Contemporary Clinical Trials 112 (2022) 106650

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

The protocol of the Application of Economics & Social psychology to improve Opioid Prescribing Safety trial 2 (AESOPS-2): Availability of opioid harm

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ARTICLE INFO

Keywords:
Opioid use disorder
Randomized control trial
Behavioral economics
Nudges

ABSTRACT

Background: High levels of opioid prescribing in the United States has resulted in an alarming trend in opioid-related harms. The objective of Trial 2 of the Application of Economics & Social psychology to improve Opioid Prescribing Safety (AESOPS-2) is to dampen the intensity and frequency of opioid prescribing in accordance with the Centers for Disease Control and Prevention recommendation to "go low and slow". We aim to accomplish this by notifying clinicians of harmful patient outcomes, which we expect to increase the mental availability of risks associated with opioid use.

Methods: The trial is multi-site. Random assignment determines if prescribers to persons who suffer an opioid overdose (fatal or nonfatal) learn of this event (intervention) or practice usual care (control). Clinicians in the intervention group receive a letter notifying them of their patient's overdose. The primary outcome is the change in clinician weekly milligram morphine equivalent (MME) prescribed in a 6-month period before and after receiving the letter. Additional outcomes are the change in the proportion of patients prescribed at least 50 daily MME and in the proportion of patients referred to medication assisted treatment. Group differences in these outcomes will be compared using an intent-to-treat difference-in-differences framework with a mixed-effects regression model to estimate clinician MME.

Discussion: The AESOPS-2 trial will provide new knowledge about whether increasing prescribers' awareness of patients' opioid-related overdoses leads to a reduction in opioid prescribing. Additionally, this trial may better inform how to reduce opioid use disorder and opioid overdoses by lowering population exposure to these drugs.

Trial registration: ClinicalTrials.gov: NCT04758637

1. Background

Much of the increase in opioid prescribing rates from 1999 until the past decade was driven by a liberal attitude toward prescribing opioids for non-cancer pain [1,2]. Opioids carry significant risks of overdose and addiction, and there is evidence that non-opioid alternatives are safer and as effective [3]. Opioid harms are a concern. In 2019, there were 14,139 prescription opioid overdose deaths in the US [4]. The costs of

Abbreviations: Abbreviation, **Term**; AESOPS, Application of Economic and Social psychology to improve Opioid Prescribing Safety; CDC, Centers for Disease Control and Prevention; ED, Emergency department; IDPH, Illinois Department of Public Health; MME, Milligram morphine equivalent.

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https://doi.org/10.1016/j.cct.2021.106650
Received 9 December 2020; Received in revised form 29 November 2021; Accepted 4 December 2021
Available online 8 December 2021

prescription opioid adverse outcomes are staggering. Aggregate costs for prescription opioid harms are estimated at over $78.5 billion (in 2013 USD), and almost 25% of the aggregate economic burden is publicly funded (for instance, through Medicaid, Medicare, and veterans' programs) [5].

In 2016, the United States Centers for Disease Control and Prevention (CDC) issued the "CDC Guideline for Prescribing Opioids for Chronic Pain". The guideline encourages the use of alternatives to opioids and other practices that minimize harm to patients [6]. Despite its evidence-based recommendations, primary care clinicians, who prescribe 45% of all opioid prescriptions in the US, report practical challenges in implementing the guideline [7]. The dynamics of opioid use make following guidelines difficult. Since opioid analgesia from a given dose declines with chronic use due to tolerance, doses end up increasing the chance of harm. Over time, the primary benefit of opioids for many patients is the avoidance of withdrawal. As patients become dependent on opioids, they may misconstrue the easing of withdrawal hyperalgesia that occurs with the immediate consumption of opioids as ongoing effectiveness, and they may become reluctant to stop opioids [8]. More cautious opioid prescribing (including fewer new starts, avoidance of high doses, and slow, collaborative tapers for those already on high dose long-term therapy) may improve the balance of benefits and harms for patients. The risk of a patient forming a dependence or experiencing other downstream harms is insidious. To become a more cautious prescriber, a clinician may need to be informed that opioid risks are present and relevant to his or her own patients.

