription opioids remain staggering and nonmedical use of prescription opioids strongly predicts subsequent heroin use (Compton et al., 2016). This paper studies the interaction of medical drug markets with non-medical drug use. In contrast to cocaine and heroin markets, reduced opioid access is not a clear policy goal given that such actions may require diminishing access to patients with legitimate medical needs.

While research on the opioid crisis has established a host of characteristics which predict individual-level opioid abuse, few correlates have the potential to explain the dramatic rise in abuse over time. However, access to opioids has increased at levels proportional to the rise in overdoses and there is evidence of a positive correlation between opioid prescribing and opioid abuse (Dart et al., 2016; Bohnert et al., 2011). We calculate a 274% increase in medically-intended opioid distribution between 2000 and 2011 in the United States. This increase coincides with a substantial drop in the cost of opioids. Consumers paid 56% of the total costs for opioid prescriptions in 2000 and only 19% in 2011.[3] Recent work calculates out-of-pocket price trends for opioids and estimates that the price of a morphine equivalent dose[4] to the consumer decreased from $2.64 in 2001 to $0.54 in 2012 (Zhou et al., 2016).

The correlation between opioid supply and overdoses does not necessarily provide useful information about the causal effect of increasing supply. Areas with faster growth in opioid misuse will experience sharper increases in overdoses and that rise in misuse may drive an expansion in the state opioid supply. Alternatively, physicians may be less prone to overprescribe in states with high rates of opioid diversion,[5] suggesting the fast growth in opioid supply is associated with slower growth in misuse. The direction of bias is unknown.

We exploit large and differential geographic changes in opioid supply caused by the implementation of the Medicare Prescription Drug Benefit Program (“Part D”) in 2006, a prescription drug insurance expansion targeting older segments of the population. Part D provides voluntary outpatient prescription drug coverage to millions of Medicare beneficiaries. Several studies have shown that passage of Part D increased access and

[3]Authors’ calculations using the Medical Expenditure Panel Survey (MEPS).
[4]A morphine equivalent dose is equal to 60 morphine milligram equivalent (MME) units. Opioids vary in strength so conversion factors are applied to convert a milligram of each type of opioid into morphine equivalent units.
[5]Schnell (2018) studies how physicians respond to the existence of secondary markets.

utilization of prescription drugs among the elderly (Duggan and Morton, 2010, 2011; Zhang et al., 2009; Ketcham and Simon, 2008).

At a more aggregate level, this expansion differentially affected states based on the proportion of the population eligible for Medicare. States with a relatively large fraction of individuals gaining prescription drug coverage due to Part D experienced a relative increase in opioid supply. The resulting shifts in opioid supply are large and mimic the national growth in opioid access. This has the potential to affect the Medicare-ineligible population if a primary access point is either (1) elderly relatives or friends with multiple concurrent opioid prescriptions, or (2) diverted opioids from medical facilities, pain clinics, and pharmacies that care for elderly patients. While the elderly have a modest rate of unintentional opioid overdose deaths (Paulozzi et al., 2011), they are the legitimate medical users of more opioid prescriptions than any other age group (Volkow et al., 2011), which makes studying an insurance expansion targeting older age groups ideal.

We leverage the differential effects of the implementation of Part D on states based on pre-Part D variation in elderly shares. Our approach permits us to account for national effects associated with Part D and other secular trends while also controlling for fixed differences across states. Drawing on evidence presented below that states with higher elderly shares have higher Part D enrollment and that enrollment in Part D increased the amount of opioids prescribed to individuals 65 years and older, we test whether the overall supply of opioids increased disproportionately in high elderly share states. Once we establish that the medical distribution of opioids is higher to states with a higher elderly share after implementation of Part D, we examine whether this differential increase in opioid supply led to disparate growth in opioid abuse rates among the under-65 population as measured by overdose deaths and using a complementary measure of opioid substance abuse treatment admissions. Part D also potentially affected prescription drug access for the Social Security Disability Insurance (SSDI) population since SSDI beneficiaries are eligible for Medicare, but we show that our results are not driven by systematic behavioral changes among under-65 individuals covered by Medicare.

We assess the differential impact of Part D on under-65 opioid-related treatment admissions and overdose deaths. We find significant effects on both outcomes and there is no evidence of differential pre-existing trends. Our estimates imply that a 10% increase in medical access to opioids leads to a 7.1% increase in opioid-related mortality and a 9.6% increase in opioid-involved treatment admissions among the under-65 population. We do not find corresponding evidence that opioid *prescriptions* increased among the under-65 population disproportionately in high elderly share states, consistent with diversion as the driving mechanism and ruling out alternative mechanisms such as physician prescribing spillovers or systematically related changes in opioid access for the SSDI population. While our measure of diversion is indirect, we consider a wide range of alternative causal pathways but the evidence strongly suggests that Part D increased opioid abuse among the under-65, non-SSDI population through diversion. Extrapolating our results to the full 2000–2011 time series, our evidence suggests that 74% of the dramatic growth in opioid-related overdose deaths over this time period can be attributed to spillovers resulting from increased medical access. We conclude that diversion has played a key role in the opioid crisis.

The rest of the paper is organized as follows. In Section 2, we provide background on Medicare Part D, detail the data that we use to estimate our models, and discuss our underlying theoretical framework. Section 3 describes our empirical approach. We present results in Section 4. In Section 5, we discuss interpretation of the findings. We close in Section 6 with a summary of our main findings and the policy implications.

2. Background

2.1 Medicare Part D

On December 8, 2003, President George W. Bush signed the Medicare Modernization Act (MMA), which created Medicare Part D. Part D was implemented in 2006 and provided voluntary coverage of prescription drugs for those eligible for Medicare. The introduction of Part D was the largest expansion to Medicare since its creation and accounted for $89.8 billion in expenditures in 2015.[6] Safran et al. (2005) estimated that approximately 25% of Medicare beneficiaries did not have any prescription drug coverage prior to 2006. Part D substantially reduced the out-of-pocket price of prescription drugs for the Medicare population, and empirical evidence has found that these reduced prices increased use of prescription drugs.

A large literature has studied the ramifications of Part D on prescription drug utilization (e.g., Ketcham and Simon, 2008; Zhang et al. 2009) and drug prices (e.g., Duggan and Morton, 2010) as well as effects on nondrug medical care utilization (McWilliams et al., 2011). Most of this research focuses on the targeted population. There is far less work considering spillovers to the Medicare-ineligible population, which are potentially important given the large size of the program.[7] This paper provides evidence that Part D had important spillovers on the health of the population not covered by the program.

Health insurance expansions, more generally, may affect opioid abuse through several different and potentially off-setting channels. Health insurance increases medical care utilization (Manning et al., 1988), which could lead to more prescriptions of pain relievers for new conditions diagnosed. Alternatively, health insurance could improve access to substance abuse treatment (Maclean and Saloner, 2018, 2019). A key advantage of studying Medicare Part D, unlike recent Medicaid expansions, is that it only altered prescription drug access, not medical care utilization directly, allowing us to isolate the effects of opioid supply from changes in substance abuse treatment access and other factors.[8] By primarily studying outcomes among the Medicare-ineligible, we further disentangle the consequences of increased opioid supply from other causal impacts of prescription drug coverage.

[6]The 2016 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medicare Insurance Trust Funds: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/downloads/tr2016.pdf (accessed August 27, 2016)

[7]One exception is Alpert et al. (2015) which shows that Part D increased direct-to-consumer drug advertising (DTCA). The rise in DTCA increased prescription drug utilization in several chronic drug classes among the population ages 40–60.

[8]One possible exception is access to buphrenorphine. Buphrenorphine prescribing during our time period was relatively uncommon. We will show that there was no systematic change in buprenorphine prescribing.

2.2 Data

In this section, we discuss the sources for our data. We conduct all analyses at the state-level since our four primary measures of opioid supply and misuse can be calculated at this level. More granular metrics are also possible, but the data sets do not share any common sub-state identifiers. While it is possible to impute metrics to one uniform geography, these imputations require assumptions,[9] which we do not have to impose at the state level. The main cost of using state-level data is that we lose some variation in our measure of exposure to Part D, which may reduce power.[10] We rely on the 2000–2011 time period to narrow the sample period closer to the implementation of Part D and remain consistent across all data sets.

2.2.1 Opioid Supply—To measure supply, we rely on data which records the distribution of opioids to each state. Using prescriptions would miss a critical source of diversion given that opioids can be diverted before they are received by patients through fraud or theft. Information regarding the supply of prescribed opioids within the state is captured in the Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Orders System (ARCOS). The Controlled Substance Act of 1970 requires all manufacturers and distributors to report their transactions and deliveries of all Scheduled II (and selected Scheduled III and IV) substances to the Attorney General. ARCOS is the system that monitors and records the flows of these controlled substances as they move from manufacturers to retail distributors. We construct an aggregate measure of "opioid supply" from twelve reported opioid analgesics: fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, codeine, dihydrocodeine, levorphanol, oxymorphone, and tapentadol.[11] We convert to morphine equivalent doses drawing on standard multipliers.[12,13] A morphine equivalent dose is equivalent to one 40mg OxyContin pill.

2.2.2 Mortality—Information on opioid overdose deaths comes from the National Vital Statistics System (NVSS), a census of deaths in the United States. We code deaths as related to prescription opioid pain relievers using the ICD-10 external cause of injury codes (X40-X44, X60–64, X85, or Y10-Y14) and drug identification codes (T40.2-T40.4), which indicate death by any opioid analgesic. We aggregate the data based on state of occurrence and year. Our primary results will focus on ages 0–64, but we will also present estimates for smaller age groups and the 65+ population.

2.2.3 Substance Abuse Treatment Admissions—For complementary evidence, we use the Treatment Episode Data Set (TEDS) to study substance abuse treatment admissions. The TEDS is collected annually by state substance abuse agencies at the request of the

[9]The three sub-state geographies across the data sets are county, 3-digit zip code, and CBSA. One data set does not include any sub-state identifiers.

[10]We doubt that states represent appropriate boundaries to define markets for diverted prescription opioids but defining our markets too broadly (i.e., aggregating together multiple markets) should not be problematic as long as there is still adequate variation to detect reasonably-sized effects. Our standard errors will reflect whether there is adequate variation.

[11]Our results are not meaningfully changed if we limit this metric to the seven most commonly-misused opioids.

[12]See Piper et al. (2018) and https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-March-2015.pdf (last accessed October 5, 2019)

[13]Tramadol was not a controlled substance during this time period and, thus, is not reported in ARCOS.

Substance Abuse and Mental Health Service Administration (SAMHSA). The data contain the majority of all publicly funded substance abuse treatment admissions that occur within the United States, as all facilities that receive any government funding (federal block grant funding, state treatment dollars, or even insurance dollars from Medicaid, Medicare, or Tricare) are required to provide basic information.

Some facilities are excluded, but these exclusions are unlikely to cause problems for our empirical strategy for two reasons. First, our specifications include state fixed effects which account for persistent differences in state reporting over time. Second, it is unlikely that states more "exposed" (defined below) to Part D experienced systematic changes in the share of unobserved facilities missed by TEDS or changes in reporting beginning in 2006. In our analyses, we test this assumption by removing particularly problematic reporting states and by studying treatment admissions for other substances (e.g., alcohol or heroin), which would be also be affected by reporting changes.

We aggregate annual case-level data on admissions for the period 2000–2011. TEDS provides age in broad categories: 12–14, 15–17, 18–20, 21–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55+. Consequently, to study the impact of Part D on under-65 age groups, we rely on analyses of the 12–54 age group. We will also show results for smaller age groups as well as the 55+ group. TEDS includes information on whether the individual is retired or disabled, so we are able to remove any non-elderly with disabilities (i.e., the SSDI population) and test the sensitivity of our results to excluding this group. More details about the TEDS and the construction of our outcome variable are included in Appendix A.

2.2.4 Medical Expenditure Panel Survey (MEPS)—We also make use of data from the MEPS to empirically test alternative hypotheses. The MEPS is a set of large-scale surveys of individuals, families, and their medical providers/payers that is maintained by the Agency for Healthcare Research and Quality (AHRQ). The household data are a nationally-representative longitudinal data set which surveys households about demographics, income, health insurance, and medical claims. We use the geocoded version available in the AHRQ Research Data Center to study state-level changes over time. The Prescribed Medicines Data Files include prescription drug claims data for each person in the household surveys. These files were linked to the Multum Lexicon database to obtain therapeutic class variables. We follow Stagnitti (2015) in categorizing prescriptions as opioids.[14]

2.2.5 Other Variables—We study changes in opioid abuse as a function of the percentage of the state population ages 65+ in 2003. We choose 2003 because Medicare Part D was signed into law at the end of that year, and hence 2003 is likely free of any possible anticipation effects (Alpert, 2016). We use population data from the Census to construct our population variables. We also control for state-level demographics using data from the Census and American Community Survey, including the percent of the population that is white, percent of the population ages 25+ with no college (i.e., high school degree or less),

[14]This coding does not include tramadol during our time period, which is widely-prescribed to older individuals. However, in terms of potency, tramadol is relatively weak. According to the CMS conversion factors, a milligram of oxycodone is 15 times more powerful than a milligram of tramadol.

percent of the population ages 25+ with some college but no college degree, and 6 age shares (0–11, 12–17, 18–24, 25–44, 45–64, 65+). We also account for the state unemployment rate from the Bureau of Labor Statistics.

In analyses using our full set of controls, we also condition on a set of policy variables. The policy variables include whether the state has a prescription drug monitoring program (Prescription Drug Abuse Policy Surveillance),[15],[16] medical marijuana laws, active and legally-protected medical marijuana dispensaries (RAND Marijuana Policy database; see Powell et al., 2018; Williams et al., 2019), and laws regulating pain clinics (National Alliance of Model State Drug Laws). In Appendix Table A.1, we report the first full year[17] that each state had these policies (as of 2011).

2.2.6 Descriptive Statistics—The percent elderly in 2003 was 12.4% with a state-level standard deviation of 1.9%. This percent ranges from 6.2% in Alaska and 8.5% in Utah to 15.4% in West Virginia and 17.0% in Florida, representing a significant amount of variation across states. The geographic distribution of the percent elderly is mapped in Figure A.1.

There was substantial growth in opioid supply and abuse, as shown in Figure 1, throughout our analysis period. Distribution of opioid analgesics grew during this period, rising 274% from 2000 to 2011. Per capita opioid overdose deaths also show a significant rise, increasing by 248% between 2000 and 2011. During the same time period, substance abuse treatment admissions for opioids increased by 369%.

There appears to be a greater rise in opioid distribution and opioid deaths in the period preceding the implementation of Medicare Part D than in the period following Medicare Part D. Baseline differences account for some of this, but it is also possible that state- and national-level policies (as well as broader recognition of the dangers of lax opioid prescribing) intended to curb opioid abuse altered these trends. For example, between 2005 and 2007, an additional 14% of the U.S. population was covered by a PDMP and the first pill mill regulations were adopted, suggesting that these years represented an especially active time for meaningful changes in policy. More generally, the opioid literature has often struggled to reconcile dramatic time series trends with the widespread adoption of policies shown to alter overdose rates, often in the opposite direction. Consequently, in order to isolate the effect of changes in opioid supply from the dramatic secular trends which define the opioid crisis, it is important to account for time fixed effects while employing an empirical strategy which exploits differential geographic shocks to opioid access.

We include means for our outcomes and other variables for the pre-period in Table 1, separated by 2003 elderly share. There are some noticeable differences between the two sets of states, motivating our use of a fixed effects framework to account for these initial differences. However, opioid-related mortality is similar across the two sets of states. Before Part D, low elderly share states had 3.00 fatal opioid overdoses per 100,000 people ages 0–64. High elderly share states had 2.99 fatal overdoses per 100,000 ages 0–64.

[15]The first “must access” PDMP was adopted after our sample period.
[16]We use PDAPS coding as of December 2017.
[17]If a state adopted a policy in January, we consider that year as the first “full year.”

2.3 Theoretical Framework

A primary motivation of this paper is to understand the interaction of medical and illicit markets for opioids and the scope for diversion into nonmedical use to explain national trends in overdoses. Given a large shock to the medical distribution of opioids, the supply on the illicit market will also increase assuming that there are nontrivial rates of diversion. This supply shock drives down the costs (monetary and non-monetary) of obtaining opioids for non-medical use. Typically, such a shock to opioid access could also shift the illicit market demand curve since opioids are now easier to obtain in medical settings. However, our empirical approach shuts down this simultaneous demand shift by studying a population unaffected by the change in legal access.

We do not observe prices or quantities in illicit markets. Instead, we study the consequences of a shift in the illicit supply curve on downstream outcomes. We might suspect that a shock to the availability of opioids could have immediate effects on overdose rates if it increases initiation rates and naïve users, given a lack of sophistication and tolerance, have some propensity to overdose. Alternatively, for addictive goods, the utility of consumption is a function or prior consumption such that dependence may evolve over time and require escalation of dosages, eventually leading to lethal doses. Unfortunately, given our source of variation, there are limits to our ability to uncover specific mechanisms beyond quantifying the overall role of diversion. However, this theoretical framework suggests that the timing of the effect is especially interesting in this context, motivating our empirical model. Moreover, we may conjecture that the timing of the effects of such a supply shock may be different for treatment admissions than fatal overdoses. We study the timing of both.

3. Empirical Framework

Medicare Part D was implemented as a national program in 2006, but states were affected differentially based on the fraction of their population eligible for Medicare benefits. We use cross-state variation in the percentage of the population ages 65+ and find that this serves as a useful predictor. We fix our population share variable in 2003; identification originates solely from the introduction of Part D interacted with fixed state elderly shares. This strategy allows us to non-parametrically control for the independent effects of Part D (through year fixed effects) and fixed elderly share (through state fixed effects).[18]

3.1 Using Elderly Share as the Main Predictor

While elderly share is not a “perfect” predictor of changes in prescription drug coverage due to Part D, it does not need to be for our purposes and it has advantages over the alternatives. First, we do not exploit the predictable gains in Part D coverage for the SSDI population since this population typically had generous prescription drug coverage prior to Part D.[19] In

[18]We do not use a time-varying elderly share measure in the interaction term because there may be migration correlated with opioid abuse. For example, opioid abuse may be related to local economic downturns (Hollingsworth et al., 2017). If declining economic conditions cause younger people to disproportionately migrate out of the state (i.e., increasing the percentage of the population 65+), then this source of variation is problematic in principle. In practice, the results are similar if we use a time-varying measure of state elderly share.

[19]Individuals who have received Social Security Disability Insurance benefits for 24 consecutive months receive Medicare benefits, but many also receive benefits from Medicaid; these beneficiaries are called “dual eligible.” Prior to Medicare Part D, these dual eligible generally received prescription drug benefits through their state Medicaid program.

fact, if we replicate our "first stage" analysis below (Table 2) while also including 2003 non-elderly SSDI share interacted with post-2006, we find that this variable does not predict growth in state supply.[20]

Second, in principle, we could also exploit pre-Part D prescription drug coverage rates for the older population (similar to Dunn and Shapiro, 2019). Constructing state-specific prescription drug coverage rates for the elderly population can be difficult, typically involving small sample sizes and injecting a level of noise that can be avoided by simply relying on elderly shares. In principle, pre-Part D state-level prescription drug coverage rates among the elderly could be systematically and inversely related to elderly share such that they would unravel our first stage. However, we test the relationship between elderly share and opioid supply growth empirically and rely on the empirical relationship as our test of the appropriateness of using elderly share. There is little loss in simply using 2003 elderly share given that it predicts state-level growth in opioid supply.

