### Title

Pharmacy multidisciplinary stewardship program for high-risk patients prescribed opioids in an academic clinic.




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## ABSTRACT

### Objective

To assess observation of the Centers for Disease Control (CDC) Guideline for Prescribing Opioids for Chronic Pain within a Pharmacy Controlled Substance Clinic (PCSC) compared to usual care by resident physicians in a Primary Care Internal Medicine (IM) clinic.

### Design

Single-center, retrospective cohort.

### Setting

IM clinic within a large, academic medical center.

### Participants

Patients receiving stable opioid prescriptions for management of chronic, non-malignant pain (CNCP) were screened. Exclusions included age < 18 years old, aberrant opioid use behaviors, or malignancy-related pain. Both cohorts included 100 eligible patients.

### Interventions

Within the PCSC, a pharmacy team provided assistance to resident physicians monitoring patients receiving opioid medications.

### Main Outcome Measures

The primary outcome was application of CDC guidelines: creation of an annual patient provider agreement (PPA); annual urine drug screen (UDS); quarterly review of a prescription drug

monitoring program (CURES); and documentation of quarterly evaluation of opioid use. Secondary outcomes included risk factors for opioid-related harms.

**Results**

Respective measures from the control vs. the intervention group demonstrated: PPA creation in 28% (n=28) vs. 100% (n=100) ($p<0.001$); UDS obtained in 59.2% (n=58) vs. 90.6% (n=87) ($p<0.001$); quarterly CURES review in 26% (n=26) vs. 70% (n=70) ($p<0.001$); and quarterly evaluation of opioid use in 26% (n=26) vs. 37% (n=37) ($p=0.10$).

**Conclusions**

Pharmacy-led monitoring of patients prescribed opioids for CNCP in an academic resident clinic improves implementation of CDC guidelines. Similar multidisciplinary team integration may improve opioid prescribing safety in academic primary care settings.

## TEXT

### Introduction

Opioid prescribing and use have increased substantially over the past decades.[1] It is widely recognized that chronic pain can lead to clinical, psychological, and social consequences.[1,2] For some patients with chronic non-malignant pain (CNCP), appropriate use of opioids may lead to improvements in function, including quality of life.[3-4] However, while short-term opioid use has been shown to be appropriate and effective for some, chronic use remains controversial.[5-7] Moreover, data regarding long-term safety risks is increasing.[1,8,9] According to the American Society of Addiction Medicine, medication overdose is the leading cause of accidental death in the United States, with 70,237 fatal overdoses occurring in 2017; 47,600 deaths were specifically attributed to opioids.[10] Due to increased awareness of complications of opioid-related harms, national agencies, state Medicaid agencies, healthcare providers, individuals, and communities have amplified focus on the misuse and abuse of these agents; a national public health emergency has been declared.[11-12]

In response to this national crisis, the Centers for Disease Control (CDC) published guidelines to improve the efficacy and safety of opioid prescribing for CNCP.[1] The guideline was divided into three sections that offered direction regarding: when to initiate or continue opioid use; selection, follow up and discontinuation of opioids; and review of risks and harms of chronic opioid use.[1]

To ensure safe and effective use of these high-risk agents, the guideline encouraged careful assessment of: appropriate medication use via urine drug screen (UDS), at least annually; review of each patient's controlled substance use through the state's prescription drug monitoring program, at least quarterly; and reevaluation of high-risk medication regimens, such as doses equivalent to, or greater than, 50 morphine milligram equivalents per day (MME), concurrent use of benzodiazepines and opioids, with or without co-prescription of naloxone, and assessment of other risk factors for opioid-related harm.[5] Together, consideration of these factors contribute to comprehensive assessment of the potential benefits and risks of harm when providing chronic opioid therapy (COT) and serve to guide the development of future work.

Providing safe and effective COT can pose significant burdens on primary care clinics, and adoption of risk-reduction strategies has been limited.[7,13-19.] Furthermore, these burdens may be even greater in the academic setting, as high-risk patients with chronic pain disproportionately receive care in resident clinics.[13,20] These settings may represent an opportunity for an interdisciplinary and novel approach to patient care. While the pharmacist's role in outpatient pain management has been demonstrated, there is limited information regarding the impact of a pharmacist in the monitoring of patients on COT.[21-24] Novel clinical outcomes regarding the collaboration of providers and pharmacists in the management of monitoring and management of COT for CNCP are beginning to be explored.[25-26] Initial evidence of a pharmacist-led opioid risk assessment telephone clinic demonstrated optimistic results. Of the 148 patients assessed by a pharmacist, 32.4% (n=48) received recommendations for changes in their opioid regimens (n=66 total recommendations). Of those, reduction in their daily opioid use (33.3%, n=22) was most frequent followed by discontinuation of opioid therapy (22.7%, n=15).[23] In a study further

examining the impact of pharmacist involvement in opioid reduction, Boren observed an average decrease of 207 MME/day in patients presenting with an average MME/day greater than 50.[26] Similarly, there is a need to assess the impact of a clinical pharmacist in the collaborative management of COT, particularly in an academic clinical environment.

