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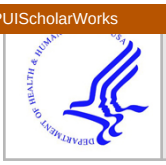

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Incident and Long-Term Opioid Therapy among Patients with Psychiatric Conditions and Medications: A National Study of Commercial Healthcare Claims

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Abstract

There is growing evidence that opioid prescribing in the US follows a pattern in which patients who are at highest risk of adverse outcomes from opioids are most likely to receive long-term opioid therapy. These patients include, in particular, those with substance use disorders (SUDs) and other psychiatric conditions. This study examined health insurance claims among 10 311 961 patients who filled prescriptions for opioids. Specifically, we evaluated how opioid receipt differed among patients with and without a wide range of pre-existing psychiatric and behavioral conditions (i.e., opioid and non-opioid SUDs, suicide attempts or other self-injury, motor vehicle crashes, and depressive, anxiety, and sleep disorders) and psychoactive medications (i.e., antidepressants, benzodiazepines, hypnotics, mood stabilizers, antipsychotics, and medications

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Supplemental Digital Content
Tables detailing generic medication names, ICD-9-CM codes, and results of sensitivity analyses.

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used for SUD, tobacco cessation, and attention-deficit/hyperactivity disorder [ADHD]). Relative to those without, patients with all assessed psychiatric conditions and medications had modestly greater odds of subsequently filling prescriptions for opioids and, in particular, substantially greater risk of long-term opioid receipt. Increases in risk for long-term opioid receipt in adjusted Cox regressions ranged from approximately 1.5-fold for prior ADHD medication prescriptions (hazard ratio [HR] = 1.53; 95% CI, 1.48–1.58) to approximately 3-fold for prior non-opioid SUD diagnoses (HR = 3.15; 95% CI, 3.06–3.24) and nearly 9-fold for prior opioid use disorder diagnoses (HR = 8.70; 95% CI, 8.20–9.24). In sum, we found evidence of greater opioid receipt among commercially insured patients with a breadth of psychiatric conditions. Future studies assessing behavioral outcomes associated with opioid prescribing should consider pre-existing psychiatric conditions.

Keywords

Adverse selection; Epidemiology; Health insurance claims; Prescription opioid analgesics

1. Introduction

Dramatic escalations in opioid analgesic use and associated morbidity and mortality have generated concern regarding the potential adverse effects of prescribed opioids [2,8,9]. In order to accurately assess opioid-related risk for these adverse outcomes, it is critical to understand which patients select or are selected for opioid therapy. There is growing evidence that prescribing in the US follows a pattern termed *adverse selection* [53]. That is, patients who are at greatest risk of adverse outcomes, including those with pre-existing substance use disorders (SUDs)—and opioid use disorders (OUDs) in particular—and other psychiatric conditions, may be more likely to be prescribed opioids for longer durations and in higher-risk regimens than are patients without these conditions [5,13,30,57,61]. This pattern contrasts with the samples enrolled in clinical trials, from which these patient groups are often excluded, as well as with opioid treatment guidelines [30,57].

Indeed, analyses of healthcare records and other studies have linked multiple psychiatric and behavioral conditions (e.g., SUDs, cigarette smoking, depression, sleep disorders, personality disorders, posttraumatic stress disorder and other anxiety disorders) and psychoactive medications (e.g., antidepressants, benzodiazepines) to opioid prescribing [6,10,12,14,18,23,27,29,32,33,35,40,43,45,51,52,56,59]. As Edlund and colleagues concluded from their analyses of patients with non-cancer pain, opioid prescribing “was more common, more prolonged, more potent, and increased more rapidly from 2000 to 2005” (p. 7) among patients with SUDs and other psychiatric problems [13]. In turn, patients with psychiatric conditions are more likely to experience overdoses and other adverse outcomes [4,60].

This study evaluated the extent to which patients with pre-existing psychiatric and behavioral conditions are more likely than are patients without those conditions to (a) fill prescriptions for opioids and (b) more important, subsequently transition to long-term opioid therapy, across therapeutic indications. Specifically, we used longitudinal healthcare claims

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data from a large, national sample to examine questions raised by prior studies. First, we examined how broadly these associations extend across a range of psychiatric conditions and psychoactive medications. Second, prescribed opioids are thought to increase risk for a number of adverse outcomes. It is possible, however, that some of these same outcomes could also occur prior to opioid therapy onset, making inferences regarding the adverse effects of opioid prescribing difficult. For example, whereas several studies implicate prescribed opioids in risk for motor vehicle crashes [22,24], it is also likely that, because they can be sources of injuries, crashes are associated with an increased likelihood of opioid receipt. We therefore included as *predictors* several factors identified as potential adverse behavioral outcomes of opioids (i.e., SUDs, depressive disorders, suicide attempts or other self-injury, and motor vehicle crashes) to evaluate the extent to which they were associated with subsequent prescription opioid receipt [2,7,17,37,39,47,49]. Finally, we examined the robustness of the predictive associations, taking into consideration painful conditions, younger patients [44,46], modeling approaches, and definitions of long-term opioid receipt.

