Post-Marketing Requirement (PMR) Study Results for Long-term Use of Extended-Release / Long-Acting Opioids in Patients with Chronic Pain

May 5, 2025

Anesthetic and Analgesic Drug Products Advisory Committee

Drug Safety and Risk Management Advisory Committee

Opioid Post-marketing Consortium (OPC)

Opioid PMR Consortium (OPC) Introduction and PMR Overview

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Adjunct Professor, Epidemiology

Harvard T.H. Chan School of Public Health

Professional Background

- Connection with PMR 3033 goes back to early design of studies
- Principal in the research firm WHISCON
- Advised the OPC
- Headed coordinating center for Study 3033-2, the large insurance-claims-based cohort
- Served as lead investigator for Study 3033-8, one of the doctor/pharmacy shopping studies

ER/LA Opioid Postmarketing Requirement Studies

PMR #	Study Description	Study Purpose
3033-1	Prospective/cross-sectional study of misuse, abuse, and addiction via POMAQ and PRISM-5-OP	Assess incidence and risk factors for misuse, abuse, addiction, overdose, and death among participants prescribed ER/LAs
3033-2	Retrospective study of overdose and death in health records, insurance claims, death records	
3033-3	Validation studies of POMAQ instrument to measure misuse and abuse: Qualitative	Develop and validate measures of misuse, abuse, and addiction
3033-4	Validation studies of POMAQ instrument to measure misuse and abuse: Quantitative	
3033-5	Validation study of PRISM-5-OP instrument to measure addiction	
3033-6	Validation of codes to identify opioid-related overdose in databases used in Study 3033-2	Validate coded medical terminologies to identify abuse/addiction, overdose, and death in databases
3033-7	Validation of diagnostic algorithm to measure abuse/addiction in administrative claims	
3033-8	Cross-sectional study of doctor/pharmacy shopping in a prescription database	Define and validate "doctor/pharmacy shopping" as outcome suggestive of misuse, abuse, and addiction
3033-9	Survey study of doctor/pharmacy shopping in a prescription database vs self-reports	
3033-10	Study of doctor/pharmacy shopping using medical record review	
3033-11	12-Month, randomized, placebo-controlled, double-blind, parallel-group clinical trial in patients with chronic pain*	

***Not part of today's discussion; ER/LA: extended release or long-acting; POMAQ: prescription opioid misuse and abuse questionnaire**

Studies Designed and Conducted with Independent Research Institutions

- Protocols collaboratively developed and agreed on after public hearings and discussions with FDA
- Experienced research centers led data collection and performed analyses
  - Kaiser Permanente Northwest (KPNW)
  - HealthCore
  - Optum Epidemiology
  - Vanderbilt University Medical Center (VUMC)
  - World Health Information Science Consultants (WHISCON)
- Institutions hold the study data

PMRs to Assess Long-Term Use of ER/LA Opioids in Patients with Chronic Pain

Observational Studies 3033-1 and 3033-2 Address Purpose of PMRs

1. Estimate the incidence of misuse, abuse, addiction, overdose, and death

2. Evaluate and quantify risk factors for these outcomes

ER/LA: extended release or long-acting

CO-7

Quantify Incidence and Predictors for Misuse, Abuse, Addiction, Overdose, Death with Long-term ER/LA Use in Chronic Pain

Study 3033-1
Prospective Original Data Collection
Rx Misuse, Rx Abuse, Addiction

Study 3033-1 Design

- 12-month prospective cohort study in new recipients of long-term opioids
- Single interview cross-sectional study of patients with long-term opioid use

Validation Studies

Outcome	Instrument	Validation Study
Rx Abuse, Rx Misuse	POMAQ	Study 3033-3/4
Addiction (OUD)	PRISM-5-OP	Study 3033-5

Study 3033-2
Retrospective Health Database
Overdose and Death

Study 3033-2 Design

- 5-year retrospective cohort study in new recipients of long-term opioids

Validation Studies

Outcome	Algorithm	Validation Study
Overdose/Death	ICD codes	Study 3033-6
~~Abuse/Addiction~~	~~ICD codes~~	~~Study 3033-7~~

ER/LA: extended release or long-acting

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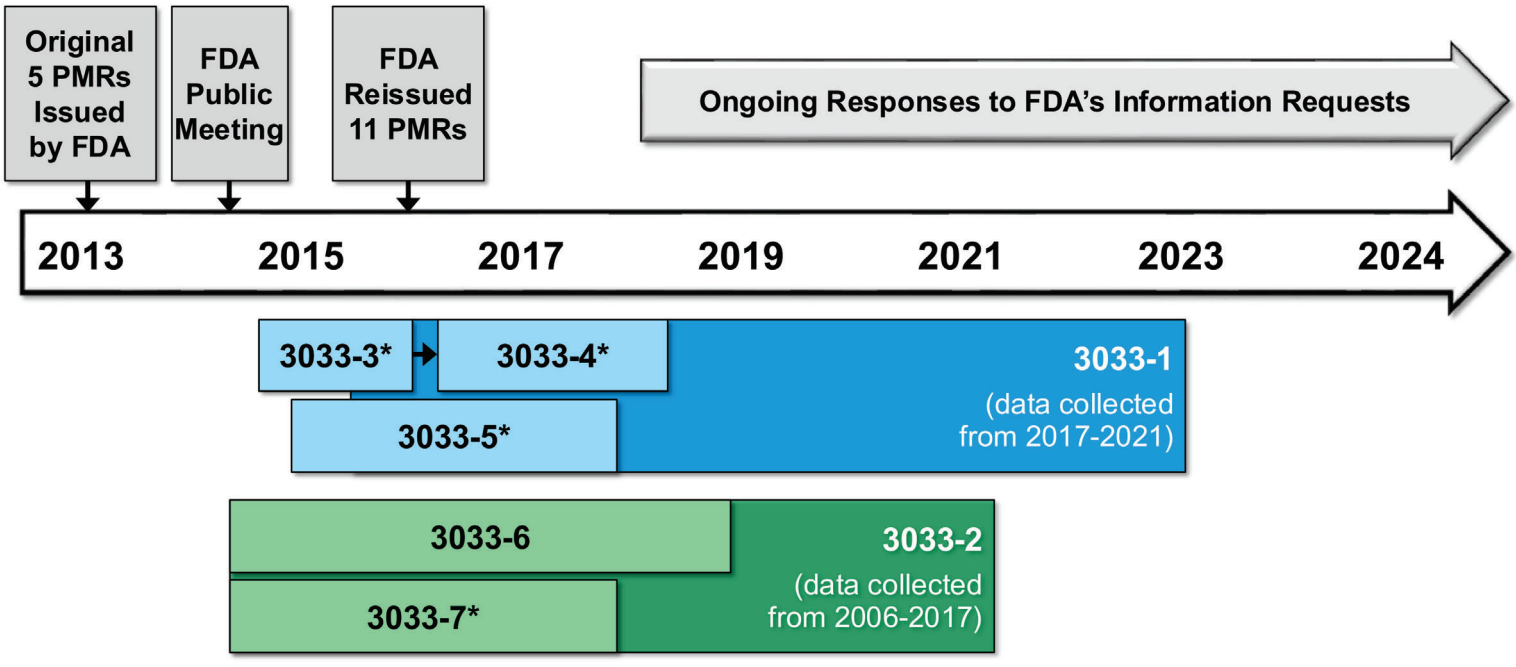
PMRs Adapted to FDA Feedback and Actions



*PMR deemed fulfilled by FDA

PMR Studies Quantified Incidence Rates and Risk Factors

- Study 1
  - 1-year cumulative risks: Rx opioid misuse (~23%), Rx opioid abuse (~9%), opioid addiction (~1.6%)
  - Similar outcome prevalences in cross-sectional study of established patients
  - Among many prespecified risk factors, prior non-opioid, non-nicotine SUD was strongest risk factor of outcomes
- Study 2
  - 5-year cumulative risk of OOD averaged 2.1% across 4 sites
  - Among many prespecified risk factors, baseline dose, prior opioid use disorder, and mental health disorders/treatments strongest independent predictors of OOD

SUD: substance use disorder; OOD: opioid-involved overdose or opioid overdose-related death

Agenda

Study 3033-1	**Bobbi Jo Yarborough, PsyD** Senior Investigator Kaiser Permanente Northwest Center for Health Research
Study 3033-2	**John D. Seeger, PharmD, DrPH** Vice President for Epidemiology, RTI-HS Adjunct Assistant Professor, Epidemiology Harvard T.H.Chan School of Public Health
Conclusions	**Alexander M. Walker, MD, DrPH** Adjunct Professor, Epidemiology Harvard T.H. Chan School of Public Health

Study 3033-1

Incidence or Prevalence of and Risk Factors for Developing Prescription Opioid Misuse, Abuse or Addiction Among Patients Prescribed Long-term Opioid Therapy

Bobbi Jo Yarborough, PsyD

Senior Investigator

Kaiser Permanente Center for Health Research

Professional Background

- Research focuses on centering experience of patients, families, and clinicians to improve care and outcomes for individuals living with mental health and substance use disorders
- Studied risks associated with prescription opioid use, including overdose prevention
- Studied outcomes associated with opioid discontinuation and tapering, including suicide
- Principal investigator for Study 1

CO-13

Study 3033-1: Prospective/Cross-Sectional Study Among Patients Prescribed Long-Term Opioids for Chronic Pain

1. Estimate the incidence of misuse, abuse, addiction
   - Using well-established, large data systems
   - Demographic and socioeconomic diversity

2. Evaluate and quantify risk factors for these outcomes
   - Prespecified demographic, psychosocial, behavioral, medical and genetic factors

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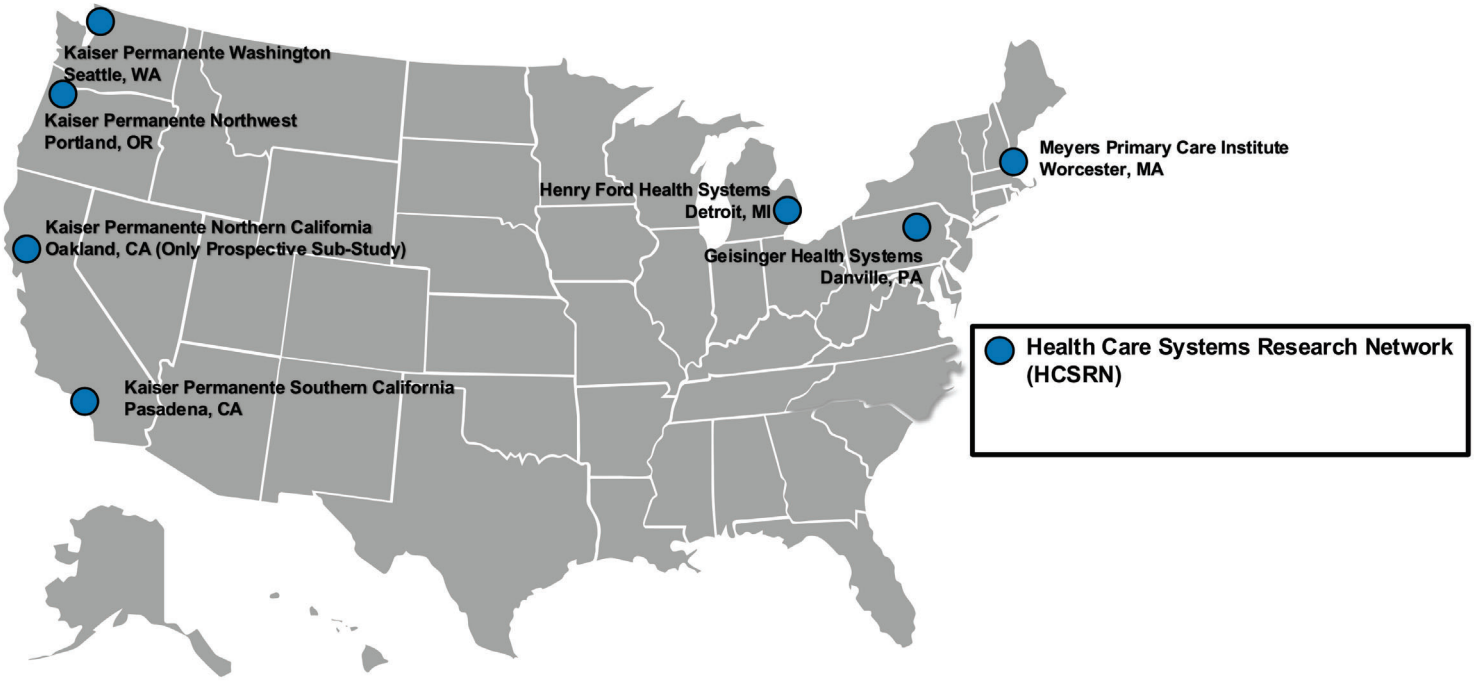
Study 3033-1 Recruitment in Established Health Systems



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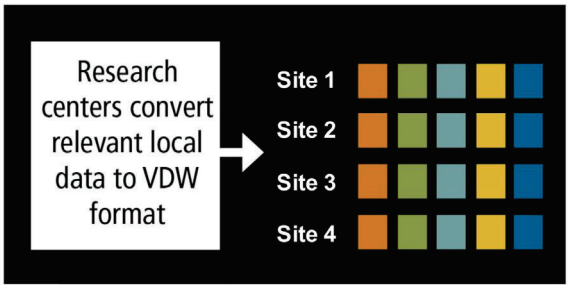
Study 3033-1 Common Data Model to Standardize EHR and Claims Data for Multi-Site Research

HCSRN VDW* allowed

- Data coordinating center to distribute set of programs to all sites with minimal site-specific modification
- Streamlined programming work at sites
- Timely return of results
- Confidence in accurate and complete capture of cleaned and standardized data
- Inclusion of more sites while still meeting study timeline

Gains in efficiencies and quality by organizing data in a common model



*Adapted from Health Care Systems Research Network; VDW: virtual data warehouse; EHR: electronic health record

