Annals of Internal Medicine ORIGINAL RESEARCH

Patterns of Potential Opioid Misuse and Subsequent Adverse Outcomes in Medicare, 2008 to 2012

Colleen M. Carey, PhD; Anupam B. Jena, MD, PhD; and Michael L. Barnett, MD, MS

Background: Providers are increasingly being expected to examine their patients' opioid treatment histories before writing new opioid prescriptions. However, little evidence exists on how patterns of potential opioid misuse are associated with subsequent adverse outcomes nationally.

Objective: To estimate how a range of patterns of potential opioid misuse relate to adverse outcomes during the subsequent year.

Design: Observational study comparing outcomes for Medicare enrollees with potential opioid misuse patterns versus those for beneficiaries with no such patterns, adjusting for patient characteristics.

Setting: Medicare, 2008 to 2012.

Patients: A 5% sample of beneficiaries who had an opioid prescription without a cancer diagnosis.

Measurements: Several measures for opioid misuse were defined on the basis of drug quantity, overlapping prescriptions, use of multiple prescribers or pharmacies, and use of out-of-state prescribers or pharmacies. The primary outcome was a diagnosis of opioid overdose in the year after a 6-month index period. Secondary outcomes included subsequent opioid-related or overall mortality.

Results: Overall, 0.6% to 8.5% of beneficiaries fulfilled a misuse measure. Subsequent opioid overdose was positively associated with successively greater numbers of prescribers or pharmacies or higher opioid quantities during the index period. For example, patients who obtained opioids from 2, 3, or 4 prescribers were increasingly more likely to have an opioid overdose (adjusted absolute risk per 1000 beneficiary-years [aAR], 3.5 [95% CI, 3.3 to 3.7]; 4.8 [CI, 4.5 to 5.2]; or 6.4 [CI, 5.8 to 6.9], respectively) than those with a single prescriber (aAR, 1.9 [CI, 1.8 to 2.0]). Subsequent overdose risk increased meaningfully with any deviation in the single prescriber–single pharmacy opioid use pattern. All misuse measures examined had a positive association with subsequent opioid overdose and death.

Limitation: Risk estimates provide measures of association and may not generalize to non-Medicare populations.

Conclusion: To fully assess patients' opioid overdose risk, clinicians should examine a wide range of misuse patterns.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2018;168:837-845. doi:10.7326/M17-3065 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 22 May 2018.

Opioid misuse has reached epidemic proportions in the United States, leading to a substantial morbidity and mortality burden (1, 2). In 2015, nearly 5% of U.S. adults misused opioids in the previous year (3). The rise of this epidemic seems to have contributed to a historic increase in deaths among middle-aged white Americans (4) after decades of decline, and recent research suggests that it may be associated with low labor market participation in the wake of the Great Recession (5). According to the National Survey on Drug Use and Health, most opioid misuse cases originated with a legitimate prescription from a provider, with the drugs either prescribed directly to the patient or obtained through diversion (6).

The scale of misuse of legitimately prescribed opioids has led to an intense focus on helping health care providers identify patients at high risk for misuse. The most prominent examples are state databases known as prescription drug monitoring programs (PDMPs) (7), which collect data from the state's pharmacies (and, in some cases, from pharmacies in other states) on all prescription opioid fills. Although PDMPs originally were designed to assist law enforcement in investigations, 49 states (excluding Missouri) and the District of Columbia have implemented a PDMP that allows access to providers, and a growing number of states are mandating that providers review PDMP data before prescribing opioids (8, 9).

In principle, PDMPs allow providers to infer a patient's risk for opioid misuse by examining details of the patient's prescription history. However, despite the wealth of opioid prescribing data contained in PDMPs, clear guidance is lacking on what specific use patterns are correlated with adverse opioid-related patient outcomes and should therefore prompt clinical attention (10–12). Previous studies on patterns of potential opioid misuse generally focused on single measures and examined only a narrow range of outcomes, potentially underestimating the depth of information present in a complex prescription history (13–16). Several metrics have been proposed to assess potential opioid misuse, including acquisition from more than 1 prescriber or pharmacy, receipt of opioids across state borders, and overlapping days of supply. However, these patterns

See also:

Editorial comment 883
Summary for Patients I-18

Web-Only
Supplement

Table 1. Characteristics of the Study Population, by Possible Opioid Misuse Measures*

Variable	No Possible Misuse Measures	Possible Misuse Measures						Multiple Possible Misuse Measures†
		>210 Days Supplied in 180 Days	Any Overlapping Claim	≥5 Prescribers	≥5 Pharmacies	Any Out-of-State Prescriber	Any Out-of-State Pharmacy	
Prevalence of misuse measures								
Prevalence, *% of half-years*	84.0	5.6	8.5	2.4	0.6	3.3	3.4	5.9
Half-years, *n*	1 622 864	109 043	165 111	46 063	12 088	63 575	66 236	114 339
Patients, *n*	605 082	45 234	88 554	28 385	7241	34 596	31 953	56 861
Patient characteristics								
Female, %	66.0	62.4	65.7	62.8	56.8	64.1	67.4	63.8
Race, %								
White‡	79.7	83.1	82.1	72.9	72.5	85.3	87.3	82.5
Nonwhite	20.1	16.8	17.8	27.0	27.4	14.6	12.6	17.4
Unknown	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.1
Mean age by enrollment category, *y*								
Age ≥65 y	76.8	75.2	76.9	73.5	71.2	76.6	77.6	76.3
Disability	51.1	50.8	50.7	47.4	45.9	50.3	51.0	49.8
Mean MED per half-year, *mg/d*	5.8	47.7	35.3	26.9	47.3	19.3	16.9	40.2
Medicare enrollment category, %								
Age ≥65 y	40.2	15.9	24.0	10.6	3.8	32.4	41.0	23.0
Disabled	8.9	16.4	12.2	12.0	15.2	15.0	12.7	14.2
Medicaid eligible, age ≥65 y	25.3	17.1	22.3	11.5	6.3	17.6	20.8	16.7
Medicaid eligible, disabled	25.6	50.6	41.5	65.9	74.7	34.9	25.5	46.0
Charlson Comorbidity Index score, %								
0	25.0	23.1	19.6	18.0	23.2	24.7	22.5	21.7
1	23.9	23.9	22.0	22.1	24.3	24.0	23.2	23.1
2	17.5	18.1	18.0	17.5	17.1	17.6	18.0	17.9
≥3	33.6	34.9	40.4	42.4	35.4	33.7	36.2	37.3