## METHODS

A need for pharmacist-provider collaboration in COT monitoring was identified in late 2015 at a large academic medical center in the Internal Medicine (IM) department. As a result, a Pharmacy Controlled Substance Clinic (PCSC) was developed to support resident physicians in the safe prescribing and monitoring of COT in patients with CNCP. The IM clinic policies on controlled substance prescribing were developed in 2015, derived from published Medical Board of California Opioid Guidelines and the proposed CDC Opioid Guidelines. Patients were most commonly referred to the PCSC for facilitation of routine refills for patients on stable regimens. However, the PCSC role grew to assist with the development of an annual patient-provider agreements (PPA), annual UDS screenings, quarterly CURES reviews, and quarterly office visits with an IM resident to evaluate COT. The team was composed of a 0.4 full-time equivalent (FTE) clinical pharmacist and 0.8 FTE pharmacy technician. The purpose of this study was to evaluate the PCSC impact on clinic policy implementation and assess integration of national recommendations in managing prescription renewals for patients on stable COT.

### *Study Design and Patient Population*

This single-center, retrospective cohort study aimed to assess integration of four select CDC guideline recommendations in the management of COT for CNCP in patients enrolled in the PCSC versus those receiving usual care by an IM resident physician.

During the period of January 1, 2016 through December 31, 2016, a total of 421 patients were initially identified as receiving chronic controlled substances. During the study period, a total of 207 (49.1%) patients were seen by the PCSC. All patients identified as receiving usual care from the IM clinic or the PCSC were screened for inclusion to meet the planned sample size of 100 each in the control and intervention groups.

The inclusion and exclusion criteria for this study aimed to include patients represented in the aims of the CDC guideline. Inclusion criteria included: age ≥ 18 years; diagnosis of CNCP; a resident physician primary care provider at the IM Clinic; and current use of a stable, opioid-based regimen with at least one opioid medication prescribed by the resident physician. Chronic opioid use was defined as ≥ 3 consecutive monthly prescriptions for opioid medications, identified through activity on the State of California prescription drug monitoring program (CURES). Stable opioid-based regimen use was determined by the resident physician. Exclusion criteria included: patients followed by the PCSC for non-opioid controlled substance, unstable opioid regimen identified through mention of tapering or adjusting therapy in electronic medical record (EMR); individuals displaying aberrant behaviors, unless specifically referred by a physician; patients with substance use disorders; and patients whose opioid medications were managed by an outside provider (Figure 1.) The study was determined to be exempt by the Institutional Review Board.

*Outcomes*

The primary outcome was percent application of a composite of four recommendations provided in the CDC Guideline for Prescribing Opioids for Chronic Pain and integrated into IM clinic policy. These objective metrics included: development of an annual patient-provider agreement (PPA), annual UDS screening, quarterly CURES review, and quarterly office visits with an IM resident to evaluate COT. Despite criticism of widespread application of the CDC Guideline to all COT patients, these objective measures were chosen as a framework to measure pharmacist impact, based on its broad reach and the lack of an alternative evidence-based construct.[27-30] Within the intervention cohort, outcomes were assessed for one year prior to enrollment, during 2015-2016, as well as after the first year of enrollment in the pharmacy clinic, during 2016-2017. Subsequently, outcomes from the first year of PCSC establishment were compared between patients in the control and intervention cohorts. Secondary outcomes assessed factors associated with elevated opioid-related risk, including average MME, concomitant benzodiazepine use, naloxone co-prescription, factors influencing drug metabolism and/or risk of respiratory depression, and substance use history as part of the clinical pharmacist role in identifying patients with potential risk factors for opioid-related harms.

Implementation of recommendations was identified through retrospective EMR review. PPA were scanned into the EMR. UDS were directly reported from the laboratory in the EMR. Review of CURES and assessment of COT were identified via review of visit notes. Average MME was calculated using the UCDMC equianalgesic dosing calculator approved by the local Pharmacy and Therapeutics Committee based on the quantity of opioids prescribed over 30 days

as identified during CURES review. Benzodiazepine use was also obtained through CURES reporting in order to capture prescription from physicians both within and outside the health system. Naloxone co-prescription was identified via prescription in the EMR. Additional factors that could increase risk for opioid-related harm were determined through retrospective review of the EMR.

*Statistical Analysis*

Categorical demographic variables in the two treatment groups were analyzed via Chi-square test. Wilcoxon rank sum test was used to evaluate differences in pain scores between groups as well as changes in MME. For the intervention cohort, McNemar's test was used to evaluate differences pre- and post-enrollment in the proportion of patients taking benzodiazepines as well as differences in UDS completion in the interventional care cohort. For the latter two measures, the signed rank test was used after residual diagnostics following a paired t-test revealed gross failures in distributional assumptions. All analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC).

Prior to creation of the PCSC, a baseline institutional rate of 25% implementation of any criteria was observed. This contributed to the identified collaboration opportunity between the IM department and pharmacy team. Given the lack of published clinical outcomes from prior studies investigating this type of clinical service, an increase to $\geq$ 50%, or double the original rate, was deemed clinically significant. The power analysis demonstrated 100 patients were required in both study arms to achieve a power of 80% to detect the expected increase with a two-sided $\alpha \leq$ 0.05.

## RESULTS

*Patient Population*

During the study period, 421 patients were identified as having received controlled substances from the IM clinic. Of these, 280 patients met inclusion screening criteria: 165 patients in the IM control cohort and 115 patients in the PCSC intervention cohort. Of those screened, a total of 80 patients were excluded. The most commonly excluded patients were those not currently receiving chronic opioid therapy. Ultimately, enrollment was stopped when a total of 100 patients were included in both the control and intervention groups (Figure 1).

Baseline characteristics were similar in both groups. Hepatic dysfunction and post-traumatic stress disorder (PTSD) occurred more frequently in the control cohort. There were no other significant differences (Table 1).