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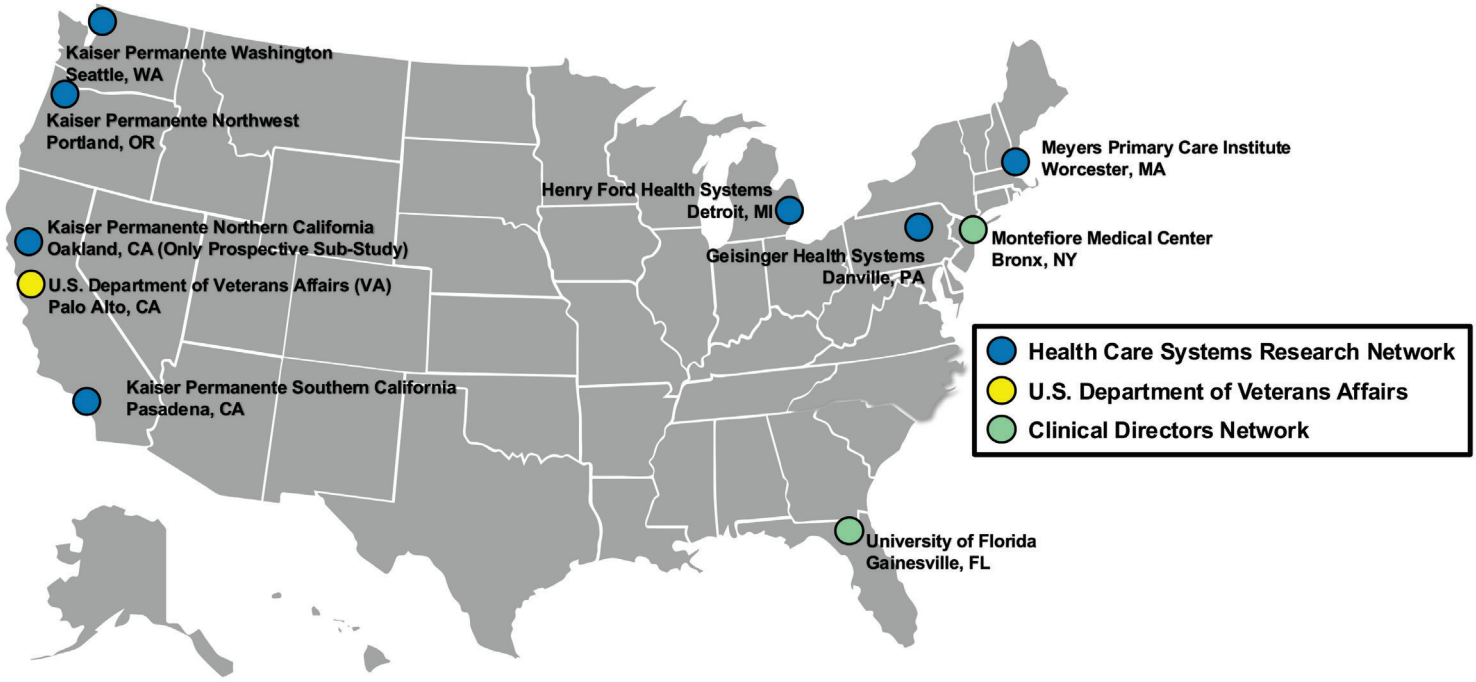
Study 3033-1 Study Sites



Study 3033-1 Site Selection Parameters

- Common data model (VDW) was a distinct advantage
- Site investigator with a history of opioid-related research
- Efficient recruitment, linkage of participant-reported outcomes to administrative data
- Survey research teams with a history of high response rates and excellent retention
- Fill geographic gaps, expand Medicaid and veteran representation
- Explored sites in Midwest and Southern regions, but they did not meet selection criteria

VDW: virtual data warehouse

Incidence of Prescription Opioid Misuse, Abuse, or Opioid Use Disorder Among Adults Newly Initiating Opioids for Chronic Pain

Study 3033-1 Prospective Study

Study 3033-1: Prospective Study Included Two Cohorts

- Study cohorts
  - ER/LA initiator: received ≥ 28 days and refilled ER/LA Rx
  - LtOT initiator: ≥ 70 of 90 days use of ER/LA and/or IR/SA
- If patient qualified for both cohorts, priority given to ER/LA initiators, as risk associated with ER/LA initial intent of PMR

ER/LA: extended release or long-acting; LtOT: long-term opioid therapy; IR/SA: immediate release or short-acting

Study 3033-1: Prospective Study Key Eligibility Criteria

- 12-month study
- Inclusion Criteria
  - Adults 18-79 years
  - English-speaking
  - Currently receiving qualifying opioid therapy
  - Evidence of consistent health care in past year
- Exclusion Criteria
  - Apparent cognitive impairment or inability to complete interview and self- or telephone-administered questionnaires
  - Unavailable for follow up
  - Current hospice care or terminal illness diagnosis in past year
  - Documented OUD or medication treatment for OUD

OUD: opioid use disorder

Study 3033-1 Evaluated Multiple Potential Risk Factors for Misuse, Abuse or Addiction

CO-21

Electronic Health Record (EHR) / Claims Data	Patient Reported Data
▪ Active opioid ingredient ▪ Abuse-deterrent ER/LA (yes, no) ▪ Dose and duration of opioid Rx ▪ Concomitant medications ▪ Co-morbidity score ▪ Type of insurance ▪ Inpatient stays ▪ Emergency Room visits ▪ Study site ▪ System type (e.g., Integrated delivery, fee-for-service) ▪ Demographic characteristics	▪ Current/past mood disorder ▪ Current/past substance use disorder ▪ Pain and functioning ▪ Health and functional status ▪ Perceived stress ▪ Social support ▪ Sleep quality **Optional Saliva Sample** ▪ OPRM1* status ▪ Cytochrome P450 (3A4, 2D6) status

*opioid receptor mu 1 gene; ER/LA: extended release or long-acting

Study 3033-1 Prospective Design (Data Collection August 2017 – October 2021)

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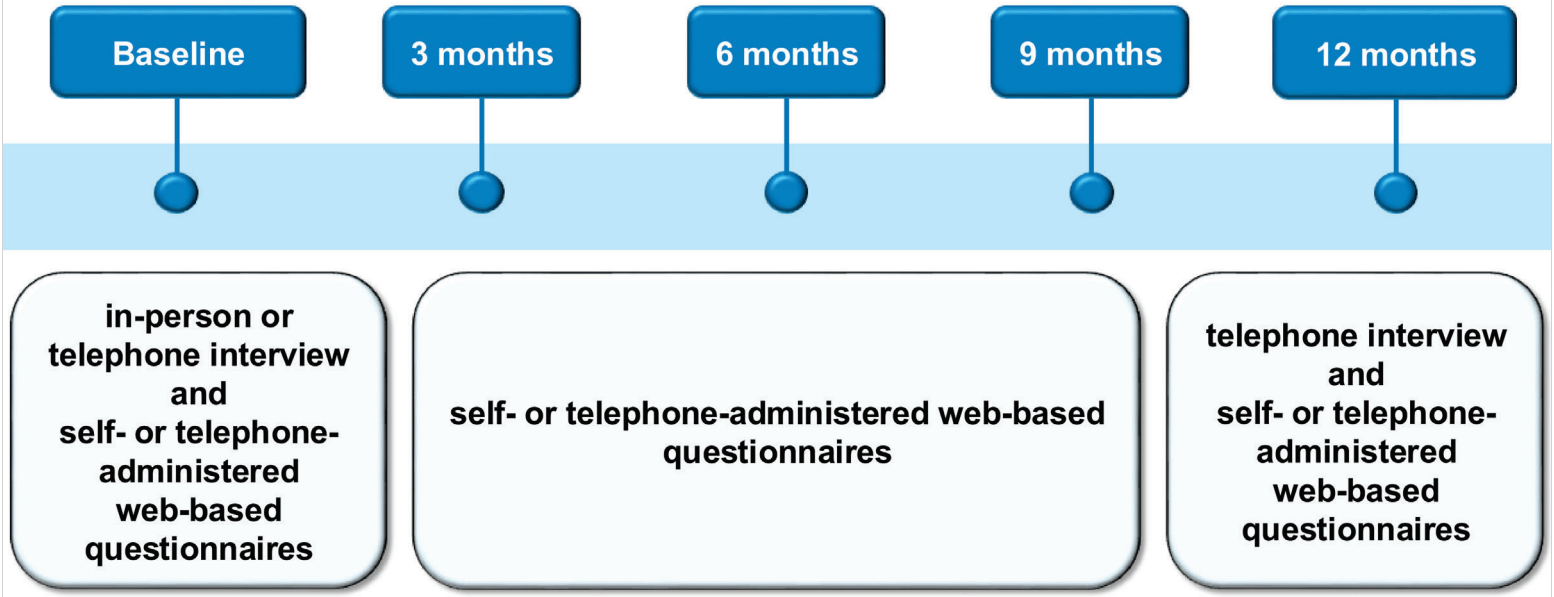

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Study 3033-1 Prospective Outcomes and Outcome Measures

Outcomes	**Primary** ▪ Prescription opioid misuse ▪ Prescription opioid abuse ▪ Addiction (assessed as OUD including pain adjusted Rx opioid use disorder or heroin use disorder) **Secondary** ▪ DSM-5 OUD
Prescription Opioid Misuse and Abuse Questionnaire (POMAQ)[1,2]	▪ Assessment used to determine misuse and abuse ▪ Modified scoring for longitudinal use in Study 1 ▪ Assessed via web-based survey or by telephone (if requested by participants)
Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 Opioid Version (PRISM-5-OP)[3]	▪ Assessment used to determine addiction (i.e., OUD) to opioid analgesics and/or heroin among patients with chronic pain who were prescribed opioids

1. Coyne et al., Curr Med Res Opin., 2018; 2. Coyne et al., Curr Med Res Opin., 2021; 3. Hasin et al., Am J Psychiatry, 2022; OUD: opioid use disorder

CO-24

Study 3033-3 and -4: Designed to Validate Prescription Opioid Misuse and Abuse Questionnaire (POMAQ)

- Study 3033-3 qualitative cognitive interview study
  - Ensured patients understood content and questions of draft POMAQ
  - Resulted in minor revisions to POMAQ after interviews
  - POMAQ demonstrated content validity
  - Considered ready for quantitative validation
- Study 3033-4 evaluated the validity and reproducibility of POMAQ
  - Cross-sectional study of 809 patients with chronic pain on LtOT
  - POMAQ demonstrated excellent test-retest reliability (~88%-100%) and construct validity
  - Determined to be a valid, reproducible tool to assess presence of misuse and abuse behaviors in Study 1

LtOT: long-term opioid therapy

Intentionality Responses Attributed to Misuse[1]

MISUSE

Intentional use of a drug for therapeutic purpose outside label directions

- I did not think that it is a problem to have a drink while taking an opioid pain medication
- I forgot I was taking an opioid pain medication
- I forgot to take my opioid pain medication
- I had more pain
- I happened to have a drink close to the time of taking my opioid pain medication
- I needed more opioid pain medication to treat my pain
- I needed more opioid pain medication to treat my pain than one doctor would give me
- I wanted to make sure I had enough opioid pain medication in case I needed it
- The dose my healthcare provider prescribed was not strong enough to treat my pain
- To feel less depressed or nervous
- To help me swallow my opioid pain medication
- To prevent withdrawal
- To reduce my stress
- To reduce the side effects of the opioid pain medication
- To save some opioid pain medication for later in case my pain gets worse
- To relax or feel mellow[2]
- To sleep better
- To treat my pain faster
- To treat the emotional hurt I was feeling
- The dose my healthcare provider prescribed was too strong to treat my pain
- To avoid getting constipated
- To celebrate a special occasion (e.g., birthday, wedding)
- I did not realize how much I was taking and ran out
- I misunderstood how much to take
- To treat other medical problems
- I misunderstood the instructions
- To unwind after a hard day[2]

1. Coyne et al., Curr Med Res Opin., 2018; 2. Originally attributed to abuse; moved to misuse after developing clinical scoring algorithm

Intentionality Responses Attributed to Abuse[1]

ABUSE

Intentional use of a drug for the purpose of achieving a positive psychological or physical effect

- To get a better feeling of high
- To feel high or stoned
- To feel more talkative/outgoing
- To boost the effect of my opioid pain medication
- I want to get more opioid medication and did not want to get caught
- To save the opioid pain medication to use more of it at once to get high
- I needed more than one doctor would give me
- I wanted to get more opioid pain medication to get high on
- It is better to get high on my prescription opioid medication when on another drug

1. Coyne et al., Curr Med Res Opin., 2018

Study 3033-5 Designed to Assess Validity of PRISM-5-OP Instrument as Measure for Addiction (OUD)

- Aim: creation of a standardized measure of OUD involving prescription opioids (among patients with chronic pain prescribed opioids) that could be used across different settings
- Study design: evaluated 606 patients from pain clinics and inpatient substance treatment that received at least 30 days of opioids for chronic pain
- Results: PRISM-5-OP instrument shown to be valid and highly reliable, demonstrating validity of pain-adjusted OUD measure involving prescription opioids

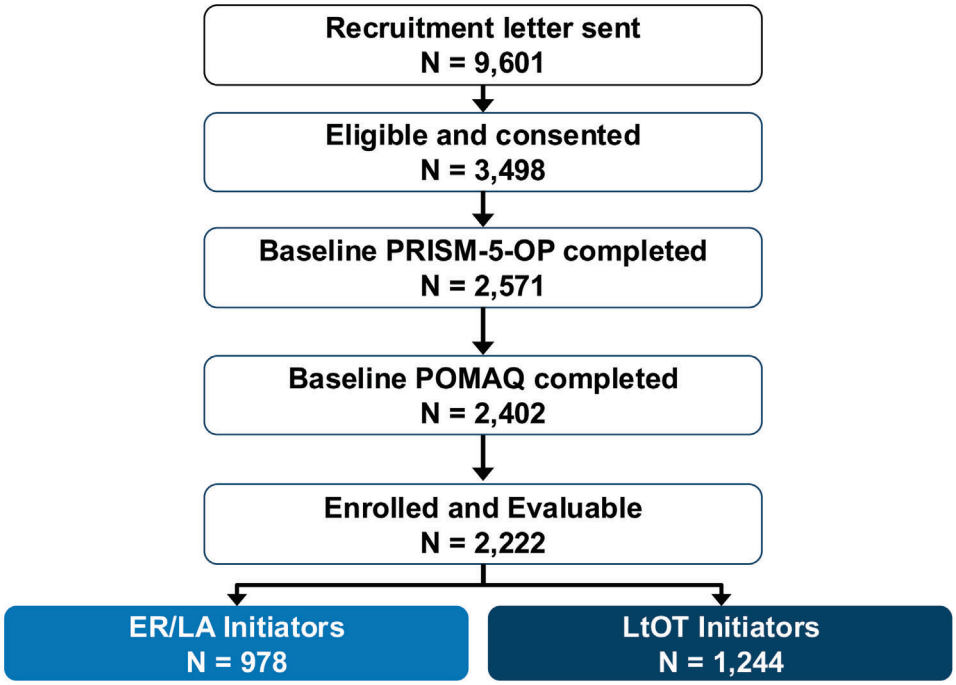
Hasin et al., Am J Psychiatry, 2022; OUD: opioid use disorder

Definitions of Misuse, Abuse, and Addiction (OUD) as Used in Study 3033-1

Misuse*	Intentional use of a drug for therapeutic purpose	▪ To reduce an aversive symptom or state in a manner outside label directions or other than prescribed or directed by a health care practitioner ▪ Patients using a drug for a condition different from that for which the drug is prescribed ▪ Patients taking more drugs than prescribed ▪ Patients using a drug at different dosing intervals
Abuse*	Intentional use of a drug for non-therapeutic purpose	▪ Sporadic or repeated use for the purpose of achieving a positive psychological or physical effect
Addiction	Pain-Adjusted OUD	▪ A pain-adjusted measure of the DSM-5 criteria of opioid use disorder involving prescription opioids where the opioids were taken other than as prescribed and for reasons other than pain relief and 4 or more criteria out of 11 were met or any DSM-5 heroin use disorder (2 or more criteria met out of 11).