MED = morphine-equivalent dosage.
* Percentages may not sum to 100 due to rounding.
† Patient half-years satisfying ≥2 possible misuse measures.
‡ 0.3% of sample has "unknown" race; these patients are grouped with nonwhites.

are not mutually exclusive, and relying on any one measure to define misuse may exclude a substantial proportion of potential misuse. Systematic empirical evidence is lacking on how the many dimensions of potential prescription opioid misuse relate to subsequent opioid-related adverse events.

Using data on Medicare beneficiaries, we examined the relationship between several patterns of potential opioid misuse and adverse opioid-related outcomes, such as opioid overdose and death. We used longitudinal data to study how 6 measures of potential opioid misuse each relate to adverse opioid-related outcomes during the following year, with the goal of identifying clinically relevant patterns of high-risk prescription opioid use.

METHODS

Study Population and Data Sources

We used prescription drug and medical claims for a 5% random sample of Medicare beneficiaries between 2008 and 2012. We included beneficiaries of all ages because the subset younger than 65 years, who are largely disabled, has a high prevalence of opioid use (17). We divided claims into half-years (6-month periods), and our analysis sample included patients who filled at least 1 opioid prescription in any half-year and were not enrolled in Medicare Advantage for any month during the current or next calendar year. We excluded persons who had cancer diagnosed in the year of the opioid fill, because many patients with advanced cancer use opioids appropriately for pain control. After sample restrictions, we noted opioid fills and adverse opioid outcomes in 1 933 232 beneficiary half-year observations between 2008 and 2012. This number represents 627 391 distinct persons who received opioids for an average of 3 half-years. The study was approved by the Cornell University Institutional Review Board for Human Participants.

Defining Opioid Prescriptions

We defined an opioid fill as an observation in the Part D (prescription drug insurance) "event file" of any drug containing an opioid analgesic ingredient, as classified by the U.S. Pharmacopeia (18). We extracted the number of days for which opioids were supplied and calculated the morphine-equivalent dosage (MED) of

total medication dispensed by using standard conversion tables (19).

Measures of Possible Opioid Misuse

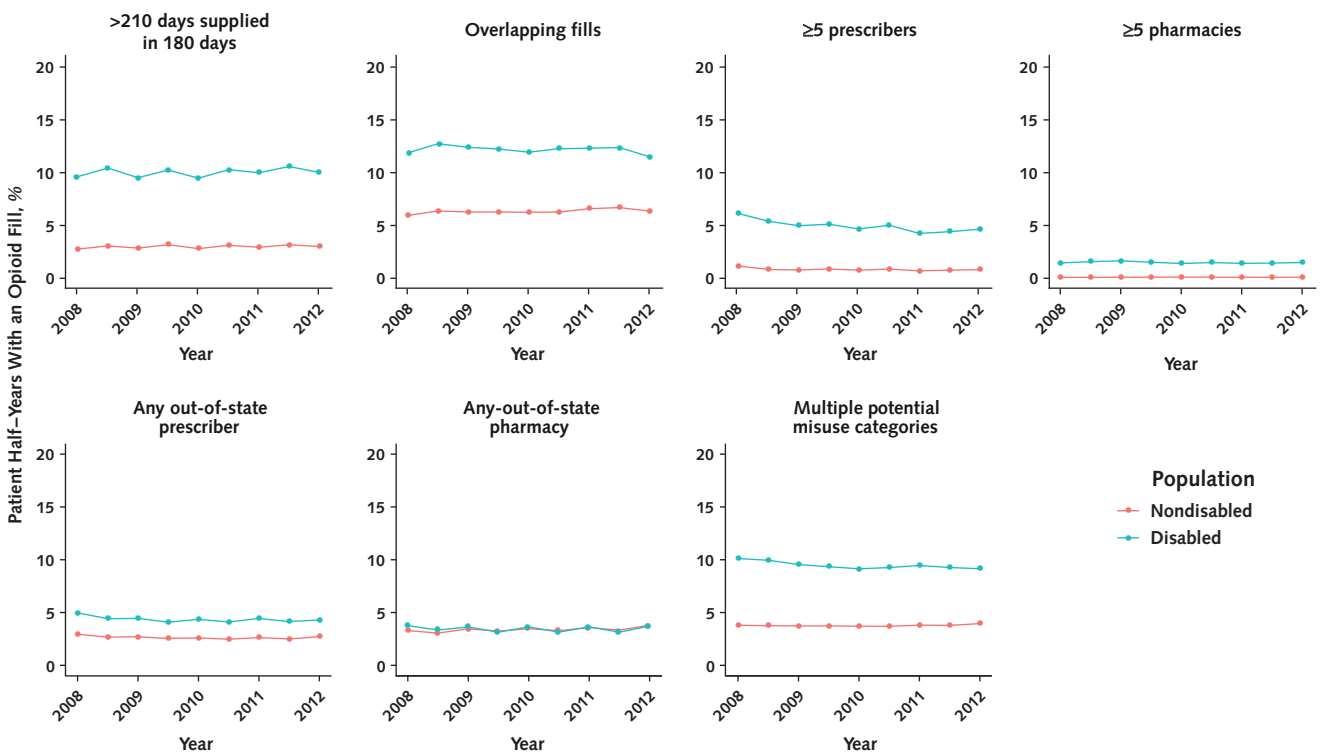
We defined 6 measures of possible opioid misuse on the basis of 3 separate dimensions of potential misuse: high prescription quantity, fragmented prescribing (sometimes referred to as "doctor shopping"), and use of out-of-state providers. These measures are not diagnostic of misuse but serve as potential markers for high-risk opioid use that may deserve scrutiny by providers. Within these misuse measures, we examined both dichotomous indicators for particularly high-risk patterns and several categorical definitions of these measures to determine whether there was a "dose–response" association.