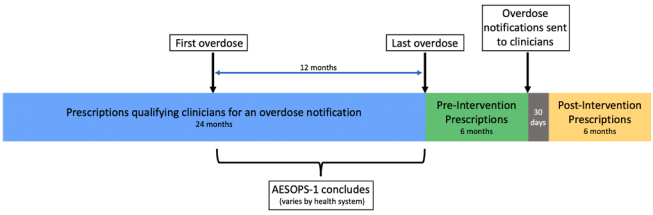
Prior work has suggested that clinicians may judge risk to patients as greater after information about a patient's fatal overdose is available to them [9]. Of course, not all clinicians prescribe to patients who suffer a fatal overdose, so the question remains whether providing feedback concerning nonfatal overdoses will have a similar impact on prescribing clinicians. Thus, the Application of Economics & Social psychology to improve Opioid Prescribing Safety (AESOPS-2) trial's objective is to test whether or not providing feedback to clinicians on both fatal and nonfatal overdoses results in more judicious prescribing of opioids. Specifically, we will measure the change in clinician weekly MME prescribed to all of their patients in 6-month periods before and after receiving overdose feedback letters. The secondary outcome is the change in the proportion of patients prescribed at least 50 daily MME.

2. Materials and methods

2.1. Overview

AESOPS-2 is a multisite, overdose-cluster randomized trial. Each overdose cluster consists of the group of physicians who prescribed opioids or DEA-scheduled drugs known to be dangerous in interaction with opioids (e.g., benzodiazepines) to the patient who had a fatal or nonfatal drug overdose. The cluster will be randomized to the control or intervention group to prevent treatment contamination.

Clinicians notified of their patient's overdose will be compared to a control group receiving no notification of their patient's overdose. All letters will be sent at one time point after data are gathered for all overdoses occurring in the preceding 12-month period and after 6 months of prescription data is gathered. The change in weekly MMEs prescribed will be measured as the difference between prescriptions written in the 6 months before and the 6 months after the intervention, with a 1-month washout period (Fig. 1). Clinicians in both study groups may receive electronic health record alerts discouraging the inappropriate prescribing of opioids during patient appointments as part of a concurrent trial, AESOPS Trial 1 (AESOPS-1) [10]. These alerts aim to encourage primary care clinicians to adhere to the "CDC Guideline for Prescribing Opioids for Chronic Pain" during visits in which a prescriber begins an order for an opioid. Clinician exposure to AESOPS-1 interventions will be recorded and included as an independent variable in our analysis. All study procedures are approved by the Los Angeles



2.2 Study sample and randomization procedures

Fig. 1. Study timeline.

County Institutional Review Board (2021–08-962).

2.2. Study sample and randomization procedures

The AESOPS-2 trial will take place in 3 diverse health systems in the U.S. – Northwestern Medicine, AltaMed Health Services, and The Children's Clinic. Northwestern Medicine is a regional health system affiliated with an academic medical center located in the Chicago region of Illinois and includes 60 primary care clinics that contain 387 clinicians with 12,552 patients using chronic opioid therapy for noncancer pain—on opioids for greater than three months. AltaMed Health Services and The Children's Clinic are in Los Angeles, California, representing private and safety-net health systems, respectively. AltaMed Medical Group has 35 clinics with 134 clinicians with 17,674 such patients. The Children's Clinic has 6 to 9 clinics containing 26 clinicians with 3307 such patients. In total, the number of noncancer pain outpatient visits where opioids are prescribed in the clinics included in the study is greater than 300,000 annually. Assuming patients on chronic opioid therapy are receiving 50 MME or more per day, we estimate more than 235 overdoses will occur during our 12-month observation period [11].

