



# Real-world misuse, abuse, and dependence of abuse-deterrent versus non-abuse-deterrent extended-release morphine in Medicaid non-cancer patients

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## ABSTRACT

**Objective:** Opioids with abuse-deterrent properties may reduce widespread abuse, misuse, and diversion of these products. This study aimed to quantify misuse, abuse, dependence, and health resource use of extended-release morphine sulfate with sequestered naltrexone hydrochloride (ER-MSN; EMBEDA<sup>®</sup>), compared with non-abuse-deterrent extended-release morphine (ERM) products in Medicaid non-cancer patients.

**Methods:** Administrative medical and pharmacy claims data were analyzed for 10 Medicaid states from 1 January 2015, to 30 June 2016. Patients were included if they received a prescription for ER-MSN or any oral, non-abuse-deterrent ERM. Index date was the date of first prescription for an ER-MSN or ERM. Abuse/dependence, non-fatal overdose, emergency department (ED) visits, and ED/inpatient readmissions were determined for each participant. An overall measure of misuse and abuse was also calculated. To account for differences in follow-up, all counts are expressed per 100 patient-years.

**Results:** There were 4,857 patients who received ER-MSN and 10,357 who received an ERM. The average age in the two cohorts was approximately 45 years old. From pre-index to follow-up, the number of patients per 100 patient-years with a diagnosis code indicating abuse or dependence increased by 0.91 (95% confidence interval [CI]: 0.85, 0.97) in the ER-MSN cohort and 2.23 (95% CI: 2.14, 2.32) in the ERM cohort. The number of patients per 100 patient-years with an opioid-related non-fatal overdose increased by 0.05 (95% CI: 0.04, 0.06) in the ER-MSN cohort compared with 0.11 (95% CI: 0.09, 0.13) in the ERM cohort. The opioid abuse overall composite score increased by 1.36 (95% CI: 1.24, 1.48) in the post-index period in the ER-MSN cohort compared to 3.21 (95% CI: 3.10, 3.32) in the ERM cohort.

**Conclusion:** Misuse, abuse, and dependence events were numerically lower in patients receiving ER-MSN compared with those receiving ERM products.

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## 1. Introduction

The increase in opioid prescriptions over the past 25 years directly correlates with an increase in opioid abuse as well as prescription opioid overdose deaths [1]. In 2016, the National Safety Council reported that '1.9 million Americans [were] addicted to opioid painkillers' [1]. Deaths involving overdose of prescription opioids were five times higher in the United States in 2016 compared with 1999, and from 1999 to 2016 there were over 200,000 deaths due to prescription opioid-related overdose [2]. In 2016, 40% of all opioid overdose deaths in the United States involved prescription opioids, and more than 46 people died every day from overdoses involving prescription opioids [2].

Opioid abuse includes multiple routes of abuse (i.e., oral, intranasal, or intravenous), utilized either separately or in combination, with or without manipulation of the medication. Manipulation (tampering) includes chewing, crushing, or

dissolving. Even though oral abuse is the most common route of abuse, there are also significant non-oral routes of abuse of extended-release opioids. For instance, Butler et al. (2013) [3] demonstrated in subjects entering substance use disorder treatment centers that non-oral routes of abuse of extended-release morphine and extended-release oxycodone are common, and in some cases exceed oral routes of abuse; note that the term oral routes of abuse does not distinguish between subjects that swallowed the drug intact or chewed the formulation. Furthermore, in an online survey of participants from the US National Health and Wellness Survey who reported abuse or non-medical use of prescription opioids, approximately half of the respondents admitted to tampering with the formulation [4]. While almost all subjects reported oral abuse of the intact drug (91%), 38.2%, 37.8%, and 32.4% of these subjects also reported snorting, chewing or injection of the drug, respectively. Addressing non-oral

routes of opioid administration is an important medical concern. Routes of administration have been shown to be a contributor to the adverse health consequences of abuse. A study of 791 opioid abusers demonstrated higher odds of intranasal, smoking, and injection administration in young opioid abusers aged 18–24; young opioid abusers also showed higher odds of HIV risk behaviors such as re-using needles, re-using needles without cleaning them, and lending needles [5]. Lastly, based on analysis of RADARS Poison Center data (2006–2014), intentional abuse exposure involving prescription opioid medication tampering associated with injection or inhalation were more likely associated with death or major medical outcome than exposures from oral ingestion (87% greater risk for injection and 76% greater risk for inhalation) [6].

