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Associations of Mental Health and Family Background with Opioid Analgesic Therapy: A Nationwide Swedish Register-Based Study

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Abstract

There is evidence of greater opioid prescription to individuals in the US with mental health conditions. Whether these associations generalize beyond the US prescription environment and to familial mental health and socioeconomic status (SES) has not been examined comprehensively. This study estimated associations of diverse pre-existing mental health diagnoses, parental mental health history, and SES in childhood with opioid analgesic prescription patterns nationwide in Sweden. Using register-based data, we identified 5 071 193 (48.4% female) adolescents and adults who were naïve to prescription opioid analgesics and followed them from 2007–2014. The cumulative incidence of any dispensed opioid analgesic within 3 years was 11.4% (95% CI, 11.3%–11.4%). Individuals with pre-existing self-injurious behavior, as well as opioid and other substance use, attention-deficit/hyperactivity, depressive, anxiety, and bipolar disorders, had greater opioid therapy initiation rates than did individuals without the respective conditions (hazard ratios from 1.24 [1.20–1.27] for bipolar disorder to 2.12 [2.04–2.21] for opioid use disorder). Among 1 298 083 opioid recipients, the cumulative incidence of long-term opioid therapy (LTOT) was 7.6% (7.6%–7.7%) within 3 years of initiation. All mental health conditions were associated with greater LTOT rates (hazard ratios from 1.66 [1.56–1.77] for bipolar disorder to 3.82 [3.51–4.15] for opioid use disorder) and were similarly associated with concurrent benzodiazepine-opioid therapy. Among 1 482 462 adolescents and young adults, initiation and

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Supplemental Digital Content

Tables with inclusion and exclusion criteria, ATC and ICD codes, additional opioid prescription information, and results of additional analyses.

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LTOT rates were greater for those with parental mental health history or lower childhood SES. Efforts to understand and ameliorate potential adverse effects of opioid analgesics must account for these patterns.

Keywords

Adverse selection; Pharmacoepidemiology; Prescription opioid analgesics; Psychiatric conditions

1. Introduction

Opioid analgesic prescription has increased and remains quite common, especially in North America [25,33], and adverse public health outcomes have raised serious concerns about opioid safety. Patients receiving greater-quantity opioid regimens are at increased risk of morbidity and mortality [7,8,17,22,47,55]. Questions remain, however, about the contribution of prescribed opioid use—versus comorbid conditions, diversion, and illicit opioid use [64]—to substance use disorder (SUD) and related harms [11,12,54]. Evaluating real-world opioid prescription patterns is therefore necessary to understanding their impact on health.

Studies of prescription in the US, often using commercial healthcare insurance records, have identified a number of predictors of opioid receipt. Critically, patients with pre-existing SUD and other mental health conditions are substantially more likely to receive long-term opioid therapy (LTOT) than are patients without those conditions [9,13,15,26,51,52]. Because such individuals may be at greater risk of harmful opioid outcomes, this phenomenon has been termed “adverse selection” [73]. A major question is whether these findings are specific to the US prescription environment or whether they reflect processes more fundamental to patients with chronic pain—and those receiving LTOT in particular. Limited large-scale healthcare-record evidence supports a similar pattern among primary care [19], post-surgical [32], and other patients outside the US. For example, benzodiazepine and other psychiatric medication use is overrepresented among prescription opioid recipients [10,24,45]. Moreover, Nordic and United Kingdom studies combining healthcare records with surveys and other clinical and population data have linked various indices of mental health (e.g., depression, smoking, SUD) to LTOT [5,21,23,27]. At present, conclusions from this literature are constrained by assessment of few mental health factors, often via self-report surveys or prescription records. To our knowledge, no study has yet comprehensively examined the course of opioid therapy among patients with mental health conditions outside the US.