2. Methods

2.1 Data Source

We used records from the Truven Health MarketScan® Commercial Claims and Encounters (MarketScan) database for 2003–2013. The MarketScan database includes de-identified inpatient, outpatient, and filled-prescription claims from commercially insured patients in the US. MarketScan records are obtained from employers and health plans and include covered employees, COBRA continuees, and early (non-Medicare) retirees, as well as spouses and dependents. About half of the US population is commercially insured, and, from 2003–2013, the MarketScan database includes approximately 143 million individual-level enrollee observations nationwide, primarily from large employers [28]. In the most recent included data year (2013), the database includes approximately 44 million individuals with enrollment data, 51.3% of whom were female and 78.1% of whom had included prescription drug coverage. Not all enrollees maintained coverage during the included years (i.e., enrollment start and end dates varied across enrollees). However, MarketScan data include enrollees' complete claims for their enrolled periods. We included only those enrollment years in which enrollees held prescription drug coverage in the MarketScan database to ensure that patients were eligible to make prescription claims. The University of Chicago Institutional Review Board has determined that this study was exempt because all MarketScan records are de-identified.

2.2 Opioid Recipient Sample

We created an incident opioid recipient cohort (i.e., patients with newly initiated opioid therapy) for our analyses [50]. In order to examine prior differences between opioid recipients and non-recipients, we compared the recipient cohort with matched non-recipient controls, whereas in order to examine which prior factors predicted subsequent long-term opioid therapy, we followed the cohort of opioid recipients only. We defined opioid recipients as patients with claims for prescriptions of any opioid drugs, using names and national drug codes used in previous opioid research in MarketScan data [42]. We excluded claims with missing or invalid fill dates and missing or improbable days supply (i.e., more

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than 180 days), consistent with that prior study [42]. We assumed that buprenorphine products were used as treatment for OUD, with the exception of transdermal buprenorphine, which was included as an opioid [38]. Methadone treatment for OUD—rather than for pain—is unlikely to be recorded in prescription claims [41].

We therefore followed prior research in including methadone as an opioid analgesic, although it was used relatively infrequently (67 210 prescriptions, or 0.2% of all opioids, in follow-up) [15,36,54]. See Table S1, Supplemental Digital Content, for a list of all included opioids. We identified 27 949 936 enrollees who first filled opioid prescriptions at age 14 or later, across any indication. Of the patients with filled opioid claims, 42.2% (n = 11 785 917) met a second inclusion criterion of having at least 12 calendar months of continuous enrollment prior to the month of the first (i.e., index) filled opioid prescription, which by definition also excluded all recipients with 2003 index prescriptions. We required patients to be at least 13 years old during this prior enrollment period to prevent the inclusion of records of uncertain validity (e.g., SUD diagnoses prior to adolescence). Of continuously enrolled patients, 87.8% (n = 10 345 694) met a third inclusion criterion of having no cancer diagnoses (except non-melanoma skin cancer) in the year before or 1.5 years after the index date. Finally, we excluded 0.3% of patients (n = 33 733) lacking enrollment coverage on or after their index date, resulting in a final sample of 10 311 961 incident opioid recipients. See Table 1 for demographic information.

We followed these patients until the end of their continuous enrollment, defined as the end of the final included month with any recorded enrollment days. Some patients dis-enrolled from included MarketScan coverage and then subsequently re-enrolled after a period without coverage. We ended follow-up for these patients at their first dis-enrollments. The median follow-up length from index fill date to end of (first) enrollment was 1.55 years (interquartile range [IQR]: 0.63–3.22). From the index date to the end of follow-up, prescriptions for hydrocodone products were filled by the most opioid recipients (72.5% of included patients), followed by oxycodone (24.2%), codeine (13.8%), tramadol (13.3%), and propoxyphene (10.1%).

