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Psychiatric risk factors for chronic high-dose opioid prescribing: register-based cohort study

Mariëlle M. C. van der Hoorn*, Gerard A. Kalkman*, Yvette M. Weesie, Femke Atsma and Arnt Schellekens

Background

Chronic high-dose (CHD) prescription opioid use is a major public health concern. Although CHD opioid use has been associated with psychiatric disorders, the causality could go both ways. Some studies have already linked psychiatric disorders to an increased risk of transitioning to chronic opioid use, and longitudinal data identifying psychiatric disorders as predictors of CHD opioid use could shed further light on this issue.

Aims

To prospectively examine the relationship between the presence of a psychiatric disorder and subsequent development of CHD opioid use in primary care patients newly receiving opioids.

Method

Data were included from 137 778 primary care patients in The Netherlands. Cox regression modelling was used to examine the association between psychiatric disorders prior to a new opioid prescription and subsequent CHD opioid use (≥90 days; ≥50 mg/day oral morphine equivalents) in the subsequent 2 years.

Results

Of all patients receiving a new opioid prescription, 2.0% developed CHD opioid use. A psychiatric disorder before the start of an opioid prescription increased the risk of CHD opioid use (adjusted hazard ratio HR = 1.74; 95% CI 1.62–1.88), specifically psychotic disorders, substance use disorders, neurocognitive disorders and multiple co-occurring psychiatric episodes. Similarly, pharmacotherapy for psychosis, substance use disorders and mood and/or anxiety disorders increased the risk of CHD opioid use. Psychiatric polypharmacy conferred the greatest risk of developing CHD opioid use.

Conclusions

Psychiatric disorders increase the risk of developing CHD opioid use in patients newly receiving prescription opioids. To reduce the public health burden of CHD opioid use, careful monitoring and optimal treatment of psychiatric conditions are advised when opioid therapy is initiated.

Keywords

Primary care; drugs of dependence disorders; opiate disorders; risk assessment; pain care.

Prescription opioids are highly effective analgesics, although evidence for long-term use in chronic non-cancer pain is lacking.[1] In Europe, the number of people receiving opioid prescriptions has increased sharply in recent years.[2] For instance, the number of opioid prescriptions in The Netherlands nearly doubled over the past decade, mainly due to the substantial increase in oxycodone use.[3] Similar to other countries,[2] the increase in opioid prescriptions was paralleled by an increase in opioid-related harm, including opioid use disorder and opioid-related mortality.[3] Although not comparable to the opioid epidemic in the USA, the increased use of prescription opioids in Europe is considered a public health concern.[2] The risks associated with long-term prescription opioid use, including misuse, overdose and addiction, against the limited evidence for their long-term effectiveness stresses the importance of carefully balancing the benefits and risks when prescribing opioids.[4] Identifying patients at risk for chronic high-dose (CHD) use of prescribed opioids could help reduce opioid-related harm.[1,4,5] Several studies show that psychiatric disorders are associated with chronic opioid use and misuse. For example, a cross-sectional study in the USA showed that over half of all opioids were being prescribed to patients with psychiatric disorders, while these patients only make up 16% of the total population.[6] However, the relationship between CHD prescription opioid use and psychiatric disorders could be bidirectional.[7] Indeed, most studies investigating the association between psychiatric disorders and chronic opioid use rely on cross-sectional data from the USA collected from specific populations (e.g. insured patients, military veterans or patients with specific conditions).[5] To our knowledge, the only longitudinal studies on this topic are by Olopoenia et al[8] and Quinn et al.[9,10] Olopoenia et al found that in patients with chronic non-cancer pain, having a psychiatric disorder was a strong risk factor for receiving CHD opioid prescriptions.[8] The study was conducted in a US sample of insured patients aged 18–65, which limits generalisability to other (European) countries. Quinn et al found a similar relation between psychiatric disorders, initiation of opioid therapy and subsequent transition to long-term opioid use in both a US and a Swedish population.[9,10] Further longitudinal studies based on representative community samples, including some from Europe, are needed to substantiate current evidence on the role of psychiatric disorders as a major risk factor for chronic opioid use.

