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Uptake of slow-release oral morphine as opioid agonist treatment among hospitalized patients with opioid use disorder

Running title: SROM as opioid agonist treatment

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Abstract

Introduction: Buprenorphine and methadone are highly effective first-line medications for opioid agonist treatment (OAT) but are not acceptable to all patients. We aimed to assess the uptake of slow-release oral morphine (SROM) as second-line OAT among medically ill, hospitalized patients who declined buprenorphine and methadone.

Methods: This study included consecutive hospitalized patients with untreated moderate-to-severe opioid use disorder (OUD) referred to an inpatient addiction medicine consultation service, between June 2018 and September 2019, in Nova Scotia, Canada. We assessed the proportion of patients initiating first-line OAT (buprenorphine or methadone) in-hospital, and the proportion initiating SROM after declining first-line OAT. We compared rates of outpatient OAT continuation (filling outpatient OAT prescription or attending first outpatient OAT clinic visit) by medication type, and compared OAT selection between patients with and without chronic pain, using Chi-squared tests.

Results: Thirty-four patients were offered OAT initiation in-hospital; six patients (18%) also had chronic pain. Twenty-one patients (62%) initiated first-line OAT with buprenorphine or methadone. Of the 13 patients who declined first-line OAT, seven (54%) initiated second-line OAT with SROM in-hospital. Rates of outpatient OAT continuation after hospital discharge were high (>80%) and did not differ between medications (p=0.4). Patients with co-existing chronic pain were more likely to choose SROM over buprenorphine or methadone (p=0.005).

Discussion and Conclusions: The ability to offer SROM (in addition to buprenorphine or methadone) increased rates of OAT initiation among hospitalized patients. Increasing access to SROM would help narrow the OUD treatment gap of unmet need.

Key words (MeSH Terms): opiate substitution treatment; opioid-related disorders; opioid epidemic; addiction medicine; hospitalists

Introduction

North America is facing a complex and devastating public health crisis involving opioids. An estimated two million Americans have opioid use disorder (OUD), and there were 46,802 opioid-involved overdose deaths in the United States in 2018.(1) As injection drug use is increasingly common, the incidence of life-threatening injecting-associated bacterial and fungal infections, such as infective endocarditis, is rapidly rising.(2–4)

Opioid agonist treatment (OAT; particularly buprenorphine and methadone) is associated with large reductions in all-cause mortality among people with OUD (5,6), and may also reduce risk for injecting-associated bacterial and fungal infections.(2,7,8) Hospitalization with these infections represents a "reachable moment" to effectively engage untreated patients into OAT.(9–13) Unfortunately, buprenorphine and methadone are not desired, tolerable, or sufficiently beneficial for all patients, and up to 50% stop within six months.(14,15) This contributes to enormous unmet need, with more than 1 million Americans estimated to have untreated OUD.(14) Innovative approaches and options are needed to reach these patients.

In an effort to close these treatment gaps, recent clinical practice guidelines in Canada(16) and in the United Kingdom(17) now advise off-label use of slow-release oral morphine (SROM) as second-line OAT, supported by randomized trials showing non-inferiority compared to methadone.(18–20) SROM may be especially helpful for patients with co-existing chronic pain who experience insufficient relief with buprenorphine or once-daily methadone.(15,21) In the United States, SROM is approved for treatment of chronic pain, but federal law prevents its use as OAT.(15) As clinical experience is limited in North America, little is known about how the

inclusion of this additional option increases engagement in care of high-risk, hospitalized patients who decline first-line OAT.

In order to explore the potential role for SROM in engaging high-risk hospitalized patients with medical complications of untreated OUD into treatment, we examined data from a series of hospitalized patients with untreated OUD in Halifax, Nova Scotia, Canada. We aimed to assess: (1) how often patients successfully started SROM as second-line OAT in-hospital, after declining first-line OAT with buprenorphine or methadone; (2) whether patients starting SROM in-hospital would be less likely to continue OAT after discharge, compared to patients starting first-line OAT with buprenorphine or methadone; and (3) whether uptake of SROM was more frequent among patients with co-existing chronic pain.