2.3 Long-Term Opioids

Consistent with prior studies, we defined long-term opioid therapy using two criteria [4,55]. First, we required that patients had filled prescriptions for more than 90 days opioid supply during a 6-month (i.e., 183 day) window. We calculated a window's days supply by summing across all filled prescriptions, under the assumption that multiple prescriptions filled on the same date were taken concurrently and, therefore, had redundant days supply. When a given prescription's days supply exceeded the end of a given six-month window, we counted only the number of days from that prescription that fell within the window for that window's count of days supply. Second, to ensure that opioid therapy was continuous, we required that these 6-month windows had no gaps of more than 32 days between the end of one prescription's supply and the beginning of the next. To maximize the number of identified long-term recipients, we permitted prescription claims from after the end of included follow-up to be included in these windows. That is, prescriptions could be included in windows when patients were without coverage but resumed or continued opioid receipt

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within six months of a prior fill date. We defined the onset of long-term opioid therapy as the fill date of the prescription that initiated the first long-term window. Thus, the long-term onset date could have occurred at any point from the index date until the end of included follow-up, including the index date itself.

2. 4 Psychiatric and Behavioral Predictors

We obtained included diagnoses (recorded with International Classification of Diseases, Ninth Revision, Clinical Modifications [ICD-9-CM] codes) from inpatient and outpatient claims. We grouped them into seven categories as follows: OUD, non-opioid SUD, depressive disorder, uncertain or definite suicide attempt or self-injury (combined), anxiety disorder, sleep disorder, and motor vehicle crashes (i.e., motor vehicle traffic accident codes). In the preparation of the MarketScan database, diagnosis codes are screened and edited to increase validity. Recorded codes that do not correspond to valid ICD-9-CM codes are treated as missing [58].

We also included the following 11 psychoactive medication classes from prescription claims: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), other antidepressants, mood stabilizers, antipsychotics, benzodiazepines, non-benzodiazepine hypnotics (i.e., eszopiclone, zaleplon, zolpidem), and medications used for OUD (i.e., buprenorphine, naltrexone), alcohol use disorder (AUD), tobacco cessation, and attention-deficit/hyperactivity disorder. We excluded tricyclic antidepressants and other antidepressants (i.e., duloxetine) commonly used in pain management from our antidepressant definitions, and we included only two mood stabilizers (lamotrigine and lithium) given that some related medications are also used to manage pain. See Tables S1 and S2, Supplemental Digital Content, for complete lists of generic drug names and diagnosis codes, respectively.

Patients met criteria for having a predictor condition or medication if the first claim with that diagnosis or medication preceded the month of the first opioid prescription fill. We required patients to be at least 13 years old at these predictor claims, with the exception of motor vehicle crashes, for which patients were required to be at least 18 years old and, therefore, eligible to have fully privileged driver’s licenses in all states.

2.5 Analytic Approach

All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC). Our first set of analyses examined the extent to which the predictor conditions and medications were associated with filled prescriptions for any opioids. To account for demographics and varying enrollment times, we compared opioid recipient cases to matched controls without opioid prescription fills. We matched cases and controls 1:1 on sex, calendar year and age of first enrollment, and number of months enrolled. Matching on months of enrollment ensured that cases and controls had matching durations of opportunity to claim psychiatric predictors (prior to the index month for cases and overall for controls). For first enrollment and months of enrollment, we again only counted years in which patients were at least 13 years old and held prescription drug coverage. To ensure sufficient matching on exact values, we randomly selected 40% of cases for these comparisons, only 0.02% of whom could not be matched

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(analytic n = 4 124 038 cases). We compared cases to matched controls using a series of separate conditional logistic regressions, with each matched-pair case and control entered as a stratum (PROC LOGISTIC), and we report estimated odds ratios (ORs) with confidence intervals (CIs) as effect sizes.

Our second set of analyses examined the extent to which the predictors were associated with transitioning from initial receipt to long-term opioid therapy among the cohort of new opioid recipients. Given differing index dates and enrollment durations, follow-up time varied across included patients and could be ended (i.e., right-censored) by either dis-enrollment from coverage included in the MarketScan database or the end of the study. We therefore modeled time to onset of long-term opioid therapy among opioid recipients with Kaplan-Meier estimates (PROC LIFETEST) and Cox proportional hazards regression (PROC PHREG) to account for right-censoring, with follow-up time starting on the index opioid prescription fill date [1]. We estimated hazard ratios (HRs) in separate Cox regressions for each predictor and added covariates for sex, index age group, and calendar year of index prescription.