This study aimed to prospectively examine the relationship between psychiatric disorders and the development of CHD opioid use in Dutch primary care patients receiving a new opioid prescription. More specifically, we investigated whether the presence of a psychiatric disorder before a new opioid prescription increased the risk of CHD opioid use. This relationship was further explored for each psychiatric disorder separately and for different categories of psychiatric drug.

Method

Data and study design

We conducted a register-based cohort study with data from the Nivel Primary Care Database (Nivel-PCD), covering 2011–2019.

* These authors contributed equally to this work.

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The Nivel-PCD contains pseudonymised routine care data from approximately 10% of all general practitioners (GPs) across The Netherlands, which forms a representative sample of the total population of Dutch GPs.[11,12] All Dutch residents are registered with one GP who oversees their medical records, provides primary care and is a gatekeeper to specialist care. The Nivel-PCD thus includes representative nationwide patient data.

The available medical information is coded using the International Classification of Primary Care, version 1 (ICPC-1) for diagnoses and the Anatomical Therapeutic Chemical Classification (ATC) for prescriptions. Data from the Nivel-PCD can be used for research purposes. According to Dutch civil law (article 7:458), no informed consent or medical ethics committee involvement is required for studies without direct personal identifiable data. As a result, this study has been approved by the applicable governance bodies of Nivel-PCD under number NZR-00319.048.

Data on median income, as an indicator of socioeconomic status, were based on the first four digits of a patient's postcode and collected from Statistics Netherlands.[13]

Sample and follow-up

Between 2011 and 2017 all patients with at least one opioid prescription were included and indexed by date of the first opioid prescription. Exclusion criteria were: (a) missing data 6 months before the index prescription, (b) enrolment in a primary care practice with less than 90% of the prescriptions coded with a valid ATC code and (c) treatment of opioid use disorder. Because of the required 6 months without opioid prescribing before the index prescription, only patients with an index prescription in July 2011 and onward were included. To allow for a 2-year follow-up period after the index prescription, data from 2011–2019 were obtained. Patients were categorised as having treatment for opioid use disorder if the first opioid prescription was for an opioid used in treatment of opioid use disorder (ATC N07BC). This selection resulted in 137 778 included participants (Fig. 1).

Psychiatric disorders

Participants with psychiatric disorders were defined as having ≥1 psychiatric episode recorded or having ≥1 prescription for a psychiatric drug 6 months before a first opioid prescription. The comparison group comprised all other participants receiving a new opioid prescription. Seven categories of psychiatric episode were created: mood and anxiety disorders; substance use disorders; psychotic disorders; neurocognitive disorders; somatisation or eating disorders; personality or gambling disorders; and multiple psychiatric episodes. Owing to limitations in the ICPC-1 coding system, the 'somatisation and eating disorders' and 'personality and gambling disorders' categories could not be subdivided into the individual disorders. Psychiatric drugs were grouped into five categories: mood and anxiety disorders (antidepressants, benzodiazepines, antiepileptics and buspirone); attention-deficit hyperactivity disorder (ADHD) (amphetamines and atomoxetine); substance use disorders (acamprosate, disulfiram, nalmefene, naltrexone, nicotine and varenicline); antipsychotics (atypical and typical antipsychotics); and multiple psychiatric drugs. Participants with more than one type of psychiatric episode or more than one type of psychiatric drug were categorised as having 'multiple psychiatric episodes' or 'psychiatric polypharmacy' respectively. Participants using tricyclic antidepressants, carbamazepine or duloxetine were not categorised as having a psychiatric disorder when there was a registered episode of neuropathy. Similarly, participants using anti-epileptics were not categorised as having a psychiatric disorder when they had an episode of epilepsy. The complete list of codes (ATC and ICPC-1) used to identify psychiatric drugs and episodes is given in Supplementary Tables 1 and 2, available at https://doi.org/10.1192/bjo.2023.54.