Overdose clusters are the units of randomization in this study. A cluster consists of all clinicians who prescribed one or more of the included scheduled drugs to the patient in the year prior to the overdose. Clustering at this level reduces contamination that might occur if individual clinicians treating the same patient are placed in different experimental groups. We will randomize clusters, stratified by the health system which defines the cluster in the year prior to the overdose event. Clinicians who practice at multiple clinics will be assigned to the clinic at which the majority of their visits occurred in the year prior to the overdose event. If clinicians belong to more than one cluster (have multiple patients with opioid-related overdoses), they will be randomly assigned to one of those patients and placed in the corresponding study group. If clinicians belonging to more than one cluster are randomized to the intervention group, they will only receive an overdose notification regarding the one patient to whom they were randomly assigned.

Randomization will be carried out using the statistical computing language R. For each of the 9 combinations of the stratification levels, we will construct numbered lists of overdose clusters. We will then employ the sample function in R to return a random permutation of each numbered list. For each list, we will draw a sample representing the largest number of overdose clusters within each clinic organization that is divisible by two (the number of study groups). We will then assign each randomly permuted cluster to a study group, repeating this process until clusters have filled the two groups of the study in equal measure. Because the number of clusters available to fill each stratification level may not always be divisible by two, these remaining clusters will be randomized to conditions separately. Allocation will be concealed until after the study groups are assigned.

2.3. Inclusion and exclusion criteria

Participants are clinicians who will be enrolled from clinical sites in

Illinois and California. Clinicians are eligible for inclusion if: 1) they prescribed a qualifying scheduled drug to a patient in the 12 months prior to their nonfatal or fatal overdose 2) the patient is 18 years old or older at the time of the overdose, 3) they practice within a health system enrolled in the study, and 4) the overdose occurs during the 12-month observation period. Qualifying prescriptions are from the CDC's National Center for Injury Prevention and Control and are listed in **Appendix A** [12]. Such prescriptions include those for one of the following scheduled drugs: opioids, benzodiazepines, muscle relaxants, or sleep aids. Prescriptions to patients in hospice or with active cancer will be excluded from the primary analysis. Cancer exclusions (ICD-10 codes) are listed in **Appendix A**. We will request a waiver of consent for clinician randomization.

2.4. Interventions

Overdose clusters will be randomized to the overdose notification group or the control group. Clinicians in the control group will receive guideline education in the form of the CDC pocket guide and no notification of a patient overdose event [13]. At Northwestern Medicine, clinicians in the intervention group receive a letter notifying them of their patient's fatal or nonfatal emergency department (ED) overdose. At AltaMed Health Services and The Children's Clinic, clinicians in the intervention group receive a letter notifying them of their patient's nonfatal ED overdose. We will identify overdoses from electronic health record data from emergency departments and state vital records. If randomized to the overdose notification group, physicians who prescribed a qualifying prescription to the deceased or surviving patient in the year prior to their overdose will be informed of the overdose via letter. The letters will alert prescribers to the patient's opioid-related overdose, recommend the use of their state's PDMP, and list evidence-based interventions to lower opioid-related overdoses. Sample letters are shown in **Appendices B and C**.

As noted above, notifying physicians of their patient's death via a letter has been previously shown to reduce opioid prescribing significantly [9]. People rely upon vivid, recent and otherwise easy to retrieve knowledge from their memory when judging probabilities and making decisions. The more easily people can call an instance of some event to mind—the more *available* it is to them—the more likely they are to judge the event to occur. The influence of availability on decision making has been identified in numerous experiments [14–17]. Moreover, when negative emotions are associated with an activity, people are influenced by the affect heuristic to judge the activity's risks as higher and benefits as lower [18]. Thus, learning of a prior patient's overdose may cause clinicians to be more wary of a future overdose when prescribing opioids, benzodiazepines, muscle relaxants, or sleep aids.

We will have a participant debrief following completion of the study. Clinicians will be sent a debriefing statement which contains the following information: a description of the nature and purpose of the study, specification of what data were collected about participants, and instructions for participants to communicate their desire for their data to be removed from the study. Additionally, closing interviews with a sample of nonfatal overdose clusters of clinicians randomized to the intervention group will be conducted upon trial completion. This qualitative assessment will be used to assess the clinician's overall experience, and if and how their relationships with patients who experienced a nonfatal overdose were impacted.