We also conducted several sensitivity analyses. First, to test and adjust for violations of the proportional hazards assumption, we included an interaction between each predictor and linear follow-up time [21]. Because of computing memory constraints, we randomly selected 10% (n = 1 031 196) of the sample for these models. Because this selection retained a reasonably large sample in absolute size, it is unlikely to have introduced substantive bias to the results. Second, to ensure that our results were not explained by comorbidity between psychiatric conditions and chronic pain conditions, we restricted analyses to the 73.8% of the sample that received painful condition diagnoses at age 13 or later. We included diagnoses (see Table S2, Supplemental Digital Content) drawn from those used in prior opioid research [54]. Third, to examine associations in an alternative modeling approach, we ran binary logistic regressions (PROC LOGISTIC) predicting long-term therapy onset within the first 1.5 years among patients with at least 2 years of enrollment. Fourth, to test whether our results generalized to younger patients, we restricted analyses to patients aged 25 or younger at index. Fifth, to test whether results depended on the definition of long-term use, we tested associations with a stricter long-term definition (i.e., at least 183 days supply within 6 months —instead of the more than 90 days criterion in the main analyses—with no gaps greater than 32 days). Finally, although all patients had at least 12 months of continuous enrollment prior to the index month, the exact duration of prior enrollment varied across patients. To test whether results were biased by differences in periods of predictor assessment prior to the index date, we tested associations with only those conditions and medications recorded in the 12 months prior to the index month.

3. Results

3.1 Comparisons of Opioid Recipients to Non-Recipients

Our first objective was to estimate the extent to which prior psychiatric conditions, motor vehicle crashes, and psychoactive medications would predict claims for any prescription opioids. Comparisons of psychiatric diagnoses between patients who filled at least one opioid prescription and matched non-recipient controls are presented in Table 2. The

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included conditions ranged in prevalence, with depressive disorders the most common (8.5% of cases) and suicide attempts or other self-injury the least common (0.1%). Across all diagnosis categories, however, prior conditions were more common among cases relative to controls. For example, patients with prior OUD or non-opioid SUD diagnoses had 16% or 11% greater odds, respectively, of receiving opioids than did patients without these conditions. Overall, these differences were modest in size, and the suicide attempts or other self-injury difference did not reach statistical significance.

Table 3 presents case-control results for psychoactive medications dispensed prior to the first opioid fill. The use of psychoactive medications varied as well, with 12.5% of cases filling at least one SSRI prescription but 0.1% of cases filling any prescriptions for medications to treat AUD. Similar to the psychiatric conditions, patients with all prior medications had between 19% (AUD) and 64% (tobacco cessation) greater odds of receiving opioids than did patients without prior medications. Notably, benzodiazepine recipients had 52% greater odds of receiving opioids than did benzodiazepine non-recipients. These associations were again relatively modest but were consistently positive across all assessed medication classes. In sum, the presence of a range of pre-existing psychiatric and behavioral problems and treatments was associated with modest increases in the odds of receiving opioids.

3.2 Long-Term Opioid Receipt

Our second objective was to estimate the extent to which prior psychiatric conditions, motor vehicle crashes, and psychoactive medications would predict receipt of long-term opioids among opioid recipients. Of the 10 311 961 incident opioid recipients, only 1.7% (n = 177 816) received long-term opioids during follow-up, whereas the remainder were censored. According to Kaplan-Meier estimates, the probability of transitioning from first fill to long-term opioids was 1.3% by 1.5 years after the first prescription fill, 2.1% by 3 years, 3.7% by 6 years, and 5.3% by 9 years. Fewer than half of long-term recipients met a stricter long-term definition (at least 183 days supply) during follow-up (n = 86 009). The likelihood of receiving long-term opioids by this stricter definition was 1.0% by 3 years.

As shown in Table 4, all diagnosis categories were positively associated with long-term opioid therapy in adjusted Cox models. That is, patients with prior psychiatric diagnoses, suicide attempts or other self-injury, and motor vehicle crashes were at greater risk of transitioning from an incident opioid prescription fill to receipt of long-term opioids than were patients without prior psychiatric conditions. Whereas for depressive, anxiety, and sleep disorders and motor vehicle crashes this increase in risk was approximately two-fold, other conditions were associated with more substantial increases in risk. Patients with prior suicide attempts or other self-injury, compared to those without, were at 2.55 times the risk of long-term opioids. Moreover, patients with prior non-opioid SUDs and OUDs were at 3.15 and 8.70 times the risk of long-term receipt, respectively.