The FDA views the development of opioids with abuse-deterrent properties as a high public health priority [7,8]. Opioids with abuse-deterrent properties are developed with the intent to curtail specific routes of abuse; while these medications are currently not abuse-proof, they are designed to help deter routes of abuse that involve tampering (chewing, crushing, or dissolving), and may have an impact on abuse and diversion rates [3,9–14]. Abuse deterrence may be achieved in a variety of ways, including making the medication difficult to crush, insoluble in water or other commonly available solvents, adding aversive agents, or combining with a sequestered opioid antagonist. A 2014 study showed that abuse-deterrent OxyContin successfully reduced abuse of the active drug, particularly in those who abused by tampering to inject or inhale the substance [15,16].

With the exception of oxycodone, little information exists regarding the impact of opioids with abuse-deterrent properties on reducing abuse or misuse of opioid products. The low patient exposure to other abuse-deterrent formulations has also made it difficult to determine any impact of these formulations on abuse, overdose, and death. The recent preferred formulary status of EMBEDA<sup>®</sup> for Medicaid patients in some states provides an opportunity to address this issue quantitatively. Once other abuse-deterrent formulations also demonstrate higher patient exposure, it will be useful to quantify the impact of other medicines. The objective of this study was to quantify the misuse, abuse, dependence, opioid-related non-fatal overdose, and health resource use in a Medicaid patient sample prescribed an abuse-deterrent formulation of extended-release morphine sulfate with sequestered naltrexone hydrochloride (ER-MSN; EMBEDA<sup>®</sup>) or non-abuse-deterrent extended-release morphine (ERM).

## 2. Materials and methods

This retrospective cohort study analyzed medical and pharmacy claims records for two cohorts of patients aged 18 years or older during the study period. The two cohorts consisted of patients on ER-MSN treatment and patients on non-abuse-deterrent ERM treatment. Patients enrolled in fee-for-service Medicaid programs in 10 separate states located throughout the country and representing around 6.1 million covered lives were examined. Administrative medical and pharmacy claims data with dates of service between 1 July 2014, and 30 June 2016 from each of the 10 states were combined into a single data source and evaluated. All data comes from post-

adjudication data sources and duplication is removed (based on unique combinations of patient, date of service, place of service, provider, and product/service performed or provided) in order to include only the latest paid claims available at the time.

Patients were included in this study if they were at least 18 years of age or older, had a history of diagnosed chronic pain (defined as greater than or equal to three months) during the baseline or study period, had a minimum of one paid claim for ER-MSN and/or non-abuse-deterrent ERM during the baseline or study period, and were continuously eligible, allowing a maximum gap of up to seven days, during the baseline period (six months prior to index date) and study period (at least six months post-index date). Patients were excluded if they were residents of a nursing home or skilled nursing facility, received hospice care at any time during the study period, or if they had any cancer diagnosis (except non-melanoma skin cancer) on separate calendar dates at least 60 days apart in study period, in order to eliminate likelihood of errant diagnosis coding.

The dispense date of the first prescription for an oral ERM product was considered to be the index date for each patient. Each patient was followed for the remainder of their eligibility through the end of the study period. Event rates were adjusted per 100 patient-years to account for the differing lengths of follow up for the included patients. Each patient had at least 6 months of follow up data.

Baseline metrics for each patient were calculated and include age at the index date as well as gender. The Charlson Comorbidity Index as well as the presence of opiates (other than ERM) was measured in the six months leading up to the index date. Baseline measures were calculated as descriptive values and presented as means, standard deviations, and medians for continuous variables and counts and percentage for discrete values.