The current study helped address this gap using nationwide register data from Sweden, where, although opioid prescription has historically been relatively conservative, use and accompanying concerns have increased [33,58]. Specifically, this study characterized opioid initiation and LTOT for up to eight years, across analgesia indications, for patients with a wide range of mental health conditions (e.g., SUD, self-injurious behavior). Additionally, we examined associations with concurrent benzodiazepine-opioid therapy, a prescription pattern that may contribute to risk of opioid overdose [76] and has therefore been discouraged in

Sweden [46,56,65] and elsewhere [14]. Finally, given clearly established genetic influences on mental health [50], as well as socioeconomic disparities in opioid prescription [44,77,78], research is needed to more fully examine family backgrounds for these patient populations [39]. We therefore incorporated register-based family mental health history and socioeconomic status (SES).

2. Methods

2.1 Registers and Cohort

We identified a cohort of adolescents and adults in Sweden who were naïve to prescription opioid analgesics, drawing data from population registers linked by Statistics Sweden [53,70]. As has been described previously, Swedish and other Nordic register data represent unique resources for epidemiology because of their whole-population coverage and potential for linkage via personal identity numbers that are assigned at birth or immigration [2,40,48]. The linked registers included: Total Population Register (including demographics, residence, and migration) [40], Swedish Prescribed Drug Register (all prescription medications dispensed outside of hospitals since July 2005) [79,82], Multi-generation Register (familial relationships for individuals born since 1932 or living in Sweden since 1961) [16], National Patient Register (nationwide inpatient hospitalizations since 1987 and outpatient specialist visits since 2001) [41], Longitudinal integration database for health insurance and labour market studies (LISA; diverse socio-economic information since 1990) [42], and Cause of Death Register (deaths since 1961) [49]. The Indiana University Institutional Review Board and the Regional Ethics Committee in Stockholm approved this study.

We included Sweden-born residents aged 13–73 years on January 1, 2007. We excluded individuals with any recorded opioid analgesics dispensed in 2005–2006, as well as those with terminal cancer or with dispensed cancer-related opioid prescriptions. We followed all individuals from January 1, 2007 through the first of emigration, death, or the end of the study (December 31, 2014), requiring at least 6 months of follow-up. The final cohort comprised 5 071 193 individuals (48.4% female), of whom 158 496 (3.1%) had less than 8 years of follow-up. The cohort represented 78.8% of the original birth cohort and 89.0% of those without registered deaths or emigrations prior to the start of follow-up.

Additionally, SES data were not available from LISA prior to 1990 [42]. In examining associations between family background and offspring opioid receipt, we therefore analyzed a sub-cohort of individuals with age-12 family-of-origin data by January 1, 2007 (i.e., those aged 13–29 years in 2007; N = 1 482 462). See eTable 1, Supplemental Digital Content, for complete inclusion and exclusion criteria.

2.2 Opioid Prescription

The Swedish Prescribed Drug Register includes dispensing dates and information on products and prescribers for dispensed prescription medications [82]. Using Anatomical Therapeutic Chemical (ATC) codes, we identified opioid analgesic prescriptions dispensed in 2007–2014, including weak opioids (i.e., codeine, dextropropoxyphene, tramadol) but not medications listed as cough and cold preparations (eTable 2, Supplemental Digital Content,

lists all included ATC codes). In order to differentiate buprenorphine and methadone dispensed as medication-assisted treatment (MAT) of opioid use disorder (OUD) from prescriptions for analgesia, we followed prior research [1,37]. Specifically, prescriptions of transdermal buprenorphine, prescriptions dispensed to adolescents (under 18 years), or prescriptions dispensed via the “ApoDos” multi-dose packaging system were considered analgesics. Other buprenorphine and methadone was counted as an analgesic only if it was prescribed by non-psychiatry providers in non-psychiatry practices.

2.2.1 Long-term opioid therapy.—Prior research has used multiple operationalizations of LTOT, and there is no single agreed-upon definition [15,81]. In Sweden, opioid prescriptions are dispensed for a maximum of 3 months supply [66]. We therefore defined LTOT as strong (i.e., not weak) opioids dispensed on 2 or more dates within a 6-month window, which is consistent with previous Swedish research and matches the 6-month windows used in some US studies [24,51,74]. Sensitivity analyses, described below, evaluated this definition.

2.2.2 Concurrent benzodiazepine therapy.—We examined concurrent benzodiazepine-opioid therapy as an index of potentially harmful deviation from opioid prescription guidelines. We defined concurrence as prescriptions dispensed within 30 days of each other, with the concurrence beginning on the later dispensing date.