We defined 2 measures to assess high prescription quantity. Recognizing that a patient may appropriately receive a prescription for a long-acting opioid plus a short-acting one for breakthrough pain, we first classified each claim as long- or short-acting and assessed quantity by using the maximum amount supplied of either type. To illustrate, our first quantity measure was whether a patient obtained more than a 210-day (about a 7-month) supply of either long- or short-acting opioids during the half-year. A person who obtained an 8-month supply of tramadol would fulfill this measure, but a person who obtained 4 months of fentanyl transdermal patches and 4 months of hydrocodone would not. Second, we defined a "claims overlap" measure according to whether a patient filled a prescription for the same opioid ingredient with the same duration of action (long- or short-acting) more than 1 week before the number of days supplied on the previous prescription were exhausted. The claim must have been for the same ingredient to exclude the possibility that a patient may have had poorly controlled pain requiring different types of opioids. For example, a patient who filled prescriptions for a fentanyl patch and hydrocodone tablets on the same day would not be coded as having overlapping claims. For sensitivity analyses, we also explored measures that did not adjust for combinations of long- and short-acting opioids (**Supplement**, available at Annals.org).

To measure fragmented prescribing, we counted the number of prescribers and the number of pharmacies from which a patient obtained opioids during the half-year. Prescribers were identified by their National Provider Identifier, and pharmacies in the Part D event file were identified by using an encrypted tag specific to individual pharmacy locations. Our main analysis focused on a binary cutoff to define potential misuse: whether a patient obtained opioids from 5 or more prescribers or 5 or more pharmacies in each half-year (20, 21).

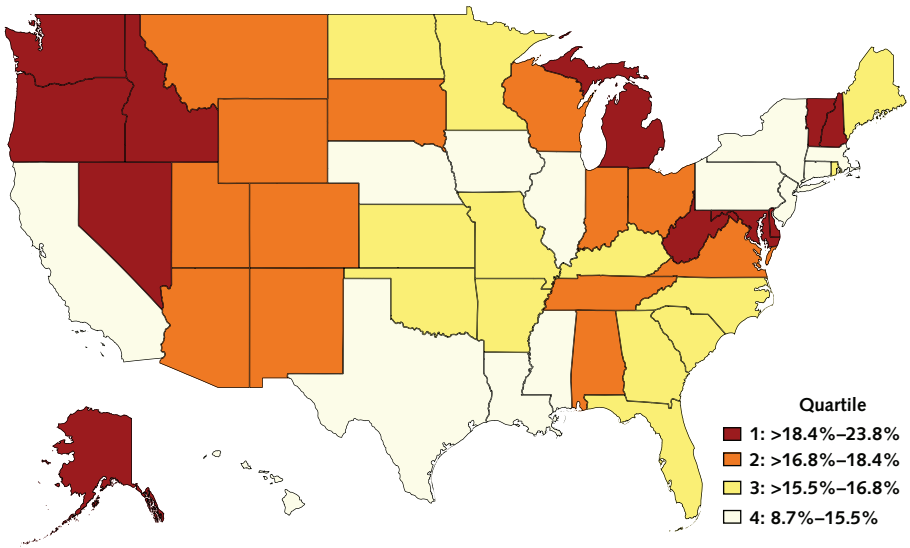
We considered 2 additional measures that involved prescriptions crossing state lines, because some per-

Figure 1. Trends in measures of possible opioid misuse, by Medicare eligibility category, 2008 to 2012.



Prevalence of measures of possible opioid misuse, as defined in Methods, from 2008–2012. Each point represents the prevalence of a measure of possible misuse during a half-year. The blue lines represent the trend for the Medicare population enrolled because of disability, and the orange lines represent all other Medicare beneficiaries.

Figure 2. State-level prevalence of possible opioid misuse measures, 2008 to 2012.



States are divided into quartiles by prevalence of any misuse measure, as defined in Methods, among prescription opioid users in each state between 2008 and 2012. Higher quartiles are colored darker on the map, and the key shows the range of prevalence of any misuse measure for each quartile.

sons may have sought to evade new state regulations by obtaining opioids from prescribers or pharmacies in another state. Because provider addresses in publicly available files might be inaccurate, we inferred a state for each prescriber on the basis of the modal state of residence each year for beneficiaries who received nonopioid prescriptions from that prescriber; we used a similar approach for pharmacies. We counted the number of opioid prescriptions a patient obtained from an out-of-state prescriber or filled at an out-of-state pharmacy.

Outcomes

Our primary outcome was any occurrence of opioid overdose, defined as the presence of any opioid overdose–related diagnosis code (also labeled as *opioid poisoning* in diagnosis descriptions [Supplement]) (14) in any position on a claim from any care setting (that is, an inpatient, an outpatient, or a carrier claim), in the year after a half-year with an opioid fill. These diagnoses included intentional and unintentional overdose or poisoning diagnoses attributed to prescription opioids, as well as suicide attempts or self-inflicted injuries involving opioids. We observed no evidence for redaction of opioid overdose claims from our data set, compared with previous work with nonredacted claims (Supplement Figure 1, available at Annals.org) (14). We measured overdoses in the full year (that is, 2 half-years) after the half-year of prescription opioid use to mimic the information available to a PDMP user observing data from the past half-year and interested in outcomes during the coming year. As a secondary outcome, we examined all-cause mortality during the year after a half-year with a Part D opioid claim. For patients with an opioid overdose incident in the subsequent 12 months, we defined an alternative secondary outcome, 30-day postoverdose mortality, for those who died of any cause during the 30 days after an opioid overdose claim. In the absence of cause-of-death data, this measure serves as a marker for deaths that may be directly related to opioids. In the Supplement, we demonstrate similar results from measuring mortality within 15 or 90 days after an overdose event.