Patients were placed into two cohorts based on the presence or absence of ER-MSN in the follow up period. Patients who used ER-MSN at any time in the follow up period were placed into that cohort. A variety of metrics were calculated based on medical claims incurred during the follow up period for each patient. These metrics are based on diagnosis codes, place of service codes, revenue codes, and discharge disposition information from submitted medical claims data and consist of the difference in counts per 100 patient-years between the baseline and follow up periods for both cohorts, as well as a 95% confidence interval.

The number of patients with a code indicating abuse or dependence (defined as 3 or more specific abuse behaviors exhibited in the past year similar to DSM-IV criteria) was assessed for the entire population based on ICD-9 or ICD-10 code in any position on the claim. The relevant codes are listed in Table 1 of the Supplemental Information. The number of opioid-related non-fatal overdoses was also counted for each cohort. Health-care utilization metrics included all-cause emergency department (ED) visits, ED or inpatient (IP) readmissions, and a composite count of all-cause ED visits or ED or IP readmissions.

## 3. Results

A total of 15,214 patients were included in the study. Of these patients, 4,857 received ER-MSN (31.9%) and 10,357 received

**Table 1.** Variables assessed in the study.

Baseline Patient Characteristics	Age
	Gender
Treatment Trends	Adherence (PDC)
	Persistence
	Switching
	Physician Specialty
	Dose
Charlson Comorbidity Index	1
	2
	3+
Concomitant Therapy	Classes ranked by proportion of patients
Healthcare Resource Utilization	Count of inpatient care
	Cost of inpatient care
	Emergency utilization
	Office visits
	Pharmacy fills
	Pharmacy spend
	Laboratory/imaging utilization
Adverse Health Outcomes	Addiction, abuse, opioid-related overdose, all opioid-related ED visits
	Outpatient/inpatient medical visits related addiction and abuse (post-ER care visits)
	MEQ, number of prescribers, number of pharmacies, number of opioid prescriptions by quarter, etc.
	Respiratory failure, alteration of consciousness, poisoning, etc.

Abbreviations: ED = emergency department; MEQ = morphine equivalent dose; PDC = proportion of days covered; ER = emergency room.

non-abuse-deterrent ERM (68.1%). The average age in the two cohorts was similar at around 45 years old (Table 2). The comorbidity burden between the two cohorts was similar with a Charlson Comorbidity Index of 1.7 for the ER-MSN group and 1.8 for the non-abuse-deterrent ERM group (Table 2).

The number of patients per 100 patient-years with a diagnosis code indicating abuse or dependence increased by 0.91 (95% CI: 0.85, 0.97) in the ER-MSN group and 2.32 (95% CI: 2.14, 2.32) in the non-abuse-deterrent ERM group from the pre-index to follow-up periods (Table 3). The number

of patients per 100 patient-years with an opioid-related non-fatal overdose increased by 0.05 (95% CI: 0.04, 0.06) in the ER-MSN group compared with 0.11 (95% CI: 0.09, 0.13) in the non-abuse-deterrent ERM group (Table 3).

The opioid abuse overall composite score (in patients per 100 patient-years), comprised of patients with an all-cause ED visit, repeat ED visit, or repeat IP readmission, increased by 1.36 (95% CI: 1.24, 1.48) in the post-index period in the ER-MSN cohort compared to 3.21 (95% CI: 3.10, 3.32) in the non-abuse-deterrent ERM group (Table 4).

**Table 2.** Baseline demographics of the ER-MSN and non-abuse-deterrent ERM cohorts.

Metric		ER-MSN Cohort	Non-abuse-deterrent ERM Cohort
N		4,857	10,357
Age	mean (SD) [median]	45.43 (9.92) [46.00]	45.52 (10.52) [46.00]
	18–20, n (%)	16 (0.3%)	90 (0.9%)
	21–30, n (%)	346 (7.1%)	796 (7.7%)
	31–40, n (%)	1,225 (25.2%)	2,519 (24.3%)
	41–50, n (%)	1,555 (32.0%)	3,220 (31.1%)
	51–60, n (%)	1,490 (30.7%)	3,094 (29.9%)
	61+, n (%)	225 (4.6%)	638 (6.2%)
Gender	Female, n (%)	3,138 (64.6%)	6,374 (61.5%)
	Male, n (%)	1,719 (35.4%)	3,983 (38.5%)
Charlson Comorbidity Index	mean (SD) [median]	1.66 (2.20) [1.00]	1.76 (2.43) [1.00]
	0, n (%)	1,871 (38.5%)	4,212 (40.7%)
	1, n (%)	1,221 (25.1%)	2,290 (22.1%)
	2, n (%)	629 (13.0%)	1,313 (12.7%)
	3+, n (%)	1,136 (23.4%)	2,542 (24.5%)
Opiate Use During Baseline	Yes, n (%)	4,338 (89.3%)	9,187 (88.7%)