2.3 Pre-Existing Mental Health

The National Patient Register includes discharge dates and diagnoses (recorded as *International Classification of Diseases* [ICD] codes) from inpatient hospitalizations and outpatient specialist visits [41]. We identified inpatient and outpatient clinical diagnoses before 2007 for OUD and other SUD, suicide attempt or other self-injury, and attention-deficit/hyperactivity, depressive, anxiety, schizophrenia spectrum, and bipolar disorders (eTable 3, Supplemental Digital Content, lists all ICD codes). We adapted ICD codes from prior opioid-related and register-based research [52,53]. As an alternative index of mental health, we also examined 2005–2006 receipt of psychoactive medications (i.e., antidepressants, antipsychotics, benzodiazepines, mood stabilizers, non-benzodiazepine z-hypnotics, and medications used in the treatment of attention-deficit/hyperactivity disorder, OUD, and other SUD). We counted as MAT of OUD only those non-analgesic buprenorphine and methadone prescriptions (defined above) dispensed from psychiatry specialists in psychiatry practices.

2.4 Family Background

In order to assess family mental health history, we identified maternal and paternal diagnoses of anxiety or depressive disorder, OUD or other SUD, and suicide attempt or other self-injury from inpatient hospitalizations prior to 2007. We also included several indices of family-of-origin SES. First, we identified the highest level of maternal and paternal education through 2006 [53]. Second, we estimated family income at offspring-age 12 (i.e., prior to the start of follow-up). We calculated family income as the mean of available maternal and paternal disposable family incomes [36]. In order to adjust for inflation or transient economic events, we created within-year decile-rank scores. Third, we included a

deprivation score for the neighborhood of residence at age 12, which we also analyzed using within-year decile-rank scores. As described elsewhere, the deprivation score was generated for each year via a principal components analysis of all 25–64-year-old neighborhood members' socioeconomic characteristics (i.e., welfare receipt, unemployment, immigration, divorce, secondary education, disposable income, crime), where neighborhood was defined using Statistics Sweden's homogenous geographic Small Areas for Market Statistics [61]. In addition to the registers described above, the neighborhood deprivation score additionally drew on the National Crime Register, which includes convictions since 1973 [18]. Fourth, we examined parental immigrant status, defined as having at least one parent born outside of the Nordic countries. Finally, we included an indicator of metropolitan residence (in Stockholm, Göteborg, or Malmö) at age 12.

2.5 Statistical Analysis

Our objective was to examine the extent to which opioid therapy rates differed among those with and without pre-existing mental health conditions and family background factors. We used a survival analysis approach in SAS 9.4 (SAS Institute, Inc.) to examine these associations because follow-up time was right censored. We calculated Kaplan Meier estimates of the cumulative incidence of opioid receipt and estimated hazard ratios (HRs) using Cox proportional hazards regressions [3]. We set censoring dates to six months prior to the end of available follow-up (i.e., the last date at which an individual was eligible to initiate a six-month LTOT window). Consistent with our previous studies, we report the cumulative incidence of opioid therapy receipt within 3 years as an index of absolute risk [51,52].

The first set of models examined associations with rates of opioid initiation, defined as first dispensed opioid. The timescale was years since January 1, 2007. The second and third sets of models examined associations with the transition to LTOT and concurrent benzodiazepine therapy, respectively. These models were limited to those who had initiated opioids, and the timescale was years since initiation. We examined each mental health condition or family factor in a separate regression because our goal was largely descriptive (i.e., characterizing opioid prescription patterns among those with and without mental health and family background factors). We included demographic covariates, which are detailed in eTable 4, Supplemental Digital Content (county of residence in 2007 [Stockholm, Västra Götaland, Skåne, or other counties], age group, sex, and—for LTOT and concurrent benzodiazepines—calendar year of opioid initiation). In the family background analyses, we accounted for the clustering of individuals born to the same mother with robust standard errors.