2.5. Measures

The primary outcome is the change in weekly morphine milligram equivalent (MME) ordered by clinicians to all of their patients pre- and post- letter intervention. Prescription opioids will be converted to MME using publicly available formulas published by the CDC [19]. Weekly MME for each clinician will be measured in the pre- and post-intervention periods as the average milligram morphine equivalents written to all of their patients in a 7-day period. The pre-intervention period begins after the 12-month observation period and consists of the 6 months before the date on which the letter is sent. The post-intervention period consists of the 6 months following the 30-day washout period after the date on which the letter is sent. The 30-day washout period is used to account for differential time until receipt and opening of the notification envelope. Prescriptions written to patients who experience an overdose will be excluded from the outcome measure.

A secondary outcome is the change in the proportion of patients prescribed at least 50 daily MME. The number of patients with a prescription of at least 50 MME per day written by the clinician represents the numerator and the total number of patients with an opioid prescription written by the clinician is the denominator for the secondary outcome during each 6-month study period. Additional outcomes include buprenorphine referrals for medication assisted therapy and access rates for referral links included in the letter. We will collect information on potential patient effect modifiers, such as prior mental health or substance use disorder diagnoses, from electronic health record data.

2.6. Data collection and management

In addition to the collection of electronic health record data, this study will collect primary data from the medical examiner's office, state vital records, and insurance claims. Opioid-related death data will be gathered from the Illinois Department of Public Health (IDPH). The process of gathering nonfatal overdose data resulting in ED visits will vary by clinic organization. Nonfatal overdose information will be collected from ED data for Northwestern Medicine and claims data for AltaMed Health Services and The Children's Clinic. Nonfatal overdose diagnoses (ICD-10 codes) are listed in **Appendix A**. Prescription data will be collected from each health system's electronic health record data.

For fatal overdoses, the retrieval of death data will occur quarterly in Illinois. Study personnel will send the IDPH a list of identifiers for patients who received an opioid prescription at a participating clinic. IDPH will use this information to identify if the patient is deceased. If so, IDPH will send back the date of death, cause of death, and whether the death was opioid-related via a secure file transfer process to Northwestern Medicine. IDPH will not send back information if a patient is not deceased. Analysts at Northwestern Medicine will link opioid-related decedents to identify opioid prescriptions and prescribers. In both states, clinicians of patients randomized to the intervention group will receive a patient overdose notification.

Proper data management is critical to this study since the primary outcomes will be captured from electronic health record or claims. All data collected in this study will be in electronic format. Each overdose will be assigned a unique identifier for the creation of the de-identified analytic dataset.

2.7. Statistical analysis plan

We will use means and medians for continuous measures for sample descriptive statistics, frequencies for count data and standard deviations, and interquartile ranges for variance. We will evaluate changes in opioid prescribing rates by group using an intent-to-treat difference-in-differences regression model on clinician morphine equivalent weekly dose. The coefficient for the group assignment and time interaction, also known as the difference-in-differences estimator, denotes MME's change for prescribers in the intervention group compared to prescribers in the control group over time. The use of a linear mixed-effects hierarchical knotted spline regression model offers a flexible way to accommodate non-linear trends in prescribing by group before and after introducing the intervention. This model places a knot at the intervention start date allowing slopes before and after the introduction

of the intervention to vary for each group. If the outcome of interest, weekly MME, is not normally distributed, then it will be natural log-transformed. If we have an excess of data clustering at zero, indicating the weeks during which a physician wrote no opioid prescriptions, we will consider using a censored regression. We will estimate the association of letter assignment and natural log-transformed weekly MME prescribed using the following model:

