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Epidemiology: Review of Final Study Report
ER/LA PMR 3033-9

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Drug Names:	Extended-Release/ Long-Acting Opioid Analgesics
Subject	PMR #3033-9 Final Study Report: "A Survey Study to Evaluate the Relation Between Doctor/ Pharmacy Shopping and Outcomes Suggestive of Misuse, Abuse, and/or Diversion"
Application Type/Number:	Multiple
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ACRONYMS

AIAA	Algorithmically-Indicated Abuse and/or Addiction
BPI	Brief Pain Inventory-Short Form
CMSD	Crowne-Marlowe Social Desirability Scale - Short Form
DPS	Doctor/Pharmacy Shopping
ER/LA	Extended Release/Long Acting
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database
IR	Immediate Release
NDA	New Drug Application
NSDUH	National Survey on Drug Use and Health
OPC	Opioid PMR Consortium
ORC	Opioid Post Marketing Research Consortium
PMR	Post-Marketing Requirement
POMAQ	Patient Opioid Misuse and Abuse Questionnaire
PPV	Positive Predictive Value
REMS	Risk Evaluation and Mitigation Strategy
SUD	Substance Use Disorder

EXECUTIVE SUMMARY

Background: In September 2013, the FDA issued a letter to sponsors of approved extended release/long acting (ER/LA) opioid analgesic new drug applications (NDAs), requiring postmarketing studies to assess the risks of misuse, abuse, addiction, overdose, and death.[1] It was anticipated that four observational studies would be necessary to answer these questions (# 2065-1 through # 2065-4). These four studies were subsequently broken into ten studies in a release and reissue[2] (studies #3033-1 through #3033-10). Three of these studies (studies #3033-8, #3033-9, and #3033-10; formerly 2065-4A, 2065-4B, and 2065-4C) aim to define and evaluate "doctor/pharmacy shopping." When applied to drugs with potential for abuse, the term "doctor/pharmacy shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers and filling them at multiple pharmacies without their coordination or knowledge. At present, there is no standard definition of doctor/pharmacy shopping, and its relation to misuse, abuse, and/or addiction has not been well characterized. However, there is also no ideal "gold" standard against which to measure the performance of doctor/pharmacy shopping metrics.

Therefore, the Opioid PMR Consortium (OPC) has conducted three complementary studies, post marketing requirement (PMR) #3033-8, #3033-9, and #3033-10, that evaluate these metrics in different settings and compare against different measures of misuse, abuse, and addiction—respectively, an administrative claims-based algorithm, patient self-report, and potentially aberrant behaviors documented in the medical record. The subject of this current review, PMR #3033-9, evaluates the association between doctor/pharmacy shopping, as defined using claims data, and abuse and misuse as measured through patient self-report using the web-based Patient Opioid Misuse and Abuse Questionnaire (POMAQ), which was developed and validated in PMRs #3033-3 and #3033-4. The 3033-9 PMR requirement is to conduct "*An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.*" The objectives, as described in the final study report, are: "*1. Investigate reasons patients go to multiple prescribers and/or pharmacies to obtain prescription opioids; and 2. To assess whether the proportion of patients reporting misuse, abuse and/or diversion, measured using a validated questionnaire, increases across doctor/pharmacy shopping categories defined a priori in Study 3033-8*."

The amended Final Study Report for PMR #3033-9, submitted by the OPC to the FDA on July 16, 2019 is the subject of this review. This version of the Final Study Report incorporates edits requested by FDA through an Information Request sent to the OPC on May 16, 2019. FDA comments for this Information Request were based on initial review of the amended Final Study Report, submitted by the OPC to the FDA on December 10, 2018.

The purpose of this review is twofold: (1) to determine whether this study fulfills PMR #3033-9, and (2) to interpret the findings of the study as they relate to doctor/pharmacy shopping outcomes metrics as a measure of possible misuse, and/or abuse.

Methods: This study used a cross-sectional self-report survey in combination with retrospective medical and pharmacy claims from the HealthCore Integrated Research Database (HIRD). The study population included adult patients with at least two opioid dispensings (immediate release (IR) or ER/LA opioid) during an 18-month period (7/1/2015-12/31/2016) identified in claims data. Patients were excluded if their charts could not be obtained, if they were on the "Do-Not-

[1] https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

[2] https://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm484415.pdf

Call" list, or if they had a known history of substance abuse identified through the HIRD administrative claims data. A four-category doctor/pharmacy shopping (DPS) classification scheme using claims data based on that developed in PMR #3033-8 was evaluated in relation to prescription opioid misuse and/or abuse defined by self-report in the POMAQ.

Results: After limiting to only patients with two or more IR or ER/LA opioid dispensings between 7/1/2015 to 12/31/2016 and applying other exclusion criteria, the sampling frame included 2.9% (n=129,650) of the total patient population; 10,081 were randomly selected and invited to participate in the study. Of those, 10.8% (n=1,085) met all screening criteria implemented at the beginning of the survey and completed the survey; most of the invited patients did not access the link (n=8,215).

The majority (78.7%; n=101,975) of patients in the sampling frame were classified into the "no shopping" category. A smaller percentage of patients were classified into the "minimal" and "moderate" DPS categories, 11.5% (n=14,954) and 7.0% (n=9,125), respectively. Only 2.8% (n=3,596) of patients in the sampling frame were classified into the "severe DPS category."[3] Patient characteristics differed according to the DPS category. Patients in the severe DPS category tended to be younger, female, more likely to have a pain diagnosis and more likely to have a diagnosis for anxiety and depression, compared to other DPS categories. This patient characteristic profile for severe shoppers was similar among patients who completed the survey and patients who were invited but did not complete the survey.

A pre-planned stratified sampling scheme resulted in approximately 271 patients in each of the four DPS categories. Among patients completing the survey (n=1085), 5.1% (n=55) reported abuse of prescription opioids, 8.0% (n=87) misuse of prescription opioids, 10.1% (n=110) reported abuse or misuse, and 2.9% (n=32) both abuse and misuse of prescription opioids. Among patients with no shopping, these numbers were 4.1%, 5.5%, and 7.8% for abuse, misuse, and abuse or misuse, respectively. There were ≤10 patients in the no shopping category with abuse and misuse (further detail was not reported for counts ≤10). These percentages were higher for patients classified with severe shopping: 5.9% abuse, 11.8% misuse, 12.6% abuse or misuse, and 5.2% abuse and misuse. However, the absolute number of patients with the abuse/misuse outcome in each category was small, ranging from only 14 to 34. Additionally, 14 patients were identified by the POMAQ as reporting diversion, but when stratified by DPS categories, all categories had 10 patients or fewer.

Only 15 patients answered "true" to visiting multiple doctors or healthcare providers in the past 3 months to get more prescription opioids. No specific reasons for visiting a doctor or healthcare provider were selected by more than ten patients. Fifty patients answered "true" to the question on using more than one pharmacy to obtain prescription opioids in the last 3 months. Reasons for using multiple pharmacies included convenience, price, insufficient stock, and concern about being caught, among others. Of note, for both questions (visiting multiple providers and multiple pharmacies), patients were restricted to only the reasons available in the survey or the "other" option. Therefore, common reasons selected are dependent on the options available for selection and may be representative of the survey options rather than the patients' perspective.

[3] No shopping: 1 prescriber (regardless of number of pharmacies), OR 1 pharmacy (regardless of number of prescribers), OR 2 prescribers and 2 pharmacies
Minimal shopping: 2 prescribers and >2 pharmacies, OR 3 or 4 prescribers and 2 pharmacies
Moderate shopping: 3 or 4 prescribers and >2 pharmacies, OR >4 prescribers and 2 pharmacies
Severe shopping: >4 prescribers and >2 pharmacies

There was a statistically significant trend from no DPS to severe DPS categories in the percentage of patients who reported (1) misuse, (2) abuse and misuse, or (3) abuse or misuse. The trend was not statistically significant for abuse or for diversion.

Results from multivariate regression analyses showed that after adjusting for covariates (potential risk factors other than DPS), patients in the severe DPS category had more than twice the odds of **misuse** compared to patients in the no DPS category (OR 2.1; 95% CI 1.1, 4.0). After adjusting for covariates, results for abuse and misuse were not significant (OR 2.78, 95% CI 0.98, 7.86). However, in unadjusted analyses, patients in the severe DPS category had nearly three times the odds of abuse and misuse compared to patients in the no shopping category (OR 2.95; 95% CI 1.05, 8.33). Despite the significant trend of misuse, misuse and abuse, and misuse or abuse, and the significant association for misuse, the total proportion of patients in the severe DPS category experiencing abuse (5.9%), misuse (11.8%), abuse or misuse (12.6%), or abuse and misuse (5.2%) was small; most of the patients in the severe DPS category were would not identified as abusing or misusing prescription opioids by self-report. Negative predictive value was high (above 90%) for most models, both adjusted and unadjusted, indicating that most patients included in the final sample without DPS behavior did not report misuse or abuse. Positive predictive values were low and the positive predictive value for the adjusted model predicting misuse was 12.1%, indicating that only about 12% of patients included in the final sample with DPS behaviors reported misuse.

Interpretations and Conclusions: This study fulfills PMR #3033-9.

Overall, this study was sufficiently designed and implemented to provide insight into a challenging area of public health. The information from this study suggests that DPS behavior is complex and likely driven by multiple clinical, behavioral and logistical factors; abuse and misuse may play a role in DPS behavior, but a multitude of other factors should be considered as well.

The study did not identify doctor/pharmacy shopping as a sufficient proxy for misuse or abuse, but it provided some insights into the patient experience. The study found the potential for lack of the provider's understanding of the patient's pain and issues of convenience and availability from the pharmacy from self-report of DPS reasons. Additionally, the results from this analysis suggest that DPS behavior is likely a reflection of multiple factors related to the potentially complex experiences of patients with chronic pain. Severe DPS was associated with increased pain and also with diagnoses for anxiety and depression. This is consistent with previous literature describing a complex interaction of other medical conditions and treatment of pain. Only misuse, and not abuse, was found to be associated with DPS in logistic regression models, although the sample size was based on a power calculation to detect an odds ratio of 2.5 or greater, larger than most results in this study. Therefore, if the study had been powered to detect a lower odds ratio, we may have detected an association between abuse and DPS.

The results from this study were intended to add to information obtained from studies 3033-8 and 3033-10. **All three studies found that the DPS measure was not able to discriminate well between patients with and without the abuse/misuse/addiction outcomes and identified DPS as a weak marker of these outcomes**.

Several limitations were identified which affect the interpretation of the study results. The lack of generalizability was a major limitation. The study excluded patients diagnosed with substance use disorder (SUD), the primary population of interest for these objectives. The study was also limited to patients with health insurance and those not paying cash for prescriptions. Although this population is not representative of the general U.S. population, it reflects the population for

which DPS metrics are most often applied. The self-report survey was subject to low response rate, resulting in a select group of patients answering the questions. Another major limitation is that the time period for measuring DPS in the claims data differed from the time period that the POMAQ was administered (time period for collecting abuse and misuse outcomes); behavior may have changed between the time when DPS and misuse or abuse were measured. A third major limitation is that limited information was obtained from self-reported reasons for visiting multiple healthcare providers since all response options had 10 or fewer patients selecting the specific reason, possibly due to reporting bias. Additionally, some important covariates, such as total number of opioid dispensings and duration of opioid therapy were not controlled for in the logistic regression models, despite being collected by investigators and associated with DPS. Finally, the outcomes of abuse and misuse were measured using self-report on the POMAQ and, although previously validated under other study conditions, may not fully capture all misuse and abuse in this study population.