Sensitivity analyses tested the robustness of the associations with opioid initiation and LTOT. First, in order to ensure that differences in predictor assessment periods did not bias the results, we restricted the pre-existing mental health condition diagnoses to the period when outpatient and inpatient records were available (2001–2006). Second, we excluded the 34 374 individuals who were ever dispensed buprenorphine or methadone to ensure that our results were not biased by misclassification of MAT vs. analgesia. Finally, we examined the sensitivity of the results to the operationalization of LTOT. Our definition, based upon previous Swedish and US studies [24,51], required only 2 dispensed strong opioid

prescriptions. If some recipients merely switched drugs because of negative reactions to an acute therapy prescription, the definition could have overestimated LTOT incidence. We therefore additionally examined a stricter definition of LTOT (i.e., strong opioids in 3 of 4 consecutive 90-day quarters) drawn from other previous Nordic research [21].

3. Results

3.1 Opioid Initiation

In this cohort of 5 071 193 adolescents and adults who were naïve to prescription opioid analgesics, the estimated cumulative incidence of initiating an episode of opioid prescription within 3 years was 11.4% (pointwise 95% confidence interval [CI], 11.3%–11.4%). As shown in eTable 4, Supplemental Digital Content, older individuals were more likely to initiate opioids than were younger individuals.

From 2007 onward, the cohort was dispensed 5 399 576 opioid prescriptions (eTable 5, Supplemental Digital Content, details the specific opioid drugs). The majority were for weak opioids, including tramadol (32.9% of dispensed prescriptions) and codeine (32.4%). Among opioid recipients, 52.3% were dispensed at least 1 prescription for a codeine-containing product, 40.1% tramadol, 20.8% oxycodone, 10.4% morphine, 9.5% dextropropoxyphene (removed from the market in 2011), 2.2% buprenorphine or methadone, and 2.2% other opioids.

Individuals with most pre-existing mental health conditions had greater rates of opioid initiation than did individuals without those conditions. These HRs, adjusted for demographics, ranged from 1.24 (1.20–1.27) for bipolar disorder to 2.12 (2.04–2.21) for OUD (Table 1). Only schizophrenia spectrum disorders were inversely associated with opioid initiation (HR, 0.84; 0.83–0.86). Moreover, relative to no conditions, the number of mental health conditions was also associated with greater initiation rates (Figure). As shown in eTable 6 and eTable 7, Supplemental Digital Content, we found comparable associations between prior psychoactive medications and initiation, as well as in sensitivity analyses examining past-6-year mental health diagnoses and excluding buprenorphine and methadone recipients.

3.2 Long-Term Opioid Therapy

Among the 1 298 083 opioid recipients prior to censoring, the estimated cumulative incidence of LTOT was 7.6% (7.6%–7.7%) within 3 years of opioid initiation and was greater among older opioid recipients (eTable 4, Supplemental Digital Content). For each mental health condition, individuals with pre-existing diagnoses had greater rates of transitioning from opioid initiation to LTOT relative to those without (Table 2). Adjusted HRs ranged from 1.66 (1.56–1.77) for bipolar disorder to 2.20 (2.15–2.25) for SUD and 3.82 (3.51–4.15) for OUD. The number of mental health conditions was again associated with greater rates of LTOT (Figure), and the relative magnitudes of all LTOT associations were greater than their respective magnitudes for opioid initiation.

Similarly, across each class of psychoactive medications, prior recipients had greater LTOT rates than did non-recipients (eTable 6, Supplemental Digital Content). As shown in eTable

8, Supplemental Digital Content, sensitivity analyses examining past-6-year mental health diagnoses and excluding buprenorphine and methadone recipients also produced comparable associations. In a test of the sensitivity of the results to the LTOT definition, we found comparable but stronger associations when we defined LTOT as strong opioids in 3 of 4 consecutive quarters. Although the cumulative incidence was lower (1.7% [1.7%–1.7%] within 3 years of opioid initiation), adjusted HRs for this definition ranged from 2.46 (2.21–2.75) for bipolar disorder to 3.54 (3.40–3.69) for SUD and 8.43 (7.44–9.55) for OUD (eTable 8, Supplemental Digital Content).