Abbreviations: ER-MSN = extended-release morphine sulfate with sequestered naltrexone hydrochloride; ERM = extended-release morphine; SD = standard deviation.

**Table 3.** Abuse/dependence and opioid-related non-fatal overdose counts in the ER-MSN and non-abuse-deterrent ERM cohorts.

Metric	Pre-Index		Follow-Up	
	ER-MSN Cohort	Non-abuse-Deterrent ERM	ER-MSN Cohort	Non-abuse-Deterrent ERM
Abuse/Dependence <sup>a</sup>	2.11 <sup>a</sup> (1.83, 2.39)	1.9 <sup>a</sup> (1.77, 2.21)	3.02 <sup>a</sup> (2.84, 3.20)	4.22 <sup>a</sup> (4.09, 4.35)
Opioid-Related Non-Fatal Overdose <sup>b</sup>	0.01 <sup>a</sup> (0.00, 0.20)	-	0.06 <sup>a</sup> (0.03, 0.09)	0.11 <sup>a</sup> (0.09, 0.13)

Data are presented as count per 100 patient-years (95% CI)

<sup>a</sup>Equation: (Follow-up – Pre-index)

<sup>b</sup>ICD-9: 304.00–304.03, 305.50–305.53; ICD-10: F11.10, F11.20, F11.21

<sup>c</sup>ICD-9: 965.09; ICD-10: T40.2, T20.4, T40.6

Abbreviations: CI = confidence interval; ER-MSN = extended-release morphine sulfate with sequestered naltrexone hydrochloride; ERM = extended release morphine; ICD = international classification of diseases.

**Table 4.** Health-care utilization in the ER-MSN and non-abuse-deterrent ERM cohorts.

Metric	Pre-Index		Follow-Up	
	ER-MSN Cohort	Non-abuse-Deterrent ERM	ER-MSN Cohort	Non-abuse-Deterrent ERM
Patients with an all-cause ED visit	3.00 <sup>a</sup> (2.66, 3.34)	3.16 <sup>a</sup> (2.89, 3.43)	4.49 <sup>a</sup> (4.27, 4.71)	5.47 <sup>a</sup> (5.32, 5.62)
ED or IP Readmit	0.76 <sup>a</sup> (0.59, 0.93)	1.05 <sup>a</sup> (0.89, 1.21)	1.85 <sup>a</sup> (1.71, 1.99)	3.06 <sup>a</sup> (2.95, 3.17)
Composite	2.73	2.87	4.09	6.08

Data are presented as count per 100 patient-years (95% CI)

<sup>a</sup>Equation: (Follow-up – Pre-index)

Abbreviations: CI = confidence interval; ED = emergency department; ER-MSN = extended-release morphine sulfate with sequestered naltrexone hydrochloride; ERM = extended release morphine; IP = in-patient.

#### 4. Discussion

We found that abuse and dependence increased in patients treated with either type of extended-release morphine formulation. The number of patients with a diagnosis code indicating abuse or dependence increased by less in the ER-MSN group when compared to the non-abuse-deterrent ERM group. Additionally, the number of patients with an opioid-related non-fatal overdose increased by less in the ER-MSN group compared with the non-abuse-deterrent ERM group.