Given the widespread use of DPS metrics, the association between doctor pharmacy shopping and misuse and abuse should be further explored in future studies. Future studies should be sufficiently powered for smaller effect sizes. These future studies should also control for additional factors such as number of opioid dispensings to minimize confounding and doctor pharmacy shopping should be measured at the same time as misuse and abuse. Additionally, future studies should investigate this association among diverse populations, including persons without insurance, or cash paying, and among persons who may have substance use disorder.

In summary, the results from this report imply that DPS (in particular, the severe shopping behavior) may serve as a screening tool to identify patients with claim-identified opioid misuse. However, due to the lack of predictive power (low PPV), it should not be used as a surrogate outcome. This finding is similar to results seen in PMR 3033-10.

1 INTRODUCTION

The purpose of this review is to determine whether the study has fulfilled the objectives of PMR 3033-9 (formerly 2065-4B), and to interpret the study findings with respect to the reasons that patients go to multiple providers and/or pharmacies. In doing so, this review will assess the relationship between doctor/pharmacy shopping using the category definitions developed in study 3033-8 and patient reported misuse and abuse, measured using a previously validated web-based survey.

1.1 BACKGROUND

This review evaluates the final report from the study to fulfill ER/LA opioid analgesic PMR 3033-9 (formerly 2065-4B), titled "*A Survey Study to Evaluate the Relation Between Doctor/ Pharmacy Shopping and Outcomes Suggestive of Misuse, Abuse, and/or Diversion.*" PMR 3033-9 is one of three PMR studies (along with 3033-8 and 3033-10) that assess DPS in relation to different measures of misuse, addiction, and/or abuse. These three studies were originally proposed to fulfill PMR 2065-4, which was issued to all holders of approved ER/LA opioid analgesic NDAs in September 2013. PMR 2065-4 required these sponsors to *conduct a study to define and validate 'doctor/pharmacy shopping' as outcomes suggestive of misuse, abuse and/or addiction.* With FDA's release and reissue of the ER/LA opioid analgesic PMRs in July 2015, these three studies became individual PMRs (3033-8, 3033-9, and 3033-10). PMR 3033-9, the subject of this review, states that the ER/LA opioid analgesic sponsors must conduct *an observational study using a validated patient survey to evaluate the association between doctor/ pharmacy shopping outcomes and self-reported misuse and abuse.* PMR 3033-8 uses coded medical terminology and other electronic healthcare data to define and validate DPS outcomes.

PMR 3033-10 uses medical record review to assess the association between DPS and patient behaviors suggestive of misuse, abuse, and/or addiction.

1.2 REGULATORY HISTORY

The first ER/LA opioid analgesic was approved by the FDA in 1987, and numerous additional NDAs have been approved since. A complete list of ER/LA opioid analgesics and NDAs issued this PMR is included in **Appendix A**. In addition to the ER/LA opioid analgesic class-wide PMRs, FDA has taken multiple regulatory actions pertaining to the entire class of ER/LA opioid analgesics. A class-wide Risk Evaluation and Mitigation Strategy (REMS) took effect in 2012, and major labeling changes and a boxed warning were announced in 2013 and finalized in 2014.

1.3 PRODUCT LABELING

Appendix B contains labeling language from the ER/LA opioid analgesic MS Contin, (extended-release morphine sulfate), including *Indications and Usage*, *Abuse and Dependence*, and the Boxed Warning. This section briefly summarizes information relevant to this review; direct quotations are *italicized*.

- *Indications and Usage: indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
- *Drug Abuse and Addiction:*
  - A schedule II, controlled substance that is liable for abuse and criminal diversion
  - *Drug-seeking* behaviors including *doctor shopping* are common among people who abuse or are addicted to opioids.
- *Boxed Warning:* [This drug] *exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing [this drug], and monitor all patients regularly for these behaviors and conditions.*

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS TO BE REVIEWED

The following materials are the subject of this review:

- Final Study Report for ER/LA PMR 3033-9 (formerly #2065-4B), titled: "*A survey study to evaluate the relation between doctor/pharmacy shopping and outcomes suggestive of misuse, abuse, and/or diversion*" version dated July 16, 2019
  - PMR 3033-9 tables and figures (Appendix B of the Final Study Report)
- Information Request sent to OPC on May 16, 2019 with responses from OPC received on July 16, 2019 (included as **Appendix C** of this review)

2.2 CRITERIA APPLIED TO REVIEW

This review evaluates the analysis described in the Final Study Report for the successful completion of the study objectives and planned analyses as described in the approved final protocol, as well as the validity and appropriate interpretation of the results, based on sound epidemiologic principles.

3 REVIEW RESULTS

3.1 STUDY OBJECTIVES

There are two objectives for study 3033-9 as described by the OPC:

- *To investigate reasons patients go to multiple prescribers and/or pharmacies to obtain prescription opioids; and*
- *To assess whether the proportion of patients reporting misuse, abuse, and/or diversion, measured using a validated questionnaire, increases across doctor/pharmacy shopping categories defined a priori in Study 3033-8.*

3.2 STUDY OVERVIEW

Study 3033-9 is one of three studies with the overall objective to define and validate possible DPS as outcomes suggestive of misuse, abuse, and/or addiction.

Study 3033-9 investigated self-reported reasons for DPS and assessed the potential association between DPS categories, as defined by claims data and based on the definition developed in Study 3033-8, and the proportion of patients reporting misuse, abuse, and/or diversion. Study 3033-9 utilized a longitudinal medical and pharmacy claims database (HealthCore Integrated Research Database; HIRD) and self-reported data collected from a web-based patient survey. The self-report survey consisted of three validated survey instruments, the Patient Opioid Misuse and Abuse Questionnaire (POMAQ), the Brief Pain Inventory (BPI), and the Crowne-Marlowe Social Desirability Scale-Short Form. Patients ages 18 years and older with at least two pharmacy claims for any opioid analgesic from 7/1/2015 to 12/31/2016 were eligible to participate in the patient survey. Participants were classified into one of the four DPS categories (no, minimal, moderate, and severe shopping) and a stratified random sampling was used to get a targeted 271 completed surveys in each shopping category. This sample size was based on a power calculation to detect an odds ratio of 2.5 or greater.

Descriptive analyses were performed for the number of eligible patients and patient characteristics for each stage of sampling and stratified by DPS category. Self-reported reasons for visiting multiple providers were described to address the first objective.

Descriptive and analytic methods were also employed to address the second objective. Cochran-Armitage tests were performed to assess trends across the shopping categories. Logistic regression was used to examine the odds of experiencing the outcome (misuse, abuse, misuse and abuse, misuse or abuse, diversion) among patients in each category. Sensitivity analyses were used to assess the degree that missing information could contribute bias and affect the results.

The study described characteristics of participants identified as conducting DPS to obtain prescription opioid analgesics. The report includes patient self-reported reasons for DPS for prescription opioid analgesics. The study identified statistically significant trends in the DPS categories for the outcome of **misuse**, but not for the outcomes of abuse, or diversion. However, only a small proportion of patients in the severe DPS category reported abuse and/or misuse and most self-reported reasons for DPS were unrelated to abuse, misuse, or diversion.

3.3 STUDY METHODS

3.3.1 Design and setting

This study was designed as a cross-sectional, web-based patient survey utilizing retrospective information from a medical and pharmacy claims database to identify and recruit eligible participants. Medical and claims information also contributed covariate and demographic information.

3.3.1.1 Selection, inclusion and exclusion criteria

Inclusion criteria:

- At least 18 years old on the date of the first IR or ER/LA opioid dispensing
- At least two pharmacy claims for any IR or ER/LA opioid analgesic on different dates during the period 7/1/2015 to 12/31/2016.
- Continuous medical and pharmacy benefits with a health plan in the HIRD during the period of 7/1/2015-12/31/2016
- Currently enrolled in the health plan, commercially insured, and survey eligible at the time the sampling frame was created
- Known email and/or physical address

Exclusion criteria:

- On the HealthCore or Anthem "Do-Not-Call" list
- Patients with known history of drug/substance abuse identified through the HIRD administrative claims data (not permissible to access their medical records)
- Additional exclusions were based on the following screening requirements:
    - Patients who did not indicate that they had read about all pertinent aspects of the study and agree to participate
    - Patients who failed to validate their name and/or date of birth
    - Patients who were unable to understand the survey questions as designed (e.g., non-English speaking, etc.)
    - Patients who stated that they had not filled at least two prescriptions for opioid analgesics in the past 18 months
    - Patients employed by Opioid Post Marketing Research Consortium (OPC) International, HealthCore, the FDA, or a pharmaceutical company that is part of the OPC

3.3.1.2 Data sources

Two main data sources contributed to this analysis: 1) patient self-report data from three validated survey instruments, and 2) medical and pharmacy claims data.

3.3.1.2.1 Patient self-reported data

Patients with at least two opioid prescription claims in the claims data and who met exclusion and inclusion criteria were recruited for participation on the self-report questionnaires using stratified random sampling. Questionnaire participants completed three different surveys: Brief Pain Inventory-Short Form (BPI), Crowne-Marlowe Social Desirability Scale - Short Form (CMSD), and Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Completion of these three surveys is reported together as "survey completion."

Questionnaires were sent to the participants as a link to a web-based survey platform either through email or on a hard copy letter to the participant's physical address. Participants who completed the survey received a $50 Amazon gift card.

3.3.1.2.2 Medical and pharmacy claims data

The HIRD includes medical and pharmacy claims from multiple health plans throughout the United States. Claims and enrollment information can be tracked for individual health plan members within HIRD. As of June 2018, HIRD included claims information from approximately 49 million persons, of which 13 million were enrolled in a health plan with medical and pharmacy eligibility. Some health plans contributing claims information to the HIRD have

prescriber limits on opioid analgesic prescriptions. Claims data does not collect information on prescriptions paid for in cash.

3.3.1.2.3 Time period

Figure 1 is adapted from Figure 1A of the Final Study Report and shows a timeline for the study period. Claims data from 7/1/2015 to 12/31/2016 were queried retrospectively for patients meeting eligibility requirements and to classify their DPS behavior. This period started in 7/1/2015 to capture the most recent 18 months of available claims data at the time that the sampling frame was defined.

Surveys were completed starting on 6/16/2017. The last survey was completed in mid-June 2018, 17.5 months after the end of the 18-month claims period (12/31/2016).

POMAQ survey questions asked for behaviors in the past three or 12 months from the day they completed the survey. Questions on the BPI asked about average pain, pain in the last 24 hours or current pain. The CMSD included questions about current or past behaviors with no specified timeframe.