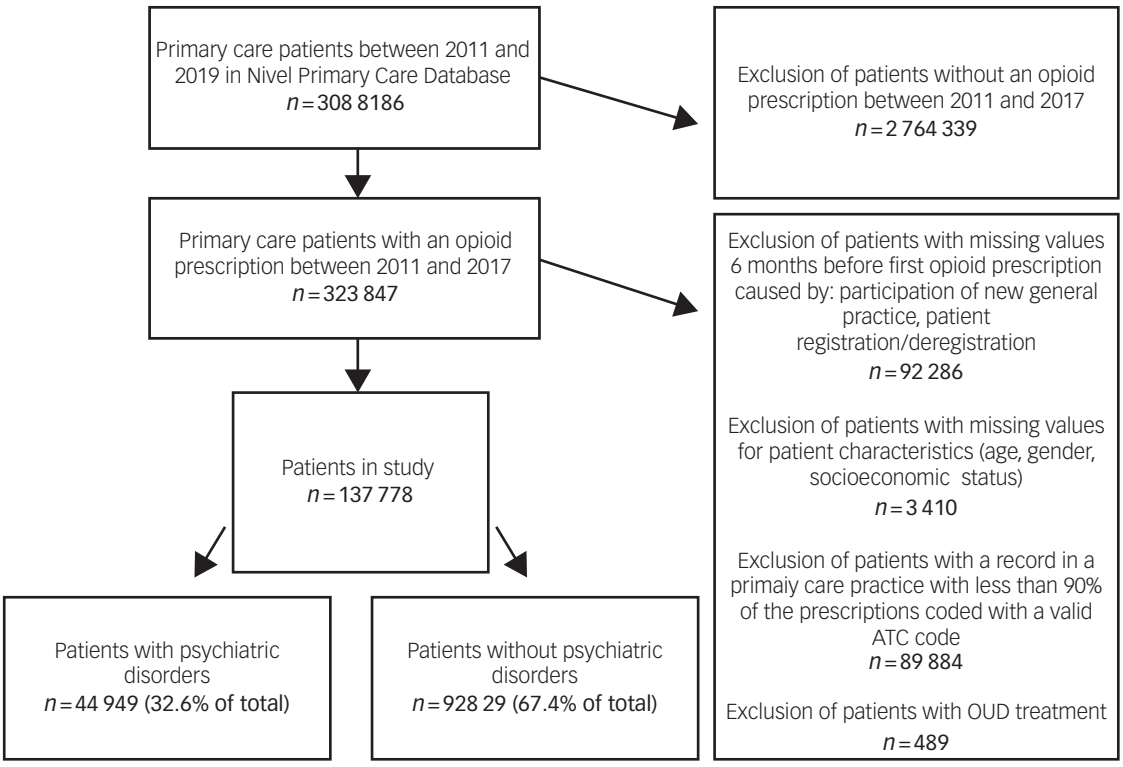

Fig. 1 Flowchart of patients in the Nivel Primary Care Database (2011–2019), excluded and included in this study. OUD, opioid use disorder.

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Chronic high-dose opioid use

Participants were followed for a maximum of 2 years on the development of CHD opioid use (Supplementary Fig. 1 shows examples). Opioids were identified using ATC codes N02A (opioids) and N07BC (drugs used in opioid dependence). CHD opioid use was defined as opioid prescriptions covering ≥90 days with an average daily dose ≥50 mg oral morphine equivalents (OME).[1] The threshold of 50 mg OME was chosen because doses above this threshold carry increased risks for adverse events.[14] The method for identifying CHD opioid use in our data-set is described in the Supplementary Methods.

Covariates

The following confounding factors were considered in the analysis: age, gender, chronic condition (excluding cancer), cancer and median income by postcode. These covariates were corrected for because they might correlate with opioid use and psychiatric disorders.[15] Age was categorised as '0–19', '20–39', '40–59', '60–79' or '80+' years. Chronic condition was defined as having one or more of the following episodes: angina pectoris, heart attack, ischaemic heart disease, heart failure, hypertension, cerebrovascular accident, arthrosis/arthritis, osteoporosis, asthma/chronic obstructive pulmonary disease and diabetes mellitus. Finally, median income by postcode was categorised as 'low–below middle', 'below middle', 'below middle–middle', 'middle', 'middle–upper middle', 'upper middle', 'upper middle–high', in line with Statistics Netherlands publications.[13]