*Primary Outcome*

Overall implementation for both cohorts were reported as a composite outcome of four CDC recommendations: creation of a PPA, annual UDS, quarterly review of CURES, and quarterly office visits to assess COT. Six patients with end-stage renal disease, two patients in the control cohort and four in the intervention cohort, were excluded from the composite analysis because they could not produce a urine sample for a UDS. Of the 194 included patients, 1% of patients (n=1) in the control cohort and 28.1% (n=27) of patients in the intervention cohort achieved the composite outcome ($p<0.001$) during the study period.

After the first year of PCSC intervention, attainment of the individual components of the composite outcome was found to differ significantly (Figure 3). Demonstration of an annual PPA, annual UDS, and quarterly review of CURES occurred in 28% (n=28), 59.2% (n=58) and 26% (n=26) of the control cohort and 100% (n=100), 90.6% (n=87), and 70% (n=70) of the intervention cohort, respectively ($p<0.001$). Quarterly evaluation of opioid use was identified in visit notes in 26% (n=26) of patients in the control cohort and 37% (n=37) of patients in the intervention cohort ($p=0.10$).

Figure 2 demonstrates the pre-post analysis of the individual components of the composite outcome for the intervention cohort (n=100). Annual PPA occurred in 27% (n=27) of patients prior to implementation of the PCSC in comparison to 100% (n=100) after enrollment ($p<0.001$). An annual UDS was completed by 37.5% (n=36) of patients prior to clinic implementation compared to 94.7% (n=91) of patients after enrollment in the 96 eligible patients ($p<0.001$). Quarterly review of CURES was documented in 3% (n=3) of patients prior to implementation versus 70% (n=70) after enrollment ($p<0.001$). Quarterly evaluation of continued therapy was documented in the assessment and plan of visit notes in 12% (n=12) prior and 37% (n=37) after enrollment ($p<0.001$).

*Secondary Outcomes*

Secondary outcomes included assessment of risk factors for opioid-related harm. Within the intervention cohort, there were significant differences pre- and post-intervention in both MME per day and benzodiazepine prescribing. Based on review of CURES data, the average prescribed opioid dose reduced by 14.0 MME/day over the study period ($p<0.001$), and the total

number of benzodiazepine prescriptions reduced by 9% (p=0.004). Concurrent use of opioids and benzodiazepines was assessed through the CURES report and identified in 20% (n=20) and 13% (n=13) of patients in the control and intervention cohorts, respectively (p=0.18; Table 1). CDC recommendations encourage concomitant naloxone prescribing with the following criteria: regimen dose ≥50 MME per day, concomitant benzodiazepine use, or history of substance abuse. Of the 100 patients in the control cohort, 70% (n=70) met these criteria, similar to 75% (n=75) of the 100 patients in the intervention cohort (p=0.43). Of note, per EMR review, 1 patient in the intervention group and no patients in the control group were identified to have been prescribed naloxone. Rates of opioid-related harm risk factors were not significantly different between the control and intervention cohorts (Table 1). Specific subsets of organ dysfunction considered as potential opioid-related risk factors are detailed in Table 2.

## DISCUSSION

We retrospectively assessed observation of four CDC guideline recommendations for patients with CNCP receiving COT following implementation of a pharmacy-led controlled substance clinic in comparison to usual care in an IM clinic. Statistically and clinically significant increases in composite measures were observed in the intervention compared to the control cohort. Achievement of individual measures was roughly two to three times more likely in the intervention cohort than control.

While rates of application of PPA, UDS, and CURES recommendations in the intervention cohort were both clinically and statistically greater compared to the control cohort, neither demonstrated consistent quarterly office visits to evaluate continued opioid prescribing. Several

reasons may underlie this observation. Resident physicians may have neglected to document evaluation of opioid therapy because of the volume of other clinical issues being addressed in a particular encounter. Thus, though evaluation of COT may have occurred during, the visit may not have met criteria for attainment of this measure in our study. Additionally, resident knowledge of clinic policy regarding opioid monitoring may have been insufficient. Pertinently, the recommendation for quarterly assessments received the lowest strength of evidence grade in the CDC guideline.[2] In considering the burdens that this recommendation poses for providers, the necessity of quarterly evaluation may be best derived from careful consideration of the needs and risk profile of the individual patient, as well as the capabilities of the healthcare system.

Secondary outcomes included objective measures for opioid-related risks. Greater than 65% (n=130) of the 200 total patients in the control cohort (63%, n=63) and intervention cohort (67%, n=67) utilized moderate- to high-risk daily regimens based on a total daily MME $\geq$ 50 per day or the concurrent use of a benzodiazepine. The FDA has warned that concomitant benzodiazepines and opioid use can contribute to respiratory depression; studies demonstrate that concomitant benzodiazepine use occurs in up to 60% of opioid-related fatal overdoses.[31-34] Identification of co-prescribing allows case-by-case risk-benefit assessment of co-prescribing.[5] We observed less than one-fourth of patients in both cohorts (20% in the control cohort vs 13% in the intervention cohort) were co-prescribed this high-risk combination. This was lower than the 27% incidence of concomitantly prescribed opioids and benzodiazepines reported by Park et al in a cohort study of veterans (N=112,069).[34]

While neither the purpose of implementing the PCSC, nor the creation of the IM policy, were aimed at reducing the use of controlled substances, statistically significant reductions were observed in both average MME/day and benzodiazepine co-prescribing. Pharmacists, in collaboration with patients, made recommendations to resident physicians for therapy de-escalation if comprehensive clinical review identified a need. This suggests adoption of a collaborative care model may lead to reductions in total opioid use, which has been similarly demonstrated by Boren et al.[26]

Identification of other opioid-related risk factors, such as a history of substance abuse, mental health disorders, hepatic, renal, or respiratory disorders should guide providers during assessment of opioid use.[1] In our populations, we observed significantly more patients with hepatic dysfunction and PTSD in the control group; however, the low numbers of patients overall may suggest that these findings are related to chance. Other opioid-related risk factors were relatively prevalent but similar between groups.