Patient Covariates

We collected information on beneficiaries regarding age, sex, race, and state of residence; whether they had dual eligibility for Medicaid and Medicare coverage; and whether they were entitled to Medicare because of age or disability. Using the medical claims, we created binary variables for each Charlson comorbidity score category based on claims in the current year (22). We also assessed a patient's average daily MED as a key measure potentially correlated with both opioid misuse and adverse outcomes (23, 24). However, because many appropriate clinical factors may influence a person's daily MED, we did not consider it to be an indicator of potential misuse; instead, we used it in some analyses as a control variable. We computed the average daily MED as the MED consumed during the half-year (total MEDs divided by 180 days) and dichotomized it at 120 daily MEDs as a threshold of clinical concern.

Statistical Analysis

We examined the association between measures of potential misuse, specified as either categories or dichotomous exposures, over the previous 6 months and adverse outcomes during the next 12 months. First, we used logistic regression controlling for all the aforementioned patient factors and the *margins* command in Stata/MP 15.1 (StataCorp) to estimate the adjusted

absolute risk (predictive margins) of successively higher values of prescribers, pharmacies, days supplied, and number of misuse measures fulfilled for subsequent adverse outcomes. Next, using the dichotomous misuse measures defined earlier, we estimated the adjusted absolute risk for each adverse outcome for beneficiaries meeting any of these dichotomous criteria, as well as their adjusted relative risk for adverse outcomes compared with beneficiaries meeting no misuse criteria. We adjusted for patient demographic characteristics and health status by controlling for age in 5-year categories, sex, white race, Medicaid eligibility, disability as the current reason for Medicare enrollment, an interaction between Medicaid eligibility and disability, Charlson diagnosis categories, and state and calendar half-year fixed effects. We estimated models with and without controls for patients' average daily MED and with misuse measures individually or all combined in the same model. We conducted subgroup analyses of Medicare enrollees who were disabled and those older than 65 years. SEs accounted for the serial autocorrelation within patients in outcomes over time (*cluster* option) (25, 26).

Role of the Funding Source

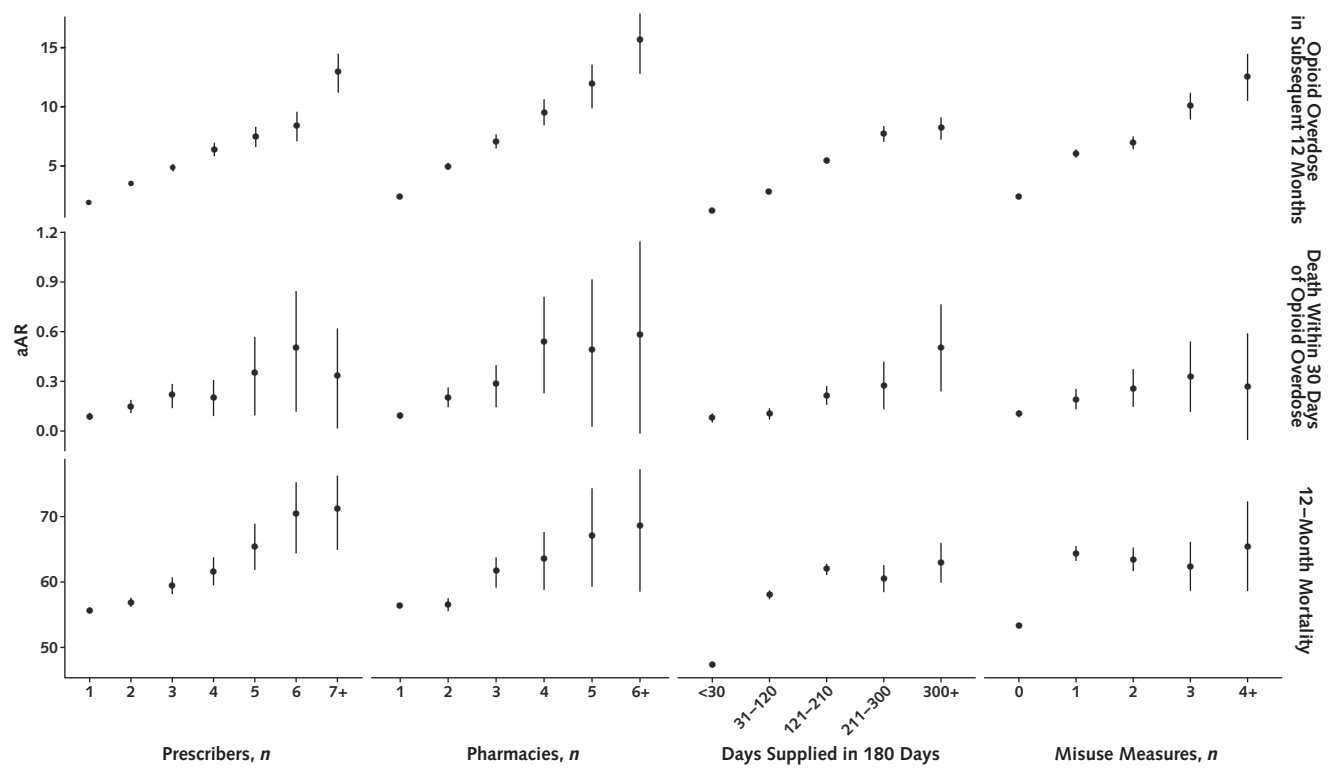
The National Institutes of Health (NIH) had no role in the design or analysis of this study.