*Modified versions from ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trials, Translation, Innovations, Opportunities, and Networks)
Smith et al., Pain, 2013; OUD: opioid use disorder

Study 3033-1 Prospective Disposition



ER/LA: extended release or long-acting; POMAQ: prescription opioid misuse and abuse questionnaire; LtOT: long-term opioid therapy

Study 3033-1 Prospective: Demographics and Baseline Characteristics of Enrolled Sample, by Cohort

	ER/LA Initiators N = 978	LtOT Initiators N = 1,244
Age ≥ 50 years	76%	72%
Sex, female	57%	59%
Race		
White	83%	78%
Black	9%	15%
Hispanic	11%	9%
Predominant opioid form		
IR/SA	60%	98%
ER/LA	40%	2%
Past-year non-opioid, non-nicotine SUD (PRISM-5-OP)	7%	8%

ER/LA: extended release or long-acting; LtOT: long-term opioid therapy; SUD: substance use disorder; IR/SA: immediate release or short-acting

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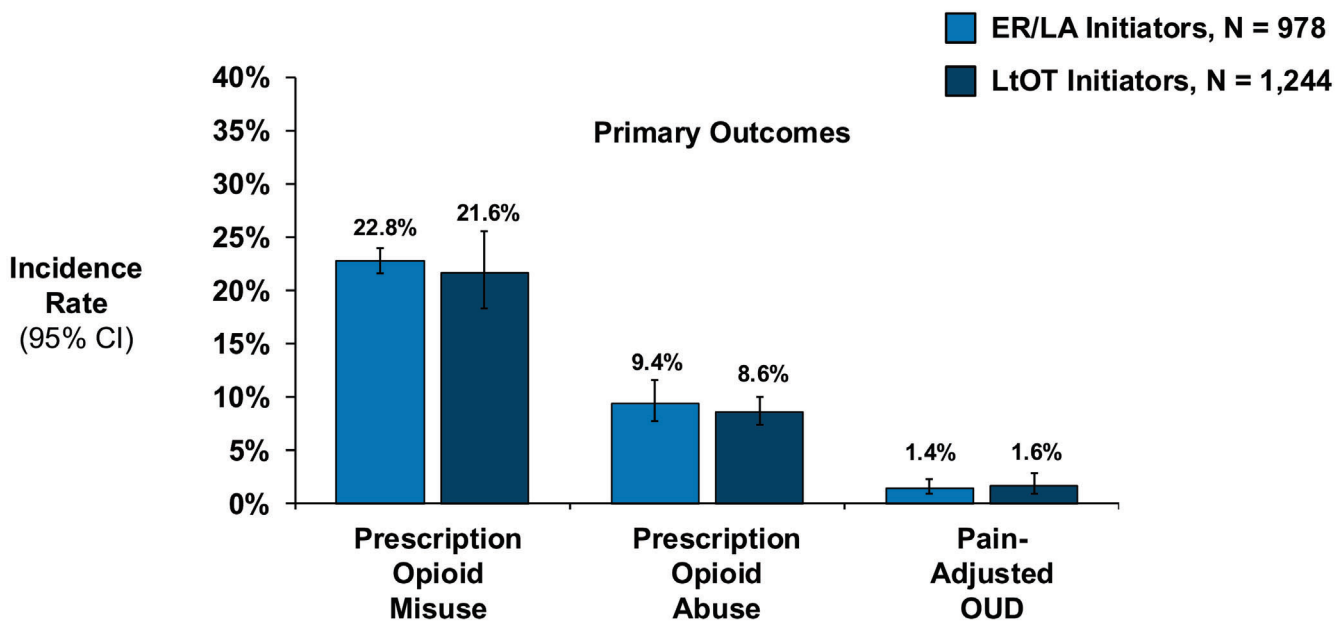
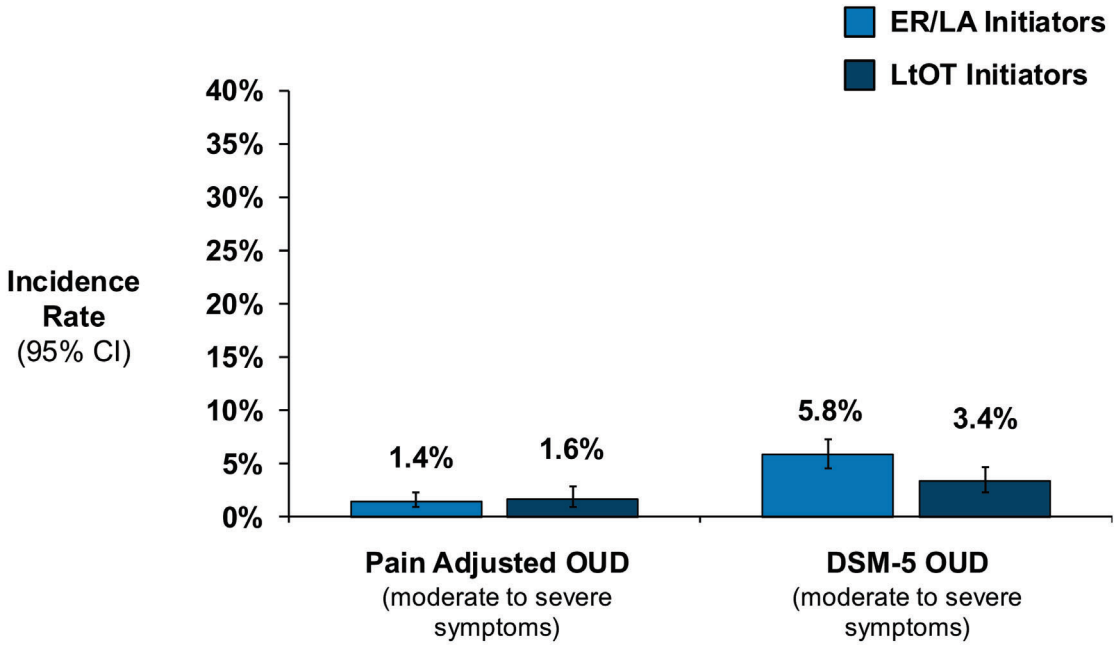
Study 3033-1 Prospective: 12-Month Cumulative Incidence of Rx Opioid Misuse, Rx Opioid Abuse, or OUD Outcome



ER/LA: extended release or long-acting; LtOT: long-term opioid therapy; OUD: opioid use disorder; CI: confidence interval

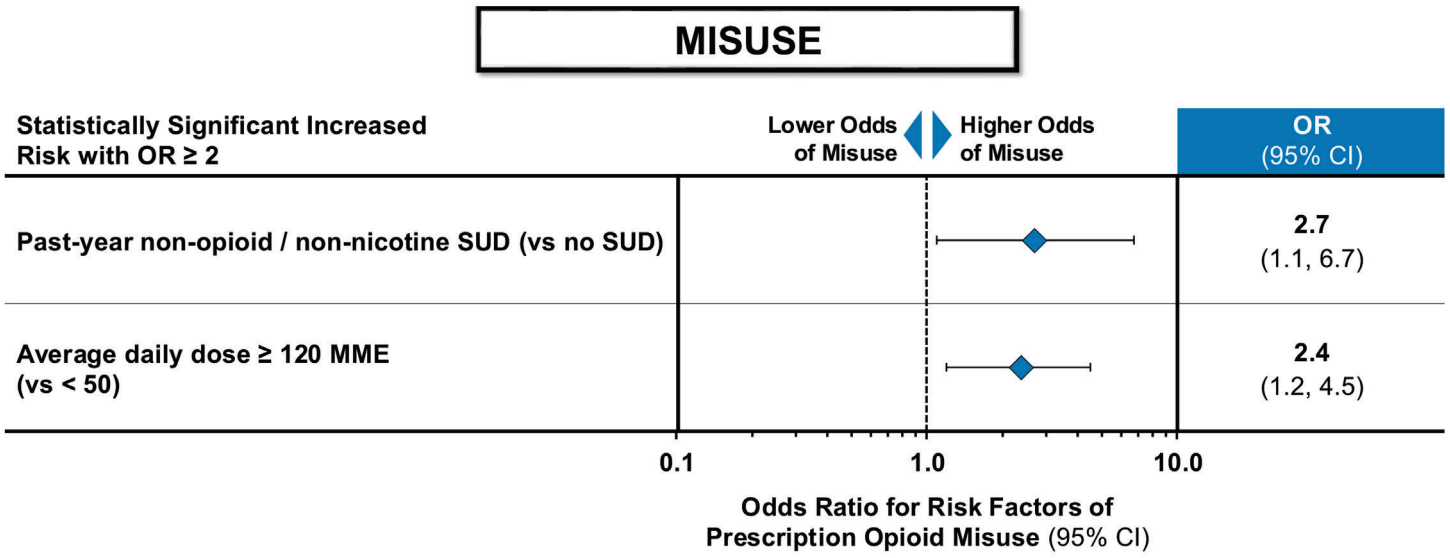
CO-32

Study 3033-1 Prospective: DSM-5 OUD Compared to Pain-Adjusted Measure for OUD



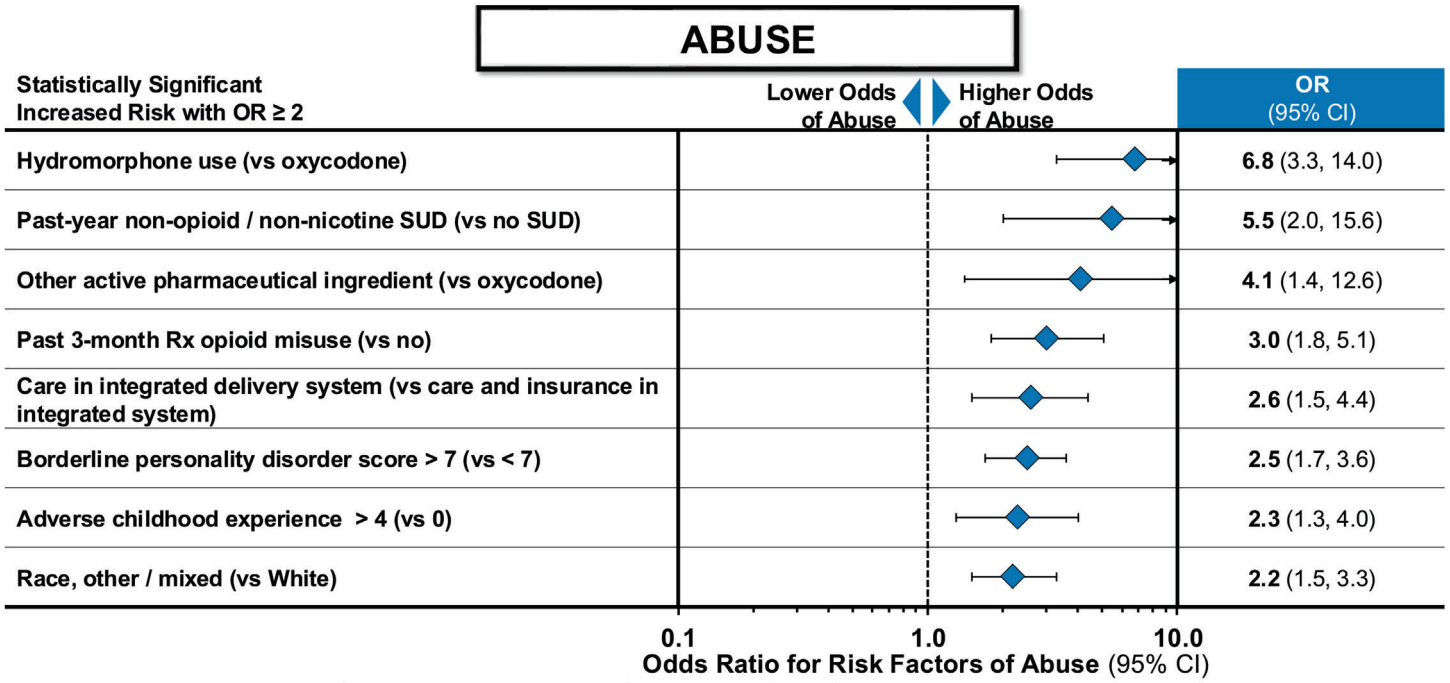
ER/LA: extended release or long-acting; LtOT: long-term opioid therapy; OUD: opioid use disorder; CI: confidence interval

Study 3033-1 Prospective: Factors that Increase Risk for Misuse (ER/LA Initiators, Fully Adjusted OR)



ER/LA: extended release or long-acting; SUD: substance use disorder; MME: milligram morphine equivalent; OR: odds ratio; CI: confidence interval

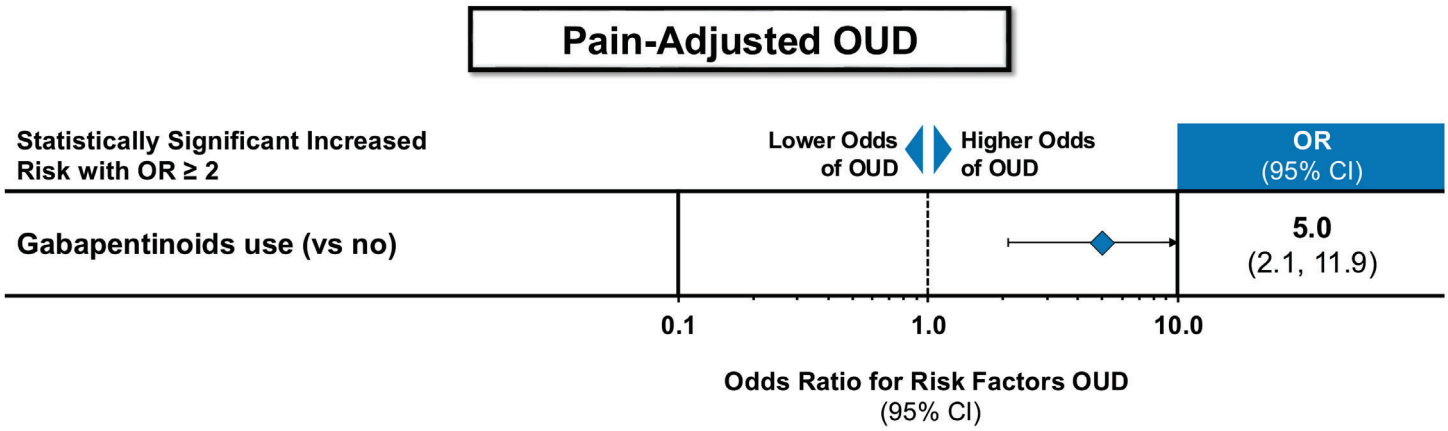
Study 3033-1 Prospective: Factors that Increase Risk for Abuse (ER/LA Initiators, Fully Adjusted OR)