3.3 Concurrent Benzodiazepine Therapy

The estimated cumulative incidence of concurrent benzodiazepine-opioid therapy was 5.7% (5.7%–5.8%) within 3 years of opioid initiation, and opioid recipients with each pre-existing mental health condition had greater rates than did recipients without the respective condition (Table 2, Figure). Adjusted HRs ranged from 3.56 (3.48–3.65) for suicide attempt or other self-injury to 6.70 (6.23–7.20) for OUD.

3.4 Family Background

Among the sub-cohort of 1 482 462 individuals with familial data (aged 13–29 years in 2007), parental mental health history was associated with differences in rates of dispensed opioid prescriptions (Table 3). Specifically, adolescents and young adults with parents who had been hospitalized for anxiety or depressive disorder, opioid or non-opioid SUD, or suicide attempt or other self-injury had greater rates of opioid initiation as well as subsequent LTOT. Adjusted HRs for opioid initiation ranged from 1.27 (1.25–1.29) for anxiety or depressive disorder to 1.41 (1.39–1.44) for suicide attempt or other self-injury. Among opioid recipients, adjusted HRs for LTOT ranged from 1.34 (1.27–1.41) for anxiety or depressive disorder to 1.44 (1.36–1.53) for SUD. As shown in eTable 9, Supplemental Digital Content, these associations persisted after adjustment for offspring mental health conditions and family SES.

We additionally found variability in opioid prescription as a function of family-of-origin SES. Individuals from lower-SES families, broadly, had greater rates of opioid therapy initiation than did those from higher-SES families. Moreover, among opioid recipients, those from lower-SES families had greater rates of transitioning to LTOT. These associations held across multiple indices of SES, including parental education, family income, and neighborhood deprivation. Whereas children of immigrants and those from metropolitan areas had modestly greater opioid initiation rates, their rates of subsequent LTOT did not differ from those with Nordic-born parents or those from non-metropolitan areas, respectively.

4. Discussion

New initiation of non-cancer opioid analgesic prescription was common in Sweden from 2007 onward. As in the US [75], receipt of LTOT was less common. An estimated 7.6% of individuals transitioned to a broader definition of LTOT—and 1.7% to a stricter definition—within 3 years of initiating an episode of opioid therapy. There were clear differences in

rates of opioid receipt among those with and without pre-existing mental health and family background factors. Individuals with diverse mental health conditions had greater rates of initiating opioid therapy and, especially, transitioning to LTOT. They also had greater rates of receiving benzodiazepines during opioid therapy, a deviation from current guidelines. Finally, opioid initiation and LTOT were also more common among those with parents with mental health conditions and those from lower SES families and neighborhoods.

The substantial associations of pre-existing mental health conditions with LTOT are consistent with our previous results from US commercial healthcare insurance claims [51,52]. Other US studies have also found greater concurrent benzodiazepine and other sedative-hypnotic use among opioid recipients with mental health conditions [63,80]. This consistency is notable given variability in populations, healthcare systems, and data sources. Indeed, there were striking differences in the composition of dispensed opioids. Whereas the weaker drugs codeine and tramadol comprised 65% of opioids in the present study, the most commonly dispensed opioids in our US data were hydrocodone and oxycodone. Despite differences in potency, however, even weaker opioids may have abuse potential [59].

There is also precedent for the current associations in previous Nordic-register-based research. Danish and Norwegian studies have found associations of, for example, smoking and benzodiazepine receipt with LTOT [5,21]. Although not all prior studies have found similar associations for substance use problems, inconsistencies may be due to differences in assessed behavior (e.g., use versus SUD), measurement (e.g., self-report versus clinical diagnosis), design (e.g., surveys versus registers), and adjustment strategies [21].

Whereas socioeconomic disparities in opioid receipt have been documented [44,77], fewer studies have examined families-of-origin in this context [39,57]. As a result, there has been uncertainty regarding underlying processes and, in particular, the direction of the associations. For example, chronic pain—or LTOT itself—might disrupt socioeconomic advancement, thereby producing associations between opioid receipt and lower SES. By showing that lower SES in childhood predicted greater opioid receipt later in life, our results suggest that the association is not exclusively caused by an individual's own pain or opioid use leading to reduced SES. Rather, individuals from lower SES backgrounds may be more likely to receive opioid prescription, perhaps because of greater risk of occupational injury or limited access to non-pharmacologic treatments. However, the familial transmission of SES, pain, and mental health results from complex genetic and social pathways that must be elucidated in order to fully understand these associations [34,68].