RESULTS

Table 1 reports the mean of patient characteristics across beneficiaries fulfilling no, any, or several measures of possible misuse. The prevalence of indicators of possible opioid misuse ranged from 0.6% (≥5 pharmacies) to 8.5% (any overlapping claims) of patients per half-year and is reported in the first row. Compared with persons who had no misuse indicators, those meeting any misuse criterion had a higher mean daily MED. Opioid users meeting misuse criteria were more likely than those fulfilling no measures to be entitled to Medicare because of disability; for example, nearly 90% of beneficiaries obtaining opioids from 5 or more pharmacies were disabled. In addition, patients fulfilling misuse measures generally had more comorbid conditions than those meeting no misuse criteria.

Of the 16% of patients in our sample who fulfilled a possible misuse measure, most had only 1 measure. However, nearly 6% of our sample met several misuse criteria; Supplement Table 1 (available at Annals.org) shows the most common misuse patterns. Among patients fulfilling more than 1 measure, the most common pattern was obtaining more than a 210-day opioid supply and having overlapping claims; the second most common pattern was obtaining opioids from both prescribers and pharmacies out of state.

Figure 3. Association between opioid use patterns and subsequent opioid-related adverse outcomes.



The figure shows the association between successively greater numbers of prescribers, pharmacies, days supplied, or misuse measures (as defined in Methods) and opioid-related outcomes in the following year. The top set of panels examines subsequent opioid overdose, the middle set subsequent death within 30 days of an overdose, and the bottom set subsequent overall mortality. In each panel, the point shows the adjusted absolute risk from a logistic regression controlling for patient covariates described in Methods. The bars around each point report the 95% CI for this estimate. aAR = adjusted absolute risk per 1000 beneficiary-years.

Table 2. Association of Possible Misuse Measures With Subsequent Opioid-Related Adverse Outcomes*

Possible Misuse Measure	Sample Fulfilling Criteria, %†	Outcome in Subsequent Year					
		Opioid Overdose		Death Within 30 Days of Overdose		Overall Mortality	
		aAR (95% CI)	Adjusted Risk Ratio (95% CI)	aAR (95% CI)	Adjusted Risk Ratio (95% CI)	aAR (95% CI)	Adjusted Risk Ratio (95% CI)
No misuse	84.0	2.33 (2.23–2.42)	1.00 (reference)	0.10 (0.08–0.13)	1.00 (reference)	53.33 (52.94–53.72)	1.00 (reference)
>210 d supplied in 180 d	5.64	8.50 (7.91–9.10)	3.49 (3.22–3.77)	0.31 (0.19–0.43)	2.98 (1.67–4.30)	63.01 (61.18–64.84)	1.20 (1.16–1.24)
Any overlapping claim	8.54	7.77 (7.32–8.23)	3.17 (2.96–3.38)	0.23 (0.15–0.31)	2.21 (1.38–3.05)	66.91 (65.63–68.19)	1.25 (1.22–1.27)
≥5 prescribers	2.38	10.04 (9.22–10.86)	4.15 (3.78–4.52)	0.32 (0.16–0.48)	2.97 (1.35–4.58)	63.99 (61.34–66.63)	1.21 (1.16–1.26)
≥5 pharmacies	0.63	12.87 (11.27–14.47)	5.46 (4.75–6.16)	0.45 (0.12–0.77)	4.25 (1.06–7.43)	64.75 (58.67–70.84)	1.22 (1.10–1.33)
Any out-of-state prescriber	3.29	5.54 (4.93–6.14)	2.34 (2.07–2.61)	0.17 (0.06–0.28)	1.61 (0.52–2.70)	58.72 (56.63–60.82)	1.10 (1.06–1.14)
Any out-of-state pharmacy	3.43	4.15 (3.59–4.71)	1.77 (1.52–2.02)	0.11 (0.01–0.20)	1.00 (0.05–1.95)	61.30 (59.32–63.28)	1.14 (1.10–1.18)

aAR = adjusted absolute risk per 1000 beneficiary-years.
* Each adjusted absolute risk estimate is from a logistic regression model controlling for patient covariates. Adjusted risk ratios comparing patients who fulfilled misuse measures with those who did not were found by using the adjusted absolute risks. SEs were clustered at the patient level in all analyses.
† Values are the prevalence of the measure of potential misuse among all patients with ≥1 opioid prescription. Percentages may not sum to 100 because patients may be classified in more than 1 category.

The prevalence of possible opioid misuse was substantially greater in the disabled population for all misuse measures except receipt of opioids from out-of-state pharmacies (**Figure 1**). Markers of misuse were largely stable over the study period. The proportion of disabled persons with opioid supplies exceeding 210 days increased slightly, from 9.6% in 2008 to 10.0% in 2012, whereas the proportion receiving opioids from 5 or more prescribers decreased from 6.1% to 4.7% during the same period. The state-level prevalence of possible opioid misuse varied considerably, both overall and within the populations of disabled persons and those older than 65 years (**Figure 2**; **Supplement Figures 2** and **3**, available at Annals.org).