Statistical analysis

Baseline characteristics were calculated at the index date, but were not statistically compared between participants with and without psychiatric disorders as this has no clinical meaning in large samples.[16]

Cox regression models were used to examine the association between psychiatric disorders and subsequent CHD opioid use within 2 years of follow-up, reported as hazard ratios (HRs) with a 95% confidence interval (CI). For each participant, the follow-up time in days was calculated from the index date to (a) fulfilling the definition for CHD opioid use, (b) the end of the 2-year follow-up or (c) loss to follow-up, whichever occurred first. Immortal time bias could not occur because assignment to groups occurred before the follow-up began. The proportional hazards assumption was tested by examination of the Kaplan–Meier and log-minus-log plots, which showed that the proportional hazards assumption holds.

To examine the effect of type of psychiatric disorder on CHD opioid use, Cox regression analyses were performed for psychiatric episodes and psychiatric drugs separately. Participants with only an ICPC-1 code for a personality disorder or a gambling disorder were excluded ($n = 662$) because a distinction between these disorders could not be made as they have the same ICPC-1 code. Furthermore, those with only a record for somatisation and eating disorders were excluded because of the small sample size ($n = 289$) relative to the other groups ($n > 400$).

A P-value of <0.05 was considered statistically significant. All analyses were conducted with R.4.0.2 for Windows. The packages survival, survminer and coxphw were used to perform Cox regression.

Results

Of the 137 778 participants with an opioid prescription, 44 949 (32.6%) had a psychiatric disorder before the first opioid prescription (Table 1, Fig. 1). The average follow-up time was 595 days. Of all participants receiving a new opioid prescription, 2.0% developed CHD opioid use. Of the 44 949 participants with a psychiatric disorder and 92 829 without, 1314 (2.92%) and 1494 (1.61%) respectively developed CHD opioid use (Table 2). Participants with a psychiatric disorder were more likely to be female, older and to have more chronic conditions, cancer and a low income than those without (Table 1). Of the participants receiving an opioid, 95 675 (69%) reached the full follow-up time of 2 years.

A psychiatric disorder was associated with an increased risk of subsequent CHD opioid use (adjusted HR = 1.74, 95% CI 1.62–1.88)

Table 1 Baseline characteristics of 137 778 primary care patients receiving an opioid

Characteristics	Participants with psychiatric disorders ($n = 44\,949$)	Participants without psychiatric disorders ($n = 92\,829$)
Age, years: *n* (%)		
0–19	460 (1.02)	2650 (2.85)
20–39	6148 (13.68)	17 019 (18.33)
40–59	15 130 (33.66)	31 859 (34.32)
60–79	15 515 (34.52)	31 658 (34.10)
80+	7696 (17.12)	9643 (10.39)
Gender, *n* (%)		
Male	16 706 (37.17)	42 013 (45.26)
Female	28 243 (62.83)	50 816 (54.74)
Chronic condition, *n* (%)[a]		
No	15 776 (35.10)	40 730 (43.88)
Yes	29 173 (64.90)	52 099 (56.12)
Cancer, *n* (%)		
No	37 054 (82.44)	81 453 (87.75)
Yes	7895 (17.56)	11 376 (12.25)
Median income by postcode, *n* (%)		
Low–below middle	271 (0.60)	405 (0.44)
Below middle	8808 (19.60)	16 799 (18.10)
Below middle–middle	1020 (2.27)	2052 (2.21)
Middle	25 657 (57.08)	52 011 (56.03)
Middle–upper middle	2882 (6.41)	7026 (7.57)
Upper middle	6177 (13.74)	14 268 (15.37)
Upper middle–high	134 (0.30)	268 (0.29)
Follow-up time, days: mean (median)	559 (730)	612 (730)

a. 'Yes' if one or more of the following comorbidities: angina pectoris, heart attack, ischemic heart disease, heart failure, hypertension, cerebrovascular accident, arthrosis/arthritis, osteoporosis, asthma/chronic obstructive pulmonary disease, diabetes mellitus.