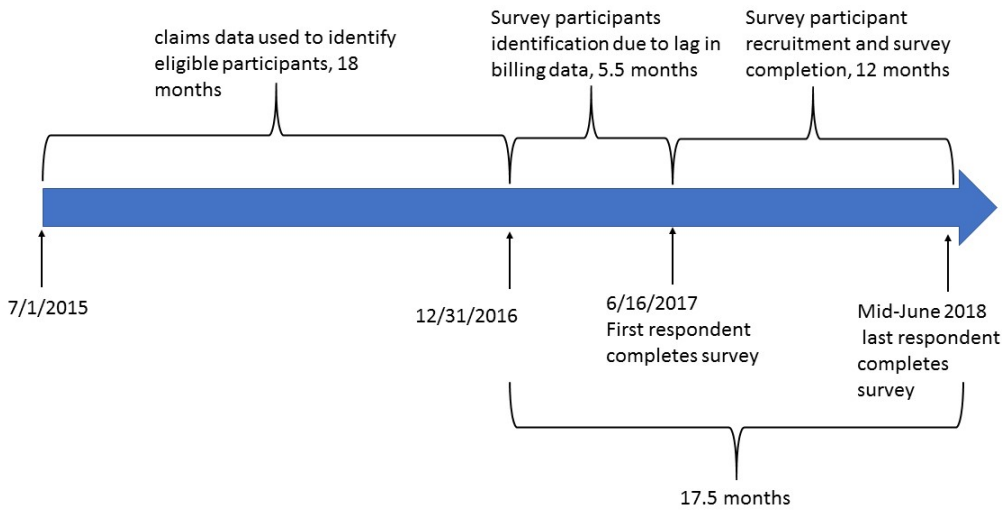

Figure 1. Study timeline adapted from Figure 1A of the Final Study Report

3.3.1.2.4 Protected health information requirements

HealthCore maintains data sharing agreements with entities providing health data to HIRD and they maintain compliance with Health Insurance Portability and Accountability Act (HIPAA). The New England IRB approved a Waiver of Authorization and the National Institutes of Health issued a Certificate of Confidentiality so that study personnel could access protected health information when contacting patients for the survey.

3.3.2 Study variables

Medical and pharmacy claims, and self-report survey data provided information for study variables.

3.3.2.1 Study variables from claims data

The claims data provided information to determine DPS (independent variable for primary analysis), factors for exclusion from survey participation, covariates and descriptive variables.

3.3.2.1.1 Independent variable- doctor/pharmacy shopping

DPS was defined based on the number of prescribers (doctors and healthcare providers) and pharmacies that the patient visited and were associated with a drug dispensing during an 18-month period according to the HIRD claims data. The doctor/pharmacy shopping categories were based on the definitions developed in PMR Study #3033-8 and adapted slightly for use in Studies 3033-9 and 3033-10 because the data source used in these studies does not contain the information that would be required to define practices or outlets. These modifications and definitions were described in detail in the August 10, 2015 report titled "OPC OSW: Study 4A - Cross-sectional Study to Define and Validate 'Doctor/pharmacy Shopping' as outcomes suggestive of abuse and/or addiction: Definitions of Shopping Behavior in Health Insurance Data for Use in Studies 4B and 4C."

Shopping categories were as follows:

1. No shopping behavior
    - 1 prescriber (regardless of number of pharmacies), OR
    - 1 pharmacy (regardless of number of prescribers), OR
    - 2 prescribers and 2 pharmacies
2. Minimal shopping behavior
    - 2 prescribers AND >2 pharmacies OR
    - 3 or 4 prescribers AND 2 pharmacies
3. Moderate shopping behavior
    - 3 or 4 prescribers AND >2 pharmacies OR
    - >4 prescribers AND 2 pharmacies
4. Severe shopping behavior
    - >4 prescribers AND >2 pharmacies

3.3.2.1.2 Other variables from claims data

Other variables collected from the claims data include age, type of opioid (IR only versus ER/LA with or without IR), average daily morphine milligrams equivalent, number of opioid dispensings, duration of opioid use, some demographic information, pain diagnoses, psychiatric diagnoses, concomitant medications with abuse potential, all-purpose health services utilization (number of doctor office visits, emergency room visits, hospitalization, and classes of medications dispensed).

3.3.2.2 Study variables from survey data

Self-report survey data provided information on abuse, misuse, abuse or misuse, abuse and misuse, and diversion (dependent variables for primary analysis), demographics, pain, and social desirability.

3.3.2.2.1 Dependent variables- abuse and/or misuse, diversion (Patient Opioid Misuse and Abuse Questionnaire)

The POMAQ (Appendix D) includes 19 items which are used to identify abuse, misuse, abuse and misuse, abuse or misuse, or diversion by self-report. Many of these 19 questions are initiated with a broad question asking about behavior in the past year. If a patient answered "Yes" to a past year behavior, they are given sub-question(s) asking about intentions for the behavior occurring in the past 3 months. If a respondent selects any item identified as misuse, abuse, or diversion without a required frequency and time period, then they are identified as having that outcome, even if only one item indicating that behavior is selected. There is no "score" or addition of items for a respondent to be considered as conducting misuse, abuse, or diversion. Likewise, if a respondent selects any item identified as misuse, abuse, or diversion with a required frequency and time period, then they are identified as having that outcome if they meet the frequency and time period requirements, even if only one item indicating that behavior is selected. The timeframe for these outcomes as determined from the POMAQ are misuse, abuse, or diversion within the last three months.

3.3.2.2.2 Other survey data

Other variables from the survey data include self-reported demographic variables for race/ethnicity, education, marital status, employment, and income.

Two additional surveys were included along with the POMAQ: The Brief Pain Inventory-Short Form (BPI) and Crowne-Marlowe Social Desirability Scale- Short Form (Appendix D). The BPI measures self-reported pain through two domains (pain intensity and pain interference) with a total of 11 items. Each item on the BPI is scored using a 1-10 scale. The Crowne-Marlowe Social Desirability Scale-Short Form includes 13 items and a summary score is calculated. A higher summary score on the Crowne-Marlowe Social Desirability Scale-Short Form indicates a stronger tendency to respond in a socially desirable manner.

3.3.3 Sample size and power

A stratified (by DPS category) random sample of patients was selected for medical record review; the target number of patients in each of the four DPS categories was 271 patients. Two hundred and seventy-two patients in moderate shopping category were recruited, leading to 1,085 patients (who completed the survey) in total.

Details of the reasoning behind the specified targets by category and relevant assumptions were included in the study protocol. Sample size requirements were calculated at varying levels of "misuse, abuse, and/or diversion" assuming the use of the Cochran-Armitage Trend Test in Proportions at 90% power and alpha=0.05. Sample size requirements were not calculated separately for abuse, misuse, or diversion.

3.3.4 Statistical analyses

Statistical analysis consisted of both descriptive and analytic methods.

3.3.4.1 Descriptive statistics

The distribution of demographic and clinical variables, BPI pain data, and misuse, abuse and diversion were stratified by DPS categories. Results were presented for participants completing the survey (all variables), survey participants invited to complete the survey but not completing the survey (some demographic and clinical variables), and patients in the sampling frame (some

demographic and clinical variables). Multiple descriptive statistics were used, such as mean, median, 25th and 75th percentiles, minimum and maximum.

3.3.4.1.1 Attrition and survey response rates

Attrition occurred at multiple steps throughout the study. Patients with at least two opioid dispensings were identified from the claims data. Exclusion criteria were applied, further decreasing the eligible sample. A stratified random sampling scheme was employed to meet sample size requirements for each level of DPS.

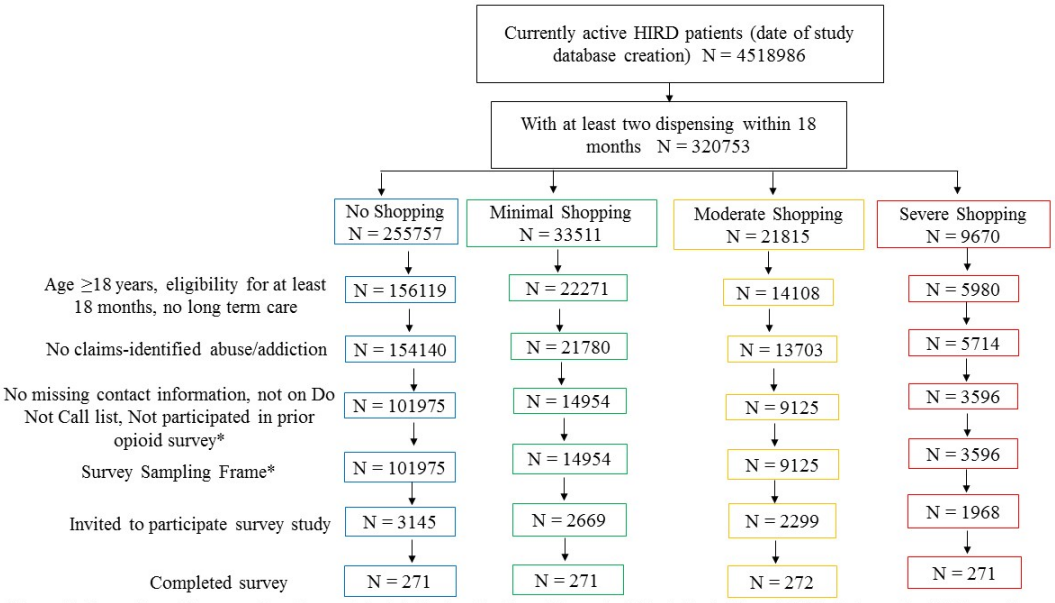

Figure 2. Formation of the sampling frame. Adapted for brevity from Figure 1 of Final Study Report 3033-9, Appendix B; N=number,
* A total of 5,544 patients who had been invited to participate in a different opioid-related survey study were excluded from the sampling frame

3.3.4.2 Analysis

3.3.4.2.1 Test for trend

The Cochran-Armitage test for trend was used to assess the statistical significance of trend in DPS categories among persons who self-reported abuse, misuse, abuse or misuse, abuse and misuse, and diversion. This analysis was conducted for all patients completing the survey and additionally stratified by pain intensity categories (BPI pain survey) and social desirability levels (Marlowe-Crowne Social Desirability Scale-Short Form).

3.3.4.2.2 Regression analysis

Logistic regression was used to assess the association between DPS and abuse/misuse outcomes. Diversion was not assessed as an outcome in logistic regression due to the small number of diversion reports. The four abuse/misuse outcomes were defined as binary variables, and as explained in the OPC response to the Information Request (May 16, 2019; **Appendix C**); due to the specification of the binary outcome variable, some participants were excluded from some analyses. Table 1, created by the reviewer, describes outcome variable specification as follows: abuse (with or without misuse) versus no abuse and no misuse; misuse (with or without abuse)

versus no abuse and no misuse; abuse and misuse versus no abuse and no misuse; and abuse or misuse versus no misuse and no abuse.

Table 1. Outcome variable specification for regression analyses

Possible combinations of abuse and misuse		Regression model outcome of interest and specification for possible combinations of abuse and misuse			
Abuse	**Misuse**	**Abuse N=1030**	**Misuse N=1062**	**Abuse and Misuse N=1007**	**Abuse or Misuse N=1085**
Yes	**Yes**	1	1	1	1
Yes	**No**	1	Excluded n=23	Excluded n=78	1
No	**Yes**	Excluded n=55	1		1
No	**No**	0	0	0	0

Source: PMR 3033-9 Final Study Report, created by reviewer with information from Final Study Report text and tables

Unadjusted and adjusted models were used for regression analysis. Both adjusted and unadjusted models used "no shopping" as the referent group for the independent variable of DPS. Covariates used for adjustment were age, gender, geographic region of residence, type of opioid used, average daily opioid dose, use of other drugs with abuse potential, history of psychiatric comorbidities, and type of pain diagnosis. Multiple steps were taken to select and retain covariates in the final adjusted models, including backward regression.