ER/LA: extended release or long-acting; SUD: substance use disorder; OR: odds ratio; CI: confidence interval

CO-35

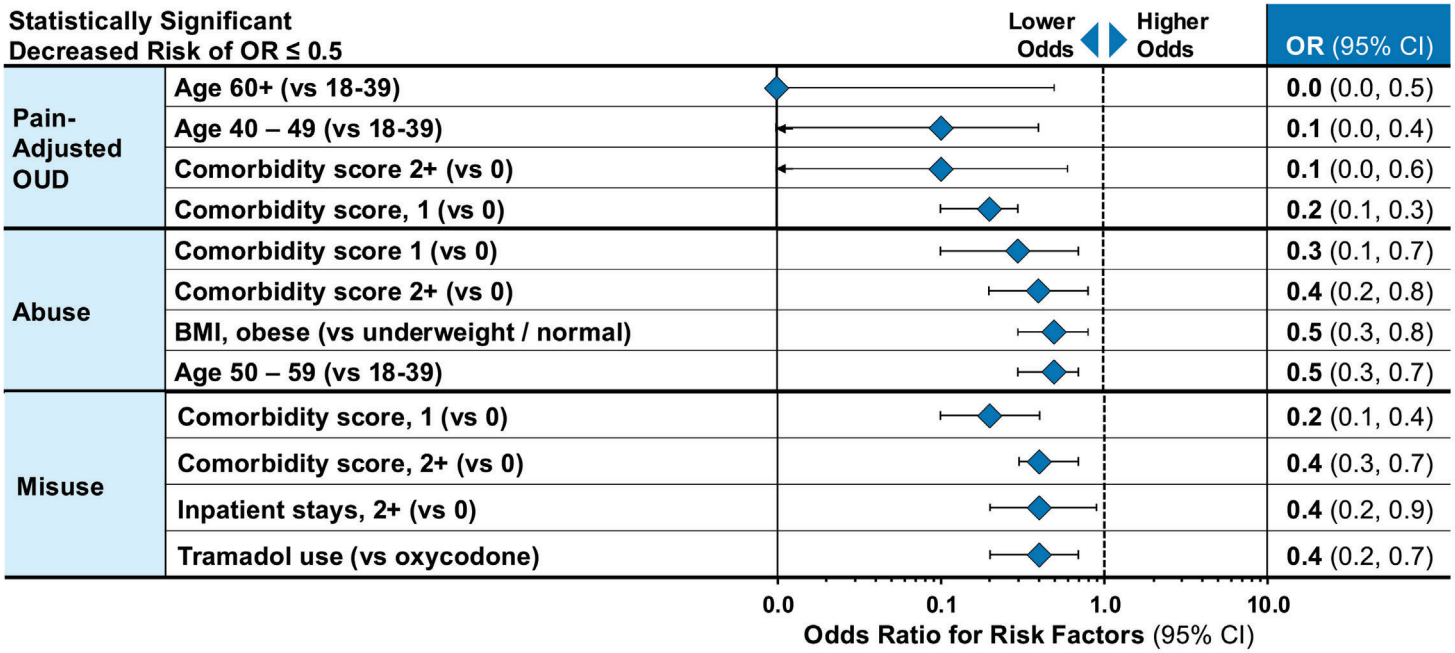
Study 3033-1 Prospective: Factors that Increase Risk for OUD (ER/LA Initiators, Fully Adjusted OR)



ER/LA: extended release or long-acting; OUD: opioid use disorder; OR: odds ratio; CI: confidence interval

CO-36

Study 3033-1 Prospective: Factors that Decrease Risk (ER/LA Initiators, Fully Adjusted OR)



Elixhauser comorbidity score: a count of medical comorbidities
ER/LA: extended release or long-acting; OUD: opioid use disorder; OR: odds ratio; CI: confidence interval

Prevalence of Prescription Opioid Misuse, Abuse, or Opioid Use Disorder among Adults with Long-term Opioid Use

Study 3033-1 Cross-Sectional Study

Study 3033-1 Cross-Sectional Study in Adults Receiving Long-Term Opioids for Chronic Pain

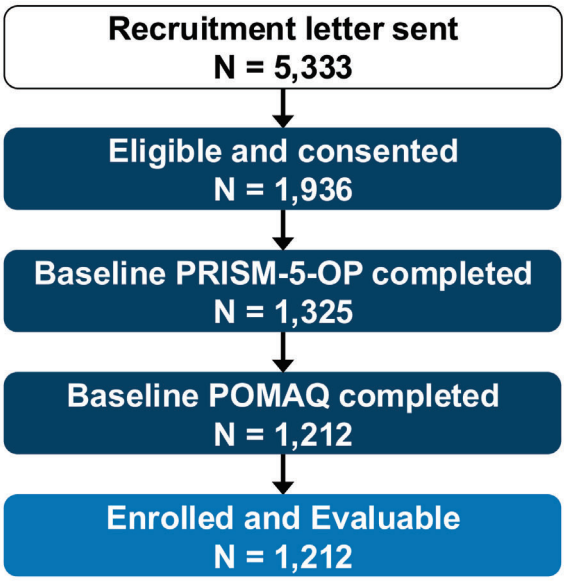
- Provided opportunity to understand risks associated with longer than 1-year exposure to opioids
- Key Eligibility Criteria
  - Prescribed opioids for pain for ≥ 12 months
  - Ability to complete interview and self-or telephone-administered questionnaires
  - Currently using prescription opioid

Study 3033-1 Cross-Sectional: Outcomes and Outcome Measures

Outcomes	Primary ▪ Past 3-month prevalence of prescription opioid misuse ▪ Past 3-month prevalence of prescription opioid abuse ▪ Past year prevalence of addiction Secondary ▪ DSM-5 OUD
Prescription Opioid Misuse and Abuse* Questionnaire (POMAQ)[1,2*]	▪ Assessment used to determine misuse and abuse ▪ Modified scoring for Study 1 ▪ Assessed via web-based survey or by telephone (if requested by participants)
Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 Opioid Version (PRISM-5-OP)[3]	▪ Assessment used to determine addiction (i.e., OUD) to opioid analgesics and/or heroin among patients with chronic pain who were prescribed opioids

1. Coyne et al., Curr Med Res Opin., 2018; 2. Coyne et al., Curr Med Res Opin., 2021; 3. Hasin et al., Am J Psychiatry, 2022; OUD: opioid use disorder
*Modified definitions of abuse and misuse adapted from Analgesic, Anesthetic, and Addiction Clinical Trials, Translation, Innovations, Opportunities, and Networks (ACTTION)

Study 3033-1 Cross-Sectional: Disposition



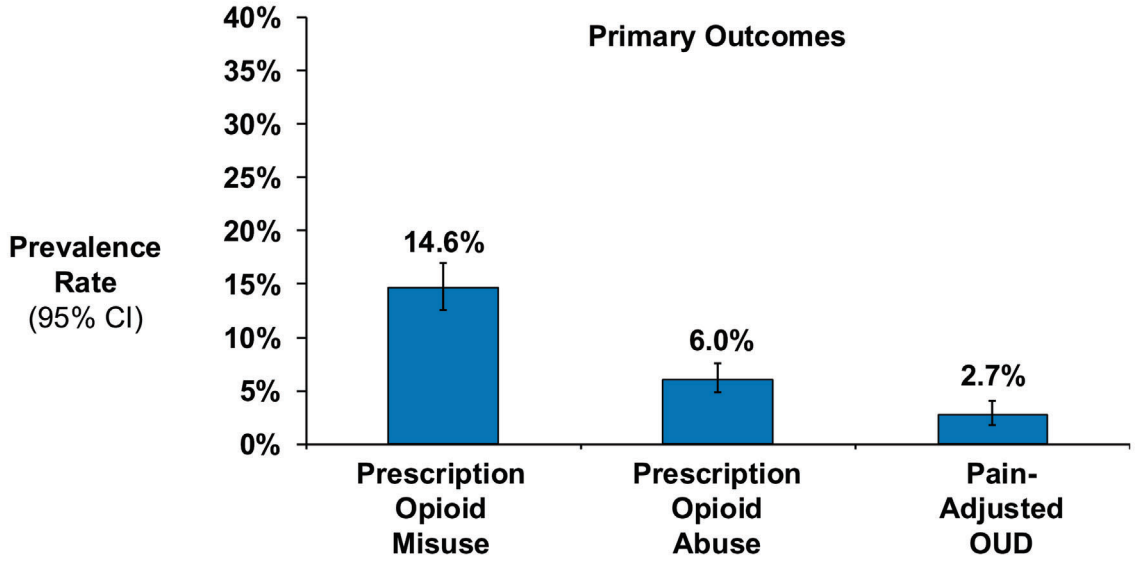
POMAQ: Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP: Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 Opioid Version

Study 3033-1 Cross-Sectional: Demographics and Baseline Characteristics

	N = 1,212
Age ≥ 50 years	80%
Sex, female	57%
Race	
White	74%
Black	12%
Unknown	10%
Hispanic	5%
Predominant Opioid Form	
ER/LA	66%
IR/SA	34%
Past-year non-opioid, non-nicotine SUD (PRISM-5-OP)	5%

ER/LA: extended release or long-acting; SUD: substance abuse disorder; IR/SA: immediate release or short-acting

Study 3033-1 Cross-Sectional: Prevalence of Rx Opioid Misuse, Rx Opioid Abuse, or OUD Outcome



N = 1,212; OUD: opioid use disorder; CI: confidence interval

Study 3033-1 Cross Sectional: DSM-5 Criteria Compared to Pain-Adjusted Measure for OUD

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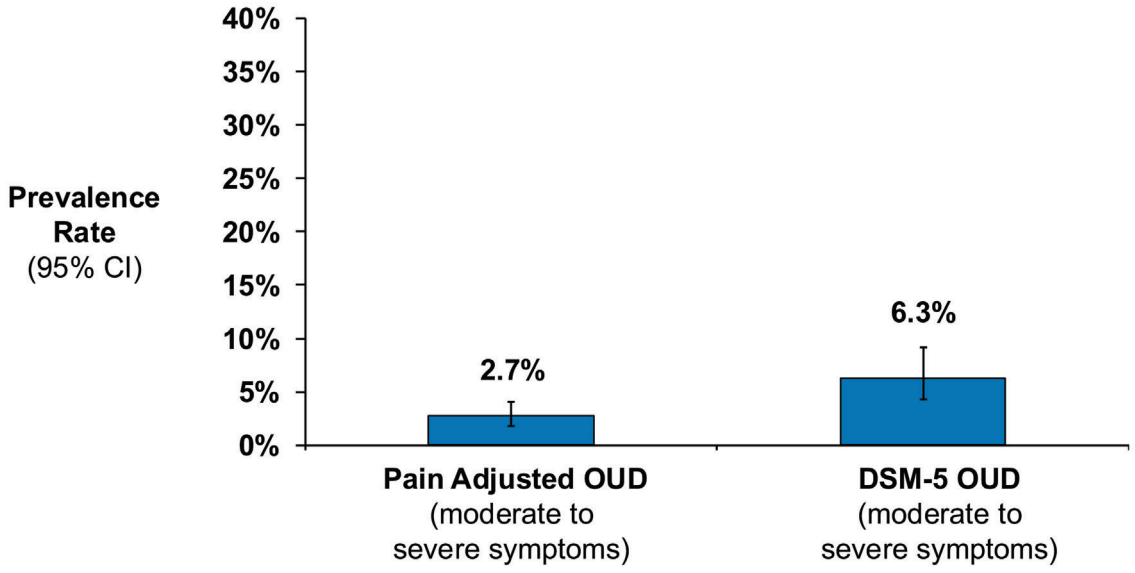

OUD: opioid use disorder; CI: confidence interval

Study 3033-1 Cross-Sectional: Factors that Increase Risk for Misuse (Fully Adjusted OR)

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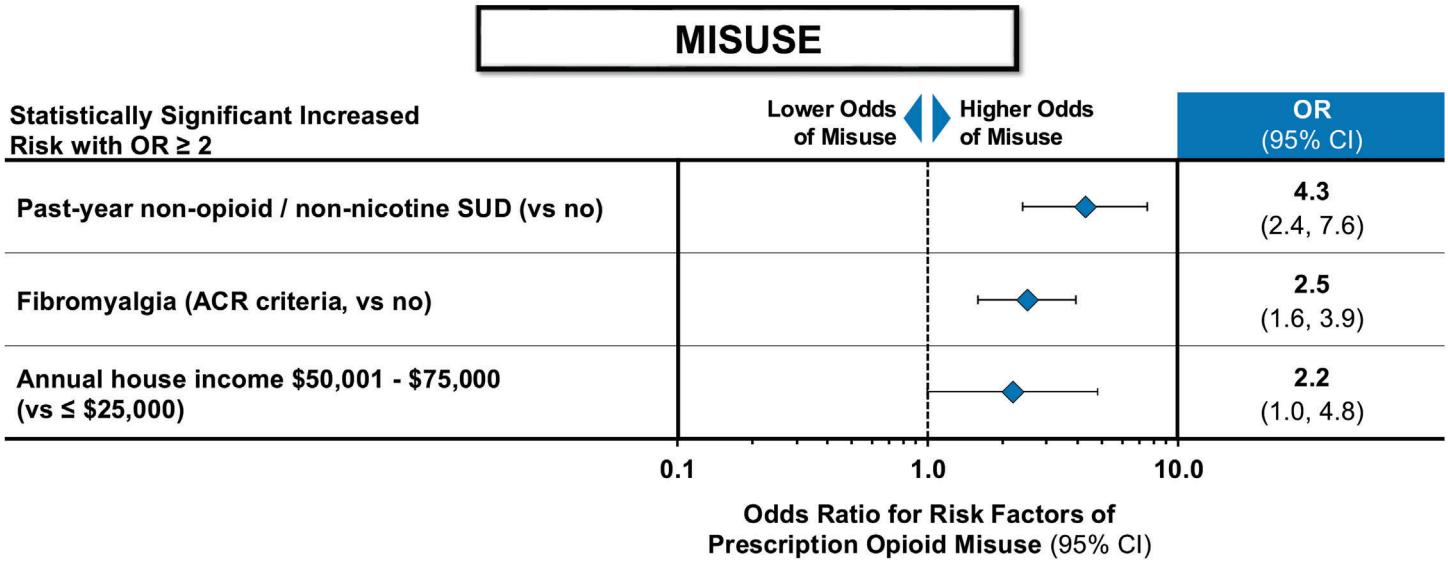