Similarly, Table 5 shows that prior psychoactive medication recipients were at greater risk of receiving long-term opioids as well. Increases in risk of long-term opioid therapy ranged from 53% for ADHD medication recipients to more than five-fold for OUD medication recipients. Benzodiazepine treatment was associated with approximately twice the risk of long-term opioid therapy.

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3.3 Sensitivity Analyses

The Cox models in the main long-term analyses assumed that the ratio of hazards between patients with and without predictors was proportional over time. To evaluate this assumption, we added an interaction between the predictor and linear time (in years) to each model. Results of these models are presented in Table S3, Supplemental Digital Content. Whereas most predictors demonstrated little violation of the assumption (i.e., yearly changes of 0.08 or less in differences in log hazard), interaction terms for OUD diagnosis ($b = -0.47$, standard error [SE] = 0.12) and OUD medication receipt ($b = -0.34$, SE = 0.14) both indicated greater risk earlier in follow-up. That is, for each year of follow-up, the estimated log hazard difference associated with OUD diagnosis decreased by 0.47, and the estimated log hazard difference associated with OUD medication receipt decreased by 0.34. At the start of follow-up, HRs were 14.08 (95% CI, 11.54–17.18) and 6.23 (95% CI, 4.74–8.19) for diagnosis and medication receipt, respectively. To illustrate the change in risk over time, we used the main effect and interaction estimates to compute HRs at year 3. Although both associations remained positive, year-3 HRs for OUD diagnosis (3.39) and medication (2.24) were substantially reduced relative to the start of follow-up. Thus, although risk of long-term opioid receipt was greater among patients with OUD diagnoses and medications than among patients without diagnoses or medications, this increase in risk was more substantial at the start of follow-up.

Additionally, because we required long-term opioid periods to be at least six months in duration, patients were at lower risk of initiating a long-term period during the final six months of their included follow-up. To test whether this requirement influenced estimates of changes in risk over time, we re-set censoring dates to six months prior to the end of observed follow-up (thereby also requiring at least six months of follow-up). Results were largely similar to those presented above, including greater risk associated with OUD diagnosis and medication earlier in follow-up and smaller changes over time in log hazard differences for other predictors. See Table S3, Supplemental Digital Content.

Further sensitivity analyses, which are presented in Table S4, Supplemental Digital Content, revealed a largely consistent pattern of associations with long-term opioids. Specifically, patients with all conditions and psychoactive medications were at increased risk of long-term opioid therapy when we (a) limited analyses to patients with painful conditions, (b) predicted onset in the first 1.5 years in logistic regression (among only those patients who had at least 2 years of follow-up), (c) limited analyses to adolescent and young adult patients only, (d) predicted a stricter definition of long-term therapy, and (e) only counted those predictor claims that occurred in the year prior to index. We note, however, that the rarity of some predictors (e.g., OUD and AUD medication) resulted in less precise estimates in adolescents and young adults. In sum, the associations between psychiatric conditions, suicide attempts or other self-injury, motor vehicle crashes, and psychoactive medications and receipt of long-term opioids persisted in younger patients and those with painful condition diagnoses and appeared robust to changes in modeling strategy and predictor and outcome definitions.

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4. Discussion

In a large, national, privately insured sample, we found that pre-existing psychiatric and behavioral conditions and psychoactive medications were associated with subsequent claims for prescription opioids. The increased odds of any opioid prescription fills among those with prior psychiatric disorders and psychoactive medications were relatively modest. The risk of long-term opioids, however, was substantially greater. It was also evident among youth and patients with painful conditions, and the risk extended to a subset of long-term recipients with at least enough days supply to fully cover a six-month window. Some of these associations, including the greater risk for long-term use than for any opioid use among patients with prior psychiatric conditions, extend prior findings in smaller datasets [5,13,27,61].

The novelty of our results is that they demonstrate the wide scope of associations between previous psychiatric and behavioral problems and long-term opioid prescription fills. That is, we found support for increased risk of long-term opioid therapy in adulthood and youth related to SUDs, suicide attempts or other self-injury, motor vehicle crashes, and depressive, anxiety, and sleep disorders, as well as a broad array of psychoactive medications—including benzodiazepines [34]. Additionally, we found that the strongest risk for receipt of long-term opioids was associated with OUD diagnoses and treatment with buprenorphine or naltrexone. Similarly, in the CONSORT study, incident long-term opioid prescribing was more common among patients with OUDs than those with other SUDs or no SUD diagnoses [61]. In our data, these associations were particularly strong in the period immediately after the initiation of opioid therapy: Patients with OUDs and buprenorphine or naltrexone prescription fills were at substantially greater risk of transitioning to long-term opioids earlier in follow-up than were patients without these conditions or medications.