3.3.4.2.3 Sensitivity analysis

Multiple sensitivity analyses were performed:

1. Covariates that were potentially correlated with items on the POMAQ were excluded from the adjusted logistic regression.
2. Doctors and pharmacies that could not be identified
    a. Doctors and pharmacies that could not be identified were assumed to be a unique doctor or pharmacy.
    b. Doctors and pharmacies that could not be identified were assumed to be the same as the most recent identifiable doctor or pharmacy that the patient visited (last observation carry forward method).
3. Restricted to survey respondents whose index date was on or before December 31, 2015.
4. Logistic regression analysis including survey participants as well as persons excluded from survey participation based on history of SUD as defined by claims. Dependent variable is abuse/ misuse (defined in claims) and independent variable is DPS (defined by claims). All patients with SUD were defined as having the abuse/misuse outcome.
5. Assessment of factors associated with study exclusion
    a. Numbers and percentages stratified by DPS shopping category
        i. All patients in sampling frame
        ii. Patients on do-not-call list (exclusion)
        iii. Patients with a history of drug/ substance abuse

iv. Patients whose responses did not satisfy screening criteria

b. Logistic regression for association of study exclusion with DPS
   i. Probability of being excluded due to being on do-not-call list
   ii. Probability of being excluded due to history of drug/ substance abuse
   iii. Probability of being excluded due to not meeting screening criteria at the start of the survey among participants invited to participate in the survey

3.4 STUDY RESULTS

3.4.1 Study population and survey response rates

Seven percent (7.1%; 320,753 out of 4,518,986) of patients who were actively enrolled in one of the health plans in the HIRD had two or more dispensings of IR or ER/LA opioid analgesics between 7/1/2015 and 12/31/2016. Among patients with at least two opioid analgesic prescriptions, nearly 67% (n=214,676) attended only one or two prescribers and one or two pharmacies, with more than a quarter of these patients (28.5%; n=61,192) only attending one prescriber and one pharmacy (data not shown; Table 1 Appendix B Final Study Report).

After applying exclusion criteria, the final sampling frame included 129,650 patients, approximately 2.9% of the total patient population and 40.4% of the patient population with two or more opioid dispensings. Table 2 in this review (adapted from Table 2 Appendix B Final Study Report) shows the overall distribution by DPS category and survey response rates by DPS category. The majority (78.7%) of patients in the sampling frame were classified into the "no shopping" category. A smaller percentage of patients were classified into the "minimal" and "moderate" DPS categories, 11.5% and 7.0%, respectively. Only 2.8% of patients with at least two prescription opioid dispensings were classified into the "severe DPS category." From the sampling frame, 10,081 patients were randomly selected and invited to participate in the study, ranging from 1,968 to 3,145 patients within each DPS category, to result in a final sample of at least 271 participants in each DPS category (moderate shopping had n=272). A total of 1,085 patients (10.8% of invited patients) completed the survey and met all screening criteria implemented at the beginning of the survey. Of the patients invited to participate in the web-based survey, 8,215 did not access the link, 215 refused or did not complete the survey and 566 failed screening questions implemented at the beginning of the survey.

The survey response rates (defined as number completing survey/ number invited to participate) for each DPS category increased slightly with DPS severity, from 8.6% among persons with no DPS to 13.8% among persons with severe DPS.

Table 2. Survey response by doctor/pharmacy shopping category

	N Total	No shopping		Minimal shopping		Moderate shopping		Severe shopping	
		N = 101975		N = 14954		N = 9125		N = 3596	
		N	%	N	%	N	%	N	%
Total patients in the sampling frame	129650	101975	78.7	14954	11.5	9125	7.0	3596	2.8
Patients invited to participate in the survey	10081	3145	31.2	2669	26.5	2299	22.8	1968	19.5
Patients never responded to recruitment attempts	8215	2556	31.1	2209	26.9	1871	22.8	1579	19.2
Maximum number of contact attempts made	8165	2555	31.3	2171	26.4	1871	22.8	1568	19.1

Survey targets met, not pursued	50	≤10		38	76.0	0	0.0	11	22.0
Patients responded to recruitment attempts	1866	589	31.6	460	24.7	428	22.9	389	20.8
Ineligible to participate based on responses to screening criteria	566	253	44.7	136	24.0	110	19.4	67	11.8
Eligible	1300	336	25.8	324	24.9	318	24.5	322	24.8
Completed survey (survey respondents)	1085	271	25.0	271	25.0	272	25.1	271	25.0
Started but did not complete survey	210	64	30.5	52	24.8	45	21.4	49	23.3
Refused/did not consent to participate	≤10	≤10		≤10		≤10		≤10	
Survey response rate	10.8%	8.6%		10.2%		11.8%		13.8%	

Source: PMR 3033-9 Final Study Report, Adapted from Table 2. Survey Response by Doctor/Pharmacy Shopping Category

3.4.1.1 Demographics

Survey respondents were more likely to be younger and female compared to survey non-respondents and all patients in the sampling frame (Table 3; adapted from Table 3 Appendix B Final Study Report). Race/ ethnicity, education, marital status, employment, income and healthcare utilization information were not available for survey non-respondents nor for the entire sampling frame.

Table 3. Demographics by survey response status

	Survey respondents N (%)	**Survey non-responders N (%)**	**Patients in the sampling frame N (%)**
	1085	8996	129650
Age category			
18 to 34	246 (22.7)	1656 (18.4)	23437 (18.1)
35 to 49	426 (39.3)	3032 (33.7)	40537 (31.3)
50 to 64	403 (37.1)	4145 (46.1)	61006 (47.1)
65 and over	≤10	163 (1.8)	4670 (3.6)
Gender			
Male	397 (36.6)	3938 (43.8)	60860 (46.9)
Female	688 (63.4)	5058 (56.2)	68790 (53.1)
Geographic Region of Residence (US)			
Midwest	368 (33.9)	2768 (30.8)	36503 (28.2)

Northwest	76 (7.0)	676 (7.5)	11838 (9.1)
South	369 (34.0)	2897 (32.2)	44481 (34.2)
West	272 (25.1)	2655 (29.5)	36828 (28.4)
Missing/ unknown	0	0	0

Source: PMR 3033-9 Final Study Report, Adapted from Table 3. Demographic Characteristics and Healthcare Utilization in the Most Recent 18 Months by Doctor/ Pharmacy Shopping Category and Survey Status

Most patients received IR opioid analgesics alone. The total number of opioid dispensings and duration of opioid analgesic use increased with increasing severity of DPS. No trend was observed in the estimated average daily dose of opioids (data not shown; Table 4 Appendix B Final Study Report).

3.4.1.2 Doctor/pharmacy Shopping

Among survey respondents, the percentages of some demographic variables varied by DPS severity. Although not assessed with statistical analysis, there was a higher percentage of female patients and patients without a high school degree in the severe DPS category. There was also a lower percentage of patients with employment (full or part time) in the severe DPS category (data not shown; Table 3 Appendix B Final Study Report).

3.4.1.3 Misuse and Abuse

Among the 1,085 patients who completed the survey, 55 (5.1%) reported abuse, 87 (8.0%) reported misuse, 110 (10.1%) reported abuse or misuse, and 32 (2.9%) reported abuse and misuse (Table 4 of this review; Table 7a Appendix B Final Study Report). All outcomes of abuse and misuse increased by increasing DPS severity. Only 14 (1.3%) of participants reported diversion. Results of diversion by DPS are not available due to low numbers.

Table 4. Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Responses

	Total N	N with Outcome		No shopping		Minimal shopping		Moderate shopping		Severe shopping	
				N = 271		N = 271		N = 272		N = 271	
	N	N	%	N	%	N	%	N	%	N	%
Misuse and abuse categories											
Abuse	1085	55	5.1	11	4.1	12	4.4	16	5.9	16	5.9
Misuse	1085	87	8.0	15	5.5	18	6.6	22	8.1	32	11.8
Abuse or Misuse	1085	110	10.1	21	7.8	23	8.5	32	11.8	34	12.6
Abuse and Misuse	1085	32	2.9	≤10		≤10		≤10		14	5.2
Diversion	1085	14	1.3	≤10		≤10		≤10		≤10	

Source: PMR 3033-9 Final Study Report, Adapted from Table 7a. Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Responses

3.4.2 Objectives

Objective 1: *"Investigate reasons patients go to multiple prescribers and/or pharmacies to obtain prescription opioids."* The study addressed the first objective through multiple

approaches. The most direct way was to ask the patients why they visited multiple prescribers and pharmacies in the last three months or last year to obtain prescription opioid analgesics using the POMAQ. Table 5 of this review (Table 7b Appendix B Final Study Report) includes the results for patient-reported reasons for visiting multiple doctors and healthcare providers. Few patients responded that they visited multiple doctors or healthcare providers in the last year (n=67) or last three months (n=15). Additionally, due to confidentiality reasons from small numbers, after stratifying by DPS severity, all reasons were reported as "≤10"; these reasons could be endorsed by anywhere from one to 10 participants. Among those reporting visiting multiple healthcare providers in the last three months, at least one person selected a reason indicating that they wanted more opioids to get high. No one selected the reason indicating a desire to sell the medication, and the majority of the other answers selected were related to seeing multiple doctors to manage the pain and their doctor not understanding the patient's pain.

Table 5: Reasons for Using Multiple Doctors or Healthcare Providers to Obtain Opioids (POMAQ)

	N Total	N Responded "True"	No shopping		Minimal shopping		Moderate shopping		Severe shopping	
			N = 271		N = 271		N = 272		N = 271	
	N	N	N	%	N	%	N	%	N	%
Visited more than 1 doctor or healthcare provider to get more prescription opioid medication in the past year	1085	67	≤10		15	5.54	18	6.62	25	9.23
Visited more than 1 doctor or healthcare provider to get more prescription opioid medication in the past 3 months	72	15	≤10		≤10		≤10		≤10	
Reason:										
I see different healthcare providers for different health problems so I ask for an opioid prescription when seeing each healthcare provider	15	≤10	≤10		0	0	≤10		≤10	
I needed more opioid pain medication to treat my pain than 1 doctor would give me	15	≤10	≤10		0	0	0	0	≤10	
I wanted to get more opioid pain medication to get high on	15	≤10	≤10		0	0	0	0	0	0
I wanted to get more opioid pain medication to sell	15	0	0	0	0	0	0	0	0	0
I wanted to get more opioid pain medication to help a friend or relative	15	0	0	0	0	0	0	0	0	0
I lost my opioid pain medication	15	0	0	0	0	0	0	0	0	0
I wanted to make sure I had enough opioid pain medication in case I needed it	15	≤10	0	0	0	0	≤10		0	0
My insurance, employment or place of residence changed and I had to change my doctor	15	0	0	0	0	0	0	0	0	0
My doctor stopped prescribing opioid pain medication	15	≤10	≤10		0	0	0	0	≤10	
I was referred to another doctor	15	≤10	0	0	≤10		≤10		0	0
My doctor does not understand my pain level	15	≤10	≤10		0	0	0	0	≤10	
My doctor thinks I may be faking my pain	15	≤10	≤10		0	0	0	0	≤10	
Other	15	≤10	0	0	0	0	≤10		≤10	

Source: PMR 3033-9 Final Study Report, Adapted from Table 7b. Reasons for Using Multiple Doctors or Pharmacies to Obtain Opioids

Table 6 of this review (Table 7b Appendix B Final Study Report) includes the results for patients asked about visiting multiple pharmacies. There were 158 patients that responded that they went to more than one pharmacy in the past year to obtain prescription opioids and 50 patients indicated this had occurred in the past three months. Similar to the question about visiting multiple doctor's offices, many of the responses were only indicated as "≤10" due to confidentiality reasons. However, among those indicating that they had visited more than one pharmacy in the past three months for opioids, convenience, price and lack of available stock were the most frequently chosen options.