3.2 Main Specification

We use the timing of Part D and cross-sectional differences in elderly share across states for identification. We estimate the specification

$$y_{st} = \alpha_s + \gamma_t + X'_{st}\beta + \delta\left[\%Elderly_{s,2003} \times 1(t \geq 2006)\right] + \varepsilon_{st}, \quad (1)$$

where y_{st} is a measure of opioid-related distribution, abuse, or mortality for state s in year t. X is the vector of time-varying covariates which includes percentage white, 6 age group shares, percent with no college, percent with some college (but no degree), and the unemployment rate. We will also include policy variables: PDMPs, medical marijuana laws, legal and operational medical marijuana dispensaries, and pain clinic regulations.

We will show results which do not include the time-varying covariates because of concerns that some of these variables may themselves be outcomes related to opioid diversion. In addition, these covariates may themselves predict differential trends in the outcomes so we will also provide results in which we permit the relationship between the covariates and outcomes to vary by year.[21] We are interested in the estimate of δ, the differential change in the outcome experienced by high elderly share states relative to low elderly share states. We expect this estimate to be positive if Part D increased opioid access and, consequently, opioid-related substance abuse.

In addition, we will present event study estimates, which lets the relationship between 2003 elderly share and the outcomes to vary by year. For these results, we will also allow the relationship between the covariates and outcomes to vary by year given recent work suggesting that this flexibility is important in such designs (Jaeger et al., 2018). Event study estimates will provide evidence about the importance of pre-existing trends while also

[20] It is estimated to have a negative (though small and statistically insignificant from zero) effect.

[21] We interact the unemployment rate and demographic characteristics with year indicators with the exception of the age share variables. Since our variable of interest is 2003 elderly share interacted with the Post dummy, including age share variables interacted with time dummies creates collinearity issues. Instead, we also include the 2003 25–44 age share interacted with time dummies. We selected this age group because it includes the population most vulnerable to the opioid crisis.

testing for the timing of the effect. The timing of the effect is interesting here given the dynamics of addiction and substance use.

Our outcome measures will be specified as per capita morphine equivalent doses, deaths per 100,000 people, or substance abuse treatments per 100,000. We weight all regressions by state population, and standard errors are adjusted for clustering at the state level.

4. Results

4.1 Part D Enrollment & Prescription Opioid Use Among the Elderly

Our empirical strategy relies on the assumption that elderly share predicts changes in state opioid supply due to Part D implementation. We will test this assumption explicitly in the next section but, here, we explore intermediate outcomes which are consistent with an increase in supply. First, we test whether high elderly share states have higher Part D enrollment per capita. We use Part D enrollment data from the CMS aggregated by state and year to study this relationship. Part D may impact access by providing prescription drug coverage to part of the population which would not have had any coverage otherwise or by providing more generous coverage to people who would have had coverage even in the absence of Part D. Both of these mechanisms are potentially important determinants of the overall increase in opioid supply. Here, we simply verify that high elderly share states have higher Part D enrollment rates after implementation.

Figure A.2 quantifies the relationship between elderly share and the Part D enrollment rate (Part D enrollment divided by state population). It shows coefficient estimates from cross-sectional year-by-year regressions of the Part D enrollment rate on 2003 elderly share between 2006 and 2011, indicating that each additional percentage point of the state population ages 65+ predicts an additional 0.4 to 0.6 percentage points of the population enrolled in Medicare Part D. This relationship grows over time, which suggests that we might expect the relationship between 2003 elderly share and our measures of opioid supply and abuse to grow over time as well. Our graphical analyses will generally find that this is the case.

Second, our empirical strategy assumes that enrollment in Medicare Part D increased the amount of opioids prescribed to individuals 65 years and older. While several papers have identified an impact of Medicare Part D on prescription drug utilization for the 65+ population, we are unaware of any published analyses looking specifically at the effects on opioid utilization.[22] To verify previous findings hold for opioids specifically, we conducted our own examination of the impact of Medicare Part D insurance on the number of opioids prescribed by comparing opioid prescriptions filled by a group of newly insured (those 66–71 years of age) to a sample of near elderly (those 59–64 years of age) in the 2002–2009 MEPS. This strategy replicates the empirical strategy found in the literature on the Part D effects on utilization. A complete description of this analysis is included in Appendix Section B. The main results and numerous sensitivity analyses demonstrate that Medicare

[22]In a recent working paper, Soni (2018) adopts a similar approach as the one that we use in this section to provide a more comprehensive analysis. She estimates an elasticity of −0.89, which is reasonably close to our estimate here.

Part D decreased the out-of-pocket price of opioids substantially (by 48%) and increased the number of annual prescriptions by 0.174 relative to the 59–64 age group (representing a 28% increase), implying an elasticity of −0.6. Alpert (2016) estimates that acute drug prescriptions increased by 23.6% for the elderly after implementation of Part D, similar in magnitude to the estimated increase in opioid prescriptions here.

This relationship suggests that Part D had the potential to increase the supply of opioids in states with high elderly share. We do not necessarily expect that the increase in prescriptions due to Part D reflects the full growth in opioid supply since opioids may be diverted before they are prescribed. However, an increase in number of prescriptions is consistent with an increase in supply.

4.2 State-Level Increases in Opioid Supply

We now turn to our main models to examine whether state elderly share is associated with an increased state supply of opioids. We estimate equation (1) using morphine equivalent doses per capita from the ARCOS data as our outcome variable and present our estimates in Table 2. We estimate that a one percentage point increase in the 2003 elderly share is associated with additional 0.8 morphine equivalent doses per person after Part D. This estimate is robust to the inclusion of the unemployment rate and demographics (Column 2). In Column (3), we add policy variable controls and the estimated effect is unaffected. Finally, in Column 4, we permit the time-varying controls to have different effects in each year. We estimate a similar relationship. The consistency of the estimates across models is suggestive that there are no time-varying confounders biasing our estimates.

Figure 2 provides the event study equivalent. While there is some evidence of a pre-existing trend prior to 2003, we observe little differential change in opioid supply between 2003 and 2005. This is followed by a sharp rise beginning in 2006 and continuing to 2010. Overall, we find convincing evidence that the introduction of Medicare Part D differentially affected the geographic supply of opioids based on elderly share. As discussed before, we do not necessarily expect that the increase in distribution to each state solely reflects increases in prescriptions to the 65+ population. For example, pharmacy theft is common,[23] and opioids are also known to be stolen at other points of the supply chain. Consequently, the ARCOS data provide a useful measure of opioid supply that would not be captured by prescriptions. Next, we analyze harms associated with this broader opioid availability.

4.3 Mortality Regression Estimates

We present our regression estimates of the differential impact of Medicare Part D on non-elderly opioid-related mortality in Table 3. The outcome variable is opioid-related deaths per 100,000 (ages 0–64). We estimate that each additional percentage point of the percentage elderly is associated with 0.28 additional deaths per 100,000 people after the enactment of Part D (Column 1), statistically significant from zero at the 5% level. In Column (2), we add state-specific time-varying controls and find that the estimate is robust to accounting for

[23]In 2014, there were over 1000 federal burglary reports of controlled substances according to https://www.deadiversion.usdoj.gov/21cfr_reports/theft/maps/DTL_Burglary_By_State_CY2014.pdf (last accessed November 13, 2017).

these factors. We control for additional policy variables in Column (3) and estimate that each additional percentage point of the percentage elderly is associated with 0.35 additional deaths per 100,000 after 2006. In Column (4), we interact the time-varying covariates with year indicators. The estimate increases further.

Next, we consider the independent effects of variation in age composition by accounting flexibly for differences in age structure. We create opioid-related deaths per 100,000 for each age under 65 (0, 1, 2,…, 64); observations are defined by state-year-age. The specification includes age-year interactions as well as state-age interactions, flexibly accounting for the effects of age composition changes in each state and the time-varying propensities of abuse by age. The estimate, presented in Column (5) of Table 3, is similar to the Column (3) estimate which uses the more aggregated approach. In general, we find that the results of this paper are insensitive to flexible controls for state age structure.

We also include an event study equivalent of equation (1) in Figure 3, permitting the effect of the 2003 elderly share to vary by year. There is little evidence of pre-existing trends. It is also worth remembering that the pre-2006 *levels* are also similar across states (as shown in Table 1). Post-implementation of Part D, there is a steady rise in mortality, generally following a similar path as the opioid distribution event study estimates (Figure 2).

Table 4 disaggregates the relationship between Part D expansion and opioid-related mortality by sex and age group. The results show that the effect is larger for men across most age groups. For men, the largest estimate is for the 30–39 age group, implying that each percentage point of elderly share leads to 0.99 additional opioid-related deaths per 100,000 people, almost three times as large as the aggregate effect shown in Table 3, Column (3). For women, the largest estimate is for the 40–49 age group. In the last row of Table 4, we present the p-value from a test of whether the estimate for men is equal to the estimate for women for the same age group.[24] At the 5% level, we can reject that the 50–59 age group estimates are the same across gender as well as the 30–39 age group estimates.

We estimate large effects for the age groups highlighted by Case and Deaton (2015), and the age profile generally follows an inverse-U shape. At ages 65+, we observe no statistically significant effects at the 5% level, suggesting no spillovers to this population. Note that even for this age group, the estimate only reflects the effect of spillovers, not the direct effect of Part D. Our variation does not originate from individual-level variation in Part D eligibility but, instead, from cross-state variation in the proportion of other people eligible for Part D. A 65 year old in a high elderly share state experiences the same gain in Part D eligibility in 2006 as a 65 year old in a low elderly share state so the direct effects of access through Part D are similar.

The age pattern of the results is consistent with pain reliever misuse rates from the 2004 National Survey on Drug Use and Health (NSDUH), shown in Appendix Figure A.3. The additional access to opioids translates to different rates of overdoses by age, and this pattern reflects differences in self-reported rates of misuse. We observe very low rates of misuse for

[24]We estimate this p-value through a clustered bootstrap.

the 65+ population, consistent with the lack of mortality effects for this age group. Appendix Figure A.4 shows the estimates for each age graphically.

4.4 Opioid Abuse Treatment Admissions

Opioid mortality, while extremely important from a public health perspective, is also a relatively rare outcome. A more common outcome indicative of problematic use or abuse of opioids is treatment admissions. In Table 5, we present estimates for opioid-related substance abuse treatment admissions for ages 12–54. The outcome variable is the number of treatment admissions per 100,000. In Column (1), we use the full sample and estimate that a one percentage point increase in the percentage of the state population ages 65+ in 2003 leads to an additional 11.5 treatments per 100,000 people after Part D. As we add controls and account for policy adoption, the estimate remains relatively consistent in Columns (2) and (3). In Column (4), we permit the effects of the covariates to vary by year. The standard errors noticeably increase, but the point estimate remains about the same.

In Column (5), we select on states reporting in all years (i.e., the “balanced sample”) and find a similar result. The consistency of the estimates between Columns (3) and (5) should reduce concerns that our estimates are driven by changes in the states reporting information to TEDS over time. In Column (6), we further adjust the sample and exclude admissions which list that the person is “Retired/Disabled.” These selection criteria should exclude the SSDI population. The estimate is relatively unaffected (eliminating the SSDI population reduces the mean of the outcome variable -- the estimates are similar in proportional terms). In this more narrowly defined population, we estimate that a one percentage point increase in the elderly population (65+) is significantly associated with 8.6 additional substance abuse treatments per 100,000 people after 2006.

As with the mortality results, we include event study estimates in Figure 3. As before, we find little evidence of pre-existing trends, followed by a rise in treatment admissions. This rise is delayed relative to the fatal overdose effect discussed above. This postponed effect relative to the mortality effect could reflect that fatal overdoses rise immediately due to unsophisticated users initiating in response to a supply shock, leading to some immediate deaths. However, those not overdosing in the short-term may take time to develop dependence issues before seeking treatment.

In Table 6, we examine the relationship across different age groups and gender, using the available age groupings in the TEDS. We observe statistically significant effects throughout the age distribution. Here, we find less evidence of differences by gender. The age heterogeneity is generally consistent with the age trajectory estimated for mortality. For both men and women, the estimates are largest for the 21–29 age group and at least twice the size of the estimated aggregate effect for ages 12–54 (Column 3 in Table 5). The point estimates steadily decrease at older ages, again consistent with Figure A.3.

Given our concern that reporting issues may obfuscate the useful information in the TEDS, we briefly summarize why we believe that the estimates in this section reflect true changes in substance abuse. First, our results are consistent when we select the sample on states that are supplying a less noisy measure of substance abuse treatments. Second, in Section 4.6.1

below, we replicate our analysis using measures of non-opioid treatments as the dependent variable. We never observe patterns similar to the trajectory observed for opioid treatment admissions. If reporting issues were the driving mechanism, then we would expect to observe similar effects on other types of treatments. While treatment admissions can also reflect treatment *access*, this evidence suggests that we are finding changes in demand for treatment.

4.5 Parameterizing the Relationship between Opioid Supply and Abuse

In this section, we parameterize the relationship between opioid supply and abuse. In the first column of Table 7, we use OLS to estimate the relationship between state morphine equivalent doses (MED) per capita and the state opioid mortality rate for ages 0–64. We find that each additional morphine equivalent dose per capita is associated with an increase in the number of deaths by 0.327 per 100,000 people ages 0–64.

This relationship is potentially confounded by many unobserved factors and, as discussed in the introduction, the direction of the bias is unknown. To account for these possible confounders, we instrument opioid supply with our interaction term ($\%Elderly_{s,2003} \times 1(t \geq 2006)$). The IV estimate is similar to the OLS estimate. The similarity in these estimates does not imply the absence of confounding factors but does suggest that any confounding factors cancel each other out for mortality. In Column (3), we present the 2SLS estimate for the full population (including the elderly) and estimate a coefficient of 0.287, implying that an additional morphine equivalent dose per person in a state leads to an additional 0.287 overdoses per 100,000. This estimate is smaller than the Column (2) estimate given the low abuse response of the 65+ population to additional opioid access (as shown in Table 4), but the effect size is similar in proportional terms.

In the last three columns of Table 7, we present estimates for substance abuse treatment admissions. With OLS, we estimate that each morphine equivalent dose is associated with 6.6 additional treatment admissions per 100,000 people ages 12–54. When we estimate using 2SLS, the effect increases to 11.4.

In the final column, when we estimate the relationship for the population ages 12+, we find that each additional per capita morphine equivalent dose increases the substance abuse treatments by 6.9 treatments per 100,000 people. This effect is similar in proportional terms to the estimate for the 12–54 population. The Table 7 estimates imply that a 10% increase in opioid supply increases opioid-related mortality rates (for ages 0–64) by 7.1% and substance abuse treatment admission rates (for ages 12–54) by 9.6%.[25]

4.6 Robustness Tests

We test the sensitivity of our results to several factors. We previously addressed concerns about state age composition (Table 3, Column 5). Here, we consider other possible mechanisms, such as concurrent shocks in the demand for opioids, state insurance expansions during this time period, and confounding reporting trends.

[25]To calculate these estimates, we use the mean value in 2006–2011 for each outcome as the baseline. The mean for per capita morphine equivalent doses during this time period is 12.4.

4.6.1 Concurrent Supply-Side and Demand-Side Shocks—In this section, we study whether we observe similar results for other substances. If our opioid results are driven by some other concurrent confounding supply or demand shock affecting substance use more generally, then this shock should influence consumption of other substances. For example, if high elderly share states were disproportionately affected by the Great Recession and economic downturns are associated with increases in drug abuse, then we should observe relative rises in other drugs as well.

While our main motivation in this section is to test whether we observe similar changes in actual abuse of other drugs, these results also support the prior evidence that the rise in opioid-related treatment admissions is not an artifact of systematic changes in reporting. We find that the large and statistically significant rise in substance abuse treatment admissions is unique to opioids. Figure A.5 present event study estimates for alcohol, marijuana, heroin, and total admissions not involving opioids. There is some evidence of a differential decline in admissions in 2004, which may suggest systematic reporting changes. However, none of the other substances replicate the post-2006 jump in admissions followed by a steady increase over time. Instead, this pattern is unique to opioid-specific treatment admissions.

Figure A.6 presents event study estimates for fatal overdoses involving other substances. First, we study heroin overdoses. We do not find similar differential increases in heroin overdoses. In principle, a shock to prescription opioid availability could decrease substitution to heroin, but we observe little evidence of such substitution either. Next, we examine cocaine overdose rates and again find no evidence of differential increases beginning in 2006. We also examine all overdoses not involving prescription opioids. We exclude overdoses involving only unspecified drugs (T50.9) in this measure due to concerns that we may inadvertently include unspecified opioid overdoses in this measure. Again, we do not estimate a similar pattern of results. Instead, only opioid-related mortality (and treatment admissions) appear to differentially rise post-2006 and gradually increase over time, consistent with the differential gradual increase in Part D enrollment and opioid supply. In addition, we also study alcohol-related poisonings in Figure A.6.[26] There is little relationship between changes in alcohol-related poisonings and state elderly share.

Finally, we analyze other deaths of despair studied in Case and Deaton (2017). These event study estimates are presented in Figure A.7. We study these outcomes to test for the possibility that elderly share is correlated with some systematic shock to “despair” (i.e., economic conditions, cultural institutions, etc.) beginning in 2006. First, we study suicides, excluding overdoses. Second, we study alcohol-related liver disease mortality. In both cases, we do not estimate similar relationships with elderly share. The results in this section generally suggest that high elderly share states were not differentially impacted by other factors beginning in 2006 which would independently increase substance use or other risky behaviors which may increase mortality.

[26]Because code F10.0 was discontinued in 2007 and thereafter coded as an external cause, it is necessary to include F10.0 and F10.1 in our measure of alcohol poisoning deaths.

4.6.2 Insurance Expansions and Pill Mill Crackdowns—

We study a large prescription drug expansion and its differential effects at the state-level. During our time period, there were also large state-level health insurance expansions. In 2006, Massachusetts enacted a health care reform law which expanded health insurance to nearly the entire population. In 2008, Oregon expanded its Medicaid program. In the other direction, Tennessee disenrolled a large number of Medicaid enrollees in 2005. In addition, Florida had a unique rise in opioid abuse due to the prevalence of pill mills in the state before the 2011 crackdown.[27] We test whether any specific state is driving our estimates. Figure A.8 provides mortality estimates while excluding one state at a time. While there is some variability in the estimates, they are rather consistent in magnitude and always statistically significant from zero at the 5% level. We find little evidence that any specific state is driving our results.

4.6.3 Buprenorphine Access—

We interpret our estimates as reflecting the consequences of a shock to prescription opioid supply given that Part D only affected prescription drugs. One possible confounding shock is that buprenorphine, often used in medication-assisted treatment (MAT), is a prescribed drug. If this treatment was also diverted, then our results would reflect the net effect of a shock to prescription opioid supply and MAT. Given the low rate of misuse by the 65+ population, we expect that Part D had limited effects on buprenorphine supply. We test this assumption explicitly by replicating our event study specification for per capita buprenorphine grams. We present these results in Figure A.9. As expected, we observe little evidence of any relationship with elderly share over time.