Methods

Setting and design

This study includes consecutive patients with untreated moderate or severe OUD referred to a hospital inpatient addiction medicine consultation service (AMCS) at an academic, tertiary care hospital in Halifax, Nova Scotia, Canada, from June 2018 to September 2019. A description and evaluation of the AMCS is detailed elsewhere.(11)

Consistent with Canadian guidelines, the AMCS offered buprenorphine (formulated as sublingual buprenorphine-naloxone) or methadone as first-line OAT options, based on patient preference.(16) Patients who declined these were offered SROM.(16) For patients experiencing opioid withdrawal who declined all forms of OAT, the AMCS offered immediate-release

hydromorphone or morphine to relieve withdrawal symptoms and offered ongoing re-assessment for transition to OAT (with buprenorphine, methadone, or SROM) before hospital discharge.(10,21) In Halifax, outpatient OAT is available without a waiting list, so patients could continue on OAT after discharge without interruption. Buprenorphine, methadone, and SROM are all covered by public health insurance plans and start with daily-witnessed dispensing at community pharmacies.

Data collection and variables

Using hospital records, including AMCS assessments, we collected data on which OAT medications were offered and initiated in-hospital, and whether patients reported co-existing chronic pain. Patients were classified as continuing OAT after discharge if they filled their daily-dispensed, witnessed OAT discharge prescription at an outpatient pharmacy (confirmed through provincial pharmacy information system) and/or attended their scheduled OAT outpatient follow-up appointment (confirmed through report from community-based physicians).(11) This data was collected as part of a program evaluation, and we did not capture data on patient demographics or medical comorbidities, nor did we collect information on rates of long-term treatment engagement.

Data analysis

We described the frequency of initiation of first-line OAT (with buprenorphine or methadone), and second-line OAT (with SROM) among hospitalized patients referred to the AMCS. We compared rates of outpatient OAT continuation between medication types (methadone,

buprenorphine, or SROM), and compared rates of OAT initiation between patients with and without chronic pain, using Pearson's Chi-square tests.

Ethics statement

This analysis, as part of the AMCS evaluation, was deemed exempt from requirements for Research Ethics Board approval and individual patient consent by Nova Scotia Health Authority.

Results

Thirty-four patients with untreated moderate or severe OUD were referred to the AMCS during the study period; all had severe OUD and consumed opioids by injection. All 34 patients were offered buprenorphine or methadone as OAT (Figure 1). Twenty-one of the 34 patients (62%) initiated first-line OAT in hospital (10 with buprenorphine and 11 with methadone). The remaining 13 patients (38%) declined first-line OAT and were offered SROM. Seven of these 13 remaining patients initiated SROM in-hospital (54% of patients declining first-line OAT; 21% of total sample). The remaining six patients declined all forms of OAT (46% of patients declining first-line OAT; 18% of all patients). Of these six patients declining all forms of OAT, three had premature patient-initiated discharges against medical advice and three were discharged with prescriptions for other opioid analgesic medications (i.e., short- or long-acting hydromorphone) not intended as OAT.

Among patients initiating OAT in hospital, frequency of OAT continuation immediately after hospital discharge did not differ between medication types (buprenorphine: 80%; methadone: 91%; SROM: 100%, p=0.4; Figure 1).

Six patients (18% of total sample) with untreated, severe OUD reported co-occurring chronic pain; three of these six patients had chronic multisite pain and three had chronic back pain. All six patients declined buprenorphine and methadone, and then all were offered SROM. Four of these six patients initiated SROM and two declined all forms of OAT (Figure 2). Patients with chronic pain were more likely to initiate SROM than other OAT medications (p=0.005). Due to the small sample size, we repeated this analysis using the maximum likelihood ratio Chi-square test and found similar results (p=0.002).

Discussion

Among hospitalized patients with untreated moderate-to-severe OUD referred to a inpatient AMCS, we found 38% of patients declined first-line OAT (with buprenorphine or methadone), but most of these patients subsequently initiated OAT with SROM while in-hospital. Patients starting SROM in-hospital continued OAT immediately after discharge at similar rates to patients starting buprenorphine or methadone. Patients with co-occurring chronic pain were more likely to initiate SROM than buprenorphine or methadone. The ability to offer SROM, in addition to buprenorphine and methadone, increased rates of in-hospital OAT initiation from 62% to 82% of eligible patients. This highlights the value of SROM as a treatment option for high-risk patients hospitalized with medical complications of OUD, and suggests that expanding access to SROM could help combat North America's overdose death crisis.