$$log(MME)_{ijk}^{*} = \beta_1 + \beta_2 Time_{ij} + \beta_3\left(Time_{ij} - t^{*}\right)_{+} + \beta_4 Group_i + \beta_5\left(Time_{ij}{*}Group_i\right) + \beta_6 Overdose\ Type_k + \beta_7\left(\left(Time_{ij} - t^{*}\right)_{+}{*}Group_i\right) + \beta_8\left(\left(Time_{ij} - t^{*}\right)_{+}{*}Overdose\ Type_k{*}Group_i\right) + \beta_9 Trial_i + \eta + \delta_{ik} + error \quad (1)$$

where $\log(MME)_{ij}$* denotes the censored dependent variable for clinician i in week j, $Time_{ij}$ is the study week indexed by j, t* is the spline knot for the start of the intervention, $(Time_{ij}$ - t*$)_+$ is a truncated line function that is equal to $(Time_{ij}$ - t*$)_+$ when $Time_{ij} > t^*$ and 0 otherwise to allow for nonlinear trends in prescribing following the intervention, $Group_i$ is dichotomous for the overdose notification intervention group, $Trial_i$ is dichotomous and denotes if clinician i was randomized to the intervention group in a simultaneous trial of AESOPS (AESOPS-1), Overdose $Type_k$ is dichotomous for a fatal overdose, η is the clinic random effect, and δ_{ik} is the random effect for each i clinician who prescribed to patient k who suffered an overdose.

The simplified version of the logistic regression model for our secondary outcomes is shown in Eq. 2:

$$\pi_{ijk} = \beta_1 + \beta_2 Time_{ij} + \beta_3\left(Time_{ij} - t^{*}\right)_{+} + \beta_4 Group_i + \beta_5\left(Time_{ij}{*}Group_i\right) + \beta_6 Overdose\ Type_k + \beta_7\left(\left(Time_{ij} - t^{*}\right)_{+}{*}Group_i\right) + \beta_8\left(\left(Time_{ij} - t^{*}\right)_{+}{*}Overdose\ Type_k{*}Group_i\right) + \beta_9 Trial_i + \eta + \delta_{ik} + error \quad (2)$$

where π_{ij} is the proportion of interest for clinician i, $Time_{ij}$ is the study week indexed by j, t* is the spline knot for the start of the intervention, $(Time_{ij}$ - t*$)_+$ is a truncated line function that is equal to $(Time_{ij}$ - t*$)_+$ when $Time_{ij} > t^*$ and 0 otherwise to allow for nonlinear trends in prescribing following the intervention, $Group_i$ is dichotomous for the overdose notification intervention group, $Trial_i$ is dichotomous and denotes if clinician i was randomized to the intervention group in a simultaneous trial of AESOPS (AESOPS-1), Overdose $Type_k$ is dichotomous for a fatal overdose, η is the clinic random effect, and δ_{ik} is the random effect for each i clinician who prescribed to patient k who suffered an overdose. For the analysis of the change in the proportion of clinician i's patients prescribed 50 MME or more, π_{ij} in Eq. (2) measures the number of patients that are prescribed 50 daily MME or more divided by the number of patients that are prescribed an opioid by clinician i in week j. For the analysis of the change in the proportion of clinician i's patients referred to buprenorphine for medication assisted treatment, π_{ij} in Eq. (2) measures the number of patients with their first buprenorphine prescription in the numerator divided by the number of patients that are prescribed an opioid by clinician i in week j. The frequency of accessing medication assisted treatment referral links will be evaluated over time.

2.8. Power calculations

We calculated the sample size needed to achieve 0.8 statistical power for a one-tailed *t*-test at the 0.05 level of significance for a 4.8% change in the primary outcome. We chose this effect size based on 50% of the effect size in the previous availability of opioid harms study [9]. We assumed an intraclass correlation coefficient of 0.055 for clinicians and an average of 2.5 clinicians in an overdose cluster, based on half of the average number of prescribers per opioid-related decedent in the previous study [9]. 50% of the average number of prescribers per opioid-related decedent was assumed since this study will only include prescribers from participating health systems, instead of all prescribers to the patient who experienced an overdose. Weimer found high-dose opioid users were prescribed 263 (± 35) MMEs per day [20]. We conducted our analysis assuming the mean dose for high-dose opioid users in 2021 is half of Weimer's findings (131.5 MME/day) and variance is a constant proportion of the mean. Using a cluster-adjusted formula for estimating sample size, we found that with 206 clinicians (approximately 83 overdoses), we will have greater than an 80% chance to detect a 4.8% change in opioid dosage [21].