Our results support calls for coordinated or integrated mental health screening and treatment among patients with chronic pain [30]. In particular, the finding that patients with pre-existing psychiatric conditions were more likely to transition to long-term opioids suggests that thorough assessment of mental health may be valuable in this population. Several of our findings also raise concerns regarding risk of overdose. At least one study has found greater risk of drug overdose among patients with depression and stronger opioid doses [60]. Further, benzodiazepines are implicated in some opioid overdose deaths, leading the CDC guideline for opioids in chronic pain to recommend against concurrent prescribing [11,31]. We found that depressive disorders and benzodiazepine treatment were associated with roughly double the risk of transitioning to long-term opioids. Although long-term opioid receipt may not necessarily increase risk of overdose, prescription factors (e.g., maximum dose) have been linked to opioid overdose deaths, and the present associations highlight subgroups of recipients that may be at higher risk [3]. Moreover, given the breadth of psychiatric predictors, including prior suicide attempts or other self-injury, overdose risk may be exacerbated by multiple psychiatric problems and polypharmacy [60]. These findings provide further support for prescription monitoring programs and other methods of identifying and alerting clinicians to patients with higher-risk opioid prescription quantities and medication combinations, particularly when multiple providers are involved in a patient's care [9].

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Given this study's scope and level of analysis, it cannot elucidate the processes underlying observed associations between psychiatric conditions and their treatments and long-term opioids. As discussed by Howe and Sullivan [30], this pattern may result from a number of hypothetical possibilities that involve interplay among neurobiological systems, pain and psychiatric symptom comorbidities, and patient-provider interactions. One hypothesis is that patients with psychiatric disorders may be more likely to experience greater distress and demand for pain relief, which may lead providers to treat with opioids (and patients to choose to fill prescriptions for opioids) in the absence of other options perceived as viable [53]. Alternatively, given the well-established comorbidity among psychiatric and painful conditions [16], it is likely that patients with psychiatric problems are more likely to experience more severe pain symptoms or greater pain-related functional impairment, perhaps leading providers to prescribe more aggressively to address pain-related concerns. It is also possible that patients with comorbid pain and psychiatric conditions may be more likely to seek care repeatedly or from multiple treatment providers because of their greater symptom severity or perceived need for care, resulting in a higher rate of opioid receipt in aggregate. Future research evaluating clinical interactions in finer detail and examining the etiology of comorbid pain and psychiatric conditions is needed to disentangle these possibilities.

It is also important to stress that we found that each of four behaviors that have been proposed as potential harms of prescribed opioids (SUDs, depressive disorders, suicidal or self-injurious behavior, and motor vehicle crashes) actually *predicted* which patients would develop long term-use. Of course, some of these associations are unsurprising; motor vehicle crashes can result in injuries and subsequent need for pain management. We highlight, however, that even these expected associations may lead to confounding in observational studies of opioid outcomes if they are not taken into account. There are several alternative hypotheses that could explain why receipt of opioids is associated with adverse behavioral outcomes in such data (beyond true adverse effects). The current results highlight how selection related to sources of prior risk might increase opioid recipients' likelihood of behavioral or psychiatric problems regardless of the effects of opioids themselves. As noted in a recent investigation of prescribed-opioid risk for OUD, if unmeasured conditions are associated with the likelihood of opioid receipt and incident behavioral harms, they can lead to overestimation of harms [15]. Given the diverse correlates of long-term use found here, we add that it may be valuable to account for a wide range of psychiatric conditions and psychoactive medications in future studies of opioid outcomes. At the same time, however, the current results do not necessarily argue against the hypothesis that opioid prescribing contributes to these adverse outcomes. Indeed, Scherrer and colleagues [48] found evidence of bidirectional associations between changes in opioid dose and changes in the probability of depression. Rather, our results highlight the importance of using research designs that can help rule out confounding by indication and other selection factors.