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Table 2 Association between psychiatric disorders (episode and/or psychopharmacotherapy) and chronic high-dose (CHD) opioid use

Psychiatric disorders	*n*	CHD opioid use, *n* (%)	Hazard ratio (95% CI), unadjusted	Hazard ratio (95% CI), adjusted[a]
No	92 829	1494 (1.61)	1 [reference]	1 [reference]
Yes	44 949	1314 (2.92)	1.97 (1.83–2.12)	1.74 (1.62–1.88)
Psychiatric episode[b]				
No psychiatric episode	118 046	2290 (1.94)	1 [reference]	1 [reference]
Mood and/or anxiety disorder	9736	202 (2.07)	1.05 (0.91–1.21)	1.12 (0.97–1.29)
Substance use disorder	3800	122 (3.21)	1.65 (1.37–1.97)	1.65 (1.38–1.98)
Psychotic disorder	463	14 (3.02)	1.66 (0.98–2.81)	2.05 (1.21–3.47)
Neurocognitive disorder	3076	102 (3.32)	2.58 (2.11–3.14)	1.47 (1.20–1.80)
Multiple psychiatric episodes	1706	58 (3.40)	1.90 (1.46–2.47)	1.83 (1.41–2.37)
Psychiatric drug				
No psychiatric drug	100 972	1669 (1.65)	1 [reference]	1 [reference]
Pharmacotherapy for mood and/or anxiety disorder	31 184	981 (3.15)	2.02 (1.87–2.19)	1.71 (1.58–1.85)
Pharmacotherapy for substance use disorder	514	17 (3.31)	2.00 (1.24–3.22)	2.06 (1.28–3.32)
Antipsychotics	1152	25 (2.17)	1.97 (1.33–2.92)	1.64 (1.10–2.43)
Pharmacotherapy for ADHD	460	3 (0.65)	0.39 (0.13–1.21)	0.96 (0.31–2.98)
Psychiatric polypharmacy	3496	113 (3.23)	2.46 (2.04–2.98)	2.49 (2.06–3.02)

ADHD, attention-deficit hyperactivity disorder.
a. Adjusted for gender, age, median income by postcode, chronic condition (angina pectoris, heart attack, ischaemic heart disease, heart failure, hypertension, cerebrovascular accident, arthrosis/arthritis, osteoporosis, asthma/chronic obstructive pulmonary disease, diabetes mellitus), cancer.
b. Excluded: personality disorder and/or a gambling disorder ($n = 662$) and somatisation and/or eating disorders ($n = 289$).

(Table 2). Adjusted analysis per psychiatric episode showed that psychotic disorders were associated with the highest risk of CHD opioid use (adjusted HR = 2.05, 95% CI 1.21–3.47). Substance use disorder (adjusted HR = 1.65, 95% CI 1.38–1.98), neurocognitive disorder (adjusted HR = 1.47, 95% CI 1.20–1.80) and multiple psychiatric episodes (adjusted HR = 1.83, 95% CI 1.41–2.37) also increased the risk of subsequent CHD opioid use (Table 2).

Analysis by type of psychiatric drug showed that pharmacotherapy for mood and anxiety disorders (adjusted HR = 1.71, 95% CI 1.58–1.85), substance use disorders (adjusted HR = 2.06, 95% CI 1.28–3.32), antipsychotics (adjusted HR = 1.64, 95% CI 1.10–2.43) and psychiatric polypharmacy had an increased risk of subsequent CHD opioid use (Table 2). Psychiatric polypharmacy (adjusted HR = 2.49, 95% CI 2.06–3.02) carried the largest risk of developing CHD opioid use. A plot of the adjusted effect sizes of the main analysis and both sub-analyses is shown in Fig. 2.

In addition, two sensitivity analyses were performed to investigate (a) the effect of adding the total OME of the first prescription as a covariate and (b) the effect of excluding serotonin–noradrenaline reuptake inhibitors (SNRIs). The results of these analyses are presented in Supplementary Tables 3 and 4.