Taken together, the present results illustrate that the adverse-selection pattern of opioid prescription among patients with mental health and other psychosocial problems is pervasive in Sweden. In light of the cross-national generality of this finding, comorbidity and shared (i.e., transdiagnostic) liabilities in chronic pain and mental health may be more responsible for the prescription pattern than are factors specific to the US context, such as inappropriate or excessive opioid prescription [6,30]. Multiple explanations for the over-representation of depression, anxiety disorders, and SUDs in patients with chronic pain and LTOT have been proposed. There is evidence that mental health and chronic painful conditions partially share genetic, neural, and psychological mechanisms [29,34,38]. In particular, a recent review

highlighted the shared processing of reward, pain, and social bonding and stress by the endogenous opioid system [4]. This work has given rise to the hypothesis that patients with depression may self-select into—and providers may be willing to prescribe—LTOT in order to not only manage pain but also self-medicate psychological distress [71,73].

Given the breadth of mental health conditions associated with LTOT, as well as the stronger associations for SUD than for depressive or anxiety disorders, the extent to which emotion-regulation or other motivations for opioid analgesic use are mental-health-condition-specific or more general remains to be determined [69]. At its epidemiologic level of analysis, the present study cannot determine the processes that may have led to these prescription patterns. Opioid prescription decisions are proximally shaped by interpersonal interactions between patients and providers that would not be fully captured by healthcare-record data [72]. Further research with detailed clinical, genetic, or neurobiological assessment is needed to disentangle the pathways relating pain and LTOT to mental health comorbidity and other psychosocial problems.

Regardless of the specific processes, our findings provide further evidence that patients receiving opioids—and others with chronic non-cancer pain—should receive thorough mental health assessment and, when appropriate, treatment [14,43]. The findings serve to underscore the clinical complexities and needs at the intersection of chronic pain, mental health comorbidity, and psychological distress [31]. Given that LTOT is often arrived upon unintentionally and can be difficult to taper for some [20,30,35], mental health evaluation may help inform decisions to initiate or not initiate opioid therapy. Moreover, our findings add to evidence that opioid recipients with pre-existing mental health conditions may be at subsequent risk of concurrent benzodiazepine therapy, a potentially harmful outcome [67] that may increase risk of opioid overdose [76].

This study shares methodological advantages and disadvantages with other healthcare-record studies. First, we examined eight years of nationwide opioid prescriptions, although we did not assess particular analgesia indications, including somatic pain locations or pain severity or sensitivity [60]. US studies have, however, found comparable mental health associations with and without restriction to diagnosed painful conditions [26,51,52]. Nevertheless, given the likely co-occurrence of chronic pain with the mental health and familial factors considered here, our results should be interpreted as describing differences in opioid prescription patterns rather than specific mental health contributions to a causal pathway to opioid initiation or LTOT. Second, our results concern opioid prescriptions written by providers and dispensed to patients. Records do not provide explicit information about primary or secondary noncompliance or illicitly obtained medications. We also could not determine whether providers employed any risk-reduction strategies for opioid or concurrent benzodiazepine prescription. We note, though, that using a stricter LTOT criterion actually strengthened the mental health associations. Third, we examined opioid duration and strength but not dosage [28]. Fourth, we assessed diverse mental health conditions. Many registered diagnoses are validated [41], although they would not capture patients who did not obtain specialist treatment (e.g., those treated in primary care), which likely underestimated the prevalence of some conditions. However, differing predictor definitions—including psychoactive medications—produced comparable results. Fifth, we required at

least 1.5 years washout prior to the initiation of new episodes of opioid therapy [62]. Like previous healthcare-record-based opioid research [5,9,24,51], however, this study cannot ensure that the cohort had never received opioids prior to the available data. Finally, we do not know the generalizability of our family-background findings to older individuals.