4.7 Mechanisms

We interpret the relationships estimated in this paper as evidence of economically-meaningful levels of diversion, though we do not measure diversion directly. An alternative mechanism would be that Part D led to differential changes in physician prescribing patterns, generating similar increases in opioid prescribing to the under-65 population as was observed for the 65+ population. In principle, there is little support for this interpretation given that opioids were already heavily-prescribed before Part D. We would also likely expect most physician prescribing spillovers to disproportionately affect older age groups, but our age-specific results suggest stronger abuse responses at younger ages.

We test this possibility more explicitly using the geocoded MEPS (accessed at the AHRQ Data Facility). Following Stagnitti (2015) in classifying opioid prescriptions, we constructed the number of opioid prescription per person for ages 0–64 at the state level and estimated our main specification.[28] The results are presented in Table 8. When we include all of our control variables, we estimate that a state with an additional percentage of elderly experienced a decline of 0.249 prescriptions among the 0–64 population after Part D. This estimate is not statistically different from zero. Because opioid prescriptions are relatively rare for younger age groups, we replicate this analysis for the 18–64 population and present

[27] It is not clear that we would want to exclude the Florida pill mills given that it has been suggested that Part D aided the creation of the pill mills in Florida (since it is a high elderly share state) and the state's rise in abuse (e.g., Meinhofer, 2016).

[28] When this same model is estimated for the 65+ population, we find no evidence of any spillover effects for this population.

the estimates in the last column. Again, we estimate a negative and statistically insignificant effect.

These tests also support our prior evidence that SSDI is not confounding our main estimates. One alternative hypothesis is that elderly share predicts additional opioid prescriptions among the under-65 population after Part D through SSDI, resulting in more drug overdoses from direct medical access. However, we do not observe differential increases in prescriptions to the under-65 population in Table 8.

Overall, our analysis strongly suggests that the rise in abuse operates through nonmedical acquisition. We find large effects on opioid-related harms for the under-65 population without corresponding increases in prescriptions. Alternative mechanisms such as systematic price changes,[29] SSDI enrollment, and physician-prescribing spillovers are inconsistent with the available evidence.

5. Discussion

5.1 Externalities

We find that overdoses increase among a population that does not directly gain medical access to these drugs. We can interpret the costs of misuse of these diverted opioids in the same manner as the costs of cigarette smoking, as studied in Gruber and Köszegi (2001), due to time-inconsistent preferences. Gruber and Köszegi (2001) refer to the “internalities” of smoking. Our estimates refer to the harms incurred by the population that is not directly prescribed the opioids so the “internalities” of additional medical access are experienced by an “external” population. Assuming that overdoses represent evidence of time-inconsistent preferences, this combination (time-inconsistent preferences plus an external population) could lead us to interpret these results as evidence of externalities resulting from increased medical opioid access. Recent work suggests that a calculation of internalities must also factor in the utility gains of using the addictive product (Levy et al., 2018; Cutler et al., 2015). This insight would also impact any externality calculation made using these estimates. We do not pursue this calculation here.

5.2 Tradeoffs

This paper examines the negative spillovers resulting from increased medical access to opioids. Understanding these harms is critical for designing policy to curb overdoses. It is also important to consider the benefits of expanded access to pain relievers, such as reductions in severe pain among the Medicare Part D population. Given the necessary reliance on coarse self-reported measures of pain, this exercise is difficult in our context and generally beyond the scope of the paper.[30]

[29]While not shown, we also find no evidence of differential price changes. In principle, the increased demand for opioids could have increased opioid prices more in high elderly share areas. This result would work against the effects that we are finding. However, given that we do not find utilization differences among the non-elderly, it is not surprising that we do not find price differences either.

[30]Using self-reported pain measures in the Health and Retirement Study (HRS) and the same empirical strategy used in Section A.1, we find no evidence of reductions in pain resulting from Medicare Part D (in fact, we estimate rather precise zero effects).

As policymakers and medical professionals consider guidelines and regulations governing appropriate opioid prescribing, it is important to consider the benefits of opioids as an effective pain management tool. However, it is also critical for policy to internalize the spillovers to the rest of the population.

6. Conclusion

According to the CDC, 130 people die each day from an opioid overdose in the United States and at least half of those involve a prescription opioid.[31] While many federal, state and community strategies have been offered to try to counteract the tide, empirical evidence for what caused the rise of the opioid crisis in the first place has been relatively rare. This paper is the first to evaluate the extent to which policy-driven expansions in medical access, specifically insurance that reduced the cost of prescription drugs to patients, may have contributed to the opioid epidemic. By exploiting geographic variation in the location of the elderly, who were the primary beneficiaries of Medicare Part D implementation, we are able to evaluate how expansion of prescription drug benefits (independent of expansions in access to medical care) might have influenced the dramatic rise in drug overdoses. Part D provides a rare opportunity to mimic dramatic national trends in medical opioid supply and observe the spillover effects while conditioning on time fixed effects.

Evidence from SAMHSA (2015) indicates that friends and relatives are the primary source of prescription opioid medication, and elderly with multiple concurrent prescriptions are an easy target for some individuals interested in diverting opioids into the black market. Our results are consistent with these stylized facts and provide evidence about its causal relationship with opioid-related overdoses. It is important to acknowledge that our findings are most relevant to the first wave of the opioid crisis. Given the wider availability of heroin and illicitly-manufactured fentanyl (Pardo et al., 2019), a large increase in the supply of prescription opioids could have very different effects today. It may increase initiation rates which, due to the existence of mature illicit opioid markets, leads to even larger increases in overdoses. Alternatively, additional access to prescription opioids for nonmedical use may substitute for more potent illicit opioids, minimizing the rise in overdoses.

We interpret our results as indirect but clear evidence of diversion from the medical market to the illegal nonmedical use market. Opioid distribution in the United States increased between 2000 and 2011 by 274% while opioid-related overdose mortality rates increased by 248% over the same time period. Extrapolating our results to the national context should be done with caution and we highlight that our estimates reflect the effects of increases in opioid access for the 65+ population, which may involve a higher diversion rate than similar changes to opioid supply for other populations. With this caveat, our Table 7 (Column 3) estimates imply that the increased access to opioids explains 74% of the rise through diversion. Our treatment admission results (Table 7, Column 6) imply that the national growth in opioid supply explains 75% of the national rise in opioid treatment admissions. Attributing these magnitudes to unintentional spillovers does not rule out the importance of more direct, complementary mechanisms. Opioid overprescribing may lead to high addiction

[31] https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis (last accessed on March 21, 2019)

rates which are then exacerbated by nonmedical opioid access through diversion. Our results imply that the diversion component is a critical driver of the opioid epidemic. It also suggests that opioid supply is an important driver of this crisis.

The implications of these findings is that, unless supply side mechanisms become more effective at reducing the opportunities for diversion of these prescription opioids from patients (by reducing overprescribing, enforcing PDMPs, educating physicians on inappropriate prescribing, and managing utilization), the opioid crisis will continue to worsen. While the opioid crisis has recently transitioned to heroin and illicit fentanyl, there is still great interest in understand the role of prescription opioids in the crisis, especially since prescription opioids remain a crucial component of the current rate of overdoses, involved in almost 15,000 overdoses per year. Optimal policy must account for the spillovers of improving medical care access to drugs that are easy to abuse and divert.

Acknowledgments

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APPENDIX

Appendix A: Additional Details for TEDS Data

The TEDS data contain the majority of all publicly funded substance abuse treatment admissions that occur within the United States, as all facilities that receive any government funding (federal block grant funding, state treatment dollars, or even insurance dollars from Medicaid, Medicare, or Tricare) are required to provide basic information. Private facilities that only treat non-publicly insured individuals and that receive no federal or state grant monies are the only facilities that are supposed to be excluded. However, states differ in the scope of facilities covered due to differences in agencies responsible for licensing, certification and accreditation, and disbursement of public funds for treatment. Moreover, the scope of admissions captured by those facilities that do report to TEDS also varies across states, as some states only report admissions for clients that were treated with public funds while others report all admissions from within the facility (SAMHSA, 2013). In the main text, we provide several reasons why these differences across states should not affect our results.

The unit of observation in the TEDS is an admission, and information is retained on the primary, secondary, and tertiary substances reported at the time of the admission, as well as client demographics, expected source of payment, treatment setting, and treatment characteristics. We include two substance categories in our metric of opioid abuse: “non-prescription methadone” and “other opiates and synthetics.” The latter category includes “buprenorphine, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like

effects." We include all admissions in which one of these drugs is included as primary, secondary, or tertiary substances. Our results do not change meaningfully if we only count primary substance or if we exclude non-prescription methadone.

Appendix B: Did Part D increase opioid prescriptions among the 65+ population?

Several papers compare changes in prescription drug utilization for the 65+ population after the implementation of Medicare Part D to utilization changes for individuals under 65. This approach isolates the effect of Part D from other secular trends in drug utilization. The literature consistently finds that Part D increased overall prescription drug utilization, but there is no research focusing specifically on opioid prescriptions. A necessary condition for our empirical strategy is that Medicare Part D increased opioid prescriptions for the 65+ population.

We use the Medical Expenditure Panel Survey (MEPS) to study changes in the number of opioid prescription for ages 66–71 relative to ages 59–64. We exclude age 65 in this analysis since those individuals are partially-treated. We follow Stagnitti (2015) by defining opioid prescriptions as those with therapeutic subclasses "narcotic analgesics" and "narcotic analgesic combinations." We use the 2002–2009 data files and consider each claim as a prescription, which is standard in this literature (see Alpert, 2016). The MEPS surveys households for two consecutive years so we account for the panel structure by adjusting standard errors for clustering. We estimate the following specification:

$$y_{iat} = \theta_a + \gamma_t + \rho[1(a \geq 65) \times 1(t \geq 2006)] + \varepsilon_{st}, \quad (2)$$

where y_{iat} represents the number of opioid prescriptions filled by individual i at age a in year t. The specification includes age and year fixed effects. The parameter of interest is the coefficient on the interaction of the implementation of Part D and an indicator for ages 65+.

We present the main estimates in Column 1 of Table A.1. The estimate implies that individuals ages 65+ increased the number of annual prescriptions by 0.174 more prescriptions than individuals ages 59–64. This estimate is statistically significant at the 5% level. While the literature often uses large data sets of pharmacy claims, we are able to statistically reject that there was no effect even with our relatively small sample.

We replicate this analysis in Column 2 but exclude ages 63 and 64. Alpert (2016) provides evidence of important anticipation effects with respect to Medicare Part D. Excluding these ages should reduce concerns that the control group is also "treated" by Part D because they defer some treatments until they are eligible for Medicare. We find similar estimates when we exclude 63–64 year olds. Alpert (2016) shows that the anticipation effects occurred in 2004–2005 since Part D was announced at the end of 2003, providing individuals the opportunity to alter prescription drug utilization given the intertemporal price changes. In Column 3, we exclude 2004 and 2005 from the analysis and estimate a similar effect. In Column 4, we exclude 2004–2004 and ages 63–64. Again, we observe similar effects.

We have also estimated the above models using Poisson regression to estimate proportional effects. The evidence (not shown) is consistent with the estimates presented in Table A.1, which is not surprising given that the pre-Part D utilization rates between these two groups are relatively similar.

In Panel B of Table A.1, we present corresponding estimates of the effect of Part D on the price of opioids. Part D decreased out-of-pocket prices for the 65+ population, driving the increased utilization. We estimate

$$\ln(p_{idat}) = \theta_{da} + \gamma_{dt} + \varphi[1(a \geq 65) \times 1(t \geq 2006)] + \upsilon_{st}, \quad (3)$$

where p_{idat} is the out-of-pocket price of National Drug Code (NDC) d purchased by individual i of age a in year t. We control for interactions based on NDC-age and NDC-year. Each observation is an opioid prescription purchased in the sample for ages 59–71 (excluding 65). We adjust our standard errors using two-way clustering (Cameron et al., 2011) by individual and by NDC.

The estimates are consistent whether we account for anticipation effects. Our main estimate (Column 1 in Panel B) implies that individuals ages 65+ experienced a 48% reduction in out-of-pocket payments relative to the 59–64 population after the implementation of Part D.

Thus, we find evidence that Part D decreased the price of opioids for the Medicare-eligible population and that this price decrease led to an increase in the number of prescriptions. In Section 4.2, we study whether this individual-level increase in opioid access can be observed at a more aggregate level by studying whether elderly share predicts increases in state opioid supply. We find that higher elderly share states experienced relative increases in opioid supply after Part D implementation.

Overall, using multiple data sets and empirical strategies, the evidence strongly suggests that the supply of opioids increased faster in high elderly share states after Medicare Part D.

References (included in Appendix but not in main paper):

Cameron, A. Colin, Jonah B. Gelbach, and Douglas L. Miller, “Robust Inference With Multiway Clustering,” *Journal of Business & Economic Statistics*, 29 (2011), 238–249.

Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Behavioral Health Statistics and Quality, “Treatment Episode Data Set (TEDS): 2001–2011. State Admissions to Substance Abuse Treatment Services,” (Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013).

Appendix Figures and Tables

Figures

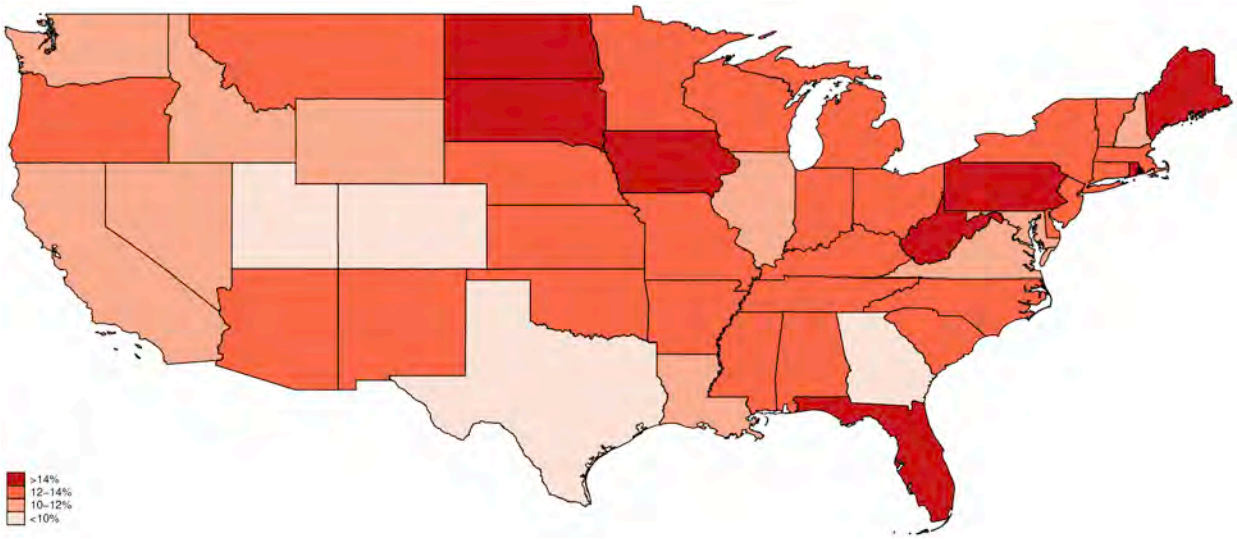

Figure A.1:
Elderly Share in 2003

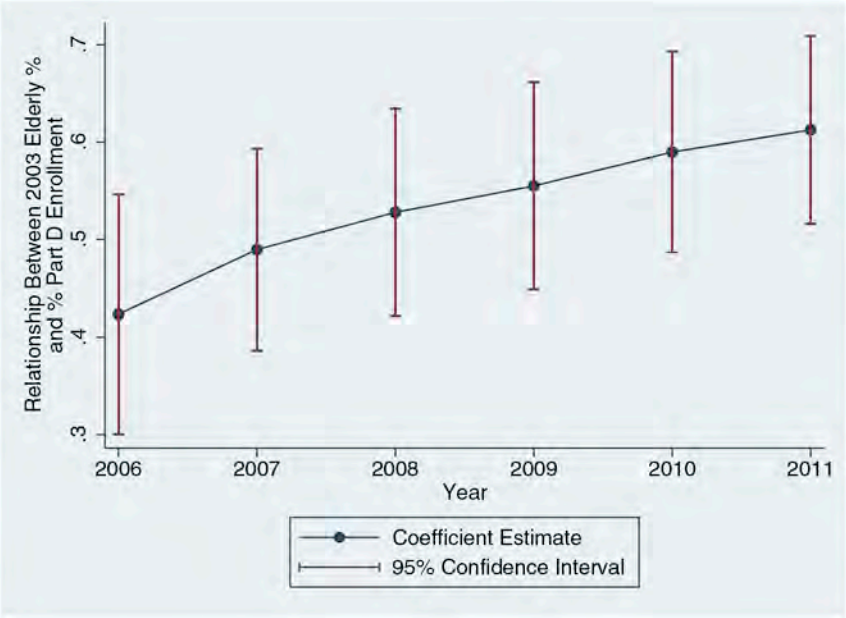

Figure A.2:

Relationship between % Elderly in 2003 and % Enrolled in Part D

Notes: We regress the percentage of the population enrolled in Part D on the percentage of the 2003 population ages 65+. We perform this cross-sectional regression by year.

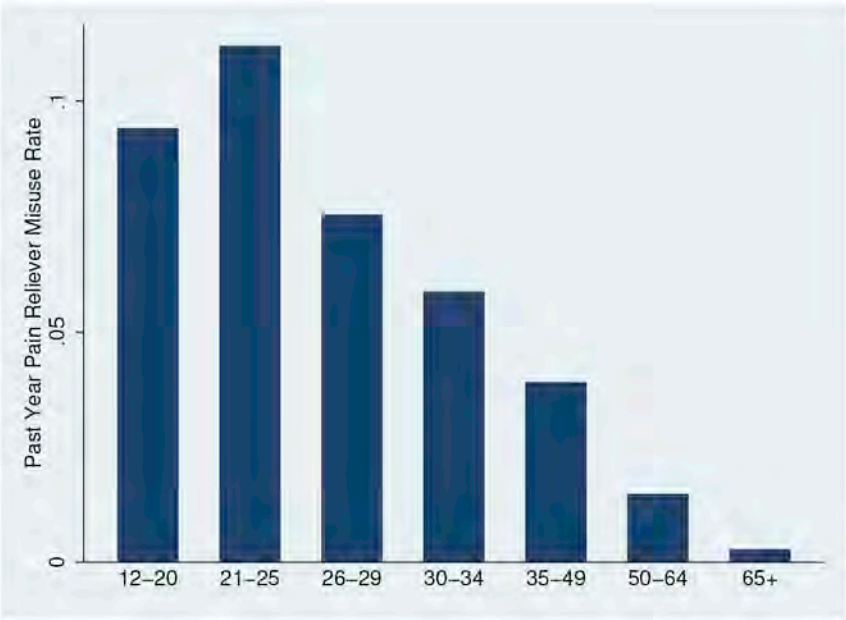

Figure A.3:
Pain Reliever Misuse Rate in 2004 by Age Group
Source: 2004 National Survey on Drug Use and Health

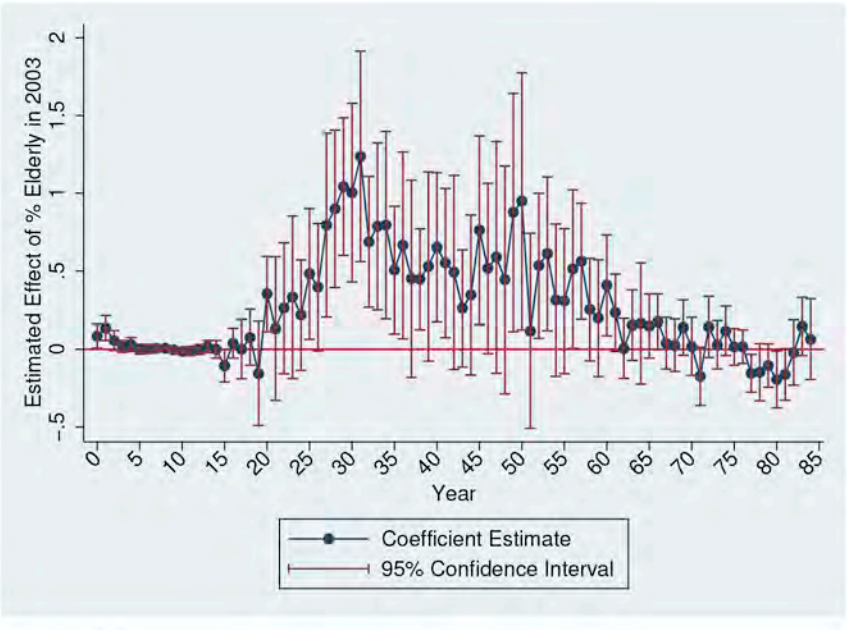

Figure A.4:

Relationship between % Elderly in 2003 and Mortality Rate by Age

Notes: We estimate equation (1) for each age between ages 1 and 85. The models include all covariates, including the policy variables. Confidence intervals are adjusted for within-state clustering.