There are several potential reasons for these observations. Since ER-MSN was the preferred formulary product, most patients in whom an ER morphine product was prescribed likely received ER-MSN. However, several factors could affect the drug received by the patient. For example, a prescriber could decide to use the abuse-deterrent product in patients with an increased risk of substance abuse. This is not the intended use, but a common clinician perception – an “abuse-deterrent” drug should be used in a patient with high risk for abuse. This bias would tend to elevate abuse rates in the group receiving ER-MSN. Conversely, a patient who intends to abuse a product may subtly try to influence the prescriber to use a non-abuse deterrent formulation, which would tend to increase abuse rates in the ERM group. The final population that received ER morphine likely represents a unknown mixture of users at high or low risk. However, the relatively short time period of study should limit differential bias over time, meaning that the bias would be expected to be constant between the two groups throughout the study period.

Whether a low- or high-risk patient, an opioid with abuse-deterrent properties offers potential benefits. Most patients do not abuse their medication. An abuse-deterrent formulation is expected to reduce the street value of the drug and thereby attractiveness of the drug for theft [17]. Further, if the user finds themselves attracted to the drug, the ADF properties discourage them from tampering with the product. In contrast, abusers posing as a patient (‘doctor shoppers’) may well request a non-abuse deterrent formulation, which can alert the prescriber to their hidden intent.

It is important to note that certain limitations in this study impacted the conclusiveness of the results, as they may not represent the full picture. This study was completed using administrative medical and pharmacy claims data. Services rendered or products dispensed, but not billed, will not be included in this data. Services or products not billed may include physician services provided pro bono, or any service or product included in a cash transaction. Claims data provide codes for billing purposes and may not represent all diagnoses for a given patient. Additionally, diagnoses may also be subject to provider interpretation and bias.

Formularies vary from state to state and can heavily dictate provider choice of prescribed agents. Not all providers are able to choose between opioids with abuse-deterrent properties and opioids without abuse-deterrent properties. Patients were not randomized to drugs and therefore the study groups could differ in ways that were not measured. Additionally, different states have different formulary status for specific drugs, including ER-MSN. ER-MSN had preferred ERM product status in some states for the entire study period, in some states for part of the study period, and in other states for none of the study period. The ability to assess differences in ER-MSN and non-abuse-deterrent ERM cohorts by formulary access group would minimize this bias. However, due to contractual limitations, the identities of the states included in the study must remain blinded, and thus a state-by-state assessment by coverage policy could not be conducted.

Although several opioid analgesics with approved labeling for abuse deterrence are available commercially, they have had low utilization to date. The preferred formulary status of ERM was an unique opportunity to include enough patients for analysis. The low utilization of abuse-deterrent products to date means that the abuse-deterrent efficacy of abuse-deterrent products cannot be studied or will take many years to assess under ‘real-world conditions.’ There are likely many reasons for the lack availability. Strong discordant opinions about the appropriateness of abuse-deterrent products have emerged. Proponents view abuse-deterrent opioids like seat belts: a tool reduce to reduce harms from the medication by reducing chewing, snorting, and injection. Opponents contend that the research available has not proven the products effective and allege that an abuse-deterrent formulation might increase prescribing due to a false sense of security. There is also concern about as potentially ‘pushing’ abusers to other drugs like heroin. Another reason is formulary status. Many third-party payers have made abuse deterrent products difficult or impossible to prescribe.

#### 5. Conclusion

Misuse, abuse, and dependence of standard non-abuse-deterrent ERM products or an opioid with abuse-deterrent properties were evaluated in a Medicaid non-cancer population. The results show that misuse, abuse and dependence events were numerically lower in patients receiving ER-MSN compared to those receiving non-abuse-deterrent ERM products. The main limitation of the study is that state formularies drive prescribing choice, so physicians were not always able to choose between opioids with abuse-deterrent properties and opioids without abuse-deterrent properties. However, as utilization of these products increases over time, more robust differences may be observed between opioids with abuse-deterrent properties and opioids without abuse-deterrent properties. Although it was not the intent



of the study, we can report that the incidence of abuse, dependence, and overdose was low in both ER-MSN and non-abuse-deterrent ERM groups for the durations observed.

### Geolocation information

Provision of geolocation information is not possible due to the required confidentiality discussed in the Materials and Methods.

### Data availability

Data are available on request due to privacy/ethical restrictions.

### Funding

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### Declaration of interest

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