Discussion

This study aimed to prospectively investigate the association between psychiatric disorders and the development of chronic high-dose (CHD) opioid use in a representative large general

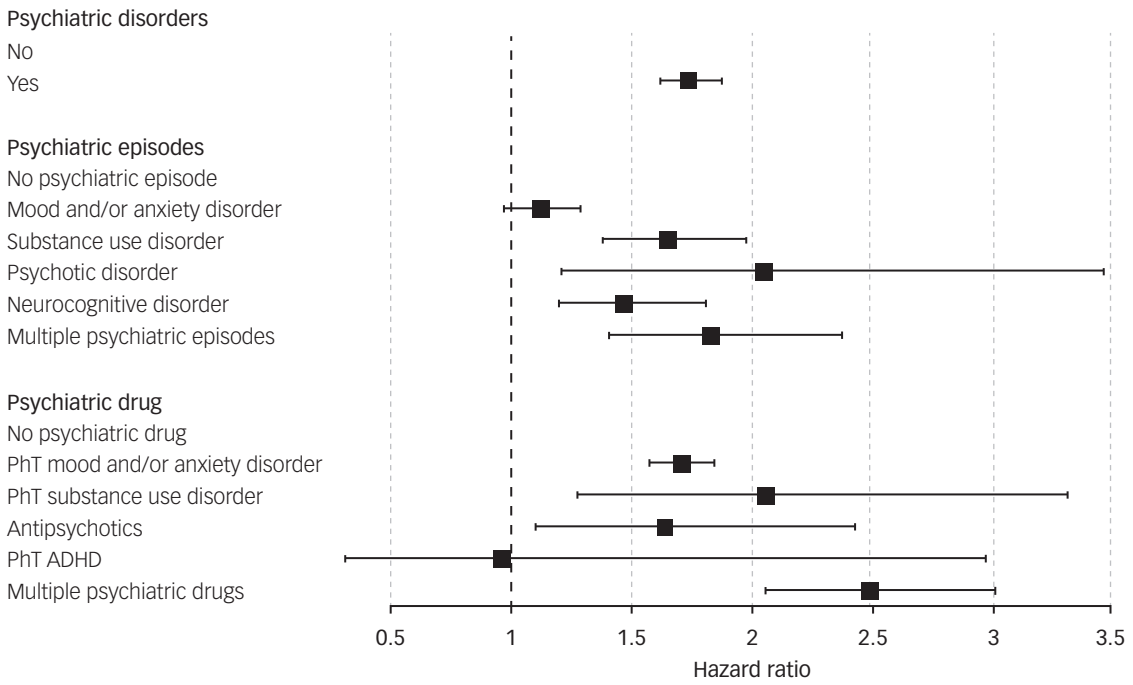

Fig. 2 Association between psychiatric disorders (episode and/or psychopharmacotherapy) and chronic high-dose opioid use: adjusted hazard ratios. PhT, pharmacotherapy; ADHD, attention-deficit hyperactivity disorder.

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population sample ($n = 137\,778$).[17] In this cohort of primary care patients, 2.0% of those newly receiving an opioid prescription developed CHD opioid use during follow-up. Participants with psychiatric disorders were at greater risk of developing CHD opioid use than those without psychiatric disorders. Specifically, psychotic disorders, substance use disorder, neurocognitive disorders and multiple psychiatric episodes increase the risk for CHD opioid use. Similarly, the use of drugs for mood and anxiety disorders, psychosis and substance use disorder, and psychiatric polypharmacy, increased the risk for CHD opioid use. Overall, having a psychotic disorder and receiving psychiatric polypharmacy had the highest adjusted hazard ratios (2.05 and 2.49 respectively).

Our findings align with previous cross-sectional studies indicating an association between opioid misuse and psychiatric disorders.[18,19] Several mechanisms might explain this association. For example, the emotional distress associated with psychiatric disorders might predispose to chronic pain and subsequently prolonged opioid use.[7] Shared neurobiological mechanisms might also play an important role.[20] For instance, serotonin is involved in mood regulation, pain processing and analgesia.[21] Disruption of serotonergic pathways could contribute to psychiatric disorders (e.g. depression) as well as chronic pain.[21] Other shared risk factors for psychiatric disorders and chronic pain are traumatic childhood experiences and poor socioeconomic status.[7,20] Finally, decreased effectiveness of opioids in people with psychopathology might also play a role in the increased risk for CHD prescription opioid use in patients with psychiatric disorders.[7]

In this study, psychiatric polypharmacy showed the strongest association with subsequent CHD opioid use. Using multiple psychiatric drugs might indicate multiple or more severe psychiatric conditions. Therefore the observed highest hazard ratio in multiple psychiatric episodes and psychiatric polypharmacy might hint at a dose–response relationship, further suggesting causality.