Successively higher numbers of prescribers, pharmacies, or days supplied were associated with a higher risk for subsequent opioid-related adverse outcomes (**Figure 3**). For example, a person who obtained opioids from 2, 3, or 4 prescribers in 6 months had a greater risk for an opioid overdose in the next year (adjusted absolute risk per 1000 beneficiary-years [aAR], 3.5 [95% CI, 3.3 to 3.7]; 4.8 [CI, 4.5 to 5.2]; or 6.4 [CI, 5.8 to 6.9], respectively) than a person with only 1 prescriber (aAR, 1.9 [CI, 1.8 to 2.0]). For all outcomes, any deviation from a single prescriber, single pharmacy, or short treatment duration was associated with an increased risk for an adverse outcome in the following year. Moreover, the risk increased successively as patients fulfilled more misuse measures (**Figure 3**). We also examined the relationship between these outcomes and increasing levels of 3 other measures: MED quantity, use of out-of-state prescribers, and use of out-of-state pharmacies (**Supplement Figure 4**, available at Annals.org). As expected, MED quantity was associated with increasing risk, whereas out-of-state prescriber and pharmacy use was less consistently associated with adverse outcomes.

Nearly every misuse measure was positively correlated with a clinically meaningful higher risk relative to no misuse for each opioid-related adverse outcome during the next year (**Table 2**). For example, a person with more than a 210-day opioid supply for 6 months had an aAR of 8.5 (CI, 7.9 to 9.1) for opioid overdose during the next year, 0.3 (CI, 0.19 to 0.43) for death within 30 days of an opioid overdose, and 63.0 (CI, 61.2 to 64.8) for subsequent overall mortality. Among the 6 measures considered, patients obtaining opioids from 5 or more pharmacies had the highest aAR for a subsequent overdose (12.9 [CI, 11.3 to 14.5]) or death within 30 days of an overdose (0.5 [CI, 0.1 to 0.8]) (**Table 2**). The use of out-of-state providers (prescribers and pharmacies) was associated with an increased risk for subsequent overdose or death, but the relative risk was lower for these measures than for those capturing excessive quantity or shopping behavior.

We examined the increased risk for subsequent opioid overdose associated with each misuse measure separately for the subpopulations of disabled persons and those older than 65 years (**Table 3**). Adjusted absolute risk estimates were much higher in the disabled subpopulation, both for persons with a measure of potential misuse and those with no measures. We also repeated our analysis of the association between each misuse measure and subsequent adverse outcomes for states in the lowest and highest quartiles of misuse (**Supplement Table 2**, available at Annals.org). The absolute risks associated with measures of potential misuse were similar for both quartiles.

We performed several other sensitivity analyses. Adjusting for continuous and binary measures of average daily MED resulted in modestly attenuated but similar associations between misuse measures and adverse outcomes (**Supplement Tables 3** and **4**, available at Annals.org), suggesting that the associations we ob-

served were not driven primarily by a higher daily MED among patients with potential markers of misuse. Removing our adjustment for combinations of long- and short-acting opioids in the days-supplied and overlapping-claims measures did not substantively influence our findings (**Supplement Table 5**, available at Annals.org). In assessing death proximate to an opioid overdose, measuring mortality in the 15, 30, and 90 days after the overdose resulted in generally similar estimates of relative risk (**Supplement Table 6**, available at Annals.org). Finally, the absolute risk associated with use of out-of-state prescribers and pharmacies was similar regardless of a patient's distance from a state border (**Supplement Table 7**, available at Annals.org).

DISCUSSION

In this observational analysis of a large Medicare cohort over 5 years, we found that patterns of potential opioid misuse were common; largely stable over time; and associated with a higher risk for adverse opioid-related outcomes in the following year, including opioid overdose, all-cause mortality, and death within 30 days of an opioid overdose diagnosis (that is, plausibly linked to opioid use). We observed increased risk with nearly any deviation in opioid treatment from a single in-state prescriber and pharmacy. Of note, we also observed a dose–response relationship such that more extreme patterns of potential misuse were associated with more risk than less extreme behaviors. All 6 measures were associated with clinically significant increases in adverse outcomes, suggesting that a broad range of patterns may be informative in identifying patients with high-risk opioid use.

This study advanced previous evidence on high-risk opioid prescribing patterns by systematically assessing a range of measures of use-based misuse and studying how each measure related to clinically relevant outcomes in the following year. We characterized opioid use with 6 unique measures across the domains of excessive quantity, use of multiple providers, and use of out-of-state providers. In addition, we evaluated possible misuse across a continuum of intensity, whereas earlier studies generally used dichotomous indicators or single measures (13–16). Finally, our analysis differs from others in leveraging longitudinal claims data to model patient risk in the subsequent, rather than contemporaneous, period. This approach is analogous to the clinical task prescribers face when using PDMP databases.

We observed an increased risk for adverse outcomes even when the number of prescribers or pharmacies was well below "conventional" thresholds for suspicious opioid use patterns (20, 27). It is crucial to note that our results do not imply that any patient who deviates from a single prescriber or pharmacy is misusing opioids or should be denied appropriate pain control. Many possible explanations exist for these use patterns that do not involve misuse. For example, patients who are hospitalized or visit the emergency department several times for any reason may easily accumulate several opioid prescribers. However, our results do suggest that greater numbers of providers, pharmacies, or days supplied in a short period should prompt further history taking with regard to opioid use and possible counseling on safe practices with controlled substance prescriptions.