Our findings that SROM is a valuable tool to engage untreated hospitalized patients and narrow the OUD treatment gap is consistent with prior research in out-of-hospital settings. Offering choice among a variety of options is consistent with principles of patient-centered care and shared decision-making, increases satisfaction and engagement in addiction treatment, and is associated with improved outcomes.(22–24) We did not collect specific information on reasons for medication choices, but patients with chronic pain were more likely to select SROM than first-line OAT. This finding is also consistent with prior evidence, as common reasons for declining buprenorphine or methadone include side effects or ongoing cravings, substance use, or intolerable pain despite optimized doses.(15,21) Other treatment options for OUD, including supervised injectable OAT and injectable naltrexone, are not available in the study setting, and were therefore not offered to AMCS patients. Injectable long-acting buprenorphine was also not available during the study period.

In Canada(16) and in the United Kingdom(17), SROM is recommended as a specialist-led, second-line approach to OUD treatment. As experience with SROM increases, recommendations may change to increase access. Meta-analyses of randomized controlled trials suggest that SROM is non-inferior to methadone treatment at reducing opioid use, with comparable safety profiles.(18–20) SROM has been used as OAT in several European countries since the 1990s.(15,25) For the patients in our study, SROM was initiated by hospital-based medical trainees supervised by community-based addiction physicians, which could be a model for hospitals that do not yet have specialist AMCS.(11) In the United States and in Australia, changes to federal and state laws should be considered to facilitate SROM for OAT.

This study had limitations. Our sample included patients with OUD at an academic medical centre who agreed to AMCS consultation. This may limit generalizability to other hospital settings, though prior research suggests most hospitalized patients with OUD are interested in reducing substance use.(13) As this study was conducted within a program evaluation, we did not capture data on patient demographics or medical comorbidities, nor information on rates of long-term treatment engagement. However emerging evidence suggests in-hospital initiation and continuation of OAT improves long-term engagement, compared to outpatient referral only.(10,12,13,21) We also included consecutively referred patients (rather than a prospectively recruited cohort) and had a relatively small sample size (34 patients), though we do not know of any other hospital-based studies examining uptake of SROM for OAT.

Conclusions

The ability to offer SROM (in addition to buprenorphine or methadone) as OAT increased rates of in-hospital OAT initiation and continuation after hospital discharge. This highlights the value of SROM as a treatment option for medically ill, hospitalized patients with OUD. Increasing access to SROM would help narrow the OUD treatment gap of unmet need.

Acknowledgments

We live and work in Mi'kma'ki and along the Wolastoq, the ancestral and unceded territory of the Mi'kmaq and the Wolastoqiyik. We are all treaty people.

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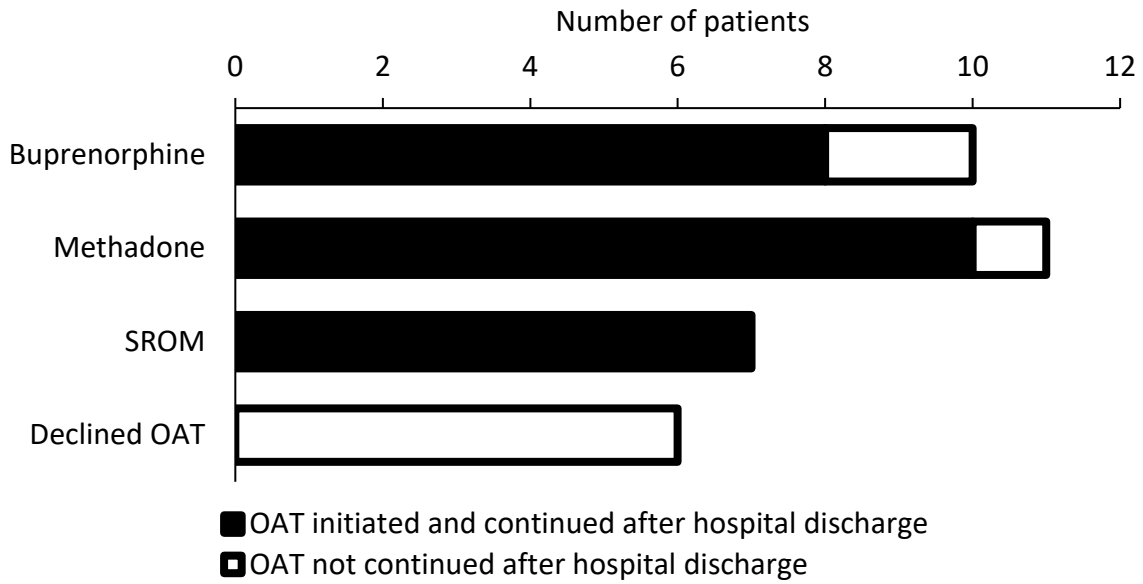
Figure captions