2.9. Safety assessment plan

The NIH has established a Data Safety and Monitoring Board for AESOPS Trials 1 and 2. The board consists of individuals with expertise in opioids, overprescribing, biostatistics or research methods. When notified of an unanticipated event following the intervention, the board will convene and make a decision as to whether the study should continue. Data for patients who abruptly stopped chronic opioid therapy, had an emergency department eligible study visit with a diagnosis that could represent a serious complication of untreated pain, died, or left the health system will be extracted from study site electronic health records and reported to the Data Safety and Monitoring Board. In accordance with CDC guidelines, adverse events are defined as an abrupt discontinuation of opioids for persons whose most recent prescription exceeds 49 MME daily dose; or as reported to study staff [22]. If there is a significant difference in the prevalence of these adverse events or overdoses between the treatment and control groups, the differences will be reported to Data Safety and Monitoring Board and in the publication of the study results. Annual reports of our safety measures will be delivered to our Data Safety and Monitoring Board.

3. Discussion

Through AESOPS-2, we will evaluate the impact of the availability of harms intervention on opioid prescribing. Clinicians from more than 101 clinics in 3 clinical organizations will be randomized to the letter intervention or control group. Those randomized to the intervention group will receive a letter notifying them of a patient's opioid-related overdose. We hypothesize that clinicians randomized to the intervention group will have lower opioid prescribing after receiving the intervention, measured as MME/day, compared to the control group, as has been shown previously with prescribers to decedents [9]. This trial will be the first to evaluate the impact of a feedback letter nudge on opioid

prescribing when sent to prescribers of patients with nonfatal overdoses. The inclusion of prescribers to patients with nonfatal overdoses broadens this scalable and cost-effective intervention's reach and potential impact.

AESOPS-2 will be pivotal in understanding and developing methods to increase adherence to the CDC guideline and Oregon Pain Guidance pain management guidelines. Our study aims to increase prescribers' assessment of risk but does not seek to increase the accuracy of risk assessment given the limited accuracy and effectiveness of clinical tools in identifying patients at low versus high risk of opioid misuse or abuse [23]. Through our secondary analysis of the change in the proportion of patients prescribed at least 50 daily MME, we can evaluate how the feedback letter nudge alters high-risk opioid prescribing. Taken together, these findings will contribute to a better understanding of how to prevent future incidents of opioid use disorder and opioid overdoses by reducing opioid exposure in clinical populations.

A potential limitation of this study is imperfect adherence to the assigned intervention. This can manifest in clinicians not reading or receiving the letters or sharing information about an overdose event across groups. Another limitation of this study is its exclusion of patients with nonfatal overdose events who do not present to the emergency departments of Northwestern Medicine, AltaMed Health Services, or The Children's Clinic. Additionally, insurance coverage for alternative treatments of chronic non-cancer varies by a patient's insurance plan. To address this limitation, we will evaluate if the share of a clinician's patients by insurance type is significantly associated with the clinician's average weekly MME ordered. To address potential confounding of the association between the AESOPS-2 intervention and opioid prescribing changes, our models will control for clinic-level variation, clinician-level variation, and clinician exposure to AESOPS-1 interventions.

Author declaration

1. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.
2. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.
3. We confirm that neither the entire paper nor any of its content has been submitted, published, or accepted by another journal. The paper will not be submitted elsewhere if accepted for publication in the Journal.
4. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.
5. We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.
6. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Funding

This work was supported by National Institutes of Health 4R33AG057395-03.