SUD: substance use disorder; ACR: American College of Rheumotology; OR: odds ratio; CI: confidence interval

Study 3033-1 Cross-Sectional: Factors that Increase Risk for Abuse (Fully Adjusted OR)

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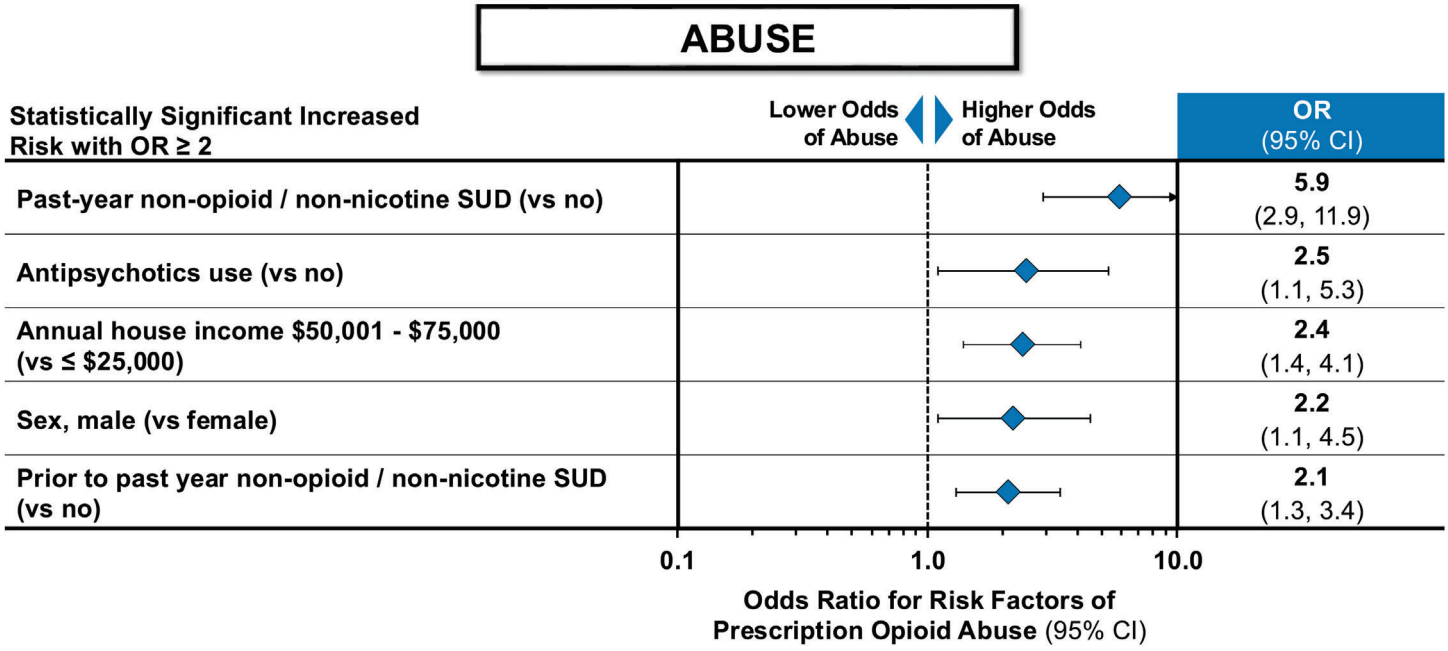

SUD: substance use disorder; OR: odds ratio; CI: confidence interval

Study 3033-1 Cross-Sectional: Factors that Increase Risk for OUD (Fully Adjusted OR)

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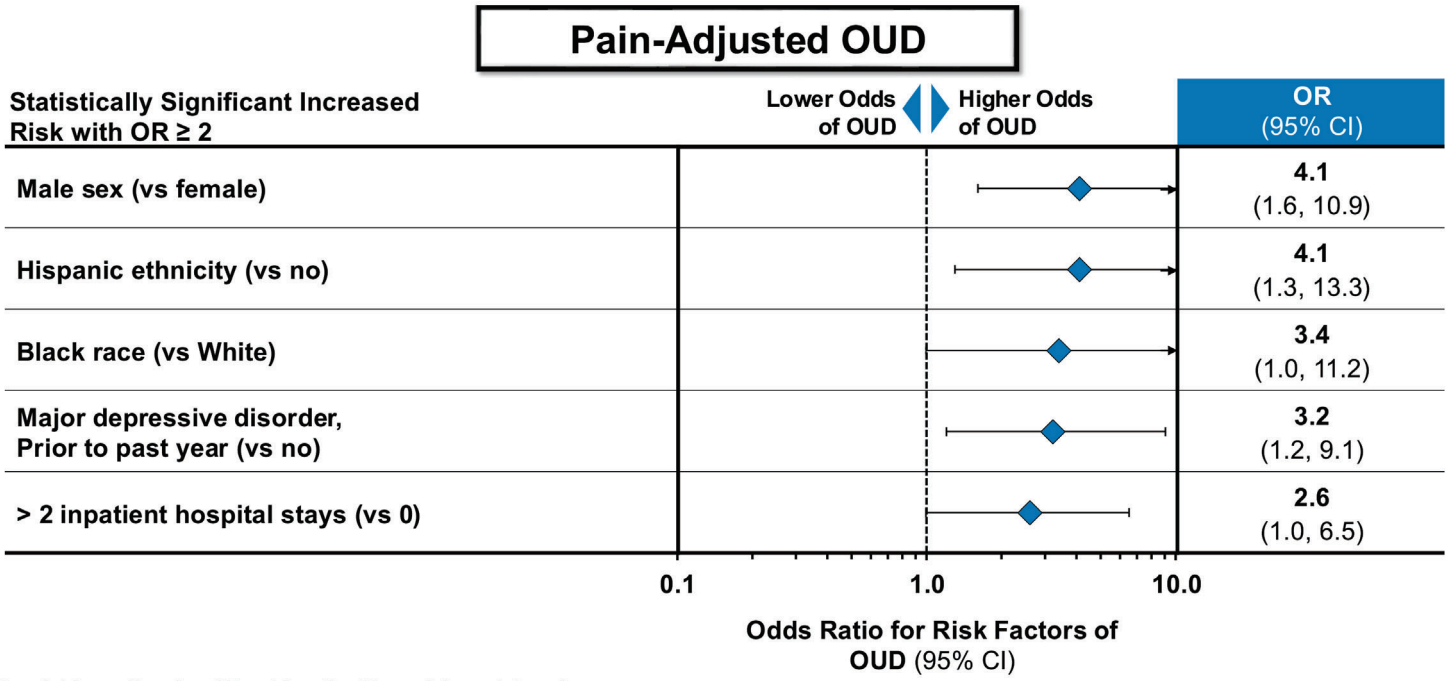
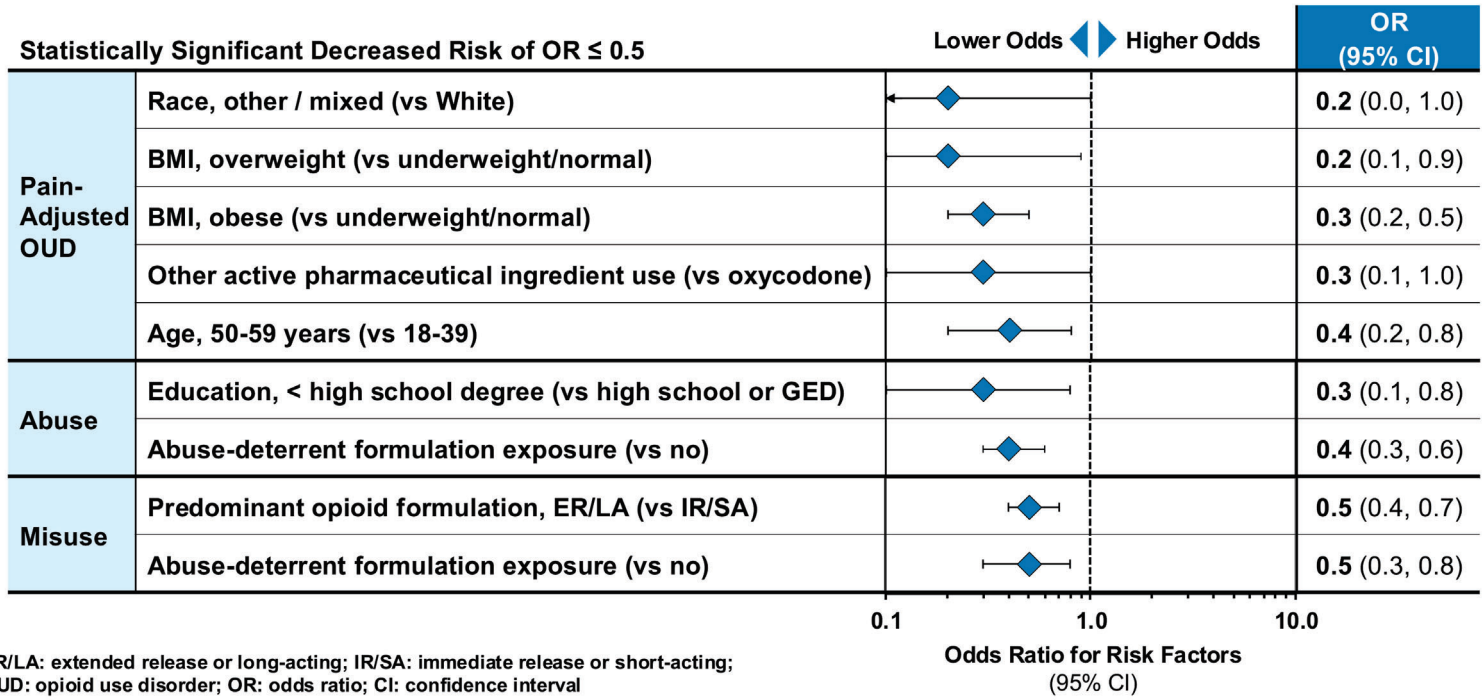


OUD: opioid use disorder; OR: odds ratio; CI: confidence interval

Study 3033-1 Cross-Sectional: Factors that Decrease Risk (Fully Adjusted OR)



ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting; OUD: opioid use disorder; OR: odds ratio; CI: confidence interval

Study 3033-1: Strengths and Limitations

Strengths

- Extensive data systems and experienced study teams
- Used validated instruments to quantify and characterize outcomes
- Diverse participant groups included
- Longitudinal analyses
- Robust estimation of incidence
- Extensive list of risk factors explored

Limitations

- Observational study (i.e., potential bias or misclassification)
- Low statistical power to detect significant differences across small subgroups for risk factors
- Did not study dose changes/ discontinuation, illicit use, suicide

Study 3033-1: Data Collected Inform Post-Marketing Requirements Regarding Abuse, Misuse, and Addiction

- Takeaways from both prospective and cross-sectional studies
  - Established incidence and prevalence rates among patients prescribed long-term opioids
  - Evaluated numerous potentially important risk factors
    - Having a non-opioid, non-nicotine SUD within past year most associated with increased risk of any outcome
- Risk factor findings align with published literature

SUD: substance use disorder

Study 3033-2

Incidence and Prognostic Factors for Opioid-involved Overdose or Opioid Overdose-Related Death (OOD)

John D. Seeger, PharmD, DrPH

Vice President for Epidemiology, RTI-HS
Adjunct Assistant Professor, Epidemiology
Harvard T.H.Chan School of Public Health

CO-51

Professional Background

- 25-year history at Optum, with final role as CSO
- Research focused on safety of pharmaceuticals and vaccines
- Started as Optum site investigator for Study 3033-2
- Principal investigator for Study 3033-2 since 2021

CO-52

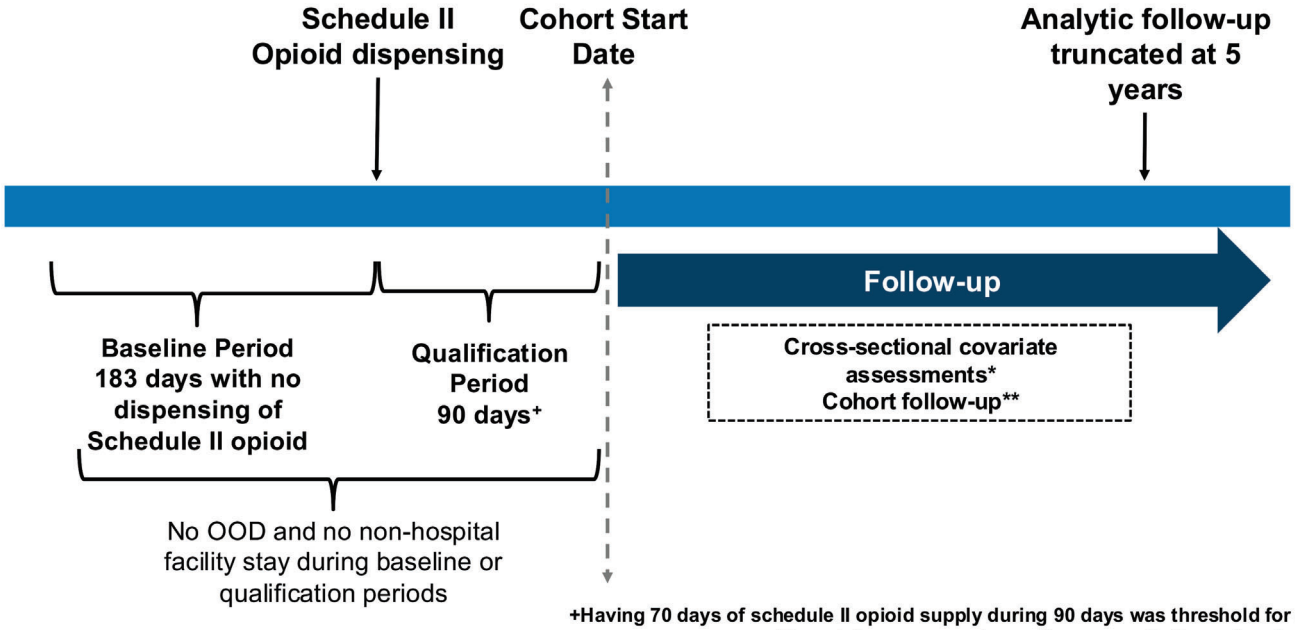
Study 3033-2: Retrospective Study Using Health Records, Insurance Claims, Death Records to Address PMRs