Notably, prescription rates of naloxone were low pre- and post-PCSC intervention. This finding represents opportunities for improved naloxone access and may reflect barriers, such as provider awareness, patient acceptance, or payor coverage. This identified care gap could be improved with expansion and revision of the pharmacist-run clinic, as well as addressing other noted impediments.

There is limited evidence regarding the use of pharmacists to manage COT in collaboration with primary care physicians. One practice research report by Norman et al details creation of a

pharmacist-managed pain clinic in a primary care setting.[25] While clinical outcomes have yet to be reported, the structure of the clinic appears similar to that described in the present study. Additionally, Boren et al found reductions in MME/day, optimization of opioid and non-opioid therapies, and increased patient access while utilizing and interdisciplinary approach.[26] The use of a pharmacist, pharmacy resident, and pharmacy students to prescribe and manage non-controlled medications under a collaborative practice agreement, conduct counseling visits with patients, and optimize nonpharmacological pain control further promotes collaboration between primary care physicians and pharmacists. While incorporation of a pharmacist in controlled substance management remains novel, numerous studies have reported improvements in clinical outcomes in a variety of other chronic conditions frequently encountered in the primary care setting.[35-37] These studies suggest interprofessional collaboration between pharmacists and physicians can improve outcomes, eliminate gaps in care, and extend the abilities of the primary care physician. In this case, where many patients were referred by IM resident physicians specifically for COT, establishing a clinic with a targeted scope may have contributed to the stronger outcomes from the PCSC as compared to the IM clinic. The success of the PCSC may further represent the benefit of establishing multidisciplinary programs with targeted interventions.

While our study was not designed to assess them, additional potential benefits of a multidisciplinary team observed during this pilot may deserve future study. Although pharmacists cannot currently bill for services, integration of the PCSC extended significant support to the prescribing physician. During PCSC office visits, pharmacists reviewed the risks of high-dose opioid use, collaborated on opioid tapering plans with interested patients, and made

recommendations to optimize nonopioid treatment when appropriate. The time spent in these visits may have allowed physicians to complete other billable appointments. The pharmacy team also addressed insurance rejections, facilitated solutions to overcome medication access barriers, completed prior authorization requests, and investigated pharmacy fill histories when CURES results were in question. Additionally, as resident physicians frequently rotate outside of the IM clinic, the pharmacy team assisted with interval COT management and refills and promoted continuity of care within a sensitive disease state. Notably, since creation of the original PCSC, pharmacy-supported COT management has been expanded to several additional health system community (non-resident) clinics and one Family Practice clinic within this health system. While the original aim of the study was to assess integration of objective opioid use measures included in the CDC guideline recommendations, the unintended impacts of reducing COT and concomitant benzodiazepine prescribing as well as broader health system adoption of the PCSC model highlights the value of interdisciplinary collaboration at this institution.

Efforts to combat the opioid epidemic are commendable but should be constructed with best practices and patient needs in mind. Since the dissemination of the 2016 CDC guidelines, the authors have published a commentary in the *New England Journal of Medicine* (*NEJM)* cautioning against misinterpretation and misapplication of the guidelines' recommendations.[26] This statement, along with other critiques, serve as reminders to the medical community that guidelines should be applied judiciously.[27-30] A consensus panel report established that, while there is reason to support the CDC guidelines, specific attention must be paid to ensure recommendations are not inflexibly applied to patient populations within, or outside of, its

intended scope.[29] One should also note the CDC Guidelines are comprised of type 3 or type 4 evidence. Type 3 evidence is based on observational studies or randomized clinical trials with notable limitations; type 4 evidence is based on clinical experience, observational studies with important limitations, or randomized clinical trials with several major limitations. Based on the interpretation of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, these evidence types carry limited to very little confidence in the estimate of effect, respectively.[38] Thus, it remains uncertain if application of these recommendations may improve the patient-important outcome of reducing opioid-related harms.

This study is limited by its single center, retrospective design and related risks of bias. Inconsistencies in knowledge and practices amongst the resident physicians may have resulted in underreporting of measure application. Despite training, there may have been gaps in resident education. Additionally, chart review revealed that the PCSC pharmacy team often reviewed CURES reports on behalf of the resident physicians, confounding interpretation of implementation. While the outcome metric increased significantly during the study, the observed 25% baseline rate may be explained by lack of specific departmental policies, robust national practice guidelines, or inconsistent emphasis on specific outcome measures during training. We also recognize implementation of a dedicated pharmacy team may not be feasible in many practice settings.

## CONCLUSIONS

Integration of a pharmacy-led controlled substance clinic significantly improved implementation of CDC recommendations for COT of CNCP in an academic, resident-based IM clinic.

Collaborative interprofessional partnerships with pharmacists to assist COT may improve care outcomes and extend capabilities of primary care physicians. However, COT programs must cautiously appraise existing guidelines and evidence to ensure patient-centered care in appropriate populations.

Areas of need highlighted by this study include improved workflows to ensure quarterly primary care visits, consistent documentation practices in the EMR, and strategies to utilize data to implement plans to mitigate opioid-related risks. Primary amongst these efforts is development of programs to expand naloxone co-prescribing.