Our findings also have implications for optimizing the design of PDMP interfaces to help prescribers interpret PDMP records. For example, PDMPs might design patient "dashboards" that sum the number of days supplied and number of prescribers or pharmacies for easy interpretation by clinicians, which ideally could be inte-

Table 3. Association of Possible Misuse Measures With Subsequent Opioid Overdose in the Subpopulations of Persons Aged ≥65 Years and Disabled Persons*

Possible Misuse Measure	Opioid Overdose in Subsequent Year					
	Subpopulation Aged ≥65 Years			Disabled Subpopulation		
	Sample Fulfilling Criteria, %†	aAR (95% CI)	Adjusted Risk Ratio (95% CI)	Sample Fulfilling Criteria, %†	aAR (95% CI)	Adjusted Risk Ratio (95% CI)
No misuse	88.26	1.11 (1.03–1.20)	1.00 (reference)	76.83	4.65 (4.42–4.88)	1.00 (reference)
>210 d supplied in 180 d	2.99	6.04 (5.13–6.96)	5.36 (4.49–6.23)	10.03	14.86 (13.75–15.96)	3.14 (2.87–3.41)
Any overlapping claim	6.34	4.08 (3.58–4.58)	3.58 (3.11–4.06)	12.17	14.56 (13.61–15.51)	3.05 (2.81–3.28)
≥5 prescribers	0.84	6.76 (5.26–8.26)	6.02 (4.64–7.41)	4.93	18.90 (17.30–20.50)	3.97 (3.59–4.34)
≥5 pharmacies	0.1	10.19 (5.74–14.63)	9.13 (5.11–13.16)	1.49	24.77 (21.64–27.90)	5.28 (4.58–5.98)
Any out-of-state prescriber	2.64	2.66 (2.03–3.29)	2.38 (1.80–2.96)	4.35	10.90 (9.57–12.22)	2.33 (2.03–2.62)
Any out-of-state pharmacy	3.4	1.53 (1.06–2.01)	1.37 (0.94–1.80)	3.47	8.99 (7.64–10.35)	1.93 (1.62–2.23)

aAR = adjusted absolute risk per 1000 beneficiary-years.
* Each adjusted absolute risk estimate is from a logistic regression model controlling for patient covariates. Adjusted risk ratios comparing patients who fulfilled misuse measures with those who did not were found by using the adjusted absolute risks. SEs were clustered at the patient level in all analyses.
† Values are the prevalence of the measure of potential misuse. Percentages may not sum to 100 because patients may be classified in more than 1 category.

grated directly into an electronic health record. Prescription drug monitoring programs also might consider whether to alert prescribers when a patient meets 1 of the criteria we examined. These steps could facilitate clinically meaningful use of the growing number of PDMPs that mandate provider access (21).

Our analysis had several limitations. First, our sample was limited to Medicare beneficiaries with Part D coverage from 2008 to 2012, so our results may not be generalizable to other populations or other periods. However, although older Medicare enrollees have a low risk for opioid misuse or adverse outcomes, disabled beneficiaries have a high prevalence of mental illness and may have unrelieved physical pain, both of which are associated with opioid misuse (14, 17, 28). Likewise, our data end in 2012; misuse patterns and their relationship to the outcomes may have evolved since then. Second, this observational study did not establish causality and should not be interpreted as having done so. However, noncausal associations may be clinically useful in understanding the relationship between opioid use patterns and adverse outcomes if unobserved confounders remain stable over time. Therefore, the misuse measures we examined should be considered predictors rather than mediators of opioid-related adverse events. Third, the study was limited by its reliance on claims-based measures. It is possible that our measure of opioid overdose is an undercount (29). In addition, during our sample period, Part D plans did not cover benzodiazepines, so we could not observe any association between their co-prescription with opioids and the risk for adverse outcomes. We did not directly examine the use of nonprescribed opioids or heroin, although we may have observed overdoses resulting from these agents.

In conclusion, in a large national sample of Medicare beneficiaries, we identified several potential markers of opioid misuse that were independently associated with an elevated risk for subsequent opioid overdose and death. Our results imply that a wide range of opioid use patterns beyond conventional definitions of possible opioid misuse may justify clinician attention. Further research should examine the types of clinical interventions for patients with high-risk patterns of opioid use that might improve patient safety without causing unintended consequences, such as driving patients to illicit opioid use.

From Cornell University, Ithaca, New York (C.M.C.); Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, and National Bureau of Economic Research, Cambridge, Massachusetts (A.B.J.); and Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital, Boston, Massachusetts (M.L.B.).

Grant Support: By NIH Early Independence Award 1DP5OD 017897-01 (Dr. Jena).

Disclosures: Dr. Jena reports grants from the NIH during the conduct of the study and personal fees from Pfizer, Hill-Rom Services, Bristol-Myers Squibb, Novartis Pharmaceuticals, Vertex Pharmaceuticals, and Precision Health Economics outside the submitted work. Dr. Barnett has a patent for a method using physician social networks based on common patients to predict cost and intensity of care in hospitals, with royalties paid. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-3065.

Reproducible Research Statement: *Study protocol:* Not applicable. *Statistical code:* Available from Dr. Carey (e-mail, colleen.carey@cornell.edu). *Data set:* Available through a Data Use Agreement with Centers for Medicare & Medicaid Services (www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/Data-Disclosures-Data-Agreements/Overview.html).

Corresponding Author: Michael L. Barnett, MD, Harvard T.H. Chan School of Public Health, Department of Health Policy and Management, 677 Huntington Avenue, Boston, MA 02115; e-mail, mbarnett@hsph.harvard.edu.

Current author addresses and author contributions are available at Annals.org.