We see several limitations to the present study. First, we focused on predictors of opioid receipt rather than on specific indications for opioid therapy, and we did not assess pain severity, although the long-term results persisted when we examined only those patients with recorded painful conditions. Second, our sample was restricted to patients with commercial insurance. It thereby excluded individuals aged 65 years or older and those with Medicaid,

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other sources of healthcare, or no insurance, and our data cannot speak to patterns of opioid receipt outside the US [19,20]. At the same time, though, the sample was national and large enough that we could use an incident user cohort design and examine rare predictors and long-term opioid receipt without excessive loss of precision [50]. Third, we assessed psychiatric conditions via service claims, meaning that only those patients who sought or otherwise received diagnoses or treatments could be identified as having those conditions. As a result, these data probably underestimate the prevalence of SUDs and other psychiatric conditions [25,26]. Fourth, our results should be interpreted as relating to prescriptions filled by patients rather than prescriptions written by providers. Patients may also have filled but not taken medications or, conversely, received medications outside of the included prescriptions. For example, the high risk of long-term opioids among patients with OUD diagnoses or medications may indicate that these patients were more likely to seek greater quantities of opioids early in their treatment course. Alternatively, however, their OUD diagnoses or treatments may have reflected an unobserved history, perhaps known to providers but not apparent in these data, of heavy prescription opioid use prior to their first recorded opioid fill. Fifth, given the large number of insurers included in the MarketScan database, it is possible that individuals who left one employer and subsequently joined another MarketScan-covered employer were counted as multiple enrollee observations. Finally, we required a 12-month washout period prior to the incident opioid prescription, which excluded a large proportion of opioid recipients and may have led to an underestimation of the rate of long-term opioid therapy in the entire recipient cohort.

Taken together, our results add to existing evidence that risk of long-term opioid receipt associated with psychiatric and behavioral conditions is widespread and relates to multiple diagnoses and psychoactive medications. Our findings support the ideas that clinical practice has deviated from the ‘careful selection’ under which most clinical trials are conducted and that thorough mental health assessment and intervention should be considered in conjunction with the use of long-term opioid therapy [30]. Although the accumulated findings suggest that pre-existing psychiatric conditions must be accounted for in future observational studies of behavioral opioid harms, they also highlight the value of pharmacoepidemiologic research in understanding the impact of opioid prescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics of Opioid Recipients

Age in years	Male		Female	
	n	%	n	%
14–18	545 527	5.3%	569 741	5.5%
19–25	497 501	4.8%	650 405	6.3%
26–35	769 478	7.5%	1 095 957	10.6%
36–45	1 010 629	9.8%	1 175 156	11.4%
46–55	1 110 394	10.8%	1 239 706	12.0%
56–64	794 324	7.7%	853 143	8.3%
Total	4 727 853	45.8%	5 584 108	54.2%

Note. Age at first opioid prescription fill.

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Table 2

Prior Psychiatric Diagnoses among Opioid-Recipient Cases and Matched Non-Recipient Controls

Prior Diagnosis	Cases with Diagnosis		Controls with Diagnosis		OR (95% CI)
	n	%	n	%	
OUD	5600	0.1%	4834	0.1%	1.16 (1.12–1.20)
SUD	56 163	1.4%	50 785	1.2%	1.11 (1.10–1.12)
Depressive disorder	350 677	8.5%	291 238	7.1%	1.23 (1.22–1.23)
Suicide attempt/Self-injury	3676	0.1%	3541	0.1%	1.04 (0.99–1.09)
Anxiety disorder	285 502	6.9%	247 491	6.0%	1.17 (1.16–1.17)
Sleep disorder	275 618	6.7%	201 574	4.9%	1.40 (1.40–1.41)
Motor vehicle crash[a]	10 528	0.3%	9099	0.3%	1.16 (1.13–1.19)

Note. Included ns for cases and controls were each 4 124 038. A complete list of diagnosis codes is available in Table S2, Supplemental Digital Content. OR = odds ratio. CI = confidence interval. OUD = opioid use disorder. SUD = non-opioid substance use disorder.

[a]Motor vehicle crashes include patients aged 18 years or older at first enrollment (n = 3 532 157 cases and controls).