## CONFLICTS OF INTEREST

The authors do not have any conflicts of interest to disclose.

**LEGENDS FOR FIGURES**

Figure 1. Patient Selection. Patients from the Internal Medicine (IM) Clinic and Pharmacy Controlled Substance Clinic (PCSC) were screened for a planned inclusion of 100 patients per arm.

Figure 2. Percent attainment of individual measures in the intervention group pre- and post-PCSC enrollment

*For Annual urine drug screen (UDS), N=96 as four patients were unable to produce urine for a UDS and thus excluded from the specific metric analysis.

Patient provider agreement (PPA), State of California prescription drug monitoring program (CURES)

Figure 3. Percent attainment of individual measures

*For annual urine drug screen (UDS), N=98 in the control group and N=96 in the intervention group as six patients were unable to produce urine for a UDS and thus excluded from the specific metric analysis.

Patient provider agreement (PPA), State of California prescription drug monitoring program (CURES)

## REFERENCES


1. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: National Academy of Sciences; 2011.
2. Gaskin DJ, Richard P. The economic costs of pain in the United States. In: relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: National Academies Press; 2011.
3. Dillie KS, Fleming MF, Mundt MP, French MT. Quality of life associated with daily opioid therapy in a primary care chronic pain sample. *J Am Board Fam Med*. 2008;21(2):108-17.
4. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Current Med Res Opin*. 2005;21(10):1555-1568.
5. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – united states, 2016. *MMWR Recomm Rep*. 2016;65(No. RR-1):1-49.
6. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16:405-16.
7. Starrels JL, Becker WC, Weiner MG, Li X, Heo M, Turner BJ. Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. *J Gen Intern Med*. 2011;26:958-64.
8. Chou R, Deyo R, Devine B, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. *Evid Rep Technol Assess (Full Rep)*. 2014;218:1-219.
9. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015;162(4):276-286.

10. National Institute on Drug Abuse. Drugs involved in U.S. overdose deaths, 2000 to 2016. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed March 23, 2019.

11. Department of Health & Human Services. NIH Launches HEAL initiative, doubles funding to accelerate scientific solutions to stem national opioid epidemic. https/www.nih.gov/news-events/news-releases/nih-launches-heal-initiative-doubles-funding-accelerate-scientific-solutions-stem-national-opioid-epidemic. Published April 4, 2018. Accessed June 8, 2018.

12. Department of Health & Human Services. HHS acting secretary declares public health emergency to address national opioid crisis. https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html. Published October 26, 2017. Accessed June 8, 2018.

13. Khalid L, Liebschutz JM, Xuan Z, et al. Adherence to prescription opioid monitoring guidelines among residents and attending physicians in the primary care setting. *Pain Med.* 2015;16:480-7.

14. Becker WC, Starrels JL, Heo M, Li X, Weiner MG, Turner BJ. Racial differences in primary care opioid risk reduction strategies. *Ann Fam Med.* 2011;9:219-25.

15. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *Am J Prev Med*. 2015;49:409-13.

16. Khodaee M, Deffenbacher B. A look at the burden of opioid management in primary care. *J Fam Pract*. 2016;65:E1-E6.

17. Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA. Opioids and the treatment of chronic pain in a primary care sample. *J Pain Symptom Manage*. 2001;22(3):791-6.

18. McCarberg BH. A critical assessment of opioid treatment adherence using urine drug testing in chronic pain management. *Postgrad Med*. 201;123(6):124-31.

19. O'Rorke JE, Chen I, Genao I, Panda M, Cykert S. Physicians' comfort in caring for patients with chronic nonmalignant pain. *Am J Med Sci*. 2007;333(2):93-100.

20. Colburn JL, Jasinski DR, Rastegar DA. Long-term opioid therapy, aberrant behaviors, and substance misuse: comparison of patients treated by resident and attending physicians in a general medical clinic. *J Opioid Manag.* 2012;8:153-60.

21. Dole EJ, Murawski MM, Adolphe AB, Aragon FD, Hochstadt B. Provision of pain management by a pharmacist with prescribing authority. *Am J Health Syst Pharm.* 2007;64:85-9.

22. Bruhn H, Bond CM, Elliott AM, et al. Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial. *BMJ Open.* 2013;3(4):e002361.

23. Jacobs SC, Son EK, Tat C, Chiao P, Dulay M, Ludwig A. Implementing an opioid risk assessment telephone clinic: outcomes from a pharmacist-led initiative in a large veterans health administration primary care clinic, December 15, 2014-March 31, 2015. *Subst Abus*. 2016;37(1):15-9.

24. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*. 2007;8(7):573-84.

25. Norman JL, Kroehl ME, Lam HM, et al. Implementation of a pharmacist-managed clinic for patients with chronic nonmalignant pain. *Am J Health Syst Pharm*. 2017;74(16):1229-1235.

26. Boren LL, Locke AM, Friedman AS, Blackmore CC, Woolf R. Team-based medicine: incorporating a clinical pharmacist into pain and opioid practice management. *PM R*. 2019; 11(11):1170-1177 epub.

27. Centers for Disease Control and Prevention. Media statement: CDC advises against misapplication of the guideline for prescribing opioids for chronic pain. https://cdc.gov/media/releases/2019/s0424-

advises-misapplication-guideline-prescribing-opioids.html Published April 24, 2019. Accessed December 20, 2019.