References

1. **National Institute on Drug Abuse.** America's addiction to opioids: heroin and prescription drug abuse. 2014. Accessed at www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse on 13 October 2016.
2. **Okie S.** A flood of opioids, a rising tide of deaths. N Engl J Med. 2010;363:1981-5. [PMID: 21083382] doi:10.1056/NEJMp1011512
3. 1.5 million adults have serious mental illness and misused opioids in the past year. The CBHSQ Report. 25 January 2017. Accessed at www.samhsa.gov/data/sites/default/files/report_2734/Spotlight-2734.html on 21 June 2017.
4. **Case A, Deaton A.** Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci U S A. 2015;112:15078-83. [PMID: 26575631] doi:10.1073/pnas.1518393112
5. **Krueger AB.** Where have all the workers gone? Working paper. 2016. Accessed at www.bostonfed.org/-/media/Documents/economic/conf/great-recovery-2016/Alan-B-Krueger.pdf on 21 June 2017.
6. **Substance Abuse and Mental Health Services Administration.** Opioids. 2014. Accessed at www.samhsa.gov/atod/opioids on 21 June 2017.
7. **Gugelmann HM, Perrone J.** Can prescription drug monitoring programs help limit opioid abuse? JAMA. 2011;306:2258-9. [PMID: 22110107] doi:10.1001/jama.2011.1712
8. **Haffajee RL, Jena AB, Weiner SG.** Mandatory use of prescription drug monitoring programs. JAMA. 2015;313:891-2. [PMID: 25622279] doi:10.1001/jama.2014.18514
9. **Prescription Drug Abuse Policy System.** PDMP administration. 2017. Accessed at http://pdaps.org/dataset/overview/prescription-monitoring-program-laws-1408223428/57d6fe3fd42e07632add60c7 on 21 June 2017.
10. **Islam MM, McRae IS.** An inevitable wave of prescription drug monitoring programs in the context of prescription opioids: pros, cons and tensions [Editorial]. BMC Pharmacol Toxicol. 2014;15:46. [PMID: 25127880] doi:10.1186/2050-6511-15-46
11. **Rutkow L, Turner L, Lucas E, Hwang C, Alexander GC.** Most primary care physicians are aware of prescription drug monitoring programs, but many find the data difficult to access. Health Aff (Mill-

wood). 2015;34:484-92. [PMID: 25732500] doi:10.1377/hlthaff.2014.1085
12. **Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA.** Who uses a prescription drug monitoring program and how? Insights from a statewide survey of Oregon clinicians. J Pain. 2014;15:747-55. [PMID: 24787089] doi:10.1016/j.jpain.2014.04.003
13. **Jena AB, Goldman D, Weaver L, Karaca-Mandic P.** Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. BMJ. 2014;348:g1393. [PMID: 24553363] doi:10.1136/bmj.g1393
14. **Meara E, Horwitz JR, Powell W, McClelland L, Zhou W, O'Malley AJ, et al.** State legal restrictions and prescription-opioid use among disabled adults. N Engl J Med. 2016;375:44-53. [PMID: 27332619] doi:10.1056/NEJMsa1514387
15. **Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC.** Opioid shopping behavior: how often, how soon, which drugs, and what payment method. J Clin Pharmacol. 2013;53:112-7. [PMID: 23400751] doi:10.1177/0091270012436561
16. **Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC.** Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. Drug Saf. 2012;35:325-34. [PMID: 22339505] doi:10.2165/11596600-000000000-00000
17. **Morden NE, Munson JC, Colla CH, Skinner JS, Bynum JP, Zhou W, et al.** Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. Med Care. 2014;52:852-9. [PMID: 25119955] doi:10.1097/MLR.0000000000000183
18. The U.S. Pharmacopeial Convention. 2017. Accessed at www.usp.org on 22 June 2017.
19. **Dowell D, Haegerich TM, Chou R.** CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696] doi:10.1001/jama.2016.1464
20. **U.S. Government Accountability Office.** Medicare part D: instances of questionable access to prescription drugs. GAO-11-699. 4 October 2011. Accessed at www.gao.gov/products/GAO-11-699 on 23 June 2017.
21. **Buchmueller TC, Carey C.** The effect of prescription drug monitoring programs on opioid utilization in Medicare. Am Econ J Econ Policy. 2018;10:77-112.
22. **Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al.** Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676-82. [PMID: 21330339] doi:10.1093/aje/kwq433
23. **Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al.** Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305:1315-21. [PMID: 21467284] doi:10.1001/jama.2011.370
24. **Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al.** Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152:85-92. [PMID: 20083827] doi:10.7326/0003-4819-152-2-201001190-00006
25. **Angrist JD, Pischke JS.** Mostly Harmless Econometrics: An Empiricist's Companion. Princeton, NJ: Princeton Univ Pr; 2008.
26. **Angrist JD, Pischke JS.** Mastering 'Metrics: The Path from Cause to Effect. Princeton, NJ: Princeton Univ Pr; 2014.
27. **Centers for Medicare & Medicaid Services.** Analysis of proposed opioid overutilization criteria modifications in Medicare part D. 2017. Accessed at www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Proposed-Opioid-Overutilization-Criteria-Modifications-v-02012017.pdf on 28 July 2017.
28. **Hughes A, Williams MR, Lipari RN, Bose J, Copello EAP, Kroutil LA.** Prescription drug use and misuse in the United States: results from the 2015 National Survey on Drug Use and Health. NSDUH Data Review. September 2016. Accessed at www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm on 14 February 2018.
29. **Rowe C, Vittinghoff E, Santos GM, Behar E, Turner C, Coffin PO.** Performance measures of diagnostic codes for detecting opioid overdose in the emergency department. Acad Emerg Med. 2017;24:475-83. [PMID: 27763703] doi:10.1111/acem.13121

Current Author Addresses: Dr. Carey: 298 Martha van Rensselaer Hall, Cornell University, Ithaca, NY 14850.
Dr. Jena: Harvard Medical School, Department of Health Care Policy, 180 Longwood Avenue, Boston, MA 02115.
Dr. Barnett: Harvard T.H. Chan School of Public Health, Department of Health Policy and Management, 677 Huntington Avenue, Boston, MA 02115.

Author Contributions: Conception and design: C.M. Carey, A.B. Jena, M.L. Barnett.
Analysis and interpretation of the data: C.M. Carey, A.B. Jena, M.L. Barnett.
Drafting of the article: C.M. Carey, A.B. Jena, M.L. Barnett.
Critical revision for important intellectual content: C.M. Carey, A.B. Jena, M.L. Barnett.
Final approval of the article: C.M. Carey, A.B. Jena, M.L. Barnett.
Statistical expertise: C.M. Carey.
Administrative, technical, or logistic support: A.B. Jena, M.L. Barnett.
Collection and assembly of data: C.M. Carey.