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Table 3

Prior Psychoactive Medications among Opioid-Recipient Cases and Matched Non-Recipient Controls

Prior Medication	Cases with Medication		Controls with Medication		OR (95% CI)
	n	%	n	%	
OUD medication	5166	0.1%	4314	0.1%	1.20 (1.15–1.25)
AUD medication	3641	0.1%	3066	0.1%	1.19 (1.13–1.25)
Tobacco cessation	45 838	1.1%	28 154	0.7%	1.64 (1.62–1.66)
SSRI	515 435	12.5%	375 777	9.1%	1.44 (1.43–1.44)
SNRI	89 773	2.2%	63 858	1.5%	1.42 (1.40–1.43)
Other antidepressant	235 299	5.7%	160 595	3.9%	1.50 (1.49–1.51)
Benzodiazepine	409 110	9.9%	282 008	6.8%	1.52 (1.51–1.53)
Hypnotic	194 360	4.7%	129 734	3.1%	1.53 (1.52–1.54)
ADHD medication	117 234	2.8%	89 547	2.2%	1.33 (1.32–1.34)
Mood stabilizer	33 184	0.8%	25 429	0.6%	1.31 (1.29–1.33)
Antipsychotic	53 729	1.3%	44 156	1.1%	1.22 (1.21–1.24)

Note. Included ns for cases and controls were each 4 124 038. A complete list of generic medication names is available in Table S1, Supplemental Digital Content. OR = odds ratio. CI = confidence interval. OUD = opioid use disorder. AUD = alcohol use disorder. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin-norepinephrine reuptake inhibitor. ADHD = attention-deficit/hyperactivity disorder.

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Table 4

Associations between Prior Psychiatric Diagnoses and Long-Term Opioid Receipt

Prior Diagnosis	Long-Term Opioids by Year 3		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	No diagnosis	Diagnosis		
OUD	2.1%	11.3%	6.49 (6.11–6.89)	8.70 (8.20–9.24)
SUD	2.1%	5.3%	2.63 (2.55–2.70)	3.15 (3.06–3.24)
Depressive disorder	2.0%	3.7%	1.90 (1.87–1.92)	1.94 (1.91–1.96)
Suicide attempt/Self-injury	2.1%	3.5%	1.67 (1.45–1.93)	2.55 (2.21–2.94)
Anxiety disorder	2.0%	3.6%	1.82 (1.79–1.85)	1.92 (1.89–1.95)
Sleep disorder	2.0%	4.1%	2.08 (2.05–2.11)	1.78 (1.75–1.80)
Motor vehicle crash[a]	2.3%	3.5%	1.67 (1.55–1.80)	1.99 (1.85–2.14)

Note. Kaplan-Meier estimates of probability of long-term receipt onset by year 3. HR estimates from Cox regression. Adjusted models control sex, index age group, and calendar year of index date. A complete list of diagnosis codes is available in Table S2, Supplemental Digital Content. HR = hazard ratio. CI = confidence interval. OUD = opioid use disorder. SUD = non-opioid substance use disorder.

[a]Motor vehicle crashes include patients aged 19 years or older at index (n = 9 196 693).

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Table 5

Associations between Prior Psychoactive Medications and Long-Term Opioid Receipt

Prior Medication	Long-Term Opioids by Year 3		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	No medication	Medication		
OUD medication	2.1%	8.9%	4.79 (4.46–5.14)	5.27 (4.90–5.65)
AUD medication	2.1%	7.9%	3.72 (3.42–4.06)	3.07 (2.82–3.35)
Tobacco cessation	2.1%	4.6%	2.12 (2.05–2.19)	1.79 (1.73–1.85)
SSRI	1.9%	3.6%	1.84 (1.82–1.86)	1.71 (1.69–1.73)
SNRI	2.1%	4.3%	2.04 (2.00–2.09)	1.79 (1.74–1.83)
Other antidepressant	2.0%	4.3%	2.13 (2.10–2.16)	1.88 (1.85–1.91)
Benzodiazepine	1.8%	4.5%	2.37 (2.35–2.40)	2.05 (2.03–2.08)
Hypnotic	2.0%	4.8%	2.37 (2.33–2.40)	1.97 (1.94–2.00)
ADHD medication	2.1%	1.9%	0.89 (0.86–0.91)	1.53 (1.48–1.58)
Mood stabilizer	2.1%	3.9%	1.86 (1.79–1.94)	2.02 (1.94–2.10)
Antipsychotic	2.1%	5.2%	2.47 (2.40–2.54)	2.71 (2.64–2.79)

Note. Kaplan-Meier estimates of probability of long-term receipt onset by year 3. HR estimates from Cox regression. Adjusted models control sex, index age group, and calendar year of index date. A complete list of generic medication names is available in Table S1, Supplemental Digital Content. HR = hazard ratio. CI = confidence interval. OUD = opioid use disorder. AUD = alcohol use disorder. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin-norepinephrine reuptake inhibitor. ADHD = attention-deficit/hyperactivity disorder.