It is important to note that patient reported reasons for visiting multiple providers or visiting multiple pharmacies are restricted by the options that were available for patients to select in the survey.

Table 6: Reasons for Using Multiple Pharmacies to Obtain Opioids (POMAQ)

	N Total	N Responded "True"	No shopping		Minimal shopping		Moderate shopping		Severe Shopping	
			N=271		N=271		N=272		N=271	
	N	N	N	%	N	%	N	%	N	%
Went to more than 1 pharmacy to obtain prescription opioid medication in the past year	1085	158	15	5.5	29	10.7	50	18.4	64	23.6
Went to more than 1 pharmacy to obtain prescription opioid medication in the past 3 months	180	50	≤10		≤10		15	26.8[#]	22	31.4[#]
Reason:										
I lost my opioid pain medication	50	0	0	0	0	0	0	0	0	0
My prescription was changed to a different dose or medication	50	≤10	≤10		0	0	0	0	≤10	
I wanted to make sure I had enough of my opioid pain medication in case I needed it	50	≤10	0	0	0	0	0	0	≤10	
My insurance changed and I had to change my pharmacy	50	≤10	≤10		≤10		≤10		≤10	
I needed more opioid pain medication to treat my pain	50	≤10	0	0	0	0	0	0	≤10	
I wanted to get more opioid pain medication and did not want to get caught	50	≤10	0	0	0	0	0	0	≤10	
A pharmacy refused to fill my opioid pain prescription	50	0	0	0	0	0	0	0	0	0
I use several different pharmacies for convenience	50	27	≤10		≤10		≤10		13	59.1
My regular pharmacy did not have	50	13	≤10		≤10		≤10		≤10	

enough of my opioid pain medication										
I do not want the pharmacist to know how much opioid pain medication I take per month	50	≤10	0	0	0	0	0	0	≤10	
I always try to get the best price so I go to different pharmacies	50	12	0	0	≤10		≤10		≤10	
Other	50	12	≤10		≤10		≤10		≤10	

Source: PMR 3033-9 Final Study Report, Adapted from Table 7b. Reasons for Using Multiple Doctors or Pharmacies to Obtain Opioids
Note: #To account for skip patterns, the % were calculated as number reported Yes or Not Sure to visiting more than 1 pharmacy in the past 3 months out of number reported Yes or Not sure to visiting more than 1 pharmacy in the past 12 months.

In addition to the survey requesting reasons for visiting multiple prescribers and pharmacies, DPS was also stratified by demographic factors (previously described) and factors likely to affect a patient's need for prescription opioids, such as pain diagnoses, pain scores (BPI), psychiatric comorbidities and medication use. Among patients in the severe DPS category, a higher percentage of patients were found to have specific pain diagnoses and some psychiatric disorders compared to lower severity shopping categories. The percentages of patients in the severe shopping category reporting abdominal, chronic and neuropathic pain were at least double compared to the percentage reporting this pain in the no shopping category (Table 7 of this review; Table 4 Appendix B Final Study Report). Anxiety and depressive disorders were also nearly double among persons with severe DPS compared to persons with no DPS shopping (46.9% vs 24.0% for anxiety and 35.8% vs 17.3% for depressive disorder; data not shown; source PMR 3033-9 Final Study Report Table 4).

Table 7. Clinical Characteristics in the Most Recent 18 months by Doctor/Pharmacy Shopping Category and Survey Status

	Total	Characteristic Present	No shopping		Minimal shopping		Moderate shopping		Severe shopping	
			N = 271		N = 271		N = 272		N = 271	
	N	N	N	%	N	%	N	%	N	%
Clinical Characteristics										
Pain diagnosis: Abdominal pain	1085	390	52	19.2	91	33.6	104	38.2	143	52.8
Amputation	1085	≤10	0	0.0	≤10		≤10		0	0.0
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	1085	325	61	22.5	76	28.0	99	36.4	89	32.8
Back pain	1085	572	103	38.0	130	48.0	158	58.1	181	66.8
Chronic pain	1085	376	54	19.9	77	28.4	108	39.7	137	50.6
Fibromyalgia	1085	88	11	4.1	19	7.0	28	10.3	30	11.1
Headache	1085	285	48	17.7	62	22.9	73	26.8	102	37.6
Malignancy	1085	66	≤10		15	5.5	23	8.5	22	8.1

Multiple sclerosis	1085	≤10	≤10		≤10		≤10		≤10	
Neuropathic pain	1085	298	45	16.6	75	27.7	83	30.5	95	35.1
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	1085	21	≤10		≤10		≤10		≤10	
Stroke	1085	23	≤10		≤10		≤10		≤10	
None of the above	1085	148	75	27.7	38	14.0	24	8.8	11	4.1

Source: PMR 3033-9 Final Study Report, Adapted from Table 4. Clinical Characteristics and Medication Use in the Most Recent 18 Months by Doctor/Pharmacy Shopping Category and Survey Status
N = number

Self-reported pain intensity, as measured by the BPI showed an increasing percentage of patients with severe pain with increasing severity of DPS (results not shown; Table 5 Appendix B Final Study Report). Additionally, the scores for all survey items were at least as high and most often higher for patients in the severe DPS category. For example, patients in the severe DPS category scored their worst pain in the last 24 hours with a score of 6.3 (average) compared to a score of 4.5 (average) among patients in the no DPS shopping category.

Patients were also asked about other factors related to opioid use which may help understand the reasons that they may increase or decrease behaviors indicative of DPS (data not shown in this review; Table 7a Appendix B Final Study Report). The majority of patients reported that they used less opioid than prescribed in the past year (n=621; 57.3%); there was a higher percentage among patients with no DPS compared to severe DPS (no DPS: 67.5% vs. severe DPS 45.8%). For all DPS categories, most patients responded that they did not think they had a problem with their prescription drug, ranging from 93.7% (n=254; severe DPS) to 97.1% (n=263; no DPS). The most frequently reported reasons for concern about their opioid use was "I may have a problem stopping my opioid pain medication" (n=27; 55.1%) and "I think I may be addicted" (n=24; 49.0%).

The Marlow-Crowne Social Desirability Scale was used to assess the potential for varying social desirability to affect self-reporting of potentially socially unacceptable behaviors. The distribution of patients within each of the social desirability levels did not seem to increase or decrease by DPS category. Moreover, the severe DPS category was similar to all patients completing the survey (Table 8; Table 6 Appendix B Final Study Report).

Table 8. Marlow-Crowne Social Desirability Scale-Short Form

Social Desirability	All survey respondents N (%)	No Shopping N (%)	Minimal Shopping N (%)	Moderate Shopping N (%)	Severe Shopping N (%)
Low	398 (36.7)	95 (35.1)	101 (37.3)	102 (37.5)	100 (36.9)
Moderate	311 (28.7)	81 (29.9)	80 (29.5)	72 (26.5)	78 (28.8)
High	376 (34.7)	95 (35.1)	90 (33.2)	98 (36.0)	93 (34.3)
Total	1085	271	271	272	271

Source: PMR 3033-9 Final Study Report, Adapted from Table 6. Marlow-Crowne Social Desirability Scale-Short Form

Objective 2: *"Assess whether the proportion of patients reporting misuse, abuse and/or diversion, measured using a validated questionnaire, increases across doctor/ pharmacy shopping categories defined a priori in Study 3033-8."* This study addressed this objective using descriptive analyses, Cochran-Armitage test for trend, and logistic regression. Sensitivity analyses provided additional information on the potential for bias.

Pain intensity and social desirability were considered as potential confounding factors in the association between misuse and abuse and DPS category. Pain intensity was found to be associated with both DPS behavior (previously discussed) and the outcome of misuse or abuse. The percent of patients with severe pain among patients reporting abuse (43.6%), misuse (51.7%), and abuse or misuse (22.7%) was about twice the percent with no or mild pain reporting these behaviors. This difference was even higher for the percent with severe pain compared to no or mild pain among persons reporting abuse and misuse (Table 9; Table 7c Appendix B Final Study Report). This suggests that that having severe pain intensity may be associated with abuse and misuse, although there was no test of significance to formally explore this association.

Table 9. Abuse, misuse or diversion by pain severity

	Total	No or mild pain, N (%)	Severe pain, N (%)
Total	1085	346 (31.9)	470 (43.3)
Abuse	55	13 (23.6)	24 (43.6)
Misuse	87	21 (24.1)	45 (51.7)
Abuse or misuse	110	25 (22.7)	58 (52.7)
Abuse and misuse	32	≤10	11 (34.4)
Diversion	14	≤10	≤10

Source: PMR 3033-9 Final Study Report, Adapted from Table 7c. Misuse, abuse and/or diversion by doctor/pharmacy shopping category

Social desirability did not seem to be associated with DPS categories (previously discussed; Table 8 of this review); however, it did seem to be associated with the outcome of misuse or abuse. The percent of patients in the low social desirability category (indicating less of a tendency to respond in a socially-desirable manner) was disproportionately high among those who reported abuse, misuse, misuse and abuse, and misuse or abuse compared to the percent of persons reporting these outcomes in the moderate or high social desirability categories (Table 10; PMR 3033-9 Final Study Report, Table 7c). Not surprisingly, this association between self-report of abuse and misuse with social desirability scores suggests that self-reporting behaviors of abuse and misuse, less socially-desirable behaviors, may be affected by reporting bias, specifically, a reluctance by some patients (those with a higher tendency to report socially-desirable behavior) to report abuse or misuse.

Diversion could not be assessed as a potential confounding variable since there were fewer than 10 patients in each of the low, moderate or high social desirability categories (Table 10; PMR 3033-9 Final Study Report, Table 7c).

Table 10. Abuse, misuse or diversion by social desirability category				
	Total	Low social desirability N (%)	Moderate social desirability N (%)	High social desirability N (%)
Total	1085	398 (36.7)	311 (28.7)	376 (34.7)
Abuse	55	38 (69.1)	12 (21.8)	≤10
Misuse	87	48 (55.2)	21 (24.1)	18 (20.7)
Abuse or misuse	110	63 (57.3)	27 (24.5)	20 (18.2)
Abuse and misuse	32	23 (71.9)	≤10	≤10
Diversion	14	≤10	≤10	≤10
Source: PMR 3033-9 Final Study Report, Adapted from Table 7c. Misuse, abuse and/or diversion by doctor/pharmacy shopping category				

The percent of patients who reported abuse, misuse, abuse or misuse, and abuse and misuse was highest among patients with severe DPS (Table 11 of this review; Table 7c Appendix B Final Study Report). Among patients in the no DPS shopping category, 4.1% reported abuse, 5.5% reported misuse, 7.8% reported abuse or misuse, and very few (≤10) reported abuse and misuse. Among patients in the severe shopping category, 5.9% reported abuse, 11.8% reported misuse, 12.6% reported abuse or misuse, and 5.2% reported abuse and misuse. The test for trend was significant for all outcomes except abuse. There were insufficient numbers to report diversion by DPS category and the test for trend for diversion by DPS severity was not significant, likely due to low number of participants reporting diversion.