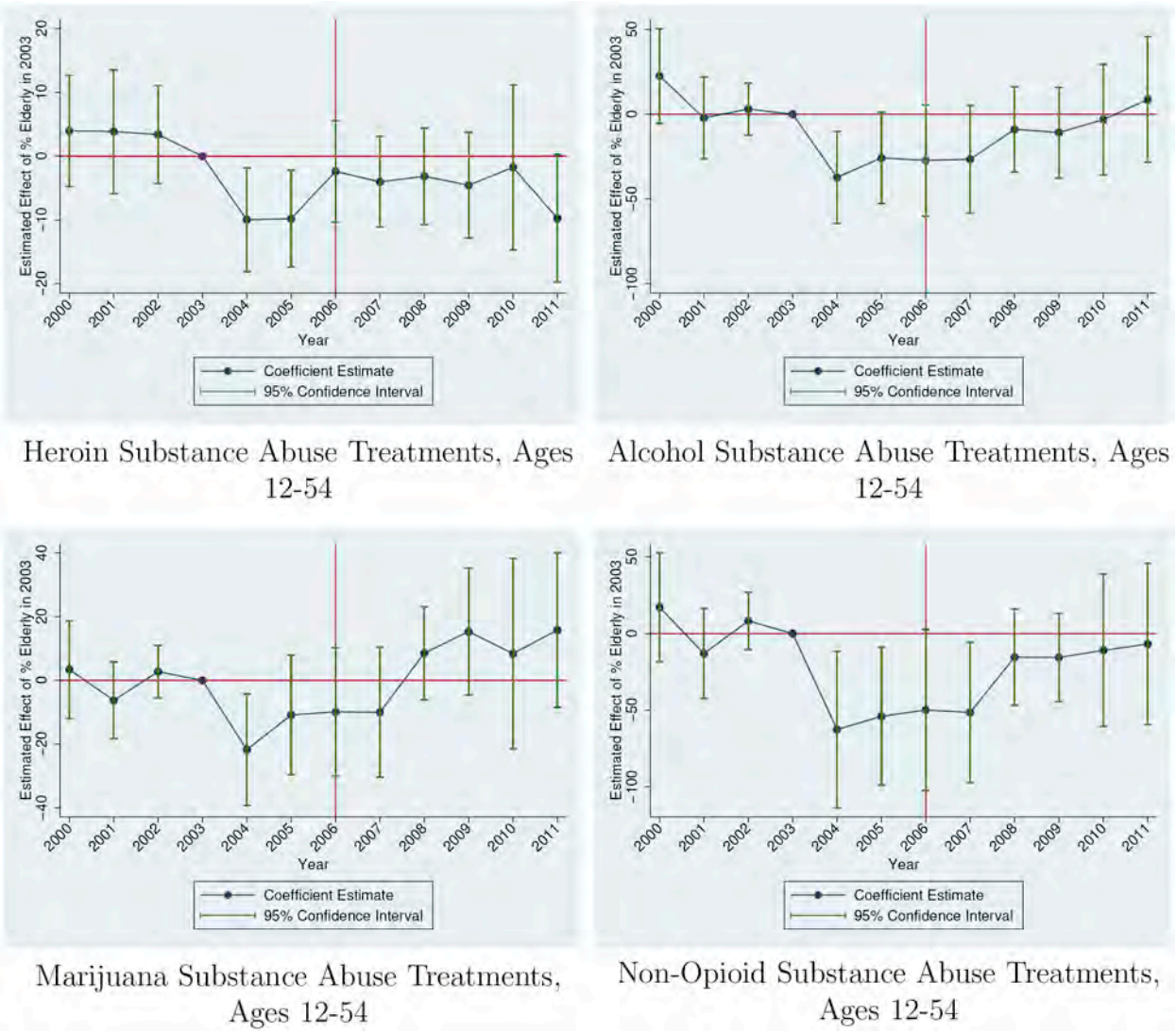

Figure A.5:
Placebo Event Studies using TEDS
Sources: Treatment Episode Data Set (2000–2011)
Notes: Outcomes are defined as per 100,000 people. Each estimate refers to the effect of 2003 Elderly Share in that year. All specifications include controls for time and state fixed effects. We also include all controls used in Table 3, Column 4. Regressions are population-weighted. Estimates are normalized to 0 in 2003. 95% confidence intervals adjusted for clustering at the state level.

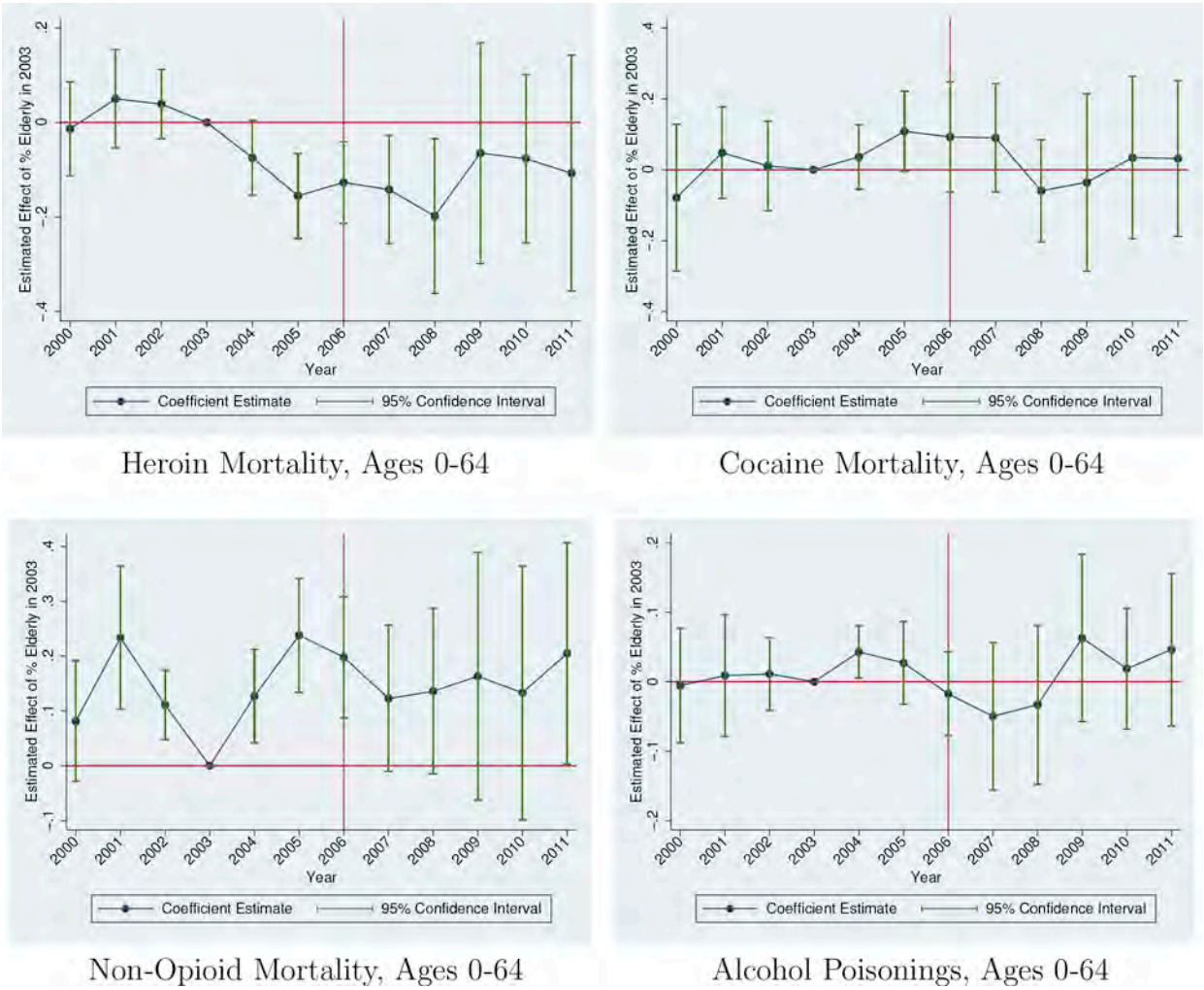

Figure A.6:

Event Studies for Overdoses not involving Prescription Opioids and Alcohol Poisoning Deaths

Sources: National Vital Statistics System

Notes: Mortality is defined as per 100,000 people. Each estimate refers to the effect of 2003 Elderly Share in that year. All specifications include controls for time and state fixed effects. We also include all controls used in Table 3, Column 4. Regressions are population-weighted. Estimates are normalized to 0 in 2003. Non-opioid overdoses exclude overdoses involving opioids and unspecified drugs. 95% confidence intervals adjusted for clustering at the state level.

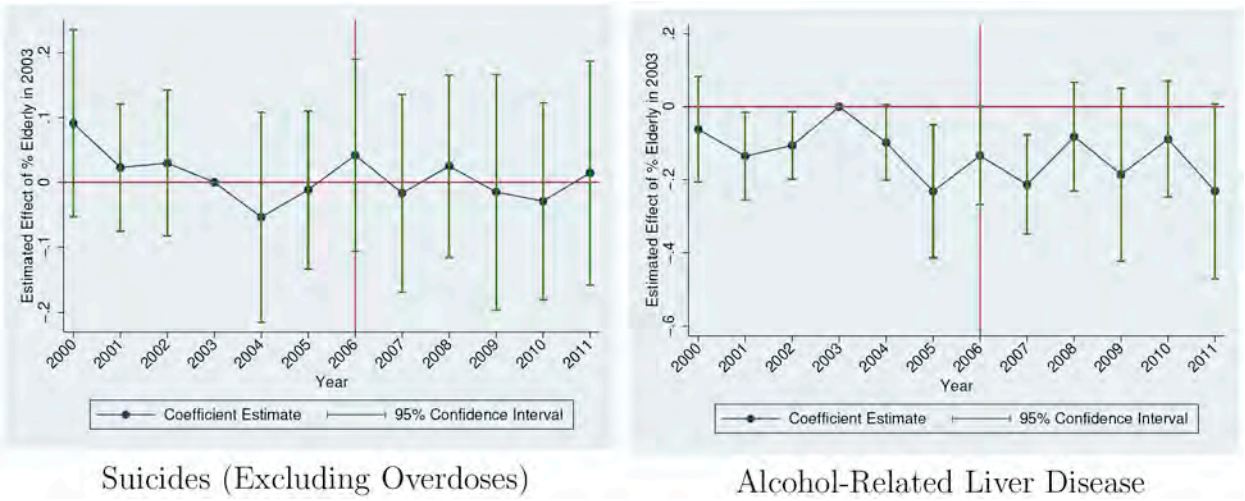

Figure A.7:

Event Studies for Other Deaths of Despair

Sources: National Vital Statistics System

Notes: Mortality is defined as per 100,000 people. Each estimate refers to the effect of 2003 Elderly Share in that year. All specifications include controls for time and state fixed effects. We also include all controls used in Table 3, Column 4. Regressions are population-weighted. Estimates are normalized to 0 in 2003. 95% confidence intervals adjusted for clustering at the state level.

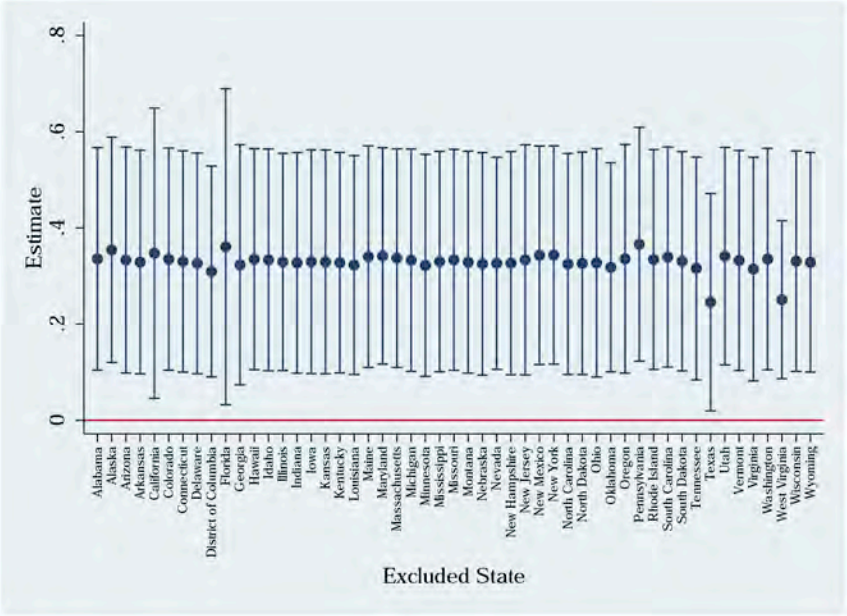

Figure A.8:

Mortality Estimates When Excluding One State

Notes: We replicate our main mortality result while excluding one state at a time. Each estimate above is marked by the state that is excluded. 95% confidence intervals adjusted for clustering at the state level.

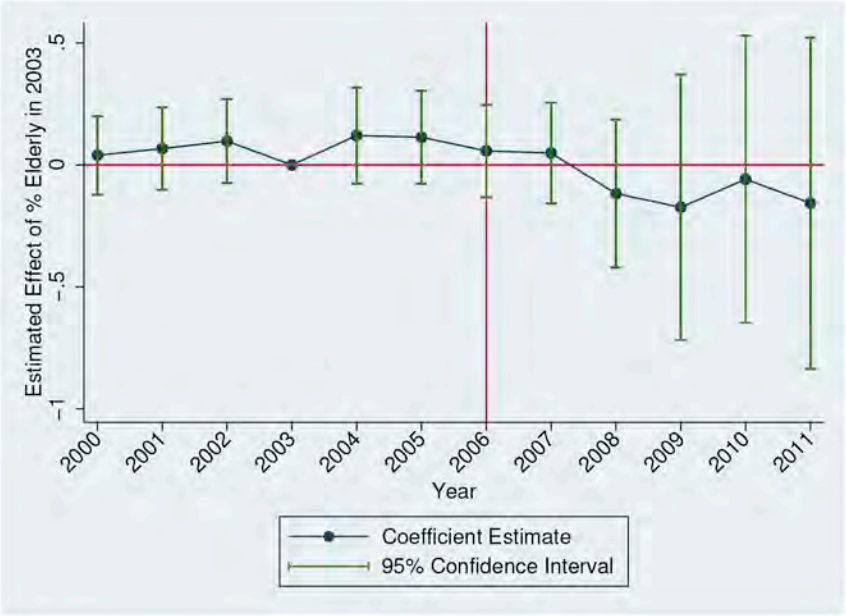

Figure A.9:
Event Study Estimates for Buprenorphine Distribution
Sources: ARCOS
Notes: The outcome is buprenorphine grams per capita. Each estimate refers to the effect of 2003 Elderly Share in that year. All specifications include controls for time and state fixed effects. We also include all controls used in Table 3, Column 4. Regressions are population-weighted. Estimates are normalized to 0 in 2003. 95% confidence intervals adjusted for clustering at the state level.

Tables

Table A.1:

State Policies: First Full Active Year (up to 2011)

State	PDMP	MML	Active and Legal Dispensaries	Pain Clinic Regulations
Alabama	2005			
Alaska	2009	2000		
Arizona	2008	2011		
Arkansas				
California	1997	1997	2004	
Colorado	2006	2001	2011	
Connecticut	2007			
Delaware	2011			
District Of Columbia		2011		
Florida	2010			2011
Georgia				
Hawaii	1997	2001		
Idaho	2001			

State	PDMP	MML	Active and Legal Dispensaries	Pain Clinic Regulations
Illinois	2001			
Indiana	1994			
Iowa	2007			
Kansas	2009			
Kentucky	1999			
Louisiana	2007			2006
Maine	2004	2000		
Maryland		2004		
Massachusetts	1992			
Michigan	2002	2009		
Minnesota	2008			
Mississippi	2007			
Missouri				
Montana		2005		
Nebraska				
Nevada	1996	2002		
New Hampshire				
New Jersey	2011	2011		
New Mexico	2005	2008	2010	
New York	1998			
North Carolina	2006			
North Dakota	2008			
Ohio	2006			
Oklahoma	1991			
Oregon	2010	1999		
Pennsylvania	2002			
Rhode Island	1997	2006		
South Carolina	2007			
South Dakota	2011			
Tennessee	2003			
Texas	1998			2010
Utah	1996			
Vermont	2007	2005		
Virginia	2004			
Washington	2008	1999		
West Virginia	1996			
Wisconsin	2011			
Wyoming	2004			

We list the first *full* year that the state has an active law. If a state adopted a law in January, then we count that year as the first full year. If a state enacted a policy after 2011 (the end of our sample period) or never adopted the policy, then we do not list an adoption date.

Table A.2:

Did Part D Increase Opioid Prescriptions Among the 65+ Population?

Panel A: Opioid Prescriptions				
	(1)	(2)	(3)	(4)
(Age ≥ 65) x (Year ≥ 2006)	0.174** (0.089)	0.191** (0.096)	0.181* (0.094)	0.177* (0.099)
Age Fixed Effects	Yes	Yes	Yes	Yes
Year Fixed Effects	Yes	Yes	Yes	Yes
Years (2002–2009)	All	All	No 2004–2005	No 2004–2005
Ages (59–71)	All	No 63–64	All	No 63–64
N	23,190	19,205	17,754	14,694
Panel B: ln(Price)				
	(1)	(2)	(3)	(4)
(Age ≥ 65) x (Year ≥ 2006)	−0.476*** (0.121)	−0.459*** (0.114)	−0.491*** (0.142)	−0.488*** (0.142)
NDC x Year Fixed Effects	Yes	Yes	Yes	Yes
NDC x Age Fixed Effects	Yes	Yes	Yes	Yes
Years (2002–2009)	All	All	No 2004–2005	No 2004–2005
Ages (59–71)	All	No 63–64	All	No 63–64
N	11,995	9,978	9,230	7,697

Notes:
*** Significance 1%,
** Significance 5%,
* Significance 10%.