Appendix A. Qualifying prescriptions and diagnoses exclusions

Qualifying Prescriptions	**Link**
Excluded Cancer Diagnoses	**Link**
Nonfatal Overdose Diagnoses	**Link**

Appendix B. Sample Death Notification Letter to Clinician

Date

Dear *(Name of Prescriber)*,

This letter is to inform you that your patient, {Name, Date of Birth}, died on {Date}. Prescription opioid overdose was either the primary cause of death or contributed to the death.

Northwestern Medicine is tracking outcomes for patients on opioids and other scheduled drugs.

A significant proportion of overdoses are due to the combination of opioids with a sedative medication. Patients may obtain legitimate prescriptions for opioids, benzodiazepines, muscle relaxants, and sleep aids from more than one prescriber. When taken in any combination, these medications put patients at greater risk of overdose and death. Many fatal and non-fatal overdoses are a result of long-term therapeutic prescribing or of combined prescription medications with drugs obtained from other sources.

Our aim is to alert clinicians to the potential dangers of opioid medications and how common death from misuse of these medications is in Chicago and throughout Illinois.

Northwestern Medical Group would like to remind you that Illinois has a prescription drug monitoring program called the Illinois Prescription Monitoring Program (ILPMP) which *helps prescribers avoid prescribing controlled substances when they are likely to do more harm than good.*

ILPMP contains information about whether and when other clinicians have prescribed controlled substances to your patient within the last 12/36 months. With few exceptions, prescribers are

required by state law to check the ILPMP when prescribing opioids. **Review of the ILPMP.**

could alert you to problematic medication usage, potential addiction or diversion, and help inform safe medication prescribing and monitoring.

This information is available through Epic and at {ILPMP link}.

You may show your commitment to being a safe prescriber by using the following evidence-based interventions to lower overdose rates:

1. **Avoid co-prescribing** an opioid and a benzodiazepine. Opioids and benzodiazepines can have additive central nervous system depressant effects.

2. **Avoid opioid prescribing for chronic pain and avoid/minimize opioid prescribing for acute pain.** According to the Centers for Disease Control and Prevention (CDC), clinicians should avoid opioids for chronic pain, and when necessary for acute pain, start with the lowest effective dose of immediate-release opioids. Three days or less is often sufficient to address acute pain. Opioids should not be considered first-line or routine therapy for chronic pain.

3. **Taper opioids to safer doses.** The CDC recommends that for patients already on long-term high-dose opioid therapy, taper to a dose that is lower than 50 morphine milligram equivalents (MME) and consider slow opioid tapers as well as pauses in the taper if needed for long-term users.

4. **Avoid "the 90-day cliff."** One California study found that nearly 70% of patients who died of prescription-related overdoses were prescribed scheduled drugs for 3 consecutive months.[1] The CDC recommends opioids should be discontinued if benefits do not outweigh risks (if realistic goals for pain and function have not been met).

5. **The CDC recommends prescribing naloxone** to patients on higher than 50 MME of opioids per day.

This letter is meant to be informative only and there is no expectation of a reply. We understand that learning of your patient's death can be difficult. We hope that you will take this as an opportunity to join us in preventing future deaths from drug overdose.

Sincerely,

Quality Medical Officer at Northwestern Medicine

Appendix C. Sample Nonfatal Overdose Notification Letter to Clinician

Date.

Dear *(Name of Prescriber)*,

This is a courtesy notification to inform you that your patient, {Name, Date of Birth}, visited the ED on {Date} with an opioid overdose.

{Institution Name} is tracking outcomes for patients on opioids and other scheduled drugs. A significant proportion of overdoses are due to the combination of opioids with a sedative medication. Patients may obtain legitimate prescriptions for opioids, benzodiazepines, muscle relaxants, and sleep aids from more than one prescriber. When taken in any combination, these medications put patients at greater risk of overdose and death. Many fatal and non-fatal overdoses are a result of long-term therapeutic prescribing or of combined prescription medications with drugs obtained from other sources.