1. Quantify the incidence of overdose and death (OOD)
   - Among long-term users of Schedule II opioids
   - Overall and evolution over time
   - Expected to be rare events – need a large study for precision
   - Observational retrospective study most informative and timely

2. Evaluate risk factors for OOD outcomes
   - Prespecified demographic, psychosocial/behavioral, medical and genetic factors
   - Identify confounders of individual risk factor / outcome relationships
   - Formulation (ER/LA vs IR/SA) as risk factor
   - Effect modifiers not included

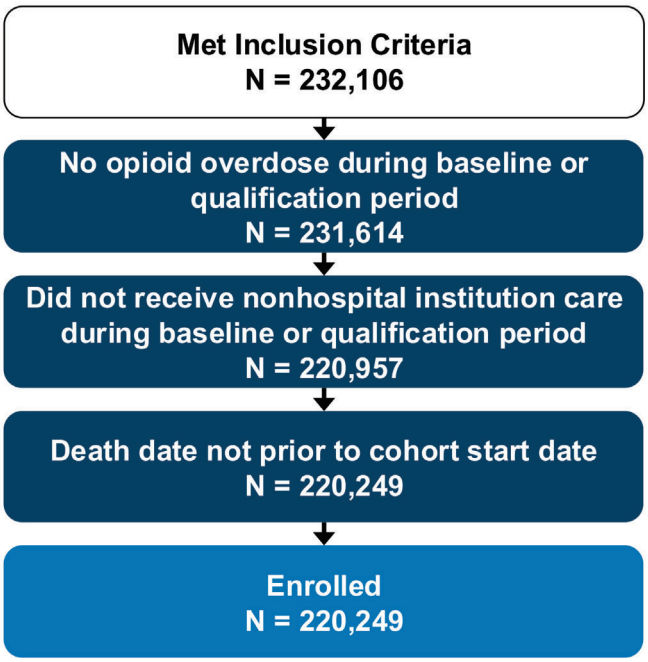
OOD: opioid-involved overdose or opioid overdose-related death; ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting

Study 3033-2: Retrospective Study Design (Dispensings Between October 2006 – December 2016)



+Having 70 days of schedule II opioid supply during 90 days was threshold for qualification
*Covariate assessments continue annually through cohort follow-up;
**Events that terminate follow-up: disenrollment, end of study (12/31/2017), OOD, death, non-hospital facility stay (other than for treatment of substance abuse) day preceding 80th birthday

Study 3033-2: Disposition



CO-55

3033-2 Sites Included Regions Across the US at Different Levels of Risk for OOD

	HealthCore (Commercial Health)	Optum (Commercial Health)	KPNW (Managed Care)	VUMC (Medicaid)
% of Total Cohort	37%	25%	5%	33%
US Census Region	Regional Distribution of Site			
Northeast	13%	5%	-	-
Midwest	29%	23%	-	-
South	32%	57%	-	100% (Tennessee)
West	26%	15%	100% (Oregon, Washington)	-

OOD: opioid-involved overdose or opioid overdose-related death

CO-56

Study 3033-2: Data Source Selection

- Data source features
  - Large size with well-defined demographic and regional characteristics
  - Complete or nearly complete information on provider, facility, and pharmacy services provided to members
  - Experience working with US claims data or as translated to FDA's Sentinel Common Data Model
  - Ability to go beyond administrative data: access medical records and link to state vital statistics records or the National Death Index (NDI)
  - Provided diversity in healthcare settings and reimbursement

Study 3033-2: Quantitative Outcomes

Primary Outcome	▪ Cumulative risk for OOD for entire population ▪ Proportional hazard models for predictors of risk using a. each covariate b. each demographically adjusted covariate c. all covariates together
Secondary	▪ Characteristics of long-term users at Cohort Start Date ▪ Characteristics of long-term users throughout follow-up ▪ Cumulative risk and incidence in covariate-defined strata ▪ No Schedule II opioid use for > 30 days prior to initiation of opioid ▪ Switched to or added ER/LA or IR/SA to an existing IR/SA regimen

OOD: opioid-involved overdose or opioid overdose-related death; ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting

Study 3033-6: OOD Algorithm Using Simple ICD Codes Proved Most Robust

- Purpose: improve on a published algorithm[1] that identified OOD using ICD codes for opioid "poisoning"
- Investigators examined additional variables to improve specificity / sensitivity
  - Prescription medications
  - Hospitalization
  - Opioid use
  - Substance abuse
  - Chronic pain diagnosis
  - Mental health conditions
- Multivariable statistical analysis using LASSO and CART found no combination of these improved performance compared to medical chart review

1. Green et al., Pharmacoepidemiol Drug Saf, 2017

LASSO: least absolute shrinkage and selection operator; CART: classification and regression tree; OOD: opioid-involved overdose or opioid overdose-related death; ICD: international classification of diseases

Study 3033-6: Performance Characteristics

- 1,172 charts from Kaiser Northwest reviewed for development dataset
- Excellent performance

Performance (%)	
Metric	**Value** (95% CI)
Sensitivity	**97.9** (96.0, 99.0)
Specificity	**88.9** (85.6, 91.6)
PPV	**89.2** (86.4, 91.5)

- In a large portability assessment of > 1,400 charts, 3 of 4 sites + Kaiser Washington showed similar results: PPV = 87.4 (85.0, 89.3)
- Algorithm adopted into Study 3033-2

PPV: positive predictive value; CI: confidence interval

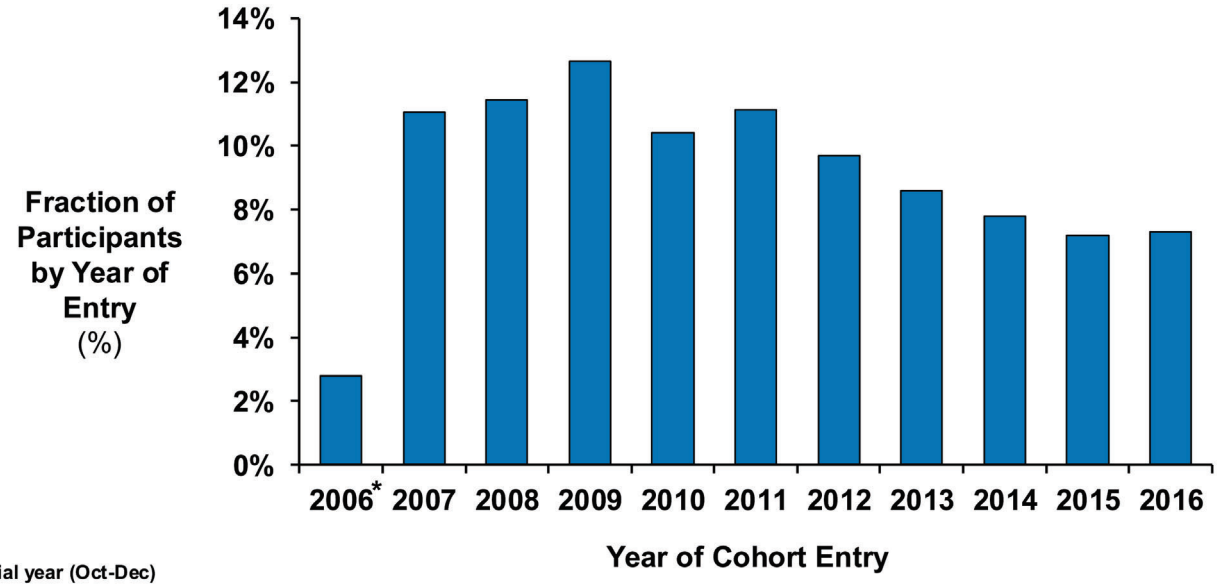
Study 3033-2: Cohort Characteristics

Covariates		Description
Prior to Cohort Start Date	**At Cohort Start Date**	**During Follow up**
▪ Pain-causing conditions ("clustered" using previous publication[1])	▪ Demographic (age, sex, year, US census region)	▪ Pain-causing conditions
▪ Substance use disorders		▪ Substance use diagnoses
▪ Mental health disorders		▪ Mental health disorders
▪ Concomitant non-opioid medications		▪ Concomitant non-opioid medications
		▪ Prescription opioid frequency and dose

1. Mayhew et al., J. Pain, 2019

Study 3033-2: Accrual Over Time

- Follow-up goes through 2017
- Later entrants tended to provide shorter durations of follow-up



*Partial year (Oct-Dec)

Study 3033-2: Demographics and Prior Medications at Cohort Start Date for Long-term CII Opioid Users

	Overall Cohort N = 220,249
Age ≥ 45 years	65%
Female	51%
U.S. Census Region	
South	59%
West	19%
Midwest	16%
Northeast	6%
Prior Medications	
Antidepressants	34%
Benzodiazepines	32%
Muscle relaxants	32%
Gabapentinoids	21%
Antipsychotics	6%

Study 3033-2: Prior Diagnoses at Cohort Start Date for Long-term Schedule II Opioid Users

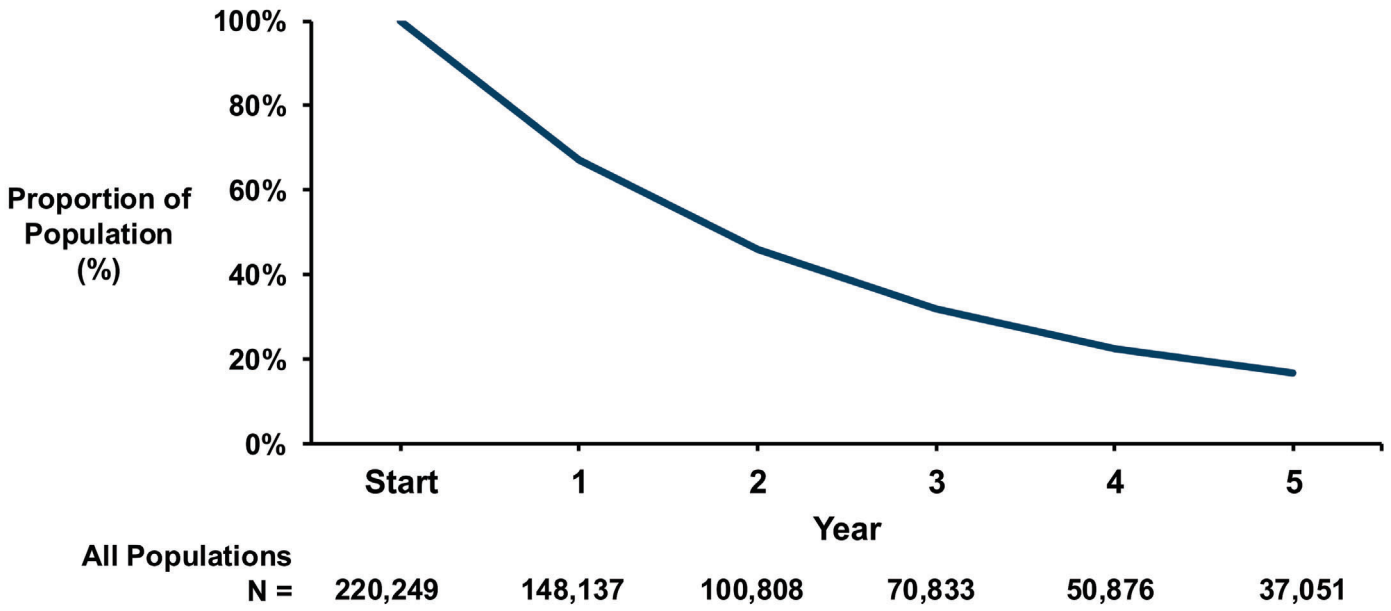
	Overall Cohort N = 220,249
Prior Pain Diagnoses (>20%)	
Back	57%
Limb/extremity/joint	57%
Abdominal, bowel	27%
Fracture, contusions, sprains, strains	26%
Neck	22%
Musculoskeletal, chest	21%
Other painful conditions	21%
Prior Mental Health Diagnoses	
Depression	27%
Anxiety	25%
Psychosis	8%
Prior Substance Use Disorder Diagnoses	
Other substance use disorder	6%
Alcohol	5%
Opioid	4%

Study 3033-2: Most Common CII Opioid Received at Cohort Start Date

	Overall Cohort N = 220,249
IR/SA Opioid as Principal Molecule	84%
Hydrocodone	59%
Oxycodone	22%
Hydromorphone	1%
ER/LA Opioid as Principal Molecule	16%
Fentanyl	5%
Morphine	4%
Oxycodone	4%
Methadone	1%

ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting

Study 3033-2: Cohort Size by Year of Follow-up



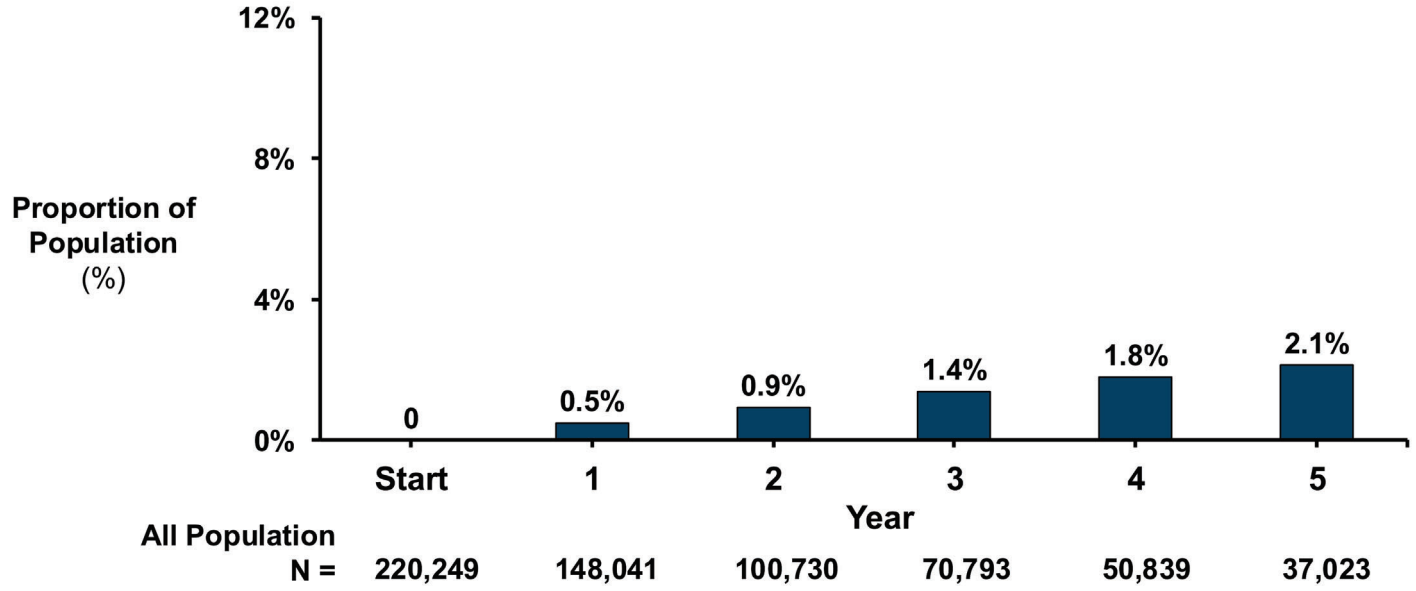
Study 3033-2: Follow-up and OOD Incidence