In Panel A, each observation is an individual-year and standard errors in parentheses are adjusted for clustering at individual level. In Panel B, each observation is a prescription and standard errors are adjusted for two-way clustering at individual- and NDC-level. Age 65 excluded in all regressions.

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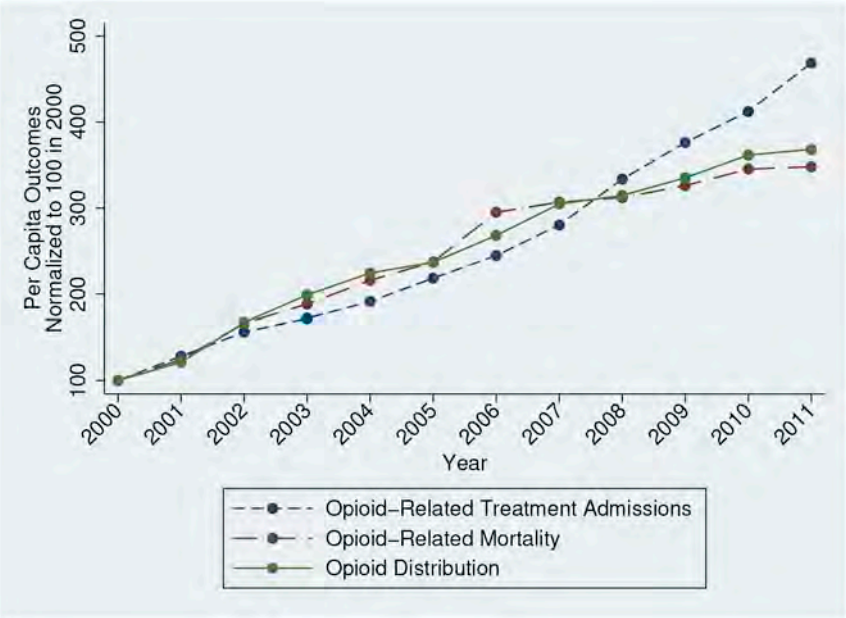

Figure 1:

Opioid Use and Abuse

Notes: We use ARCOS data to generate per capita opioid distribution, NVSS to create per capita opioid-related mortality, and TEDS to calculate per capita substance abuse treatments for opiates. We normalize each time series to 100 in 2000.

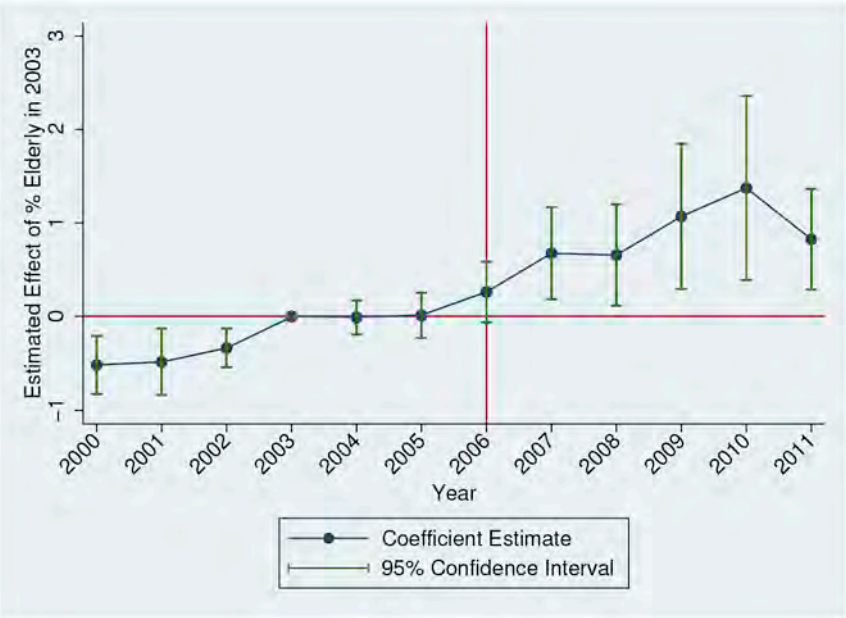

Figure 2:

Opioid Distribution: Event Study

Notes: We estimate equation (1) but allow the effect of Elderly Share in 2003 to vary by year, normalizing the coefficient for 2003 to zero. The outcome is morphine equivalent doses per capita. State and time fixed effects included. We also include all controls used in Table 2, Column 4. 95% confidence intervals adjusted for clustering at the state level.

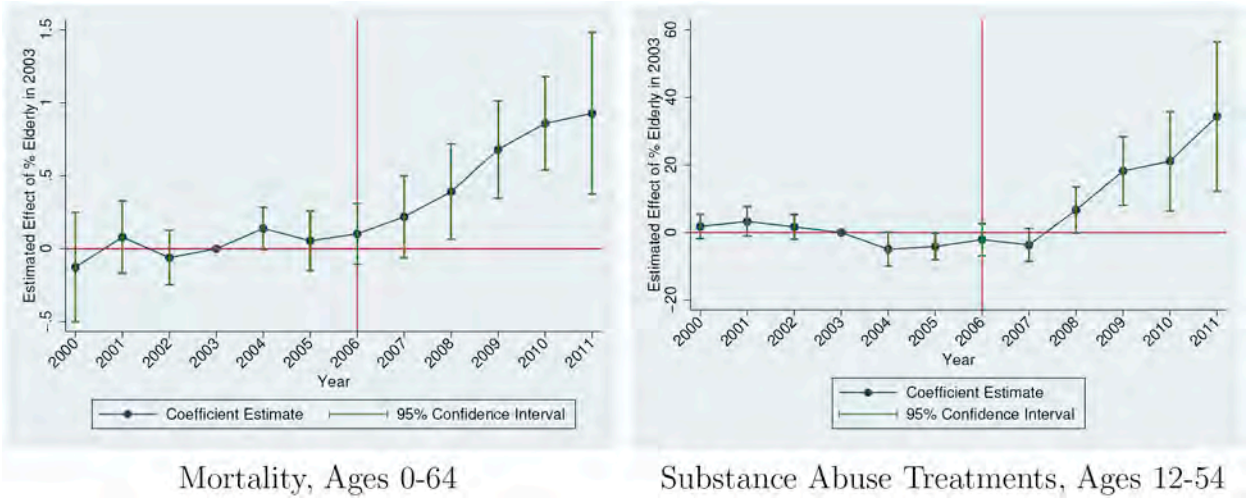

Figure 3:

Main Event Study Estimates

Sources: National Vital Statistics System (2000–2011) and Treatment Episode Data Set (2000–2011)

Notes: Outcomes are specific to opioid-related mortality and opioid-related substance abuse treatments (per 100,000). Each estimate refers to the effect of 2003 Elderly Share in that year. All specifications include controls for time and state fixed effects. We also include all controls used in Table 3, Column 4. Regressions are population-weighted. Estimates are normalized to 0 in 2003. 95% confidence intervals adjusted for clustering at the state level.

Table 1:

Summary Statistics for 2000–2005

	Low Elderly Share	High Elderly Share	P-Value
Outcomes			
Opioid Deaths per 100,000	2.75	2.63	0.805
Opioid Deaths per 100,000, Ages 0–64	3.00	2.99	0.981
Substance Abuse Treatment Admissions per 100,000	31.4	49.7	0.043
Substance Abuse Treatment Admissions per 100,000, Ages 12–54	40.7	67.7	0.026
Morphine Equivalent Doses per capita	6.13	7.47	0.009
Covariates			
Unemployment Rate	5.41	4.94	0.033
% Ages 0–11	17.2%	15.7%	0.000
% Ages 12–17	8.9%	8.5%	0.003
% Ages 18–24	10.2%	9.5%	0.001
% Ages 25–44	29.6%	28.2%	0.001
% Ages 45–64	23.0%	24.1%	0.007
% Ages 65+	11.1%	14.0%	0.000
% No College	43.0%	43.6%	0.639
% Some College	28.0%	26.5%	0.129
% White	63.3%	74.1%	0.064
% Ages 65+ in 2003	11.3%	13.3%	0.000

Notes: All statistics are weighted by the population. States are divided into groups based on 2003 elderly share. “P-Value” refers to the hypothesis that the means in the low and high elderly share states are equal (adjusted for clustering at the state level).

Table 2:

Medical Supply of Opioids

Outcome:	**Morphine Equivalent Doses Per Capita**			
	(1)	(2)	(3)	(4)
% Elderly_{2003} × Post	0.824*** (0.202)	1.042*** (0.122)	0.966*** (0.119)	0.953*** (0.255)
State time-varying controls × Year Fixed Effects	No	Yes	Yes	Yes
	No	No	No	Yes
Policy Variables	No	No	Yes	Yes
N	612	612	612	612

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Mean outcome = 9.67. Controls included in all models but not shown: state fixed effects and year fixed effects. State time-varying controls include the unemployment rate, % white, 6 age group shares, % no college, and % some college (but no degree). When these covariates are interacted with year indicators, the age group shares are not due to collinearity concerns (given the interaction term of interest). Instead, we also include the 2003 share ages 25–44 interacted with year indicators. Policy variables include whether the state has a PDMP, a medical marijuana law, legal and operational medical marijuana dispensaries, and pain clinic regulations.

Table 3:

Opioid-Related Mortality, Ages 0–64

Outcome:	Opioid-Related Mortality per 100,000				By Age
	(1)	(2)	(3)	(4)	(5)
% Elderly$_{2003}$ × Post	0.282** (0.120)	0.330*** (0.117)	0.354*** (0.130)	0.445*** (0.141)	0.357*** (0.124)
State time-varying controls × Year Fixed Effects	No	Yes	Yes	Yes	Yes
	No	No	No	Yes	No
Policy Variables	No	No	Yes	Yes	Yes
N	612	612	612	612	39,780

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

State and year fixed effects included in all models. Standard errors in parentheses adjusted for clustering at state level. Mean outcome = 4.33 in all columns. All regressions weighted by population. In Column (5), observations are defined by state-year-age and the outcome is the number of opioid-related deaths per 100,000 in that cell. State time-varying controls include the unemployment rate, % white, 6 age group shares, % no college, and % some college (but no degree). When these covariates are interacted with year indicators, the age group shares are not included due to collinearity concerns (given the interaction term of interest). Instead, we also include the 2003 share ages 25–44 interacted with year indicators. Policy variables include whether the state has a PDMP, a medical marijuana law, legal and operational medical marijuana dispensaries, and pain clinic regulations. The last column also include state-age and age-year fixed effects.

Table 4:

Opioid-Related Mortality by Age Group

Outcome:	**Opioid-Related Mortality per 100,000**						
			Panel A: Men				
Age Group:	**10–19**	**20–29**	**30–39**	**40–49**	**50–59**	**60–64**	**65+**
% $Elderly_{2003}$ × Post	−0.008 (0.048)	0.547** (0.208)	0.985*** (0.309)	0.497* (0.264)	0.596*** (0.221)	0.217* (0.109)	−0.002 (0.024)
Mean Outcome:	1.13	7.02	7.83	9.79	7.15	2.72	0.82
			Panel B: Women				
Age Group:	**10–19**	**20–29**	**30–39**	**40–49**	**50–59**	**60–64**	**65+**
% $Elderly_{2003}$ × Post	−0.007 (0.018)	0.421*** (0.155)	0.413** (0.167)	0.603** (0.270)	0.269* (0.148)	0.171** (0.078)	0.023 (0.035)
Mean Outcome:	0.35	2.52	4.34	6.89	5.52	2.53	0.87
P-Value (Men=Women)	0.922	0.434	0.042	0.384	0.008	0.816	0.450

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

N=612 for all cells. Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Other controls included: state fixed effects, year fixed effects, the unemployment rate, % white, 6 age group shares, % no college, % some college, PDMP, medical marijuana law, legal and operational medical marijuana dispensaries, and pain clinic regulations.

Table 5:

Opioid-Related Substance Abuse Treatments, Ages 12–54

Outcome:	Opioid-Related Treatment Admissions Per 100,000					
	(1)	(2)	(3)	(4)	(5)	(6)
% Elderly$_{2003}$ × Post	11.540** (4.699)	11.925*** (2.679)	10.918*** (2.880)	9.852** (4.825)	9.849*** (3.375)	8.571*** (3.098)
State time-varying controls × Year Fixed Effects	No	Yes	Yes	Yes	Yes	Yes
	No	No	No	Yes	No	No
Policy Variables	No	No	Yes	Yes	Yes	Yes
Sample	Full	Full	Full	Full	Balanced	Balanced
Population	All	All	All	All	All	No SSDI
Mean Outcome:	86.69	86.69	86.69	86.69	87.91	82.13
N	587	587	587	587	516	516

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Controls included in all models but not shown: state fixed effects and year fixed effects. State time-varying controls include the unemployment rate, % white, 6 age group shares, % no college, and % some college (but no degree). When these covariates are interacted with year indicators, the age group shares are not included due to collinearity concerns (given the interaction term of interest). Instead, we also include the 2003 share ages 25–44 interacted with year indicators. Policy variables include whether the state has a PDMP, a medical marijuana law, legal and operational medical marijuana dispensaries, and pain clinic regulations. “Balanced” uses the sample of states reporting to TEDS in all years 2000–2011. The “No SSDI” population excludes individuals reporting labor force participation of “Retired/Disabled.”.

Table 6:

Opioid-Related Substance Abuse Treatments by Age Group

Outcome:	**Opioid-Related Treatment Admissions Per 100,000**					
			Panel A: Men			
Age Group	**12–20**	**21–29**	**30–39**	**40–49**	**50–54**	**55+**
% Elderly$_{2003}$ × Post	4.857* (2.718)	23.827** (8.964)	15.669*** (4.496)	3.728** (1.577)	2.157** (0.930)	0.060 (0.339)
Mean Outcome:	58.14	182.37	107.62	73.43	47.82	9.90
			Panel B: Women			
Age Group	**12–20**	**21–29**	**30–39**	**40–49**	**50–54**	**55+**
% Elderly$_{2003}$ × Post	5.703*** (1.428)	30.068*** (6.554)	15.156*** (3.114)	3.422** (1.302)	1.610** (0.762)	−0.094 (0.139)
Mean Outcome:	36.13	143.68	95.89	58.32	29.20	4.69
P-Value (Men=Women)	0.716	0.588	0.696	0.696	0.458	0.616

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

N=587 for all cells. Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Other controls included: state fixed effects, year fixed effects, the unemployment rate, % white, 6 age group shares, % no college, % some college, PDMPs, medical marijuana laws, legal and operational medical marijuana dispensaries, and pain clinic regulations.

Table 7:

Relationship Between Opioid Supply and Harms

Outcome:	**Deaths Per 100,000**			**Admissions Per 100,000**		
	(1)	(2)	(3)	(4)	(5)	(6)
MED Per Capita	0.327*** (0.061)	0.355*** (0.130)	0.287** (0.113)	6.567*** (2.183)	11.359*** (3.181)	6.921*** (2.130)
Ages	0–64	0–64	All	12–54	12–54	12+
Estimator	OLS	IV	IV	OLS	IV	IV
Mean Outcome (2006–2011)	5.61	5.61	5.03	121.71	121.71	89.23
N	612	612	612	587	587	587

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Other controls included: state fixed effects, year fixed effects, log unemployment rate, % white, 6 age group shares, % no college, % some college, PDMPs, medical marijuana laws, legal and operational medical marijuana dispensaries, and pain clinic regulations. The excluded instrument is % $\text{Elderly}_{2003} \times$ Post. MED = morphine equivalent doses. The mean MED per capita in 2006–2011 was 12.4.

Table 8:

Geocoded MEPS Analysis

Prescriptions for Under-65 Population				
Outcome:	**Prescriptions Per Person**			
% Elderly$_{2003}$ × Post	0.410 (1.397)	0.096 (1.602)	−0.249 (1.651)	−1.417 (2.129)
State time-varying controls	No	Yes	Yes	Yes
PDMP Laws	No	No	Yes	Yes
Ages	0–64	0–64	0–64	18–64
N	609	609	609	609

Notes:

*** Significance 1%,

** Significance 5%,

* Significance 10%.

Standard errors in parentheses adjusted for clustering at state level. All regressions weighted by population. Not all states have data in each year so we have 609 observations, instead of 612. Controls also included but not shown: state fixed effects and year fixed effects.

Clinical Policy: Critical Issues Related to Opioids in Adult Patients Presenting to the Emergency Department

Clinical Policy Endorsed by the American Society of Addiction Medicine (July 27, 2020)

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Opioids:

Benjamin W. Hatten, MD, MPH (Subcommittee Chair)
Stephen V. Cantrill, MD
Jeffrey S. Dubin, MD, MBA
Eric M. Ketcham, MD
Daniel P. Runde, MD
Stephen P. Wall, MD, MSc, MAEd (Methodologist)
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Members of the American College of Emergency Physicians Clinical Policies Committee (Oversight Committee):

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Richard Byyny, MD, MSc (Methodologist)
Christopher R. Carpenter, MD, MSc
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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in opioid management in adult patients presenting to the emergency department. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients experiencing opioid withdrawal, is emergency department-administered buprenorphine as effective for the management of opioid withdrawal compared with alternative management strategies? (2) In adult patients experiencing an acute painful condition, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms? (3) In adult patients with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing a short course of opioids on discharge from the emergency department outweigh the potential harms? (4) In adult patients with an acute episode of pain being discharged from the emergency department, do the harms of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics outweigh the benefits? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Opioids are synthetic or naturally occurring substances that bind to opioid receptors in humans. Activity at the μ-opioid receptor is responsible for desired effects of both euphoria and analgesia, along with negative effects such as respiratory depression. Depending on the specific opioid administered and degree of tolerance in the patient, exposure to even small amounts of potent opioids (eg, fentanyl) is often sufficient to cause respiratory depression and death. Additional adverse effects include sedation, nausea, constipation, falls, and rapid tolerance with physical dependence.

During the past decade, drug-related deaths have surpassed motor vehicle crashes as the leading cause of injury-related death in adults in the United States.[1] The percentage of deaths related to opioids increased 292% between 2001 and 2016.[2] Within some demographic groups, opioids represent a prominent cause of death; for individuals aged 24 to 35 years, opioids caused 20% of deaths.[2] In this age group, drug-induced death was the leading cause of death, exceeding that caused by motor vehicle crashes, firearms, cardiovascular disease, and neoplasm.[3] The rate of increase was initially correlated with availability of prescription opioids. In subsequent years, presumably as the medical community has become more aware of the consequences of opioid availability, the rate of increase in opioid prescription-related deaths has slowed or even declined.[4] Unfortunately, opioid-related deaths have not ceased because cheap and widely available heroin appears to have replaced prescription opioids for many individuals with opioid use disorders (OUDs).[5,6] Fentanyl and its derivatives added to or substituting for heroin are a causal factor in driving the death rate even higher.[7]

Between 2001 and 2010, emergency department (ED) visits in which opioids were administered or prescribed increased from 20.8% to 31.0%.[8] This correlated with a broader shift toward opioid-based pain management in the larger community of medicine and was not an issue unique to emergency medicine. However, trends in ED opioid prescribing appear to have stabilized and may have peaked.[9] In 2012, a cross-sectional study of discharged patients in 19 EDs revealed that 17% of ED visits resulted in an opioid prescription during the week studied.[10] This represents an ED contribution of 4.4% of all opioids prescribed in the US health care system in that year, down from 7.4% in 1996.[11] Despite serving as a minor source of opioids within the health care system, liberal ED opioid prescribing has been linked to problem use, dependence, and opioid-related death.[12,13] Consequently, the true relationship between ED opioid prescribing and the opioid epidemic remains unclear.