4.1 Conclusions

Understanding which patients select or are selected into opioid therapy and LTOT is necessary to assessing the real-world risk of iatrogenic SUD and other possible harms of opioid prescription. Indeed, recent reviews have underscored limitations in the literature on adverse opioid outcomes, notably including lack of adequate adjustment for confounders such as pre-existing mental health conditions [11,54]. Register-based approaches can offer the generalizability, statistical power, and rich social, familial, and health data needed for rigorous analysis of opioid harms. At the same time, although they certainly do not rule out the possibility of such harms, our findings highlight the importance, in future research, of accounting for relevant pre-existing differences between opioid recipients and non-recipients beyond their own recorded medical history, such as SES and familial mental health liability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Pre-existing mental health conditions and opioid initiation, long-term opioid therapy, and concurrent benzodiazepine-opioid therapy. Kaplan Meier estimates of cumulative incidence (%) of opioid initiation since 2007 in 5 071 193 individuals who were naïve to prescription opioid analgesics (Panel A) and, among 1 298 083 individuals initiating opioids, long-term opioid therapy (Panel B) and concurrent benzodiazepine-opioid therapy (Panel C) by number of pre-existing mental health conditions. Shaded areas are pointwise 95% confidence intervals.

Table 1.

Pre-Existing Mental Health Conditions and Opioid Initiation among 5 071 193 Individuals

Mental Health Condition	Mental Health Condition Prevalence n (%)	Association with Opioid Initiation Hazard Ratio ^a (95% CI)
Opioid use disorder	5258 (0.1%)	2.12 (2.04–2.21)
Other substance use disorder	118 725 (2.3%)	1.73 (1.71–1.74)
Attention-deficit/hyperactivity disorder	12 046 (0.2%)	1.56 (1.51–1.61)
Schizophrenia spectrum disorder	44 436 (0.9%)	0.84 (0.83–0.86)
Suicide attempt or other self-injury	93 318 (1.8%)	1.71 (1.69–1.73)
Depressive disorder	120 565 (2.4%)	1.56 (1.55–1.58)
Anxiety disorder	137 552 (2.7%)	1.58 (1.57–1.60)
Bipolar disorder	18 539 (0.4%)	1.24 (1.20–1.27)
Number of conditions		
0 [reference]	4 694 315 (92.6%)	[1]
1	258 050 (5.1%)	1.43 (1.42–1.44)
2+	118 828 (2.3%)	1.68 (1.67–1.70)
Opioid initiation (n)		1 298 083

^a Adjusted for county, sex, and age.

Table 2.

Pre-Existing Mental Health Conditions and Long-Term Opioid Therapy and Concurrent Benzodiazepine Therapy among 1 298 083 Individuals Initiating Opioids

Mental Health Condition	LTOT HR^a (95% CI)	Concurrent BZD HR^a (95% CI)
Opioid use disorder	3.82 (3.51–4.15)	6.70 (6.23–7.20)
Other substance use disorder	2.20 (2.15–2.25)	4.60 (4.51–4.70)
Attention-deficit/hyperactivity disorder	2.11 (1.90–2.35)	4.48 (4.10–4.89)
Schizophrenia spectrum disorder	1.90 (1.81–1.98)	5.61 (5.42–5.81)
Suicide attempt or other self-injury	1.88 (1.83–1.93)	3.56 (3.48–3.65)
Depressive disorder	1.72 (1.68–1.76)	4.27 (4.19–4.36)
Anxiety disorder	1.69 (1.65–1.73)	4.78 (4.68–4.87)
Bipolar disorder	1.66 (1.56–1.77)	5.58 (5.33–5.83)
Number of conditions [reference: 0]		
1	1.62 (1.59–1.65)	3.14 (3.08–3.21)
2+	2.15 (2.10–2.20)	6.56 (6.43–6.69)
Outcome (n)	116 977	80 726

^a Adjusted for county, sex, age at opioid initiation, and calendar year of initiation.

BZD, benzodiazepine. HR, hazard ratio. LTOT, long-term opioid therapy.

Table 3.