Follow-up Statistics to End of Observation

	VUMC	HealthCore	Optum	KPNW	Overall
Cohort Entrants	71,932	81,782	54,515	12,020	**220,249**
Person Years	196,801	175,529	83,524	36,926	**492,780**
OOD Events	1,978	629	287	140	**3,034**
Fatal OOD events	**330** (17%)	**107** (17%)	**57** (20%)	**15** (11%)	**509** (17%)
Cumulative Risk (95% CI)	**4.1%** (3.9%, 4.3%)	**1.5%** (1.4%, 1.6%)	**1.5%** (1.3%, 1.8%)	**1.4%** (1.2%, 1.7%)	**2.1%** (2.0%, 2.2%)
Incidence Rate (per 1,000 py) (95% CI)	**8.3** (7.9, 8.7)	**3.3** (3.0, 3.5)	**3.3** (3.0, 3.8)	**3.1** (2.6, 3.7)	**5.3** (5.1, 5.5)

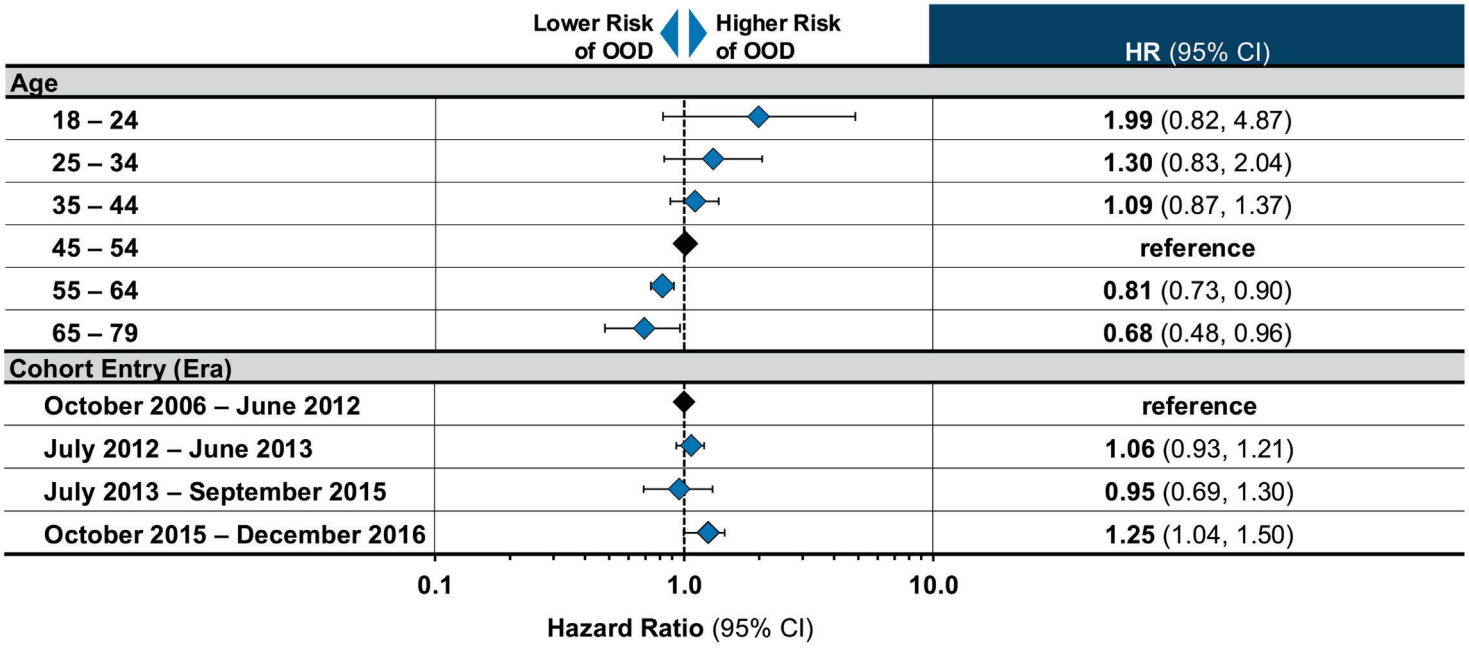
Overall Cumulative Risk is the average across sites
OOD: opioid-involved overdose or opioid overdose-related death; py: person-years; CI: confidence interval
Optum: United Health Care; HealthCore: Anthem; VUMC: Vanderbilt Univ. Medical Center, TennCare (Medicaid); KPMW: Kaiser Permanente Northwest

Study 3033-2: Cumulative OOD Risk in Patients Receiving Long-Term Opioid Therapy for Pain



OOD: opioid-involved overdose or opioid overdose-related death

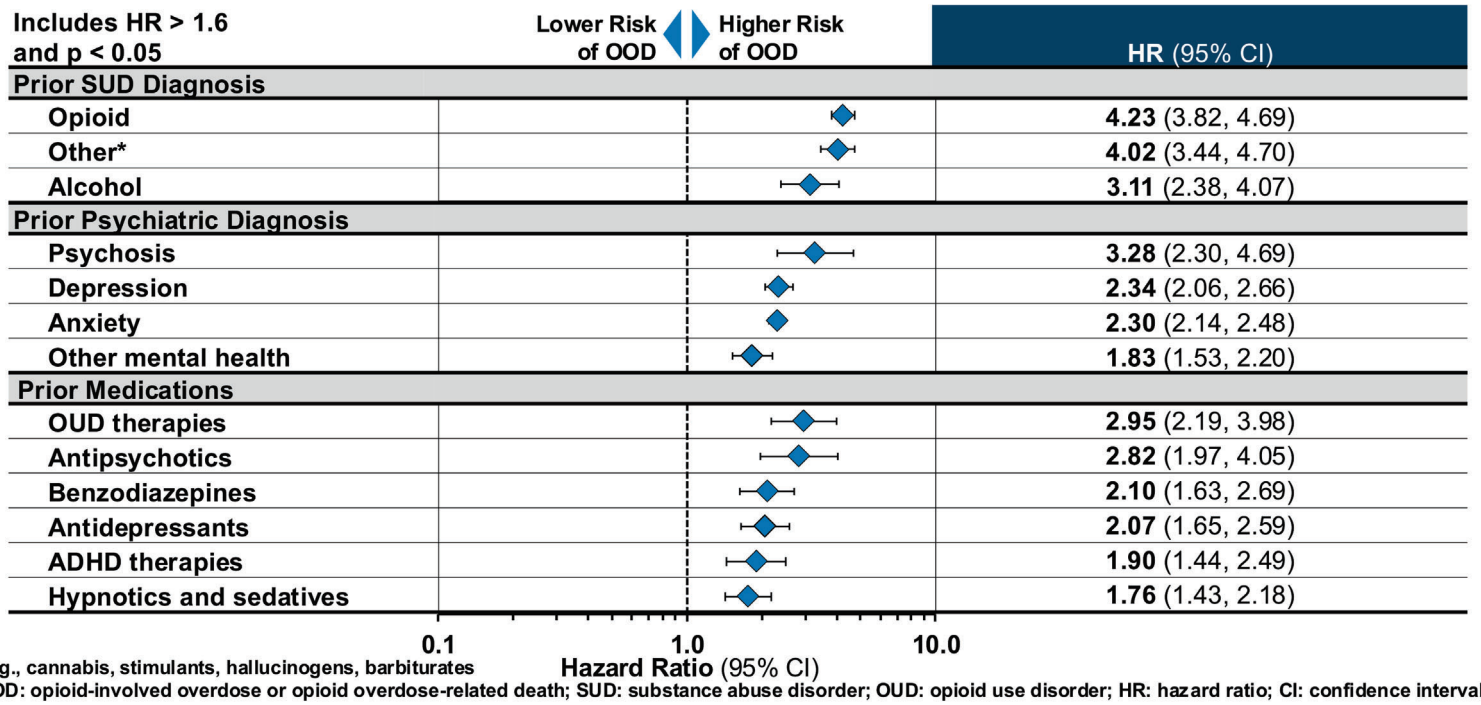
Study 3033-2: OOD by Age and Era



OOD: opioid-involved overdose or opioid overdose-related death; CI: confidence interval

Study 3033-2: Prior OUD and Psychiatric Diagnoses Predict for Overdose and Death; Aligning with Prior Literature (Adjusted for Age, Sex, Era, Region)

CO-69

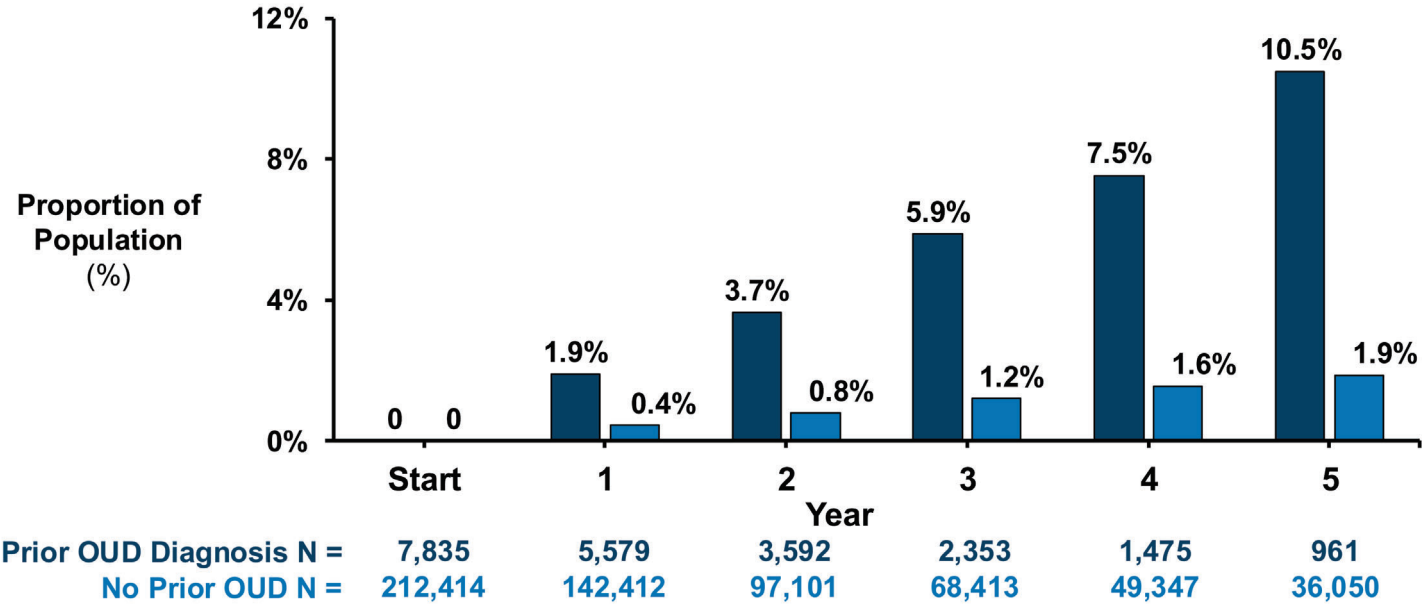


*e.g., cannabis, stimulants, hallucinogens, barbiturates

OOD: opioid-involved overdose or opioid overdose-related death; SUD: substance abuse disorder; OUD: opioid use disorder; HR: hazard ratio; CI: confidence interval

Study 3033-2: Cumulative OOD Risk by Prior OUD Diagnosis in Patients Receiving Long-Term Opioid Therapy for Pain

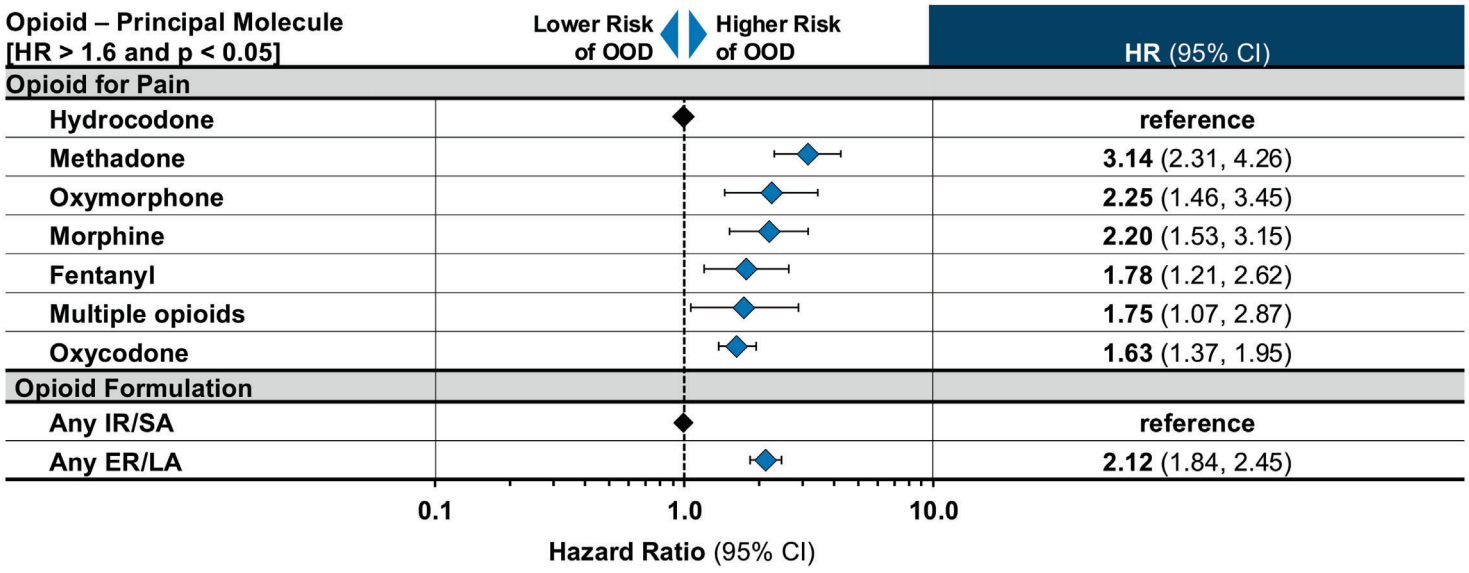
CO-70



OOD: opioid-involved overdose or opioid overdose-related death; OUD: opioid use disorder