Nevertheless, the burden of managing this problem is increasingly falling on emergency physicians, with a rising rate of substance-use-related ED visits in the United States.[14] Emergency physicians are on the front lines, regularly treating opioid overdoses and other adverse effects such as injection-drug-related complications, OUD, and opioid withdrawal. Presently, the pent-up demand for treatment of OUD overwhelms the supply of treatment professionals and programs available. With 24-hour ED availability, acute withdrawal is a common primary or secondary complaint in the ED. However, treatment of opioid withdrawal has not been emphasized in emergency physician training until recently, so many may feel unprepared to adequately treat this now common presentation.

Comprehensive opioid-prescribing guidelines supported by systematic reviews of the literature are rarely specifically targeted toward emergency physicians, with a much greater emphasis on long-term opioid use for chronic pain and quantification of opioid use in daily morphine milligram equivalents (MMEs). This metric may be clinically useful in chronic prescribing but does not translate well to concrete recommendations for ED prescribing for acute complaints; thus, policy

recommendations developed outside of emergency medicine have rarely been applicable to the ED setting. In the past decade, various cities and states have implemented policies designed to affect ED opioid prescribing. Portions of these policies relevant to the ED setting consistently focused on limiting the duration of therapy for acute complaints. Examples include Washington State (less than 14 days), New York City (3 days or less), and Ohio (3 days or less).[15-17] Vermont and Massachusetts subsequently produced regulations limiting opioid prescription duration to 7 days or less for acute complaints.[18,19] One review found 17 states with regulations concerning opioid prescribing in any setting.[20] In 2016, the Centers for Disease Control and Prevention (CDC) released national guidelines that included the following recommendation for duration of treatment of acute pain: "Three days or less will often be sufficient; more than 7 days will rarely be needed."[21] Given the national reach of the CDC guidelines, the relevance to the clinical setting, and the use of 7-day limits on duration of opioid prescribing in multiple state regulations, 7 days or less was used as a consistent definition of "short course" of prescribing within this policy.

There are no easy solutions to the opioid problem. Balancing patient comfort and preferences with the personal and societal costs associated with opioid use is a complex issue. The lack of firm regulation means that the individual emergency physician is tasked with considering individual risks and benefits of opioid prescribing.

This policy is an update of the 2012 American College of Emergency Physicians (ACEP) Clinical Policy on opioid prescribing.[22] Three of the previous critical questions from the 2012 policy were not updated in this version because of shifting focus of the guideline. These previous questions were related to utility of state prescription drug monitoring programs, opioid prescribing related to acute low back pain, and short-acting schedule II versus schedule III opioids. For this policy, the focus is on appropriate treatment regimens for acute opioid withdrawal, benefits and harms of short courses of short-acting opioids prescribed from the ED for acute and chronic pain, and co-prescribing of opioids along with other sedating medications. Opioid use for specific conditions is addressed within ACEP complaint-specific policies, the most recent example being the discussion of opioid use for acute headache discussed in the 2019 ACEP Clinical Policy on headaches.[23] In addition, this policy does not discuss naloxone prescribing from the ED, although ACEP has issued a policy statement recommending naloxone prescribing to at-risk patients being discharged.[24]

METHODOLOGY

This Clinical Policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, SCOPUS, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews were performed. All searches were limited to studies of adult humans and were published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP Clinical Policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, Consensus recommendation). Internal and external review comments were received from emergency physicians, clinical pharmacists, the American Academy of Clinical Toxicology, the American Board of Emergency Medicine, the American Society of Addiction Medicine, ACEP's Medical-Legal Committee, and ACEP's Quality and Patient Safety Committee. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this Clinical Policy; however, responses do not imply endorsement. Clinical Policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this Clinical Policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this Clinical Policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome

measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence, using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies demonstrating consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from 1 or more Class of Evidence II studies or multiple Class of Evidence III studies demonstrating consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allows adjustment when applying to patients at the extremes of risk (Appendix C).

This policy is not intended to be a complete manual on opioid management in the adult ED patient but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting in unscheduled acute care settings.

Exclusion Criteria. This guideline is not intended for use with pediatric patients.

CRITICAL QUESTIONS

1. **In adult patients experiencing opioid withdrawal, is ED-administered buprenorphine as effective for the management of opioid withdrawal compared with alternative management strategies?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. When possible, treat opioid withdrawal in the ED with buprenorphine or methadone as a more effective option compared with nonopioid-based management strategies such as the combination of α_2-adrenergic agonists and antiemetics.

Level C recommendations. Preferentially treat opioid withdrawal in the ED with buprenorphine rather than methadone.

Potential Benefits of Implementing the Recommendations:

- Adequate treatment of significant opioid withdrawal with the potential for engaging in medication for addiction treatment (also referred to as medications for OUD, or, historically, medical/medication-assisted treatment) for OUD.

Potential Harms of Implementing the Recommendations:

- Potential precipitation of opioid withdrawal after receiving buprenorphine in the patient who is opioid dependent but not yet showing signs/symptoms of opioid withdrawal, although this complication can be overcome with sufficient buprenorphine dosing.
- Adverse effects of buprenorphine, including the potential for respiratory depression, although respiratory depression is rare unless the patient is also receiving sedatives/hypnotics such as benzodiazepines.
- Given the duration of action of methadone, there is a possible increased risk of opioid toxicity in a patient given methadone in the ED who is discharged and subsequently uses additional opioids. This risk is not present with buprenorphine therapy because of its affinity for the μ-receptor and partial agonist activity, resulting in a ceiling on respiratory depression.

Key words/phrases for literature searches: benzodiazepine, buprenorphine, buprenorphine naloxone, clonidine, heroin, heroin dependence, heroin dependency, heroin withdrawal, lofexidine, methadone, methadone naloxone, methadone treatment, morphine dependence, morphine dependency, morphine withdrawal, opiate addiction, opioid analgesics, opioid-related disorder, opioid withdrawal, tapentadol, tramadol, analgesics, antiemetics, fluid therapy, oral rehydration, rehydration solutions, rehydration therapy, substance withdrawal, substance withdrawal syndrome, withdrawal syndrome, ambulatory care, outpatient care, outpatient clinic, outpatient treatment, emergency department, emergency health service, emergency room, emergency services, emergency ward, outpatient care, outpatient clinic, outpatient department, outpatient treatment, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Two hundred fifteen articles were identified in the searches. Eight articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 3 Class III studies were included for this critical question (Appendix D).

Opioid withdrawal

The common signs and symptoms of opioid withdrawal include cravings, abdominal cramping, nausea, vomiting, diarrhea, agitation, anxiety, feelings of hopelessness, dysphoria, piloerection, and myalgias. Onset of these symptoms from the last exposure to an opioid can vary according to the half-life of the opioid and the amount consumed, nominally 12 hours for heroin and up to 30 hours for methadone. Opioid withdrawal may be very uncomfortable but is rarely directly life threatening as a sole condition. However, patients are often motivated to avoid these distressing symptoms through continued hazardous opioid use.

Treatment of opioid withdrawal may be symptomatic, often involving the use of α_2-adrenergic agonists such as clonidine or lofexidine as well as antiemetics, atypical antipsychotics, and other medications targeting the withdrawal symptoms. However, appropriate use of buprenorphine or methadone effectively alleviates withdrawal symptoms. Initial dosing may also serve to initiate medication for addiction treatment (MAT) for OUD.

Buprenorphine

Buprenorphine is a semisynthetic derivative of the opioid alkaloid thebaine that is a more potent (25 to 40 times) and longer-lasting analgesic than morphine, with a half-life of 24 hours or more. It appears to act primarily as a partial agonist at μ-opioid receptors. Buprenorphine was first synthesized in 1966 as a synthetic opioid analgesic. Prescribing for pain indications is controlled in a fashion

similar to that of other opioids given that it is currently a Schedule III drug in the United States.

Buprenorphine was approved by the Food and Drug Administration for the treatment of OUD/opioid dependence in 2002. Initially, severe restrictions were placed on the administering and prescribing of buprenorphine to treat OUD. The Drug Addiction Treatment Act of 2000 allowed the Secretary of Health and Human Services to provide a waiver (commonly termed the "X-waiver") to physicians to administer and prescribe buprenorphine for the treatment of OUD if they have completed a special 8-hour training course. However, any Drug Enforcement Administration-licensed physicians who have not achieved the waiver may still administer buprenorphine in the ED to treat patients in opioid withdrawal, with the following restrictions:

"[They may] administer (but not prescribe) narcotic drugs to patients for the purpose of relieving acute withdrawal symptoms while arranging for the patient's referral for treatment, under the following conditions:

- Not more than one day's medication may be administered or given to a patient at one time
- Treatment may not be carried out for more than 72 hours
- The 72-hour period cannot be renewed or extended."[25]

(Note: "arranging for patient's referral for treatment" is not further described or clarified; this is frequently interpreted as a minimum obligation to provide the patient with treatment referral information in written form.)

Although individual institutions have developed internal treatment plans, there is no nationwide standard protocol for treating opioid withdrawal in the ED with buprenorphine. One example of a buprenorphine-based algorithm is included below (Figure), although no specific protocol has been well studied in the ED environment.

Methadone

Methadone is a synthetic, long-acting, Schedule II opioid used to treat OUD and is also used for pain management. Outpatient prescription for OUD is strictly controlled and drugs may be dispensed only as part of an opioid treatment program. However, like buprenorphine, methadone administration to treat OUD for up to 72 hours is allowed without participation in an opioid treatment program. Before the widespread availability of buprenorphine, ED administration of a single dose of methadone was considered the most effective opioid-based therapy to treat acute withdrawal. Nevertheless, because of its long duration of action (hours to days) lasting beyond the ED visit, as well as the potential to interfere with ongoing opioid treatment program adherence, methadone administration to alleviate acute opioid withdrawal is not common in many EDs.

Nonopioid treatment for opioid withdrawal

Nonopioid treatment for opioid withdrawal may include the administration of α_2-adrenergic agonists, antiemetics, benzodiazepines, and antidiarrheals. α_2-Agonists for treatment of symptomatic patients with nonhypotensive opioid withdrawal include clonidine and lofexidine. Nausea and vomiting may be treated with promethazine or other antiemetics. Benzodiazepines may help reduce catecholamine release during withdrawal and help alleviate muscle cramps as well as anxiety. Diarrhea can be treated with loperamide.

Effectiveness of buprenorphine in the treatment of opioid withdrawal

Gowing et al,[27] in an updated Cochrane review (Class III), assessed 27 studies using buprenorphine for the treatment of withdrawal that satisfied their criteria for inclusion. The majority of these studies were on inpatient populations. They concluded, based on quality of evidence ranging from very low to moderate, that patients receiving buprenorphine for withdrawal/detoxification compared with clonidine or lofexidine (α_2-adrenergic agonist approved in the United States in 2018) had less severe signs and symptoms of withdrawal, had fewer adverse effects, and were more likely to stay in treatment longer. They also concluded that buprenorphine is probably similar in effectiveness to tapered doses of methadone in the treatment of opioid withdrawal.

Meader,[28] in a 2010 meta-analysis of 20 randomized controlled trials (Class III), determined that buprenorphine and methadone were the most effective methods of opioid detoxification, with the former potentially being most effective. This was followed by lofexidine and clonidine, respectively. The duration of treatment in these studies ranged from 3 to 30 days, which makes direct translation to the ED setting less certain.

In a Class III systematic review, Amato et al[29] compared tapered-dose methadone with multiple other treatment modalities, one of which was buprenorphine. They found that slow tapering of long-acting opioids can reduce severity of withdrawal symptoms. Seventeen of the 23 studies included in the meta-analysis were inpatient based, again with uncertain applicability to ED care.

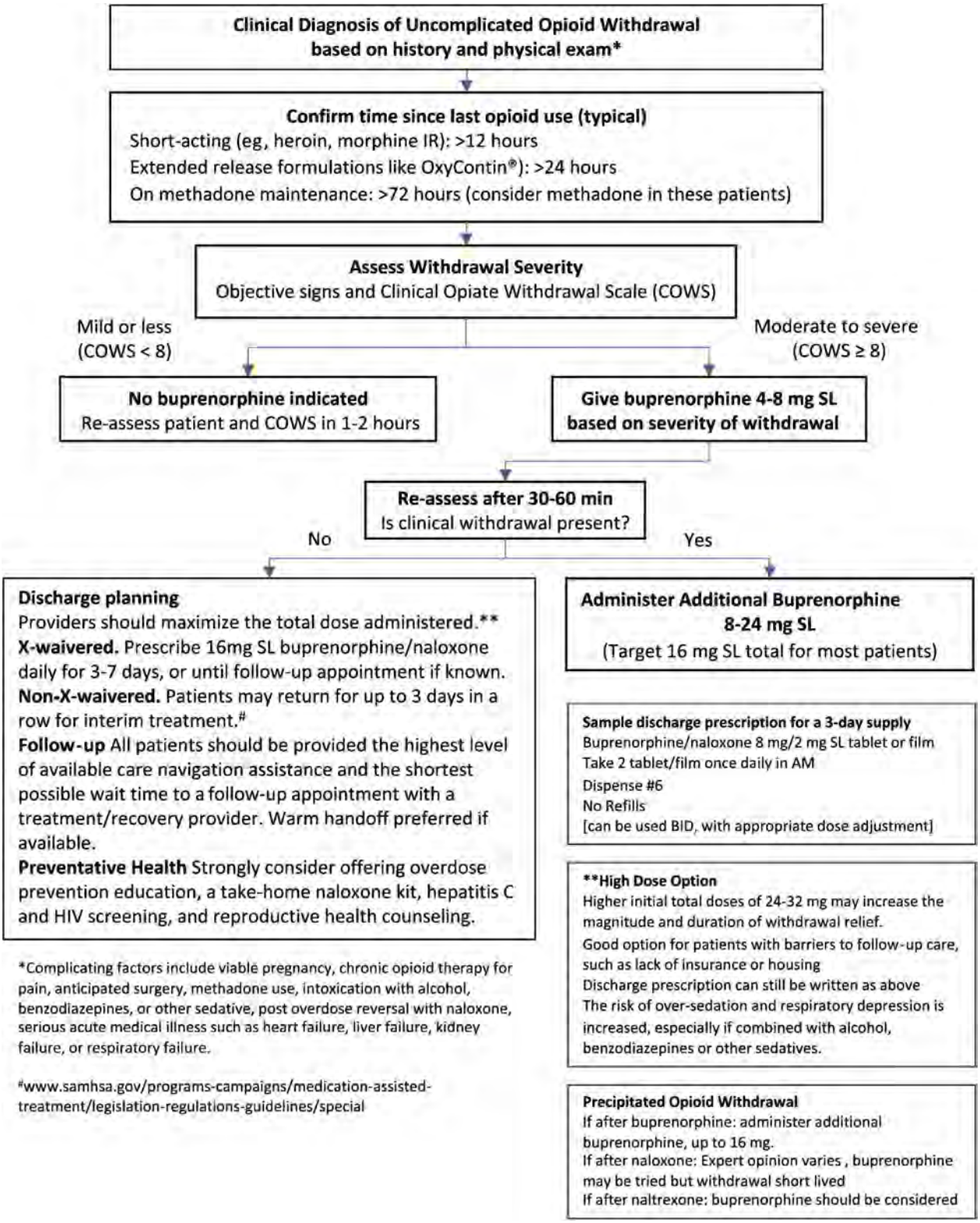

Figure. Algorithm for treatment of opioid withdrawal.[26] (Used with permission). *The Clinical Opiate Withdrawal Scale (COWS) can be found in Appendix E.

Medication for addiction treatment

Medication for addiction treatment is the use of Food and Drug Administration–approved medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of substance use disorders. For patients with OUD, this treatment may involve the administration of methadone, buprenorphine, or extended-release naltrexone. This approach has demonstrated effectiveness and saves lives.[30] Medication for addiction treatment has been initiated in many EDs, with the typical goal of continuation of the program on an outpatient basis.[31-33] These programs have demonstrated better short-term improvement in treatment and illicit opioid use rates over referral only or brief intervention.

Cautions in using buprenorphine to treat opioid withdrawal in the ED:

- Buprenorphine should be administered only to patients in active opioid withdrawal as confirmed by history and physical examination. Because of its high binding affinity and partial agonist properties, it may induce significant withdrawal symptoms if the patient is currently receiving opioids and not yet in withdrawal. In addition, particular care is required when transitioning from methadone to buprenorphine because of risk of severe and prolonged precipitated withdrawal. Several tools (such as the Clinical Opiate Withdrawal Scale) may be used to assist in the assessment of severity of withdrawal.[34]
- Comprehensive data on buprenorphine dosing in opioid withdrawal in the ED are evolving. Monitoring best practices related to buprenorphine is prudent as these are continuing to evolve. Additional useful information on buprenorphine use in withdrawal is also available at http://www.drugabuse.gov/ed-buprenorphine and http://www.medicine.yale.edu/edbup.

Summary

Although there is a paucity of quality studies concerning the administration of buprenorphine to treat opioid withdrawal in the ED, several systematic reviews (based mainly on inpatient studies) would imply that buprenorphine administration is a safe and effective treatment for opioid withdrawal and potentially superior to other modalities of opioid withdrawal treatment.

Future Research

Future areas of research should include the following:

- Clinical trials to evaluate the effectiveness and safety of treating ED patients in opioid withdrawal with buprenorphine are needed.
- Further studies to better determine the best ED induction dose of buprenorphine before ED discharge are needed.
- Evaluation of injectable depot buprenorphine in the ED for subacute opioid withdrawal treatment after discharge is needed.
- Determination of appropriate use of buprenorphine after withdrawal has been precipitated by naloxone as well as the utility of administering buprenorphine as an alternative to naloxone in the setting of acute opioid overdose, given its affinity for opioid receptors, partial agonist activity at those receptors, and ceiling on respiratory depression.

2. **In adult patients experiencing an acute painful condition, do the benefits of prescribing a short course of opioids on discharge from the ED outweigh the potential harms?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Preferentially prescribe nonopioid analgesic therapies (nonpharmacologic and pharmacologic) rather than opioids as the initial treatment of acute pain in patients discharged from the ED.

For cases in which opioid medications are deemed necessary, prescribe the lowest effective dose of a short-acting opioid for the shortest time indicated.

Potential Benefits of Implementing the Recommendations:

- By limiting the number of opioid prescriptions written on discharge from the ED and limiting the duration of therapy, emergency physicians may be able to reduce the incidence of patients who develop opioid dependence and misuse, including death from opioid overdose.
- Minimizing opioids for acute conditions may prevent patients from developing unnecessary adverse effects when alternative medication or therapies with less severe adverse effects are available.
- Prescription of nonopioid therapies avoids the potential for development of opioid-induced hyperalgesia and resulting long-term challenges in providing effective pain management.

Potential Harms of Implementing the Recommendations:

- Excessive limitations on opioid prescribing for ED patients may lead to cases of inadequate pain management.