Family Background, Opioid Initiation, and Long-Term Opioid Therapy among Adolescents and Young Adults

Family Background Factor	Prevalence n (%)	Initiation HR ^a (95% CI)	LTOT HR ^b (95% CI)
Parental mental health			
Anxiety or depressive disorder	104 433 (7.0%)	1.27 (1.25–1.29)	1.34 (1.27–1.41)
Substance use disorder	80 915 (5.5%)	1.41 (1.39–1.43)	1.44 (1.36–1.53)
Suicide attempt or other self-injury	65 509 (4.4%)	1.41 (1.39–1.44)	1.41 (1.32–1.50)
Highest parental level of education			
Less than 9 years	17 364 (1.2%)	1.34 (1.30–1.39)	1.06 (0.91–1.23)
9 years	66 230 (4.5%)	1.39 (1.37–1.42)	1.32 (1.22–1.42)
Any upper secondary	727 446 (49.1%)	1.26 (1.25–1.27)	1.27 (1.22–1.32)
Less than 2 years post-secondary	92 727 (6.3%)	1.07 (1.05–1.09)	1.06 (0.97–1.15)
At least 2 years post-secondary [reference]	551 169 (37.2%)	[1]	[1]
Postgraduate	27 526 (1.9%)	0.85 (0.82–0.88)	0.93 (0.79–1.10)
Family income in childhood			
Lowest income decile	148 256 (10.0%)	1.33 (1.31–1.36)	1.34 (1.24–1.45)
Decile 2	148 190 (10.0%)	1.28 (1.26–1.30)	1.28 (1.18–1.38)
Decile 3	148 226 (10.0%)	1.23 (1.21–1.25)	1.26 (1.16–1.36)
Decile 4	148 353 (10.0%)	1.16 (1.14–1.18)	1.22 (1.13–1.33)
Decile 5	148 266 (10.0%)	1.11 (1.09–1.13)	1.18 (1.09–1.28)
Decile 6	148 122 (10.0%)	1.10 (1.08–1.12)	1.08 (0.99–1.18)
Decile 7	148 205 (10.0%)	1.10 (1.08–1.12)	1.09 (1.00–1.19)
Decile 8	148 269 (10.0%)	1.07 (1.05–1.09)	1.13 (1.04–1.22)
Decile 9	148 394 (10.0%)	1.05 (1.03–1.07)	1.01 (0.92–1.10)
Highest income decile [reference]	148 181 (10.0%)	[1]	[1]
Neighborhood deprivation in childhood			
Least deprived decile [reference]	148 234 (10.0%)	[1]	[1]
Decile 2	148 273 (10.0%)	1.05 (1.03–1.06)	1.01 (0.93–1.09)
Decile 3	148 257 (10.0%)	1.04 (1.02–1.06)	1.06 (0.98–1.15)
Decile 4	148 244 (10.0%)	1.06 (1.05–1.08)	1.08 (1.00–1.18)
Decile 5	148 210 (10.0%)	1.08 (1.06–1.10)	1.06 (0.97–1.15)
Decile 6	148 307 (10.0%)	1.10 (1.08–1.12)	1.11 (1.03–1.21)
Decile 7	148 219 (10.0%)	1.11 (1.10–1.13)	1.11 (1.02–1.20)
Decile 8	148 273 (10.0%)	1.14 (1.13–1.16)	1.18 (1.09–1.28)
Decile 9	148 168 (10.0%)	1.15 (1.13–1.17)	1.16 (1.07–1.25)
Most deprived decile	148 277 (10.0%)	1.27 (1.24–1.29)	1.23 (1.14–1.33)
Parental immigration	146 714 (9.9%)	1.03 (1.02–1.04)	1.01 (0.96–1.07)
Metropolitan residence in childhood	435 188 (29.4%)	1.09 (1.08–1.10)	0.98 (0.93–1.03)
Offspring ^c (n)		1 482 462	273 824

Family Background Factor	Prevalence n (%)	Initiation HR ^a (95% CI)	LTOT HR ^b (95% CI)
Outcome (n)		273 824	13 314

^a Adjusted for county, sex, and age.

^b Adjusted for county, sex, age at opioid initiation, and calendar year of initiation.

^c Sub-cohort of individuals aged 13–29 in 2007 with familial data.

HR, hazard ratio. LTOT, long-term opioid therapy.