Table 11. Misuse and abuse by Doctor/Pharmacy Shopping Category											
	N Total	**N with Outcome**	**No shopping**		**Minimal shopping**		**Moderate shopping**		**Severe shopping**		**Test for trend**
			N = 271		**N = 271**		**N = 272**		**N = 271**		
	N	**N**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Proportion of patients with misuse and abuse											
Abuse	55	55	11	4.1	12	4.4	16	5.9	16	5.9	0.241
Misuse	87	87	15	5.5	18	6.6	22	8.1	32	11.8	0.006
Abuse or misuse	110	110	21	7.8	23	8.5	32	11.8	34	12.6	0.031

Abuse and misuse	32	32	≤10	≤10	≤10	14	5.2	0.037
Diversion	14	14	≤10	≤10	≤10	≤10		0.636

Source: PMR 3033-9 Final Study Report, adapted from Table 7c. Misuse, Abuse, and/or Diversion by Doctor/Pharmacy Shopping Category

Using logistic regression, there was a significant association between DPS and some of the abuse/ misuse outcomes (Table 12; adapted from Table 8 Appendix B Final Study Report; Table 1 of this review provides additional detail on model specifications with regard to outcomes). In crude models, patients in the severe DPS category had more than two times the odds of misuse (OR 2.25; 95% CI 1.19, 4.26) and had almost three times the odds of abuse and misuse (OR 2.95; 95% CI: 1.05, 8.33) compared to patients in the no DPS shopping category. Covariates retained in the adjusted models included pain (chronic pain), psychiatric disorders (bipolar, depression, alcohol use), geographic region, medication of abuse potential (only amphetamines were retained after covariate selection) but inclusion varied by model. Total number of opioid dispensings and total duration of opioid use were assessed as potential covariates for the models. Results from the adjusted models were similar to the crude models, but the magnitude of the odds ratio was attenuated in all models and the odds ratio for the model assessing abuse and misuse was no longer significant. The model assessing misuse remained significant after including covariates; patients in the severe DPS category had 2.12 (95% CI: 1.11, 4.04) times the odds of misuse compared to patients in the no DPS category, after adjusting for bipolar disorder, alcohol use and geographic region.

Table 12. Logistic regression results for the association between doctor/pharmacy shopping and abuse/misuse outcomes

	Doctor/pharmacy shopping group		
Model outcomes	**Minimal versus none** **OR (95% CI)**	**Moderate versus none** **OR (95% CI)**	**Severe versus none** **OR (95% CI)**
Unadjusted models			
Abuse versus no abuse and no misuse **N=1030**	1.10 (0.48, 2.54)	1.52 (0.69, 3.33)	1.53 (0.70, 3.37)
Misuse versus no abuse and no misuse **N=1062**	1.21 (0.60, 2.45)	1.53 (0.77, 3.02)	2.25 (1.19, 4.26)
Abuse and misuse versus no abuse and no misuse **N=1007**	1.41 (0.44, 4.51)	1.25 (0.38, 4.15)	2.95 (1.05, 8.33)
Abuse or misuse versus no abuse and no misuse **N=1085**	1.10 (0.60, 2.05)	1.59 (0.89, 2.83)	1.71 (0.96, 3.03)
Adjusted models			

Abuse versus no abuse and no misuse **N=1030**	0.91 (0.39, 2.13)	1.18 (0.52, 2.65)	1.14 (0.50, 2.61)
Misuse versus no abuse and no misuse **N=1062**	1.20 (0.59, 2.45)	1.50 (0.76, 2.98)	**2.12 (1.11, 4.04)**
Abuse and misuse versus no abuse and no misuse **N=1007**	1.27 (0.40, 4.10)	1.13 (0.34, 3.78)	2.78 (0.98, 7.86)
Abuse or misuse versus no abuse and no misuse **N=1085**	0.98 (0.52, 1.84)	1.35 (0.74, 2.45)	1.27 (0.70, 2.31)
Source: PMR 3033-9 Final Study Report, adapted from Table 8. Relation between doctor/pharmacy shopping category and each outcome (abuse, misuse, abuse and misuse, abuse or misuse)			

Model performance was assessed using the C-statistic and pseudo R-Square value. The adjusted model outperformed the crude model and the covariate models for all abuse/misuse outcomes (data not shown; Table 9b Appendix B Final Study Report). Sensitivity, specificity, positive predictive value, and negative predictive value were also reported (data not shown; Table 10 Appendix B Final Study Report). Negative predictive value was high for all models, both unadjusted and adjusted, with most negative predictive values above 90%, indicating that most patients included in the final sample without DPS behavior did not report misuse or abuse. However, positive predictive values (PPV) were low. The PPV for the adjusted model predicting misuse indicated that only about 12% of patients included in the final sample with DPS behaviors reported misuse.

Sensitivity analyses

Multiple sensitivity analyses were performed.

1. In the sensitivity analysis excluding items potentially correlated on the POMAQ (alcoholism, anxiety, depression, use of medications with abuse potential) from the adjusted logistic regression, the results were similar to the primary analysis. Patients with severe DPS had increased odds (OR: 2.27; 95% CI: 1.20, 4.31) of misuse compared to persons without any DPS, after adjusting for region only. Patients with severe DPS also had increased odds of abuse and misuse (OR: 2.95; 95% CI: 1.05, 8.33) compared to patients without DPS, but no covariates were retained in this model. Abuse and abuse or misuse models were not significantly associated with DPS for any category of DPS.

2. Results from the two sensitivity analyses to assess potential bias from doctors and pharmacies that could not be identified (prescriber or pharmacy identifier is missing), either by assuming them to be unique or by assuming them to be the same as the previous identifiable doctor or pharmacy, did not differ from the main study findings (data not shown; Table 11c Appendix B Final Study Report).

3. After restricting the study population to survey participants with at least 12 months of follow-up, the number of participants in each outcome category decreased. The direction of the associations remained similar to the main analysis, but the associations were no longer significant (data not shown; Table 14 Appendix B Final Study Report).

4. Descriptive analyses and logistic regression were conducted to assess the association between abuse/ misuse as defined in claims (dependent variable) and DPS defined in claims (independent variable) including all survey participants (n=1,085) and all persons excluded based on a history of SUD or abuse/misuse as defined in claims (n=15,764). The findings from this analysis are not straightforward; there was a higher proportion of persons with the outcome (abuse/misuse) in the no DPS category (data not shown; Table 13 Appendix B Final Study Report). The Study Final Report provided a weak explanation behind the findings: "the proportion of patients with the outcome in the no shopping category was inflated, driven by the large number of patients with claims indicative of drug/substance abuse in the category." However, one explanation of this potentially perplexing finding may be that patients with misuse or abuse may represent a different population than patients without misuse or abuse; management for these patients might restrict patients to a single pharmacy or doctor (e.g., lock-in program), limiting some patients to the low DPS category.

5. Table 12 of Appendix B in the Final Study Report includes information on the patients who were excluded from the sampling frame and univariate logistic regression models to assess the association between exclusion and DPS. One group presented in this table are patients excluded due to claims indicative of abuse/misuse (n=15,764), stratified by DPS. Patients with SUD (excluded) were more likely to doctor pharmacy shop compared to patients in the sampling frame (no SUD) (10.9% compared to 2.8%, respectively), although the percentage of patients with SUD in the severe DPS category was still a minority. Over 58% (n=9,214) of patients with SUD were in the no DPS category. The logistic regression analyses showed that this exclusion factor selectively excluded patients in the severe DPS category, which could potentially bias the results.

3.5 INTERPRETATION OF RESULTS

Overall, this study was sufficiently designed to provide insight into a challenging area to study in public health. The information from this study suggests that DPS behavior is complex and likely driven by multiple clinical, behavioral and logistical factors; abuse and misuse may play a role in DPS behavior, but the multitude of other factors should be considered as well.

This study provides insights into patient experiences for those engaging in DPS behaviors. Patients in the severe DPS category differed from patients in less severe DPS categories by multiple factors. The highest percent of patients with severe pain intensity was in the severe DPS category, suggesting that patients conducting severe DPS behaviors might have more inadequately controlled pain than patients in the lower severity or no DPS categories. This is also supported by information from claims data, which suggests that the percent of patients with certain types of pain was highest in the severe DPS category. Other factors associated with more severe DPS from the claims data are certain psychiatric conditions and medication use, factors which can complicate the management of the pain and are associated with opioid misuse.

Additionally, the POMAQ responses provided insight into potential reasons for DPS. Although the responses were limited to what was available in the survey and had limited cell sizes, selected responses suggest a lack of doctor understanding or feeling that the doctor thinks they are faking their pain and needs related to administrative issues (referral, insurance change, etc.). No patients reported reasons for DPS indicating that they intended to sell medications, however, 34 patients acknowledged that they have shared, stolen or traded opioid medication in the past year. The weak connection of DPS with misuse and abuse could either be a reflection of the reluctance to self-report socially less desirable behavior or it could be a reflection of a lower risk profile patient population and lack of generalizability to the general US population. Patients visiting multiple pharmacies self-reported convenience, pricing and insufficient stock as reasons for visiting multiple pharmacies. However, any interpretation should consider potential reporting bias where patients may be reluctant to report less-desirable or illegal behavior. Additionally, the study results may be affected by selection bias; insurance claims data do not capture patients using cash to pay for prescriptions, a behavior previously identified as associated with doctor pharmacy shopping (Cepeda, Fife, Chow, Mastrogiovanni, & Henderson, 2012). Additional data sources, such as Prescription Drug Monitoring Programs (PDMP) data should be considered for future studies.

These results are consistent with prior literature describing the complex relationship between chronic pain and psychiatric conditions (Sullivan, 2018). Further, as indicated by the low PPV and the overall low prevalence of abuse and misuse in this population, the majority of patients in the moderate and severe DPS categories do not report misusing or abusing opioids.

The study included multiple sensitivity analyses, which mostly supported the primary findings of the study, suggesting a robustness to the findings. However, the sensitivity analysis assessing the impact of excluding patients with claims indicating SUD, showed that this exclusion factor selectively excluded patients in the severe DPS category, which likely biased the results.

Finally, the study was powered for a larger effect size than was observed for most analyses. If the study had been powered for a smaller effect size, it is possible that more associations may have achieved statistical significance and additional patterns or lack of thereof would have been revealed.

Strengths and limitations

3.5.1 Strengths

The study included multiple sensitivity analyses to assess potential biases. Most of the sensitivity analyses demonstrated a robustness to the primary analyses. The sensitivity analyses assessing the potential for the way that unidentified doctors and pharmacies were categorized demonstrated no unexpected findings and the models did not differ from those in the primary analysis.

This analysis included claims data as well as three self-reported surveys to capture a wide range of information from the patient. Self-report survey data included reasons for visiting multiple providers, self-reported multiple visits to doctors or pharmacies, and pain scores. Additionally, the Marlowe-Crowne Social Desirability Scale provided information on the amount that unwillingness to self-report negative social behavior may contribute to misclassification. From this survey, we found that social desirability was associated with misuse and abuse reporting (patients with less of a tendency to respond in a socially-desirable manner were disproportionately high among those who reported misuse/abuse outcomes). By including both

self-report survey data and claims data, the study was able to assess both self-report patient reasons for DPS as well as clinical and prescription information, such as diagnoses and duration, dose and type of opioid.