Of the specific psychiatric disorders, participants with a psychotic disorder had the highest risk of developing CHD opioid use after an initial opioid prescription. This was confirmed by the medication analyses, which also showed this association for antipsychotic drug use. These findings contrast with previous research showing decreased pain sensitivity in people with a psychotic disorder.[22,23] Furthermore, Owen et al[19] found that people with psychotic disorders are less often diagnosed with chronic pain conditions and less often receive opioids than the general population. A potential explanation for the discrepancies between the results of Owen et al and our data is a difference in study design. Our study examined the risk of CHD use after an initial opioid prescription, whereas Owen et al examined the initiation of opioid treatment. People with psychotic disorders might be less likely to receive an opioid, but once opioid treatment is initiated, they could have an increased risk for CHD use. This is in line with previous research showing an increased risk of overdose in people using antipsychotics and opioids concomitantly.[24]

An increased risk for CHD opioid use in people with psychotic disorders might be related to an increased addiction liability.[25] Indeed, the prevalence of substance use disorders is higher in people with a psychotic disorder than in the general population, in part due to shared genetic liability between the two conditions.[26] In addition, people with a psychotic disorder might continue using opioids to reduce psychotic symptoms.[27] Interestingly, antipsychotics have been shown to have a protective effect against substance use disorders in people with psychotic disorders.[28] This effect could be caused by reducing the rewarding effects of opioids by antipsychotics.[29] Our results show an increased risk of CHD opioid use in participants using antipsychotics, yet with a smaller hazard ratio than for a psychotic episode. However, the number of patients with a psychotic disorder and CHD opioid use in our data-set is limited, which precludes drawing strong conclusions.

In line with existing literature,[5] substance use disorder increased the risk of developing CHD opioid use. Previous research showed that approximately half of the people who use drugs illicitly reported pain as a reason for substance use.[30] Substance use disorder predating CHD opioid use might thus reflect a type of self-medication before initiation of prescription opioids. Alternatively, people with pre-existing substance use disorder liability might also be at increased risk of CHD prescription opioid use or misuse when exposed to prescription opioids.[25,31]

We found an increased risk of CHD opioid use only in participants receiving pharmacological treatment for mood and anxiety disorders and not in those with an episode of a mood and anxiety disorder (irrespective of medication use). This contrasts with existing literature, showing rather consistently that people with mood and anxiety disorders have an increased risk of developing opioid misuse.[5] This association has been explained by overlapping stress-related mechanisms between pain and internalising disorders resulting in lower pain thresholds[5] and by the antidepressant properties of opioids.[32] That we only observed this association for pharmacotherapy for mood and anxiety disorders might be explained by a difference in severity of the disorder. In The Netherlands, pharmacotherapy is mainly considered in people with severe depression or anxiety, whereas milder forms are usually treated with psychological interventions only.[33,34]

Our results also show an increased risk of CHD opioid use after an initial opioid prescription in participants with neurocognitive disorders (i.e. delirium, Parkinson's disease and dementia), although in the literature neurocognitive disorders are often associated with reduced prescription opioid use.[35,36] An inability to clearly express pain due to cognitive impairment might explain undertreatment with opioids.[35] But once opioid treatment is initiated it might also decrease the likelihood of discontinuation to avoid undertreatment.

Strengths and limitations and future research

When interpreting the current results, several strengths and limitations should be considered. A major strength of this study is the use of a large nationwide longitudinal data-set representative of a general population and a prospective study design. However, this study also has several weaknesses.