28. Dowell D, Haegerich T, Chou R. No shortcuts to safer opioid prescribing. *N Engl J Med.* 2019;80(24):2285–7.

29. Kroenke K, Alford D, Argoff C et al. Challenges with implementing the centers for disease control and prevention opioid guideline: a consensus report. *Pain Med*. 2019; 20(4):724-735.

30. Stanton M, McClughen D. C. Three steps forward and two steps back: impacts of government action on people with pain and those who treat them. [Published online ahead of print October 19 2019]. *Pain Manag Nurs.* 2019.

31. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171:686-91.

32. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med*. 2015;49:493-501.

33. Federal Drug Administration. FDA drug safety communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-risks-and-death-when-combining-opioid-pain-or Published August 31, 2016. Accessed September 20, 2017.

34. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ*. 2015;350:h2698.

35. Hirsch JD, Steers N, Adler DS, et al. Primary care-based, pharmacist-physician collaborative medication-therapy management of hypertension: a randomized, pragmatic trial. *Clin Ther*. 2014;36(9):1244-1254.

36. Isetts BJ, Buffington DE, Carter BL, Smith M, Polgreen LA, James PA. Evaluation of pharmacists' work in a physician-pharmacist collaborative model for the management of hypertension. *Pharmacotherapy*. 2016;36(4):374-384.

37. Wallgren S, Berry-Cabán CS, Bowers L. Impact of clinical pharmacist intervention on diabetes-related outcomes in a military treatment facility. *Ann Pharmacother.* 2012;46(3):353-357.

38. Ahmed F. *U.S. Advisory Committee on Immunization Practices Handbook for Developing Evidence-based Recommendations*. Version 1.2. Atlanta, GA: Centers for Disease Control and Prevention (CDC); 2013.

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541 **TABLES**
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543 **Table 1. Baseline Demographics**
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| | Control Group N=100 | Intervention Group N=100 | *P* value |
|---|---|---|---|
| **Age in years, mean (SD)** | 61 (11) | 61 (11) | 0.86* |
| **Male gender, n (%)** | 39 (39) | 48 (48) | 0.20 |
| **Morphine Milligram Equivalents, mean (SD)** | 94.7 (125.9) | 108.7 (149) | 0.48* |
| Low ≤ 49, n (%) | 51 (51) | 37 (37) | |
| Moderate 50-89, n (%) | 23 (23) | 24 (24) | |
| High ≥ 90, n (%) | 26 (26) | 39 (39) | |
| **Regimen Risk†, n (%)** | | | 0.81 |
| Low | 37 (37) | 33 (33) | |
| Moderate | 22 (22) | 22 (22) | |
| High | 41 (41) | 45 (45) | |
| **Using multiple concurrent opioids, n (%)** | 28 (28) | 27 (27) | 0.88 |
| **Using concomitant benzodiazepine prescription, n (%)** | 20 (20) | 13 (13) | 0.18 |
| **Naloxone candidate‡, n (%)** | 70 (70) | 75 (75) | 0.43 |
| **Anxiety, n (%)** | 16 (16) | 15 (15) | 0.85 |
| **Congestive Heart Failure, n (%)** | 8 (8) | 7 (7) | 0.79 |
| **Depression, n (%)** | 49 (49) | 37 (37) | 0.09 |
| **Hepatic dysfunction, n (%)** | 7 (7) | 0 (0) | 0.007§ |
| **History of substance abuse, n (%)** | 24 (24) | 19 (19) | 0.39 |
| **Pain score, median (IQR)** | 5 (0, 8) | 5 (0, 7) | 0.49‖ |
| **Post-Traumatic Stress Disorder, n (%)** | 5 (5) | 0 (0) | 0.02¶§ |
| **Obstructive sleep apnea, n (%)** | 27 (27) | 21 (21) | 0.32 |
| **Central sleep apnea, n (%)** | 2 (2) | 1 (1) | 0.56 |
| **Renal dysfunction, n (%)** | 24 (24) | 16 (16) | 0.16 |
| **Respiratory dysfunction, n (%)** | 21 (21) | 13 (13) | 0.13 |
| **Current smoking, n (%)** | 24 (24) | 20 (20) | 0.50 |
| **Congestive heart failure** | 8 (8) | 7 (7) | 0.79 |

| | | | |
|---|---|---|---|
| **Concomitant alcohol use** | 26 (26) | 29 (29) | 0.57 |