Figure 1. Number of hospitalized patients with untreated opioid use disorder selecting each option for initiating opioid agonist treatment (OAT) while in-hospital. Patients who declined OAT did not start any OAT in hospital. Black/filled bars show number of patients who continued OAT after hospital discharge. SROM: Slow-release oral morphine; OAT: Opioid agonist treatment.

Figure 2. Number of hospitalized patients with untreated opioid use disorder selecting each option for initiating opioid agonist treatment (OAT) while in-hospital, stratified by whether or not they have co-existing chronic pain. Patients who declined OAT did not start any OAT in hospital. SROM: Slow-release oral morphine; OAT: Opioid agonist treatment.



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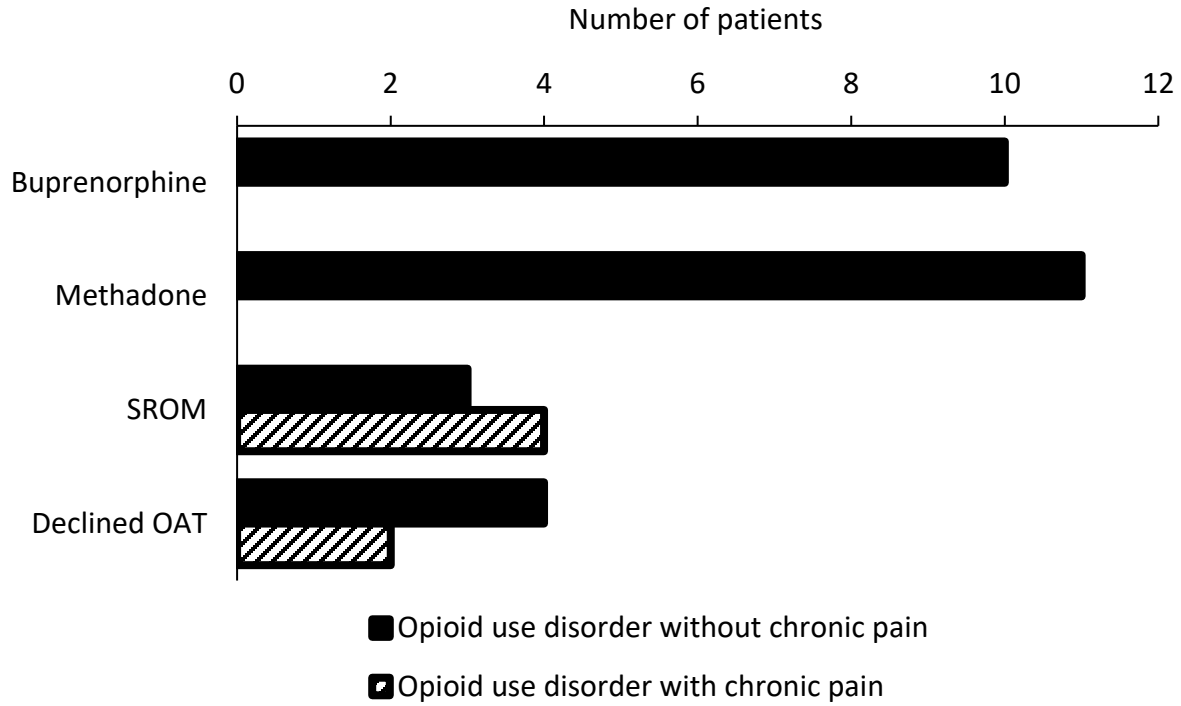

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