CO-71

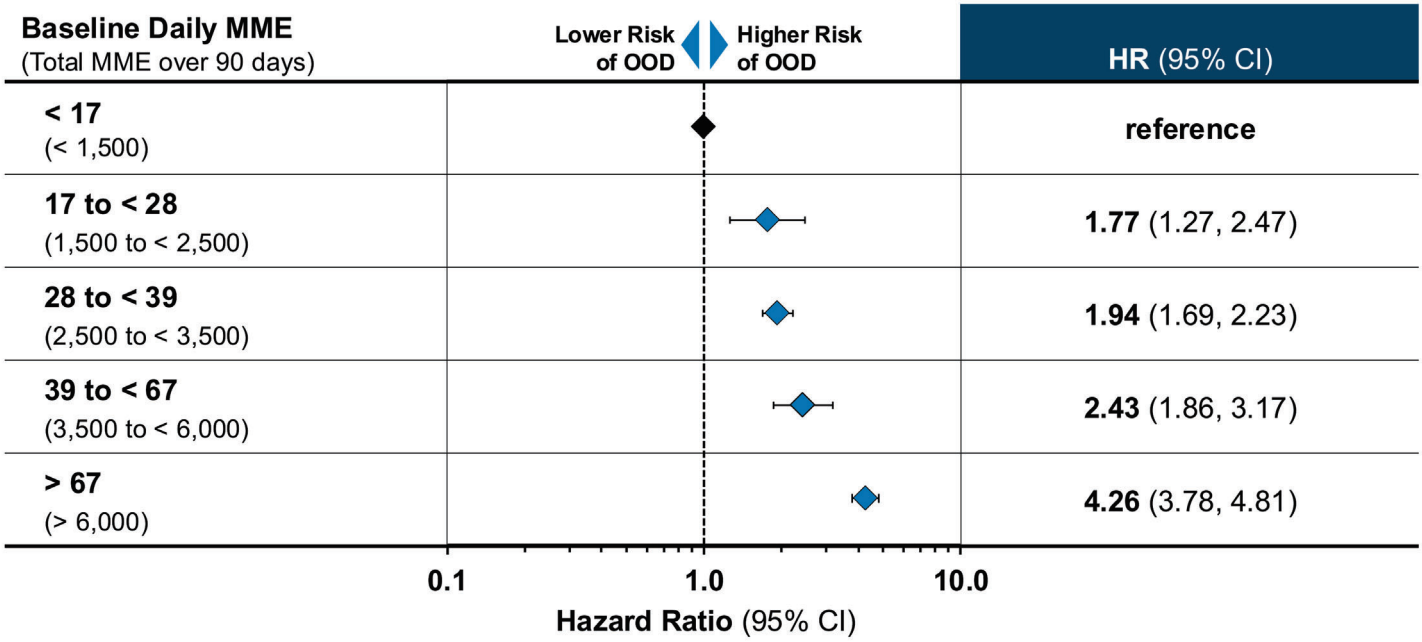
Study 3033-2: Other Risk Factors Identified that Align with Prior Literature (Adjusted for Age, Sex, Era, Region)



ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting; OOD: opioid-involved overdose or opioid overdose-related death
HR: hazard ratio; CI: confidence interval

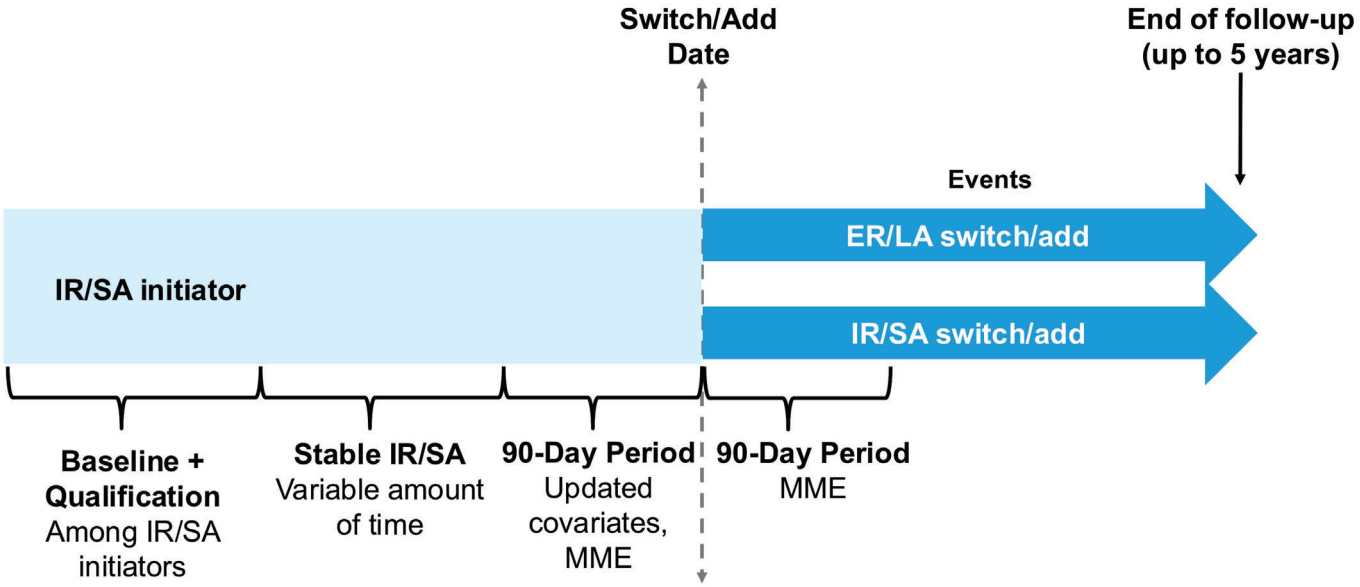
CO-72

Study 3033-2: OOD According to Baseline MME (Adjusted for Age, Sex, Era, Region)



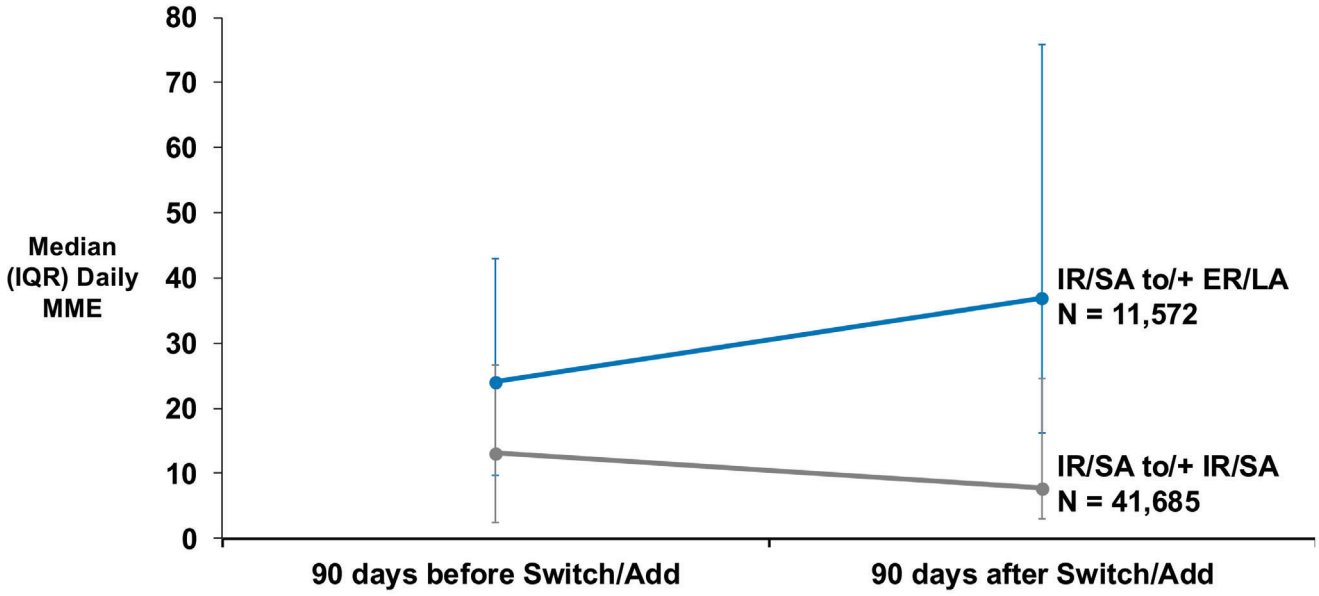
MME: milligram morphine equivalent; OOD: opioid-involved overdose or opioid overdose-related death; HR: hazard ratio; CI: confidence interval

Study 3033-2: Switch / Add Cohort



ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting; MME: milligram morphine equivalent

Study 3033-2: Switching to or Adding ER/LA Coincided with Increase in Opioid Dose



IQR: interquartile range; ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting; MME: milligram morphine equivalent

Rates in Switch/Add Cohort Higher than Primary Cohort ER/LA v IR/SA Effect Persists

	IR/SA to/+ ER/LA N = 11,572	IR/SA to/+ IR/SA N = 41,685
OOD	**333**	**812**
Person-years (1000s)	**30.3**	**111.2**
Rate per 1000 person-years	**11.0**	**7.3**

	HR (95% CI)
Unadjusted for baseline dose	**1.43** (1.09, 1.88)
Adjusted for baseline dose	**1.35** (1.02, 1.77)

ER/LA: extended release or long-acting; IR/SA: immediate release or short-acting; HR: hazard ratio; CI: confidence interval

Study 3033-2: Strengths and Limitations

Study Strengths

- Large size
- Validated OOD outcome (includes NDI linkage)
- New user cohort design with intention to treat follow-up
- Four data sources: Medicaid, managed care, and two commercial

Study Limitations

- Exposure based on recorded dispensing; actual opioid use not observed
- Did not account for opioid Rx obtained outside of insurance
- Medical characteristics inferred from diagnoses accompanying services; may not correspond to actual condition

OOD: opioid-involved overdose or opioid overdose-related death; NDI: national death index

Study 3033-2: Informs Incidence Rate and Risk Factors Regarding Opioid Overdose and Death

- People who began long-term opioids tend to continue them, at least through 5 years
  - Risk increment for OOD nearly constant over time
- Determinants of increased risk at baseline
  - High opioid dose
  - SUD and other serious mental health diagnoses and treatments
- Increased risk in those who started or switched to ER/LAs – closely correlated with higher opioid dose accompanying the switch
- Risk factor findings correspond to previous literature

OOD: opioid-involved overdose or opioid overdose-related death; SUD: substance use disorder; ER/LA: extended release or long-acting

Conclusions

Alexander M. Walker, MD, DrPH

Adjunct Professor, Epidemiology

Harvard T.H. Chan School of Public Health

PMR Studies Quantified Incidence Rates and Risk Factors

- Study 1
  - 1-year cumulative risks: Rx opioid misuse (~23%), Rx opioid abuse (~9%), opioid addiction (~1.6%)
  - Similar outcome prevalences in cross-sectional study of established patients
  - Among many prespecified risk factors, prior non-opioid, non-nicotine SUD was strongest risk factor of outcomes
- Study 2
  - 5-year cumulative risk of OOD averaged 2.1% across 4 sites
  - Among many prespecified risk factors, baseline dose, prior opioid use disorder, and mental health disorders/treatments strongest independent predictors of OOD

SUD: substance use disorder; OOD: opioid-involved overdose or opioid overdose-related death

Observational Studies Address Post-Marketing Requirements

- Studies fill previous evidence gaps related to risks associated with long-term use of prescription ER/LAs
- Used newly developed and best available scientific information
- Developed validated research measures for misuse, abuse, and addiction; confirmed validity of existing database algorithm for OOD
- For the five outcomes related to long-term opioid use in patients with chronic pain
  - Quantified incidence
  - Investigated many prespecified demographics/characteristics and confirmed strongest risk factors
- Risk factors generally align with published literature

OOD: opioid-involved overdose or opioid overdose-related death; ER/LA: extended release or long-acting

Additional Experts

Study 3033-1 Lead Biostatistician

Ning Smith, PhD
Kaiser Permanente Center for Health Research

Study 3033-3 and 3033-4 Principal Investigator

Karin Coyne, PhD, MPH
Vice President, Patient Centered Research
Evidera

Study 3033-5 Principal Investigator

Deborah Hasin, PhD
Professor of Epidemiology
Columbia University

Opioid Research Consultant

Sandra Comer, PhD
Professor of Neurobiology
Columbia University

Clinical Consultant

Charles Argoff, MD
Professor of Neurology
Albany Medical College

Clinical Consultant

Richard Rauck, MD
Carolinas Pain Institute

Post-Marketing Requirement (PMR) Study Results for Long-term Use of Extended-Release / Long-Acting Opioids in Patients with Chronic Pain

May 5, 2025

Anesthetic and Analgesic Drug Products Advisory Committee
Drug Safety and Risk Management Advisory Committee
Opioid Post-marketing Consortium (OPC)

Backup Slides Shown

Study 3033-5: PRISM-5-OP Used 3 Methods to Assess OUD

Assessment Method	Adjustments to 11 Criteria
Unadjusted measures	▪ [*Benchmark for comparison*] None. Criteria rated positive if present, without regard for "use as prescribed" or pain
DSM-5 measures	▪ Withdrawal and tolerance not rated positive (i.e., adjusted) if they occurred among participants who used opioids as prescribed, as defined in DSM-5
Pain-adjusted measures	▪ [*In addition to the DSM-5 adjustment*] DSM-5 behavioral criteria rated positive only if additional patient information from the PRISM-5-OP instrument indicated that the criteria represented addiction indicators (non-therapeutic intent) rather than treatment of pain (therapeutic intent)

Hasin et.al., 2022