Key words/phrases for literature searches: opiate, opioid, opioids, analgesia, analgesic agent, analgesics, opioid analgesics, narcotics, drug prescriptions, drug therapy, prescription drug, acute pain, pain, pain management, back pain, bone fractures, contusion, dental pain, fractures, low back pain, neck pain, sprains, strains, toothache, addiction, adverse effect, death, drug dependence, drug dependency, overdose, readmission, treatment outcome, nephrolithiasis, emergencies, emergency, emergency department, emergency health services, emergency room, emergency services, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Three hundred articles were identified in the searches. Twenty-two articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 5 Class III studies were included for this critical question (Appendix D).

Emergency physicians are tasked with determining the initial course of analgesia in patients discharged after a visit for an acute painful condition. Given the individual patient and public health risks of widespread opioid prescribing, many individuals are reconsidering the duration, dose, and even the need for opioid prescriptions. The median amount of opioid actually consumed by patients after an ED visit for an acute painful condition resulting in an opioid prescription is rather limited, at less than 50 MME.[35] Such a finding suggests that most patients find limited amounts sufficient for analgesic purposes. Furthermore, higher doses and increased duration may lead to adverse consequences. The CDC has observed that there is an increased risk for opioid-naive patients to develop long-term opioid use beginning with the third day of therapy.[36] In addition, for patients susceptible to the development of OUD, it is not clear that any opioid prescription is without risk. A survey of ED patients with current opioid dependence found that greater than one third of these patients self-reported they first became exposed to opioids through legitimate prescriptions for acute painful conditions. In 11% of the ED population with current opioid dependence, the index prescription came from an ED visit.[37] This presents a challenge for emergency physicians because there is not an accurate method of predicting which patients will develop OUD or experience adverse effects from the medication and which patients, if any, will benefit from opioid therapy at discharge. This policy does not address the administration of opioids to active patients undergoing treatment in the ED; rather, it is focused on the prescription of opioids to patients being discharged after a visit for an acute painful condition.

Although it may be difficult to predict which patients discharged from the ED with opioid prescriptions will develop OUD, there is consistent evidence suggesting that opioid-naive ED patients are at increased risk for developing OUD compared with those who have used opioids previously. In a Class III study, Hoppe et al[38] found that 17% of patients discharged from EDs leave with a prescription for opioids. Most of these prescriptions were written for patients with diagnoses of back pain, abdominal pain, and extremity injuries. Nearly all of these patients received a short course (median 15 pills) of short-acting opioids. They found that opioid-naive patients who fill a prescription for opioids have an adjusted odds ratio of 1.8 (95% confidence interval [CI] 1.3 to 2.3) that they will experience recurrent use of opioids within 1 year.[38]

Another Class III study examined opioid-naive patients treated in the ED for an ankle sprain. Delgado et al[39] reported that 4.9% (95% CI 1.8% to 8.1%) of patients prescribed greater than 225 MMEs (equivalent to 30 doses of oxycodone 5 mg) transitioned to prolonged use of opioids. Prolonged use was defined as at least 4 opioid prescriptions in the next 1 to 6 months. In contrast, 1.1% (95% CI 0.7% to 1.5%) of patients prescribed less than 75 MMEs and 0.5% (95% CI 0.4% to 0.6%) of those not receiving an opioid prescription transitioned to prolonged use.

Meisel et al[40] conducted a Class III study of ED patients without an opioid prescription in the past 12 months and found that 13.7% of those filling a new opioid prescription went on to fill persistent or high-risk opioid prescriptions in the next 12 months compared with 3.2% of those not receiving opioids at the initial visit. The highest rate of conversion to persistent or high-risk use (37.3%) was observed in patients receiving a prescription for at least 350 MMEs at the initial visit, although rates were greater than 10% even for those with an initial prescription for less than 350 MMEs. These 3 studies consistently demonstrate that the development of problem opioid use in opioid-naive patients is associated with ED prescriptions of opioids, and that this relationship strengthens with increasing amounts of opioid prescribed at the initial visit.

Although the literature examining the effectiveness of opioid prescriptions compared with nonopioid therapies after ED visits is limited, 2 Class III studies examining pain management in patients presenting with acute low back pain

were identified. Innes et al[41] conducted a multicenter, randomized controlled trial of oral ketorolac versus acetaminophen/codeine. Analgesic efficacy and functional capacity did not differ between the groups. However, compared with those receiving ketorolac, more patients in the opioid group reported at least one adverse drug events (64% versus 34%), as well as serious adverse drug events (17% versus 3%). Seven of the 59 patients receiving codeine dropped out because of the severity of adverse drug events, and only 46% had a favorable view of tolerability compared with no dropouts of the 62 patients in the ketorolac group and 70% with a favorable opinion of drug tolerability. In another Class III randomized controlled study, Friedman et al[42] showed that discharged ED patients with low back pain who received oxycodone in addition to naproxen did not have improved pain benefit after 7 days compared with those receiving naproxen alone. In addition, patients receiving oxycodone were 19% more likely (95% CI 7% to 31%) to have adverse reactions such as drowsiness, dizziness, and nausea/vomiting. Thus, in addition to the long-term risks inherent to opioid therapy, there is no evidence available demonstrating that opioids provide superior pain management compared with nonopioid therapies on discharge from the ED after a visit for an acute painful condition. Furthermore, opioids are associated with increased rates of adverse events that limit tolerability.

Summary

Opioid prescribing in the ED, even when limited to short-acting, low-potency medications for a few days of therapy, is not risk free. Patients may experience immediate adverse effects such as nausea, vomiting, over-sedation, and respiratory depression. In addition, these patients are at risk for developing an OUD, complications from chronic opioid use, and death from overdose. Therefore, opioid prescribing from the ED for an acute painful condition should be reserved for patients for whom there is a need for pain relief and alternative therapies are expected to be ineffective or are contraindicated. In those cases, anticipated risks and benefits along with alternatives should be discussed with the patient. If deemed appropriate, only low-dose, short-acting opioids with a short duration of therapy should be prescribed.

Future Research

Future areas of research should include the following:

- Methods of identifying ED patients at high risk for development of an OUD if prescribed opioids as treatment for an acute painful condition.
- Comparison of effectiveness of opioid therapy versus nonopioid analgesics/nonpharmacologic therapies in discharged ED patients treated for various acute painful conditions.
- Evaluation of educational interventions in the ED to increase patient understanding of the adverse effects of opioids and risks of dependence and opioid misuse.
- Trials evaluating efficacy and safety of more or less euphoric opioids in discharged ED patients.

3. **In adult patients with an acute exacerbation of noncancer chronic pain, do the benefits of prescribing a short course of opioids on discharge from the ED outweigh the potential harms?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Do not routinely prescribe opioids to treat an acute exacerbation of noncancer chronic pain for patients discharged from the ED. Nonopioid analgesic therapies (nonpharmacologic and pharmacologic) should be used preferentially.

For cases in which opioid medications are deemed appropriate, prescribe the lowest indicated dose of a short-acting opioid for the shortest time that is feasible.

Potential Benefits of Implementing the Recommendations:

- Avoid exposing patients to an increased risk of developing OUD.
- Avoid potential immediate adverse effects associated with opioid use; specifically, vomiting, but also nausea, constipation, dizziness, drowsiness, headache, pruritus, and dry mouth.

Potential Harms of Implementing the Recommendations:

- Withholding a treatment associated with a statistically significant, but small, improvement in pain control compared with placebo (but not to nonopioid alternatives).

Key words/phrases for literature searches: opiate, opioid, opioids, opioid analgesic, acute pain, chronic pain, musculoskeletal pain, cancer, musculoskeletal diseases, neoplasms, drug prescriptions, prescription drugs, drug administration schedule, medication adherence, opioid abuse, opioid overdose, opioid-related disorders, drug overdose, risk assessment, patient discharge, hospitalization, patient readmission, emergency room, emergency services, and variations and combinations of the key words/phrases. Searches included January 1, 2012, to the search dates of March 9, 2017, April 12, 2017, and August 8, 2018.

Study Selection: Nine hundred twenty-four articles were identified in the searches. Thirty-nine were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 3 Class III studies were included for this critical question (Appendix D).

Patients with chronic noncancer pain frequently present to the ED for treatment of acute exacerbations of their chronic pain. Unfortunately, there have been no studies that evaluate the efficacy or potential harms of prescribing a short course of opioids on discharge from the ED among this specific patient population. Although the paucity of directly applicable studies precludes giving a more definitive answer to this question, there is existing literature that allows reasonable inferences to be made about the potential risks and benefits of prescribing a short course of opioids to patients with an acute exacerbation of their chronic noncancer pain. The scope of this question specifically excludes pain management for sickle cell disease because the committee recognizes that hospitals frequently develop multidisciplinary therapeutic protocols that guide analgesia in this population, limiting emergency physician discretion. Consequently, because of concerns that studies of sickle cell patients treated in the ED may not be generalizable to other patients presenting with chronic noncancer pain, the literature search for this recommendation excluded the sickle cell population.

Three Class III studies were identified. The first of these is a systematic review by Busse et al[43] of randomized clinical trials that examined the harms and benefits of opioids for patients with chronic noncancer pain. The review examined 96 trials including 26,169 participants treated with opioids for control of their chronic noncancer pain, and the efficacy of opioids for pain control and physical functioning compared with placebo, as well as with other nonopioid analgesic options (including nonsteroidal anti-inflammatory drugs [NSAIDs], tricyclic antidepressants, anticonvulsants, and synthetic cannabinoids). The authors also considered the adverse effects (vomiting, nausea, constipation, dizziness, drowsiness, headache, pruritis, and dry mouth) of opioids therapy compared with placebo. They found that opioids did not provide a level of analgesic benefit that reached the predetermined threshold for a minimally important reduction in pain (1 cm on a 10-cm visual analog scale) compared with placebo (weighted mean difference −0.79 cm [95% CI −0.90 to −0.68 cm] on a 10-cm visual analog scale for pain). Similarly, opioids did not result in meaningful improvement in physical functioning (5 points on a 100-point Short Form-36 physical component score), with a weighted mean difference of 2.04 points (95% CI 1.41 to 2.68 points). These findings are supported by high-quality evidence from 42 and 51 randomized controlled trials, respectively. In terms of adverse effects, opioids were found to result in significant increases in all measured adverse effects, with vomiting having the most pronounced difference, 5.9% with opioids versus 2.3% with placebo (relative risk 2.50 [95% CI 1.89 to 3.30]; risk difference 3.6% [95% CI 2.1% to 5.4%]). In contrast to the evidence comparing opioids with placebo that is examined in this review, the evidence comparing opioids with nonopioid medications for analgesia was of overall low to moderate quality; however, opioids were not found to be superior to any of the comparator groups. More specifically, moderate-quality evidence found no difference between opioids and NSAIDs for either pain relief (weighted mean difference −0.60 cm [95% CI −1.54 to 0.34 cm] on the 10-cm visual analog scale for pain) or physical functioning (weighted mean difference −0.90 points [95% CI −2.69 to 0.89 points] on the 100-point Short Form-36 physical component score), but did find that opioids were associated with an increase in vomiting compared with NSAIDs (relative risk 4.71 [95% CI 2.92 to 7.60]; risk difference 6.3% [95% CI 3.2% to 11.1%]).

Beyond the immediate potential adverse effects of opioid use, there is significant concern that patients with chronic noncancer pain who are prescribed opioids are at risk of developing an OUD. There are 2 large non-ED–based retrospective studies that provide an estimation of the strength of association of opioid prescription with adverse outcomes. A 2014 Class III study[44] examined patients with a new episode of chronic noncancer pain who had not received opioids in the previous 6 months, and who carried no previous diagnosis of an OUD. In this study, Edlund et al[44] found that patients prescribed opioids had a significantly higher risk of developing OUDs compared with those not prescribed opioids, even among those who received what they termed low-dose (0 to 36 MMEs/day), acute (1 to 90 days) prescriptions (odds ratio 3.03; 95% CI 2.32 to 3.95). The risk was markedly increased for patients who received opioids for greater than 90 days, and the magnitude of the risk increased substantially in this long-term opioid use group, depending on dose (odds ratio 14.92, 28.69, and 122.45 for the low-, medium-, and high-dose groups, respectively). Individuals with a diagnosis of mental health disorders, alcohol use disorder, and nonopioid drug use disorders were also found to be at increased risk of developing OUD after being prescribed opioids for their chronic noncancer pain.

A 2017 Class III study by the CDC[36] examined the association between first opioid use among opioid-naive

patients without cancer and the likelihood that the patient would continue to use opioids at 1 year and 3 years, stratified by treatment duration, dosage, and number of prescriptions. Among patients receiving their first opioid prescription, 2.6% continued to use opioids for at least 1 year. The authors found that the probability of long-term opioid use increased markedly after only 5 days of prescription duration (and further increased at 1 month). In this population, approximately 70% of patients received an initial prescription of less than or equal to 7 days. These studies suggest that opioid prescriptions after ED visits for exacerbations of chronic noncancer pain carry an inherent risk of development of an OUD.

Summary

Although there are no studies directly examining the effect of a short prescription of opioids for ED patients presenting with an acute exacerbation of chronic noncancer pain, a large Class III systematic review of 96 randomized controlled trials (based mainly on outpatient studies) found that opioids offered no clinically significant reduction in pain or improvement in function compared with placebo or nonopioid treatment options, but did increase adverse events (most notably vomiting).[43] Additionally, two large retrospective studies found clear associations between opioid prescriptions and the development of subsequent long-term use and OUD, even with low-dose prescriptions of short duration (as little as $\geq$5 days' duration).[36,44] These data all suggest that the risks of prescribing even a short course of opioids for most ED patients with acute exacerbations of chronic noncancer pain outweigh the negligible to potentially nonexistent benefits.

Future Research

Future areas of research should include the following:

- Trials evaluating both the efficacy and potential harms of prescribing a short course of opioid medication for the treatment of acute exacerbations of chronic noncancer pain.
- Comparison of frequently prescribed opioid formulations and dosages with nonopioid alternatives, particularly NSAIDs.
- Development of tools for assessing the risk that this patient population will develop either long-term opioid use or an OUD after being prescribed a short course of opioids after ED discharge.
- Strategies for preventing opioid overdose after an ED visit for treatment of acute exacerbations of chronic noncancer pain.

4. **In adult patients with an acute episode of pain being discharged from the ED, do the harms of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics outweigh the benefits?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Do not routinely prescribe, or knowingly cause to be co-prescribed, a simultaneous course of opioids and benzodiazepines (as well as other muscle relaxants/sedative-hypnotics) for treatment of an acute episode of pain in patients discharged from the ED (Consensus recommendation).

Potential Benefits of Implementing the Recommendations:

- Reducing the severity of toxicity when opioids are combined with other centrally acting drugs.
- Preferential use of safer therapeutic alternatives.

Potential Harms of Implementing the Recommendations:

- Limited therapeutic options for patients receiving long-term opioids or muscle relaxants/sedative-hypnotics.

Key words/phrases for literature searches: opiate, opioid, opioids, analgesics, sedatives, antianxiety agents, hypnotics, muscle relaxants, baclofen, benzodiazepine, carisoprodol, cyclobenzaprine, eszopiclone, metaxalone, methocarbamol, tapentadol, tramadol, zaleplon, zolpidem, acute pain, pain, pain management, substance-related disorders, drug overdose, mortality, death, emergency, emergency department, emergency health services, emergency room, outpatient care, ambulatory care, patient discharge, patient readmission, treatment outcome, and variations and combinations of the key words/phrases. Searches included January 1, 2007, to the search dates of March 9, 2017, and August 8, 2018.

Study Selection: Four hundred articles were identified in the searches. Twenty-five articles were selected from the search results as potentially addressing this question and were candidates for further review. After grading for methodological rigor, none of the 25 articles were classified as Class I, II, or III; therefore, zero studies were included for this critical question (Appendix D).

Benzodiazepines are relatively safe when prescribed alone. However, a trend of increased mortality associated with the increased prescribing of benzodiazepines has been identified that resembles the trend of escalating overdose

mortality associated with the opioid prescriptions during the last 2 decades.[45] This burden is thought to be due to the substantial potentiation of opioid-related respiratory depression when taken in combination with centrally acting muscle relaxants/sedative-hypnotics such as benzodiazepines.[46] Emergency physicians have observed increasing rates of overdoses and drug-related deaths related to the combination of opioids and benzodiazepines.[47] Furthermore, population-based studies examining patterns of opioids and sedative-hypnotics/muscle relaxers prescribing, most prominently benzodiazepines, have identified a substantial increased risk of death when these agents are co-prescribed. In particular, the rates of death are 3- to 10-fold higher in patients co-prescribed opioids and benzodiazepines compared with opioids alone.[48,49] The literature search and evaluation process outlined in the "Methodology" section of this clinical policy yielded no directly applicable primary research study of at least a Class III level of evidence assignment. However, our understanding of the pharmacologic mechanism of these agents as well as the background literature described earlier that has examined prescribing patterns and overdose epidemiology suggests that co-prescribing is a significant danger to the ED population.

Unfortunately, there is a dearth of evidence evaluating analgesic efficacy or patient functional improvement when prescriptions for muscle relaxants (including benzodiazepines) are combined with prescriptions for opioids for acute pain when patients are discharged from an ED. However, for many common painful conditions there is a demonstrated lack of superiority when either opioids or sedative-hypnotic/muscle relaxers are prescribed compared with safer therapeutic alternatives. For example, recent meta-analyses suggest that for the treatment of acute low back pain, combination pharmacotherapy (eg, opioid with NSAID or muscle relaxant with NSAID) does not outperform monotherapy with NSAID, and that muscle relaxant drugs do not provide clinically significant additional pain relief. Furthermore, these meta-analyses suggest that co-prescribing muscle relaxants may increase risk of patient harm.[50,51] Therefore, although there is a lack of direct evidence related to ED prescribing patterns, given the increased risks of co-prescribing and lack of demonstrated benefit, the committee was able to reach consensus to develop the recommendation against routinely combining these therapies for patients being discharged from the ED after being treated for an acute episode of pain.

As the dangers of co-prescribing were being recognized in recent years, institutions focused on quality- and safety-produced guidelines, such as a recent quality measure by the National Quality Forum, titled "Safe Use of Opioids—Concurrent Prescribing" 3316e (2018), or the Department of Veterans Affairs/Department of Defense Clinical Practice Guideline for Diagnosis and Treatment of Low Back Pain (2017), which make specific recommendations against co-prescribing muscle relaxants/sedative-hypnotics (specifically benzodiazepines) along with opioids.[52,53] Moreover, the Food and Drug Administration added a black box warning in 2016 to both opioids and benzodiazepines recommending against co-prescribing these agents.[54] Unfortunately, none of these guidelines draw on studies that met inclusion criteria for this guideline.

Given the widespread potential effect on health care system policies and reimbursement, emergency physicians should become familiar with the National Quality Forum measure as its implementation increases:

National Quality Forum 3316e specifically evaluates "[p]atients age 18 years and older prescribed two or more opioids or an opioid and benzodiazepine concurrently at discharge from a hospital-based encounter (inpatient or emergency department [ED], including observation stays)."