{Institution Name} would like to remind you that Illinois/California has a prescription drug monitoring program called the Illinois Prescription Monitoring Program (ILPMP)/ California Substance Utilization Review and Evaluation System (CURES) which *helps prescribers avoid prescribing controlled substances when they are likely to do more harm than good.*

ILPMP/CURES contains information about whether and when other clinicians have prescribed controlled substances to your patient within the last 12/24 months. With few exceptions, prescribers are required by state law to check ILPMP/CURES when prescribing opioids. **Review of ILPMP/ CURES alerts safe prescribers to problematic medication usage, and potential addiction.** This information is available through Epic and at {ILPMP/CURES link}.

Emergency department visits for an overdose strongly suggest a diagnosis of opioid use disorder. The one-year mortality following an opioid overdose is high at 10%. If your patient's overdose was due to opioid use disorder, medications for opioid use disorder, such as buprenorphine/ naloxone, can be safely prescribed in any setting of care and greatly reduce mortality risks through prevention of future overdose. Medications for opioid use disorder improve your patients' chances of recovery.

You may show your commitment to being a safe prescriber by using the following evidence-based interventions to lower overdose rates:

1. **Avoid co-prescribing** an opioid and a benzodiazepine. Opioids and benzodiazepines can have additive central nervous system depressant effects.

2. **Avoid opioid prescribing for chronic pain and limit opioid prescribing for acute pain.** According to the Centers for Disease Control and Prevention (CDC), clinicians should avoid opioids for chronic pain, and when necessary for acute pain, start with the lowest effective dose of immediate-release opioids. Three days or less is often sufficient to address acute pain. Opioids should not be considered first-line or routine therapy for chronic pain.

3. **Taper opioids to safer doses.** The CDC recommends that for patients already on long-term high-dose opioid therapy, taper to a dose that is lower than 50 morphine milligram equivalents (MME) and that slow opioid tapers as well as pauses in the taper may be needed for long-term users. Discuss the benefits and risks of continued opioid therapy with patients and collaboratively form tapering plans specific to the patients' goals and concerns.

4. **Avoid "the 90-day cliff."** One California study found that nearly 70% of patients who died of prescription-related overdoses were prescribed scheduled drugs for 3 consecutive months.[1] The CDC recommends opioids should be discontinued if benefits do not outweigh risks (if realistic goals for pain and function have not been met).

5. *(For Northwestern Medicine version)* The CDC **recommends prescribing naloxone** to patients on higher than 50 MME/day of opioids.

5. *(For AltaMed Health Services and The Children's Clinic versions)* **CA law requires offering a prescription for naloxone** to patients with a history of an overdose, has an opioid use disorder or other substance use disorder, is prescribed an opioid concurrent with a benzodiazepine, or is taking higher than 90 MME/day of opioids.

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6. **Prescribed medications for opioid use disorder.** Clinicians should offer medications for opioid use disorder, such as buprenorphine/naloxone, to their patients with opioid use disorder. Physicians, physician assistants, and advanced practice nurses can file a waiver to prescribe buprenorphine for the indication of opioid use disorder by visiting the SAMHSA website (link) or by calling SAMHSA at 866–287-2728. On April 28, 2021, SAMHSA announced that it will waive the training requirement for physicians, physician assistants, and advanced practice nurses to become waivered to prescribe buprenorphine for the indication of opioid use disorder. *(For Northwestern Medicine version)* Contact {Addiction Medicine Department at Institution Name} for further information about initiating treatment for opioid use disorder. *(For AltaMed Health Services and The Children's Clinic versions)* Further, a list of local community health centers offering medications for addiction treatment is available via (http://losangelesmat.org) and a call center available to link patients with Medi-Cal and without health insurance to addiction treatment is available via the LA County Substance Abuse Services Helpline (844–804-7500).

This letter is meant to be informative only and there is no expectation of reply. We understand that learning of your patient's overdose can be difficult. We hope that you will join us in our effort to prevent future drug overdoses. Please take this as an opportunity to talk with your patient and perhaps other patients in your practice who may be at-risk.

Sincerely,

(For Northwestern Medicine version) Quality Medical Officer

(For AltaMed Health Services and The Children's Clinic versions) Los Angeles County Health Officer

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