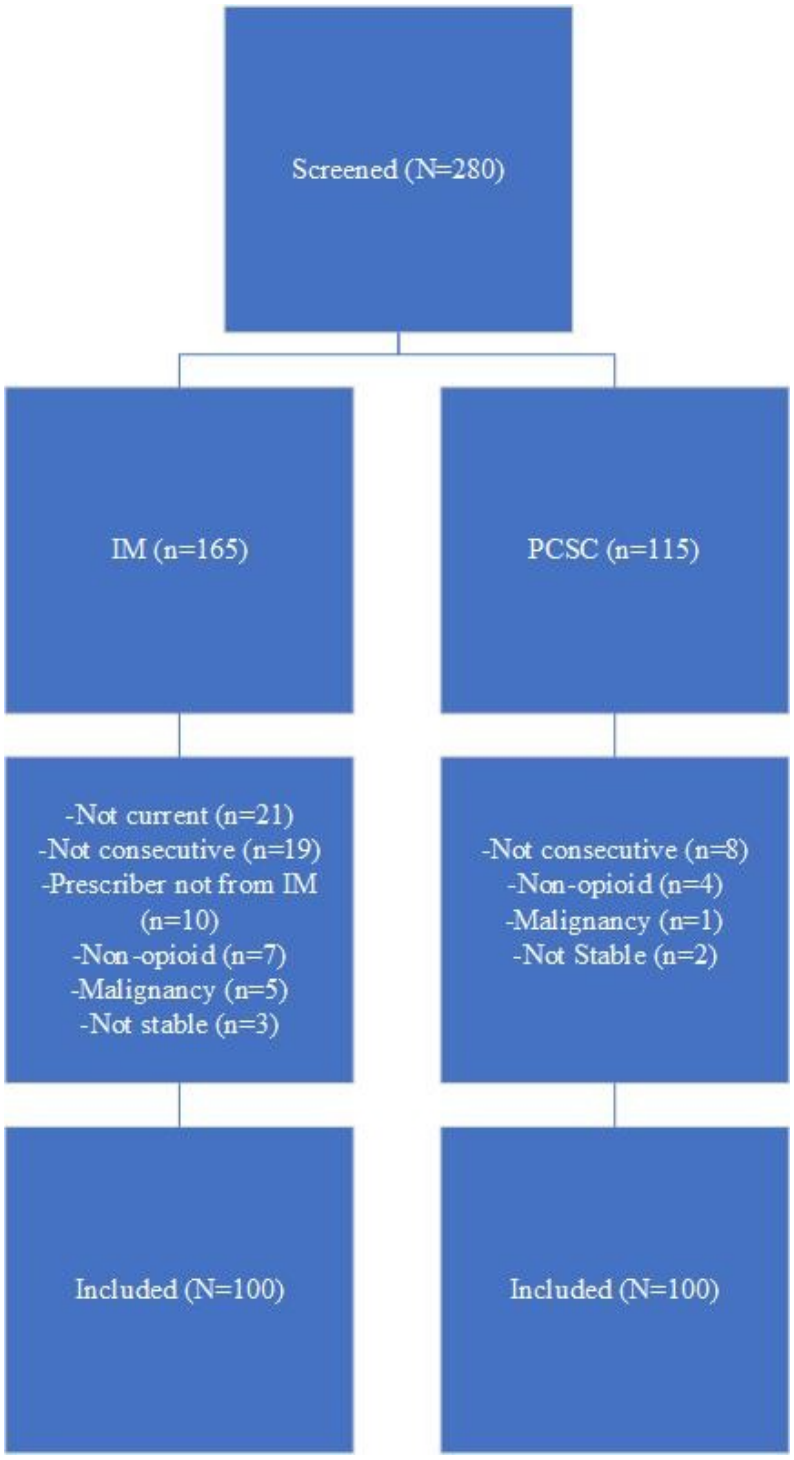
* denotes analysis via T-test;
† regimens ≥ 50 and < 90 MME were considered moderate risk while regimens ≥ 90 MME or any MME plus a benzodiazepine were defined as high risk;
‡ patients were considered to be candidates for naloxone if they met any of the following criteria: regimen dose ≥50 MME, concomitant benzodiazepine use, or history of substance abuse;
§ denotes statistical significant where p<.05;
‖ denotes analysis via Wilcoxon rank sum test;
¶ denotes analysis via Fisher's exact test; all other analyses were conducted via Chi-square tests

**Table 2. Identified Organ Dysfunction**

| Organ Dysfunction Identified | Control Group n=100 | Intervention Group n=100 |
|---|---|---|
| Hepatic, n (%) | | |
| Hepatitis C | 6 (6) | 0 (0) |
| Non fatty liver disease | 1 (1) | 0 (0) |
| Renal, n (%) | | |
| Chronic kidney disease | 22 (22) | 12 (12) |
| End stage renal disease | 2 (2) | 4 (4) |
| Respiratory (excluding obstructive sleep apnea and central sleep apnea), n (%) | | |
| Chronic Obstructive Pulmonary Disorder | 13 (13) | 9 (9) |
| Restrictive lung disease | 2 (2) | 0 (0) |
| Respiratory failure | 1 (1) | 1 (1) |
| Chronic restrictive lung disease | 4 (4) | 1 (1) |
| Chronic airway obstruction | 1 (1) | 1 (1) |
| Pulmonary fibrosis with mixed obstructive and restrictive lung disease | 0 (0) | 1 (1) |

Analyses were conducted via Chi-square tests.

## FIGURES




583
584
585 **Figure 1.** Patient Selection. Patients from the Internal Medicine (IM) Clinic and Pharmacy
586 Controlled Substance Clinic (PCSC) were screened for a planned inclusion of 100 patients per
587 arm.