Finally, the analysis was conducted in a large database, providing a large sampling frame required for describing DPS and misuse and abuse, often uncommon behaviors and outcomes. As of June 2018, HIRD included claims information from approximately 49 million persons, of which 13 million were enrolled in a health plan with medical and pharmacy eligibility.

3.5.2 Limitations

There is a lack of a "gold" standard for the outcomes of misuse, abuse and diversion. This study used the outcome of abuse and misuse as defined by self-report in the POMAQ. The POMAQ was validated for abuse and misuse in studies 3033-3 and 3033-4; the PMR requirement of PMR 3033-4 was to conduct an "*observational study to evaluate the validity and reproducibility of the POMAQ, which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use."* Study 3033-4 described misuse and abuse among patients at DoD/TriCare clinics experiencing long-term chronic pain, a different population than the one used in the current study. The PMR requirement of PMR 3033-3 was to conduct a "*prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained*." The validity of the POMAQ has not been assessed in the current study population, a general population of insured individuals for misuse and abuse.

The generalizability of the study was limited. This study was conducted using a large health insurance claims database and only commercially insured patients were included, limiting the representativeness of the population.

As previously noted, insurance claims data do not include cash payments for prescriptions. Cash payments for opioid prescriptions has been previously shown to be associated with doctor pharmacy shopping (Cepeda, Fife, Chow, Mastrogiovanni, & Henderson, 2012). Not including these prescriptions is likely to result in biased results. Because of this major limitation, future studies should utilize data sources that include cash payment prescriptions, such as data from PDMP programs.

Patients with claims indicative of SUD were excluded from this analysis. As noted in the review for 3033-10, excluding the patients with claims indicative of SUD, a high-risk patient population, reduces the external validity of the study as the findings are not likely to be representative of high-risk patient populations. However, using claims data for identifying patients with SUD is not very sensitive, meaning that it is possible that not all patients with SUD were excluded from this analysis. From the sensitivity analysis, we saw that patients with SUD were more likely to have severe DPS and inclusion of patients with SUD in the sampling frame could affect the percentage with severe DPS.

Results from a nationally representative survey, the 2015 National Survey on Drug use and Health (NSDUH), show that 12.5% of adults with prescription opioid use reported misuse in the last 12 months (Han et al. 2017). This is higher than the overall prevalence of abuse and misuse in the study population of this current analysis, 5.1% and 8%, respectively. NSDUH is a nationally representative sample which included uninsured individuals and other non-comparable populations.

The survey response rate was low (10.8%), affecting the generalizability of the study. Among the patients in the sampling frame, most invited patients did not access the link provided. Survey respondents were more likely to be female. Although characteristics of survey respondents did not appear to vary greatly by age or geographic region of residence, limited demographic information was available for comparison.

Including total number of opioid dispensings and duration of opioid analgesic use as covariates in the models could have provided additional information. The number of dispensings and duration of opioid analgesic use both increased with increasing severity of DPS but were not included in the models. Without controlling for total number of opioid dispensings, DPS may be mostly measuring frequency of opioid analgesic use, which could be associated with more opportunity for misuse/abuse measured at a later date. As such, DPS would provide a poor proxy for misuse/abuse. By including total number of opioid analgesic dispensings in the model, we could better evaluate DPS behavior as separate from other potential factors driving patients to have multiple number of opioid dispensings, such as pain and other medical conditions.

The timeframe for DPS from claims data differed from the timeframe for self-report data on the outcome (misuse and abuse). The timeframe for determining the DPS from the claims data was an 18-month period from 7/1/2015 to 12/31/2016 for all patients. This was the same time period used to determine if a patient was eligible for the study based on having at least two claims for prescription opioids. The self-report questionnaire was sent to patients after the 18-month period, with the first respondent completing the survey on 6/16/2017, nearly six months after the end of the 18-month period. The last self-report questionnaire was completed in mid-June 2018, 17.5 months after the end of the 18-month claims data period. The screening question for the self-report survey asked about prescriptions within the last 18 months and the POMAQ ascertained abuse, misuse and diversion in the past 3 months. Therefore, neither the screening question nor the outcomes ascertained by the POMAQ were assessing behaviors in the same timeframe that the DPS behavior was measured. Specifically, misuse, abuse or diversion was measured at a different time than the independent variable (DPS). Because of this, patients could have either developed or stopped misuse, abuse, diversion or DPS behaviors between the time of DPS assessment and misuse/abuse assessment.

Overall self-report information is sparse and subject to reporting bias. Accurately measuring misuse and abuse of drugs and other socially undesirable behavior is a challenge faced by all researchers of these topics. In this study, only 15 patients responded “true” to visiting more than one healthcare provider to get more prescription opioid in the past 3 months. When compared to the number of providers visited as identified in the claims data, this self-report data seems to be an underestimate of the number of patients visiting multiple providers, although the timeframe differs between these two assessments and direct comparison is not possible.

3.6 CONNECTION TO PREVIOUS STUDIES

Given that there is no ideal “gold” standard against which to validate DPS, the findings from this study were intended to add to the findings from 3033-8 and 3033-10, to enhance our overall understanding of DPS metrics and what they can tell us about opioid misuse, abuse, and addiction.

Study 3033-8 developed the DPS categories used in all three DPS PMR studies and investigated the correlation between DPS and algorithmically-indicated abuse and/or addiction (AIAA) from healthcare and pharmacy claims data. This study had similar findings to 3033-9 in that there was a positive, significant association between DPS and AIAA. However, as with 3033-9, DPS was a weak marker of abuse and addiction (as defined in claims data). Because PMR 3033-7 did not

find AIAA to perform well as a measure of abuse or addiction as recorded in the medical record, the inferential value of PMR 3033-10 was limited.

Study 3033-10 investigated the correlation between DPS and behaviors identified in the medical record possibly indicative of misuse, abuse, and/or addiction. This study also had similar findings to 3033-8 and 3033-10, in that there was a significant association between severe DPS and potentially aberrant drug behavior described in the medical record. However, as was found in 3033-8, the DPS measure did not discriminate well between patients with and without these behaviors and therefore was not a good proxy for misuse/abuse/addiction. Again, the inferential value of the study findings was limited by the fact that the measure of misuse and abuse in this study was not a validated, gold-standard measure of the outcome.

4 CONCLUSIONS

After a full review of the final study report, we have determined that the OPC has satisfactorily addressed all concerns raised by FDA in its Information Request and fulfilled the objectives of PMR 3033-9.

Patients in the severe DPS shopping category had increased odds of misuse (but not abuse) after adjusting for some potential confounding factors. However, the total proportion of patients in the severe DPS category with abuse or misuse was small, suggesting that DPS is likely a poor surrogate for identifying individuals who abuse or misuse prescription opioids. However, the effect size was smaller than anticipated and the pattern or lack of pattern may have been clearer if the study had been powered for a smaller effect size.

Although there were limitations with the self-report data and results should be interpreted with these limitations in mind, some insights into the patient experience could be drawn from the data. Reasons selected for DPS behaviors included convenience, price, and availability, among other reasons (for pharmacies), and reasons related to lack of physician understanding of the patient's pain and inadequately controlled pain (for providers). Other descriptive data showed that patients with severe DPS also tended to have increased pain and other comorbid conditions such as anxiety and depression. These findings suggest that DPS may occur more often in situations where pain management is complicated by other medical and social factors. Consistent with these findings, previous literature has described the complex relationship between depression and opioid use, abuse and addiction, with a suggested pathway through nonmedical use (Sullivan, 2019).

The association between doctor pharmacy shopping and misuse and abuse could be further explored in future studies. Future studies should be sufficiently powered for smaller effect sizes. These future studies might also control for additional factors such as number of opioid analgesic dispensings to minimize confounding, and doctor pharmacy shopping should be measured at the same time as misuse and abuse. Additionally, future studies should investigate this association among diverse populations, including persons without insurance, patients paying cash and among persons who may have substance use disorder.

This is a robust analysis using a large claims database in combination with self-report survey data. The authors included multiple sensitivity analyses to identify possible sources of bias. However, there are important limitations to consider. The study results were limited by a mis-alignment of the timeframes for the assessment of the exposure and outcome and the limited generalizability for higher-risk groups due to the use of commercial claims database and the requirement to exclude patients with SUD. Additionally, few patients self-reported reasons for DPS behavior.

The results of this study, when combined with results from the other two PMR studies, that assess DPS in relation to different measures of misuse, addiction, and/or abuse, PMR 3033-8 and 3033-10, add to our understanding of the potential association between DPS and misuse and abuse.

5 RECOMMENDATIONS

Comment to be conveyed to the sponsor:

We have determined that you have satisfactorily addressed all the concerns we raised in our Information Request and fulfilled PMR 3033-9.

6 REFERENCES

Cepeda SM, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid Shopping Behavior: how often, how soon, which drugs, and what payment method. The Journal of Clinical Pharmacology. 2012; 53(1): 112-117.

Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in the U.S. Adults: 2015 National Survey on Drug Use and Health. Ann Intern Med. 2017; 167(5): 293-301.

Sullivan M. Depression Effects on Long-term Prescription Opioid Use, Abuse, and Addiction. Clin J Pain. 2018; 34: 878-884.

8. APPENDICES

8.1 APPENDIX A. ER/LA OPIOID ANALGESIC AND NDAS ISSUED

DRUG NAME	Application Type / Number	Sponsor
Arymo ER (Morphine Sulfate)	NDA 208603	Egalet Corp
Belbuca (Buprenorphine Buccal)	NDA 207932	Endo
Butrans (Buprenorphine Transdermal)	NDA 21306	Purdue
Duragesic (Fentanyl Transdermal)	NDA 19813	Janssen
Dolophine (Methadone HCl)	NDA 6134	Roxane
Embeda (Morphine Sulfate and Naltrexone HCl)	NDA 22321	Alpharma
Exalgo (Hydromorphone HCl)	NDA 21217	Mallinckrodt
Hysingla (Hydrocodone Bitartrate)	NDA 206627	Purdue
Kadian (Morphine Sulfate)	NDA 20616	Allergan Sales LLC
Morphabond (Morphine Sulfate)	NDA 206544	Inspirion
MS Contin (Morphine Sulfate)	NDA 19516	Purdue
Nucynta ER (Tapentadol)	NDA 200533	Janssen
Opana ER (Oxymorphone HCl) - old	NDA 21610	Endo
Opana ER (Oxymorphone HCl) - new	NDA 201655	Endo
Oxycontin (Oxycodone HCl)	NDA 22272	Purdue
Targeniq ER (Oxycodone HCl and Naloxone HCl)	NDA 205777	Purdue
Troxyca ER (Oxycodone and Naltrexone)	NDA 207621	Pfizer
Vantrela ER (Hydrocodone Bitartrate)	NDA 207975	Teva
Xtampza ER (Oxycodone)	NDA 208090	Collegium
Zohydro ER (Hydrocodone Bitartrate)	NDA 202880	Pernix

8.2 APPENDIX B. RELEVANT INFORMATION FROM THE MS CONTIN LABEL

Boxed WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

MS CONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS CONTIN, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of MS CONTIN. Monitor for respiratory depression, especially during initiation of MS CONTIN or following a dose increase. Instruct patients to swallow MS CONTIN tablets whole; crushing, chewing, or dissolving MS CONTIN tablets can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of MS CONTIN, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MS CONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- Reserve concomitant prescribing of MS CONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

INDICATIONS AND USAGE

MS CONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve MS CONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- MS CONTIN is not indicated as an as-needed (prn) analgesic.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MS CONTIN contains morphine, a Schedule II controlled substance.