First, our data showed that 44% of the participants using psychiatric drugs did not have a registered psychiatric episode. Similarly, our sub-analyses showed more participants with prescriptions for psychiatric drugs ($n = 36\,806$) than episodes of psychiatric disorder ($n = 18\,781$). This is most likely caused by missing diagnoses. This might have affected our results, although we mostly overcame this limitation in our main analysis by defining psychiatric disorders using both registered episodes and psychiatric drug use. Second, some benzodiazepines were included as psychiatric drugs for anxiety or mood disorders, although they might be prescribed for mild sleeping problems. As a result, the current study might underestimate the influence of drugs for mood and anxiety disorders on CHD opioid use. Third, although we included registered drug use for ADHD, no reliable ICPC-1 code for ADHD was available. Our analyses on the effects of ADHD medication on subsequent CHD opioid use should therefore be considered explorative. Fourth, this study likely did not identify all participants with substance use disorder or those who use opioids illicitly. The resulting misclassification would probably lead to an underestimation of the overall risk of psychiatric disorders on subsequent CHD opioid prescribing. Fifth, our data do not include information on the reason for opioid prescribing. The risk for transitioning to chronic opioid use may vary per indication for the prescription opioids. For example, it might differ between postoperative and chronic pain.

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Future research should elucidate which patient populations and indications require most attention, and whether this interacts with psychiatric comorbidity. Sixth, our sensitivity analysis showed that the total OME of the first prescription did not affect the effect of psychiatric disorders on the risk of CHD opioid use (Supplementary Table 3). Seventh, SNRIs can also be used to treat fibromyalgia. A sensitivity analysis excluding these drugs did not show substantial effects of SNRIs on the association between antidepressant use and receiving a CHD opioid prescription (Supplementary Table 4). Eighth, social factors such as living alone might influence the risk of transition to CHD opioid use. However, our data-set does not include such information and it could therefore not be used as a covariate. Finally, we could not provide insight into, or adjust for the effect of, non-pharmacological strategies for pain relief. Future studies should explore the potential mitigating effects of such interventions on the risk of developing CHD prescription opioid use in people with psychiatric conditions.

Clinical implications

The association between psychiatric disorders and CHD opioid use underscores the need for an integrated approach in pain management. Strategies to prevent opioid-related harm could include screening for psychiatric comorbidity prior to opioid initiation, psychiatric consultation in case of psychiatric comorbidity and, if indicated, ongoing involvement of a psychologist or psychiatrist to treat the psychiatric condition and prevent the development of chronic or escalating opioid use.[7] Indeed, adequate pain management includes optimal treatment of co-occurring psychiatric conditions and active monitoring.[1,7,37] However, this should not result in undertreatment of pain in people with a psychiatric disorder, and opioids should not be withheld when they are indicated.

Mariëlle M. C. van der Hoorn, Msc, Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands; and Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands; **Gerard A. Kalkman**, Msc, Department of Clinical Pharmacy, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands; and Radboud Institute for Health Sciences, Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands; **Yvette M. Weesie**, Msc, Netherlands Institute for Health Services Research, Nivel, Utrecht, The Netherlands; **Femke Atsma**, PhD, Radboud Institute for Health Sciences, Scientific Center for Quality of Healthcare (IQ Healthcare), Radboud University Medical Center, Nijmegen, The Netherlands; **Arnt Schellekens**, MD, PhD, Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands; Nijmegen Institute for Scientist-Practitioners in Addiction, Radboud University, Nijmegen, The Netherlands; and Donders Institute for Brain Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence: G. A. Kalkman. Email: a.kalkman@cwz.nl

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjo.2023.54.

Data availability

Access to the underlying data in this study can be requested from Nivel Primary Care Database.

Author contributions

M.M.C.H., A.S. and G.A.K. initiated the study. G.A.K. and Y.M.W. collected and prepared the data. M.M.C.H., G.A.K., F.A. and A.S. were responsible for the concept and design of the study and the analyses. All authors were involved in the interpretation of the results. M.M.C.H. and G.A.K. were responsible for the writing of the manuscript and the other authors contributed to revisions of the manuscript. G.A.K., M.M.C.H. and Y.M.W. had full access to all the data in the study. Other authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

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Declaration of interest

None.

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