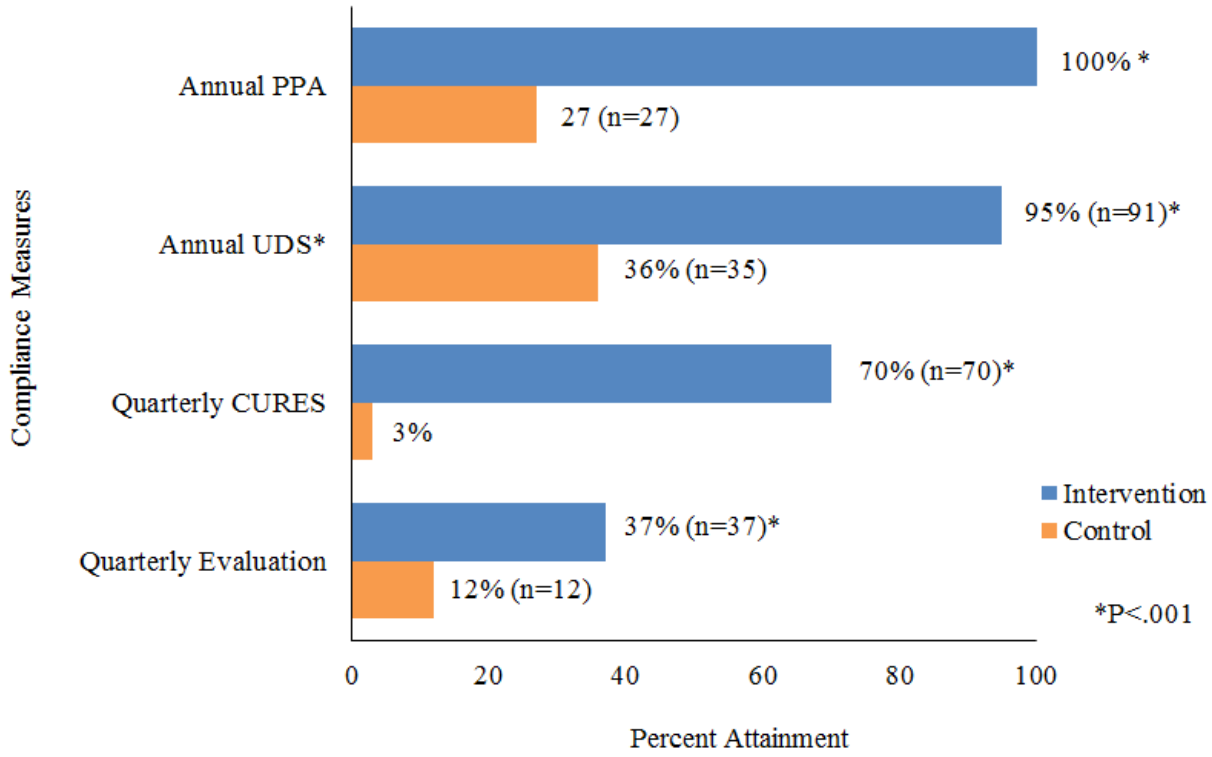



**Figure 2.** Percent attainment of individual measures in the intervention group pre- and post-Pharmacy Controlled Substance Clinic (PCSC) enrollment
*For Annual urine drug screen (UDS), N=96 as four patients were unable to produce urine for a UDS and thus excluded from the specific metric analysis.
Patient provider agreement (PPA), State of California prescription drug monitoring program (CURES)

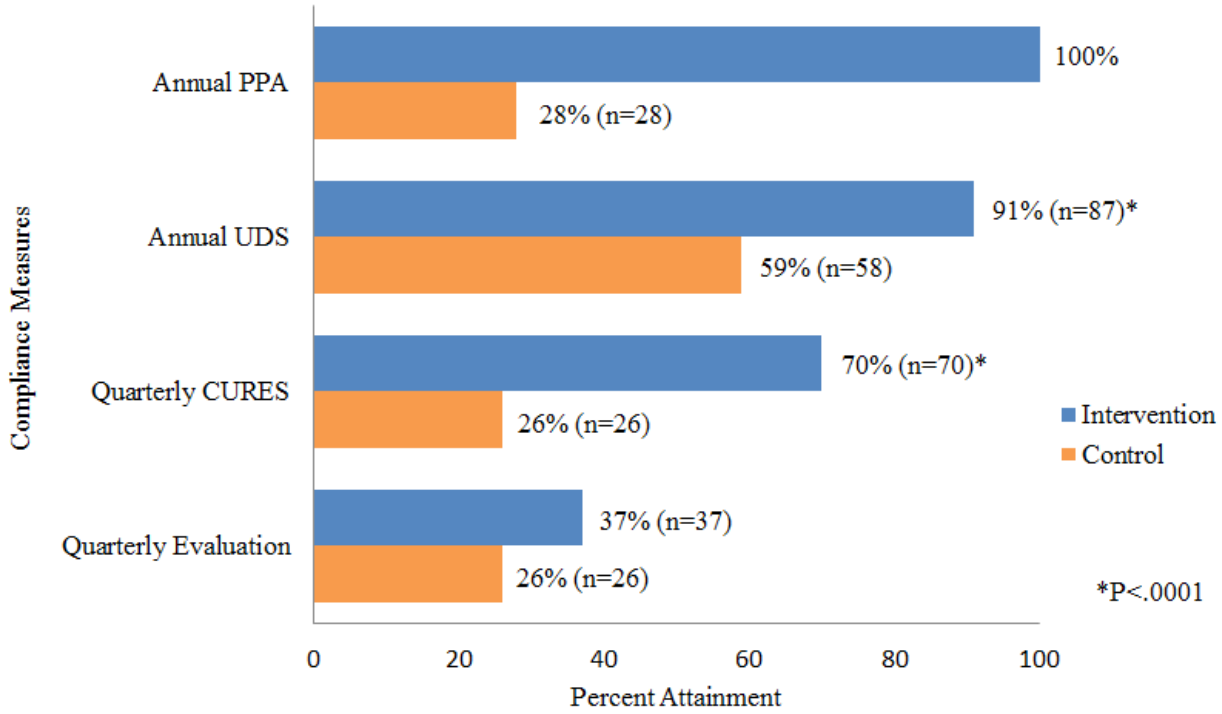



**Figure 3.** Percent attainment of individual measures
*For annual urine drug screen (UDS), N=98 in the control group and N=96 in the intervention group as six patients were unable to produce urine for a UDS and thus excluded from the specific metric analysis.
Patient provider agreement (PPA), State of California prescription drug monitoring program (CURES)