Abuse

MS CONTIN contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. MS CONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and

people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

MS CONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of MS CONTIN

MS CONTIN is for oral use only. Abuse of MS CONTIN poses a risk of overdose and death. This risk is increased with concurrent abuse of MS CONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved MS CONTIN enhances drug release and increases the risk of overdose and death.

Due to the presence of talc as one of the excipients in MS CONTIN, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

8.3 APPENDIX C. INFORMATION REQUEST AND RESPONSE

Information Request for ERLA 3033-9 Final Study Report

Having carefully reviewed the Final Study Report for PMR 3033-9, we are requesting some additional information related the description of the study population, and the first and second objectives as outlined in the approved study protocol and report.

Submit responses and revisions to the final study report (clean and tracked changes versions) no later than four weeks from the date of this email.

Note: All tables referenced in these comments refer to the tables in Appendix B of the Final Study Report.

Regarding the description of the study population:

1. Table 3: Demographic Characteristics and Healthcare Utilization in the Most Recent 18 Months by Doctor/Pharmacy Shopping Category and Survey Status: Numbers and proportions of patients in Midwest (row 20) and Northeast (row 21) geographic regions are drastically different for survey non-respondents compared to survey respondents and patients in the sampling frame. For example, the number of patients in the sampling frame in the Midwest and Northeast are 36,503 and 11,838, but among the survey non-respondents, these number are 676 (Midwest) and 2768 (Northeast).

   Verify that Table 3, rows 20 and 21 (Midwest and Northeast) are correctly specified for survey non-respondents. If accurate, explain why this difference by geographic region and response category may exist.

   Response: *Thank you for your thorough review. The results for Midwest and Northeast were incorrectly entered (switched) for survey non-respondents. We corrected this error in Table 3 of the revised report.*

2. Provide mean, median, and interquartile range (IQR) for age and healthcare utilization (Table 3) and medication use (Table 4) for all survey respondents together (N=1,085). Note that you reported a single number for IQR. IQR consists of two numbers; the 25th percentile and the 75th percentile. Present appropriate values for IQR.

   Response: *We included the 25th and 75th percentile in Table 3, Table 4, and Table 5 of the revised report where applicable.*

3. Provide clarification for missing numbers throughout Appendix B by adding a category for missing and reporting number and percent of patients with missing data for all variables with missing information.

   Examples:

   i. Two people are missing pain intensity (Table 5; 102 [no pain] + 244 [mild] + 267 [moderate] + 470 [severe] = 1083) and the total N for average score for each survey item ranges from 1080 to 1085.

   Response: *We inserted two additional rows in Table 5 of the revised report to show data for those missing pain intensity and those missing at least one of the survey items.*

   ii. Some demographic characteristics in Table 3 sum to less than 1085, for example, income categories sum to N=797.

   Response: *The significant proportion of patients missing information on self-reported income was due to a data entering error for the category of "Less than $50,000". We corrected the error in Table 3 of the revised report and now the total sums to the total number surveyed (n=1,085).*

   iii. In table 8, numbers of patients used for the analysis of any abuse, any misuse, and abuse and misuse outcome are 1030, 1062, and 1007, respectively. It is unclear why these numbers are less than the total number of the survey respondents, N=1085.

   Response: *The reason for the observed difference in the number of patients included in each analysis is due to the fact that the comparison group consisted of patients who did not report abuse or misuse. As a result, for the "any abuse" analysis, those who reported no abuse but misuse were excluded; for the "any misuse" analysis, those who reported no misuse but abuse were excluded; and for the "abuse and misuse" analysis, those who reported only abuse or only misuse were excluded.*

<u>Regarding Objective #1—To investigate reasons patients go to multiple prescribers and/or pharmacies to obtain prescription opioids:</u>

1. In Table 7b, explain why the numbers are lower for patients responding "true" for "Visited more than 1 doctor or healthcare provider to get more prescription opioid medication in the past year" (N=67) than for the denominator "Visited more than 1 doctor or healthcare provider to get more prescription opioid medication in the past 3 months" (N=72). This question also pertains to the parallel questions regarding visits to pharmacies (N=158 and N=180).

Response: *The pattern described stems from the design of the POMAQ survey. Only those who responded "True" for visited more than one doctor in the past year were asked the question whether they visited more than one doctor in the past three months. Therefore, 1,085 patients were asked whether they visited more than one doctor in the past year and only 67 were asked whether they visited more than one doctor in the past three months. The same skip pattern was also employed in the POMAQ for visiting pharmacies. Section 6.3.2 of the revised report has been clarified to provide the above information.*

Regarding Objective #2—To assess whether the proportion of patients reporting misuse, abuse, and/or diversion, measured using a validated questionnaire, increases across doctor/pharmacy shopping categories defined a priori in Study 3033-8:

1. Objective #2 includes diversion as an outcome. Although there are items related to diversion on the POMAQ, represented in Tables 7a and 7b, the Final Study Report does not include diversion in the narrative text of the results or in the discussion section. Diversion as an outcome is not specified in the PMR itself; however, it was included as an outcome in the approved study protocol and remains an outcome of interest as it is interconnected with misuse and abuse. Explain and address the inconsistency in the approved protocol, the methods section of the Final Study Report, and the actual results reported and discussed in the Final Study Report. Provide descriptive statistics (with and without stratification by doctor/pharmacy shopping, pain intensity, and social desirability as in Tables 7a-7c) and regression analysis results (as in Tables 8-10 and Figures 3-4) for diversion. Additionally, clarify how diversion was handled in the logistic regression models and if it was modeled as an outcome, as suggested in the study objectives.

   Response: *To address the inconsistency between the protocol and the statistical analysis plan, we performed additional analyses to evaluate diversion as an outcome. While the intention was to perform the same set of analyses performed for the rest of the outcomes, e.g., misuse, only 14 patients self-reported diversion. The small number of patients with self-reported diversion limited what we were able to do. As a result, we examined the proportion of patients who self-reported diversion across the shopping categories overall, stratified by pain and social desirability. We did not perform regression analysis for division as an outcome because such analyses would lack statistical power and reliability due to the small number of events per variable in the model. Updated results for diversion are included in Table 7a and Table 7c of the revised report.*

2. The FDA previously requested more detailed description for the scoring algorithm to determine abuse and misuse outcomes based on the POMAQ items. Appendix D in the latest statistical analysis plan (SAP; version 6 dated November 5, 2018) is not useful to understand how the scoring algorithm was constructed and used to ascertain the abuse, misuse, and abuse and misuse outcomes.

In the Final Study Report, provide a concise description for the scoring algorithm and a list of the POMAQ items used in the algorithm. Clarify what time frame the outcomes ascertained by the scoring algorithm represents. For example, clarify whether the abuse outcome ascertained by the scoring algorithm represents past year, past 3-months, lifetime (ever) abuse, or something else. Also provide a brief description on how the scoring algorithm has been developed and validated, or cite a study report (with a specific section and page number) providing the information.

Response: *We referenced two final reports from Study 3033-4 in Section 5.2.2 of the revised report. These two final reports include detailed information on the POMAQ survey, the scoring algorithm, and the validation of the POMAQ.*

3. Similarly, provide a scoring algorithm along with a list of items to define pain intensity category (no, mild, moderate, and severe; provided in Table 5) and social desirability category (low, moderate, and high; provided in Table 6). Cite relevant references if these scores were developed and validated from the other studies.

   Response: *We revised Sections 5.2.2, 5.5.3 and 5.6.1 to provide information on the methods used to define the pain intensity and social desirability categories and to provide the requested references.*

4. Table 7a shows that percentage of patients who endorsed the use of barbiturates among those in the severe doctor/pharmacy shopping category is 1.1%. Note that 1.1% of the total survey respondents (N=1085) is 12, which is greater than 10. However, Table 7a did not provide a number for the 1.1%. Clarify.

   Response: *The 1.1% is out of all patients in the severe shopping category and not the total. As a result, the actual number of patients reporting barbiturates use is <11.*

5. Formulation of the logistic regression model presented on page 18 of the Final Study Report is incorrect. It should have been

   $$logit\{\text{ Probability(presence of outcome = yes)}\} = \beta 0 + \beta 1 * I(\text{minimal shopping}) + \beta 2 * I(\text{moderate shopping}) + \beta 3 * I(\text{severe shopping}),$$

   where *logit* represents the logit function where $logit(p) = ln\{p/(1-p)\}$ for $0<p<1$, *ln* is the natural log function, and $I(\cdot)$ is an indicator function. Clarify if you considered $\beta 0$ (intercept) in logistic regression models. According to the formulation provided in the Final Study Report, you used logistic regression models with no intercept. Also clarify whether the reference group for the outcome only includes persons with no abuse and no misuse or persons with no outcome (e.g., persons with no abuse regardless of misuse for abuse outcome, or persons with no misuse regardless of abuse for misuse outcome).

Response: *We would like to confirm that we used a logistic regression model with an intercept term. We revised the report (Section 5.6.3) to correctly communicate the logistic regression model.*

The reference group for all outcomes in the regression analysis consisted of patients without abuse or misuse. Additional information is provided in response to comment 3iii above.

6. The outcome of abuse and/or misuse is presented in tables 7a and 7c but is not included in the regression analyses. Include the unadjusted and adjusted models for this outcome (abuse and/or misuse) in table 8.

   Response: *We added the results to Table 8. For this outcome, we performed the same set of analyses as we did for the rest of the outcomes and the results are presented in the revised Table 8, Table 9a and b, Table 10, Table 11a, b, and c, Table 14, Figure 3, and Figure 4.*

7. For analysis of *abuse and misuse* outcome, risk factors for abuse and risk factors for misuse should all be included in the full adjusted model. If this is not feasible due to the small number of patients with the outcome, consider further adjustment by geographic region, in addition to medication of abuse potential.

   Response: *We followed the same process described in Section 5.6.3 of the report to build the final adjusted model across all outcomes. Univariable analyses were performed to identify covariates to be included in an initial multivariable model, which was then reduced using manual backward elimination to a final parsimonious multivariable model. The Region variable was evaluated but was not included in the final parsimonious multivariable model.*

8. Table 11a: Sensitivity Analysis Excluding Covariates That May Be Correlated With POMAQ Items: This table only provides adjusted logistic regression results. Conduct all analyses considered in Tables 8 to 10 and Figures 2 to 4 as part of this sensitivity analysis. When you report results in Table 10 for this sensitivity analysis, also provide covariate-only model results. Note that this sensitivity analysis should be conducted for diversion outcome as well.

   Response: *The sensitivity analysis presented in Table 11a does not include results from the crude models as they were already presented in Table 8 and Table 9. As requested, we added results from the covariate-only models and the abuse or misuse models to Table 10 of the revised report. As described in our response to comment 1, under Regarding Objective #2, only descriptive analyses were performed for diversion due to small number of patients who reported the outcome.*

8.4 APPENDIX D. PATIENT SURVEYS

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