- S.4. Numerator Statement: Patients prescribed 2 or more opioids, or an opioid and benzodiazepine at discharge.
- S.6. Denominator Statement: Patients aged 18 years and older prescribed an opioid or a benzodiazepine at discharge from a hospital-based encounter (inpatient stay less than or equal to 120 days or ED encounters, including observation stays) during the measurement period.
- S.8. Denominator Exclusions: The following encounters are excluded from the denominator:
  - Encounters for patients with an active diagnosis of cancer during the encounter
  - Encounters for patients who receive palliative care orders during the encounter
  - Inpatient encounters with length of stay greater than 120 days

Denominator exceptions: None

Summary

Although there is a paucity of quality studies concerning the co-prescribing of a short concomitant course of opioids and muscle relaxants/sedative-hypnotics for acute pain in ED patients, the evolving epidemiologic data and non-ED studies suggest that in the ED, co-prescribing of these 2 classes of medications should be done with caution, and, when possible, avoided.

Future Research

Future areas of research should include the following:

- Prospective trials evaluating optimal treatment regimens for patients with specific acute pain indications (eg, acute low back pain) who are being discharged from an ED.
- Prospective trials studying the effect of the use of state pharmacy boards' prescription drug monitoring programs or ED information exchanges to improve patient selection, and reduce risk, with respect to opioid prescriptions in patients being discharged from an ED.

Relevant industry relationships: Dr. Ketcham has worked on a joint ACEP/American Society of Addiction Medicine project related to ED initiation of medication-assisted treatment that was grant funded by Indivior, the manufacturer of Suboxone. Mitigation of this potential conflict was achieved by allowing Dr. Ketcham to participate in and contribute his experience to the content development of the critical questions; however, he was not allowed to vote when establishing the final recommendations for question 1. He was assigned to work on question 4.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

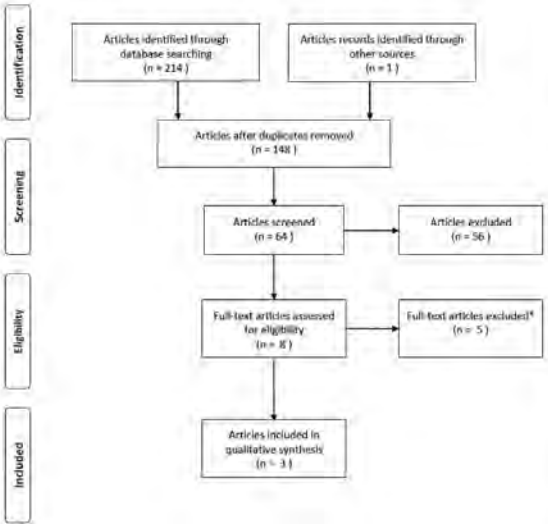
Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

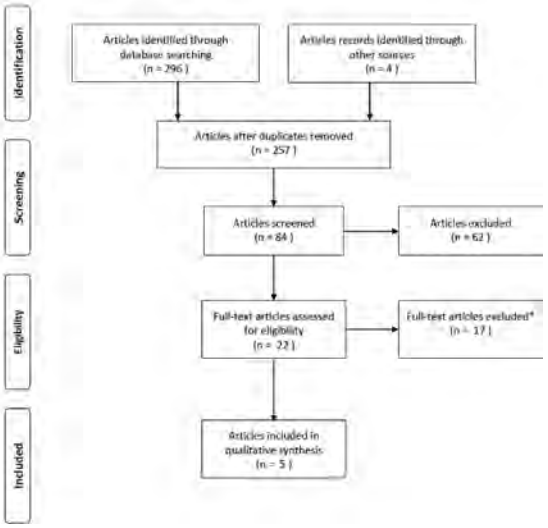
LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix D. PRISMA[55] flow diagrams.

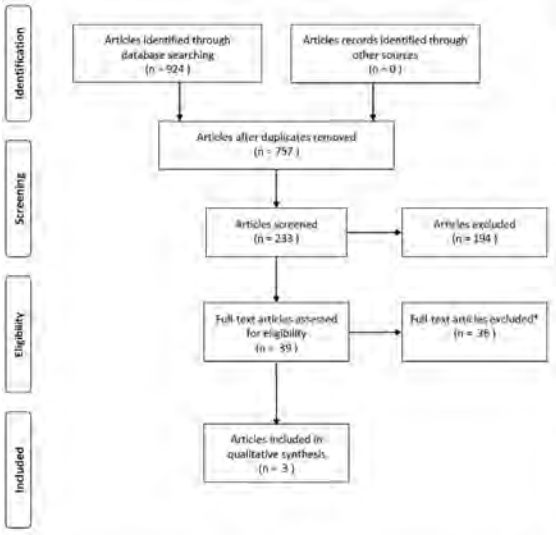
Critical Question 1 Flow Diagram



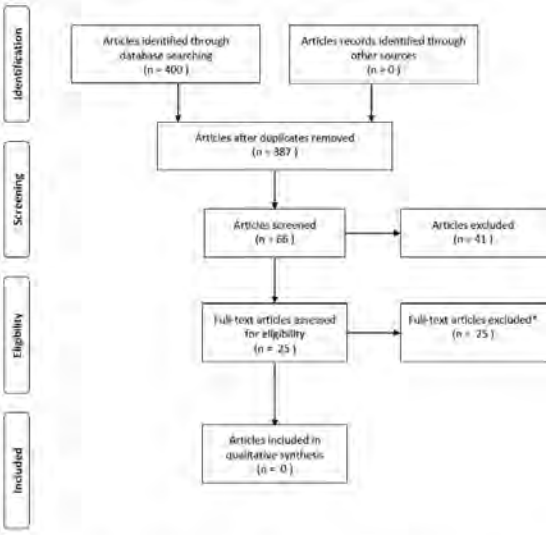
Critical Question 2 Flow Diagram



Critical Question 3 Flow Diagram



Critical Question 4 Flow Diagram



*Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question. See "Methodology" section for more detail.

Appendix E. Clinical Opiate Withdrawal Scale (COWS)[56] (Used with permission).

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gowing et al[27] (2017)	III for Q1	Systematic review of RCTs of interventions of opioid withdrawal using buprenorphine; inpatient and outpatient settings; no studies in EDs	Withdrawal treatment with buprenorphine was compared with methadone, clonidine, and lofexidine; outcome measures included intensity of withdrawal, adverse effects, and rate of withdrawal treatment completion; used standard meta-analytic approaches	Included 27 studies with 3,048 participants; meta-analysis was possible for treatment duration (similar for buprenorphine and methadone) 1.3 days and treatment completion rates,risk ratio=1.04 (95% CI 0.91 to 1.2); compared with clonidine and lofexidine, buprenorphine had lower average withdrawal scores, –0.43 (95% CI –0.58to –0.28); buprenorphine patients also stayed in treatment longer and were more likely to complete treatment, risk ratio=1.6 (95% CI 1.2 to 2.1); no significant difference in adverse events; for difference in treatment completion, number needed to treat=4 (95% CI 3 to 6); for every 4 treated with buprenorphine, 1 additional person will complete treatment compared with clonidine or lofexidine; buprenorphine is more effective than clonidine or lofexidine for managing opioid withdrawal in terms of severity of withdrawal, duration of withdrawal treatment, and the likelihood of treatment completion; buprenorphine and methadone appear to be equally effective, but data are limited	No ED studies; most study participants were men, with no outcomes based on sex; 7 studies were funded or medicines provided by a pharmaceutical company; funding source unclear for 7 studies; 12 of the studies had a high risk of bias. No meta-analysis could be done for the comparison with methadone for the outcome of withdrawal or adverse effects; quality of evidence was low or moderate for comparison of buprenorphine with clonidine or lofexidine andfor comparison of buprenorphine with methadone, and very low for dose reduction

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meader[28] (2010)	III for Q1	Systematic review of RCTs involving treatment with buprenorphine, methadone, clonidine, or lofexidine for opioid detoxification	Used a "mixed treatment comparison approach" in which treatments could be ranked; used WinBUGS software to do 80,000 MCMC simulations; main outcome measure appears to be only "completion of treatment"	23 RCTs identified with data on 2,112 patients; buprenorphine was more effective than clonidine (OR 3.95; 95% credible interval 2.01 to 7.46), but not for lofexidine (OR 2.64; 95% credible interval 0.9 to 7.5); buprenorphine may be more effective than methadone (OR 1.64; 95% credible interval 0.68 to 3.79); methadone was more effective than clonidine (OR 2.42; 95% credible interval 1.07 to 5.37) but not necessarily more effective than lofexidine (OR 1.62; 95% credible interval 0.6 to 4.58); buprenorphine had the highest probability (85%) of being the most effective treatment, followed by methadone (12.1%), lofexidine (2.6%), and then clonidine (0.01%); comparison between buprenorphine and methadone did not show a statistically significant difference	RCT settings not specified;criteria for "effective treatment" in the different studies not elucidated; seems to stress "completion of treatment" but with no information on other outcome measures such as withdrawal severity; unclear whether there were 2 independent reviewers of articles, unclear whether the quality of individual studies was assessed, and no mention of heterogeneity measurement/sensitivity analyses

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Amato et al[29] (2013)	III for Q1	Systematic review of RCTs comparing tapered methadone versus other pharmaceutical modalities for treatment of opioid withdrawal; inpatient and outpatient settings; no studies in EDs	For treatment of opioid withdrawal, tapered methadone is compared with adrenergic agonists, opioid agonists (eg, buprenorphine), anxiolytics, and placebo; outcomes: rate of treatment completion, withdrawal scores, adverse effects, relapse, abstinence at follow-up	23 trials with 2,467 patients met inclusion criteria; comparing methadone versus any other pharmacologic treatment, there was no clinical difference observed between the 2 treatments in terms of completion of treatment, 16 studies, 1,381 participants, risk ratio 1.08 (95% CI 0.97 to 1.21); number of participants abstinent at follow-up, 4 studies for tapered methadone versus buprenorphine, 390 participants, risk ratio 0.97 (95% CI 0.69 to 1.37); degree of discomfort for withdrawal symptoms and adverse events, although it was impossible to pool data for the last 2 outcomes	Although primarily directed at a review of tapered methadone for opioid withdrawal, 4 studies compared tapered methadone with buprenorphine; of these, 3 had unclear methods descriptions; 17 of the trials conducted in inpatient units; studies were not ED based
Hoppe et al[38] (2015)	III for Q2	Retrospective cohort urban academic ED in Colorado	Compared opioid-naive patients who received and filled a prescription with those who received and did not fill a prescription, and those who did not receive a prescription; defined recurrent use as having another opioid prescription filled 60 days before or 60 days after a date 5 mo after ED visit; data pulled from state prescription drug monitoring system	4,800 patients; 2,496 (52%) opioid naive; 775 (31% of opioid naive) patients filled prescription, and of these, 299 (12%) had recurrent use; for opioid-naive patients who filled a prescription vs those who did not, the OR for recurrent use was 1.8 (95% CI 1.3 to 2.3); for opioid-naive patients who received a prescription but did not fill it compared with those who did not get a prescription, the OR for recurrent use was 0.8 (95% CI 0.5 to 1.3)	Refilling a second opioid prescription does not meet definition of misuse; study limited to 1 ED setting

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Delgado et al[39] (2018)	III for Q2	Secondary retrospective analysis of national insurance claims from 2011 to 2015; describes the association between initial opioid prescription intensity and transition to prolonged use	Transition to prolonged use, defined by ≥4 opioid prescriptions 30 to 180 days after index visit; predictors: dosing of opioids (eg, >225 MMEs); performed logistic regression modeling	30,832 patients met inclusion criteria, 7,739 (25.1%) received opioid, median MME of 100 (IQR 75 to 113), tab quantity of 15 (IQR 12 to 20) and for a median of 3 days (IQR 2 to 4 days); among 25,849 with 6-mo continuous enrollment after index ED visit, 6,463 (25%) received an opioid prescription MMEs >225 (≥30 tabs of oxycodone 5 mg); adjusted prolonged opioid use was 4.9% (95% CI 1.8% to 8.1%) compared with 1.1% (95% CI 0.7% to 1.5%)	Reason for selecting the variables not explained in the model; appears there is no adjustment for clustering by provider or state; interaction terms and effect modification not disclosed; imputation not performed for missing data

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meisel et al[40] (2019)	III for Q2	Retrospective cohort study of Washington Medicaid beneficiaries with data linked from the prescription drug monitoring program between January 1, 2013, and December 31, 2015	ED visits if the ED visit did not result in an inpatient admission and the patient was opioid naive at the visit, defined as no history of opioid dispensing during the previous 12 mo; excluded observations for enrollees with a 1-y history of cancer, those who were also enrolled in Medicare or older than 64 y, children younger than 13 y, and enrollees who received any hospice or nursing home care at any time during the study period; also excluded members who were enrolled for less than 3 of the previous 12 mo; primary outcome was a composite measure of any indicator of long-term opioid use or high-risk prescription fills within 12 mo after the index visit; logistic regression model used to assess the association between measures described above and conversion to persistent or high-risk use	Among 202,807 index ED visits, 23,381 resulted in a new opioid prescription; of these, 13.7% led to persistent or high-risk opioid prescription fills within 12 mo compared with 3.2% for patients who received no opioids at the index visit; factors associated with increased likelihood of persistent opioid or high-risk prescription fills included a history of skeletal or connective-tissue disorders; neck, back, or dental pain; and a history of prescribed benzodiazepines; the highest conversion rates (37.3%)	Study limited to opioid-naive ED visits during which a new opioid prescription was written and subsequently filled; it is possible some of the index ED visit prescriptions did not originate at that time; had access to only outpatient prescription data

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Innes et al[41] (1998)	III for Q2	Double-blind RCT at 6 EDs (both university and community); convenience sample of 122; after receiving either ketorolac (10 mg orally) or acetaminophen-codeine (600mg acetaminophen, 60mg codeine, respectively); subjects evaluated at 30 and 60 min and then hourly until 6 h or until second analgesic dose; to be included, had to be well enough to be discharged in 2 to 4 h; study medication received every 4 to 6 h; pain and functional capacity evaluated for up to 7 days with telephone follow-up on day 3 or 4, and final in-person assessment at 7 to 9 days; subjects instructed to record pain relief and functional capacity daily at bedtime, and overall pain relief and medication rating at study end	Outcome of visual analog score pain was performed at discharge (calculated pain intensity difference score or pain intensity difference); subjects recorded visual analog score, functional capacity, and pain relief and functional capacity daily at bedtime, and overall pain relief and medication rating at study termination; adverse effects recorded at telephone follow-up and at end; summed pain intensity difference scores computed by weighting the length of time in hours; calculated sample size n=70 subjects in each group to discern a 20% difference in treatment groups; missing data were interpolated linearly	Ketorolac patients completed diaries for 4.4 days, acetaminophen-codeine patients for 5.2 days; after day 1, 24% of ketorolac patients and 31% of acetaminophen-codeine patients reported "a lot" or "complete" relief of pain; time to peak relief was 2.6 days for both groups; 21 of 62 (34%) ketorolac patients and 38 of 59 (64%) acetaminophen-codeine patients reported at least 1 adverse drug events; neither agent was superior in terms of analgesic efficacy	Convenience sampling; target sample size not reached; no adjustment for within-subject correlations repeated-measures outcomes; and no intention-to-treat analysis

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friedman et al[42] (2015)	III for Q2	3-arm double-blind RCT in high-volume urban academic ED	Patients presenting with acute low back pain; given naproxen plus placebo, muscle relaxer (cyclobenzaprine), or oxycodone; 10-day supply of medicine; outcome measures of improvement in Roland-Morris Disability Questionnaire and pain at 1 wk and 3 mo after initial ED visit	323 enrolled, 107 placebo, 108 cyclobenzaprine and oxycodone arms; at 1-wk follow-up, Roland-Morris Disability Questionnaire improvement was 9.8 in placebo, 10.1 in cyclobenzaprine, and 11.1 in oxycodone group, with no significant between-group differences; number of subsequent ED visits similar (3 placebo vs 1 cyclobenzaprine vs 3 oxycodone)	Patients received a 10-day course, not a 7-day course, of prescription; oxycodone group had a longer duration of low back pain before ED presentation (72 vs 48 hand 48 h); fewer patients in oxycodone group used the medications
Busse et al[43] (2018)	III for Q3	Systematic review of 96 RCTs; included trials (1) enrolled patients with chronic noncancer pain, (2) randomized them to an oral or transdermal opioid (pure opioid or a combination product) vs any nonopioid control, and (3) conducted follow-up for at least 4 wk	The primary outcomes were pain intensity (score range 0 to 10 cm on a visual analog scale for pain at the longest follow-up period; lower is better and the MID is 1 cm), physical functioning (score range, 0 to 100 points on the SF-36 PCS; higher is better and the MID is 5 points), and incidence of vomiting	N=26,169; compared with placebo, opioid use was associated with reduced pain (weighted mean difference −0.69 cm [95% CI −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID 11.9% [95% CI 9.7% to 14.1%]), improved physical functioning (weighted mean difference 2.04 points [95% CI 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID 8.5% [95% CI 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-inperiod)	Evidence was from studies of only low to moderate quality; assessment of long-term associations of opioids with chronic noncancer pain was not possible because no trial followed up with patients for longer than 6 mo; none of the included studies provided rates of developing opioid use disorder and only 2 reported rates of overdose; numerous outcomes and comparisons were evaluated, including subgroup analyses without adjustment for multiple comparisons; heterogeneity associated with pooled estimates for pain relief and functional improvement among trials of opioids vs placebo may have reduced evidence quality

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Edlund etal[44] (2014)	III for Q3	Retrospective cohort study of claims data from Health Core database from 2000 to 2005	Compared rate of developing opioid use disorder among patients with new chronic noncancer pain diagnoses who were or were not prescribed opioids	N=568,640; patients with chronic noncancer pain who were prescribed opioids had higher rate of developing opioid use disorder than those not prescribed opioids; patients prescribed opioids had significantly higher rates of opioid use disorders compared with those not prescribed opioids; effects varied by average daily dose and days' supply: low dose, acute (OR 3.03; 95% CI 2.32 to 3.95); low dose, chronic (OR 14.92; 95% CI 10.38 to 21.46); medium dose, acute (OR 2.80; 95% CI 2.12 to 3.71); medium dose, chronic (OR 28.69; 95% CI 20.02 to 41.13); high dose, acute (OR 3.10; 95% CI 1.67 to 5.77); and high dose, chronic (OR 122.45; 95% CI 72.79 to 205.99)	Included measures of painful diagnostic conditions, but no measure of pain severity or activity interference; unable to verify whether patients had an undiagnosed problem or opioid use disorder before 6 mo before opioid therapy was initiated; study included only individuals with commercial insurance

Evidentiary Table. (continued)

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Shah etal[36] (2017)	III for Q3	Retrospective convenience sample of 10% of patients in the IMS Lifelink+ database	Analyzed duration of use, number of prescriptions, and cumulative dose of patients with first-episode opioid use, time to discontinuation of opioids	N=1,294,247; 33,548 (2.6%) who continued therapy for ≥1 y; of patients who had at least 1 day of opioids, probability of continued use at 1 and 3 y was 6.0% and 2.9%, respectively	

CI, confidence interval; *cm*, centimeter; *ED*, emergency department; *h*, hour; *IQR*, interquartile range; *MID*, minimally important difference; *MME*, morphine milligram equivalent; *mo*, month; *OR*, odds ratio; *Q*, critical question; *RCT*, randomized controlled trial; *SF-36 PCS*, 36-item Short Form physical component score; *wk*, week; *y*, year.