OPEN ACCESS

University of Dundee

University of Dundee

Comparison of psychiatric comorbidity in treatment-seeking, opioid-dependent patients with versus without chronic pain

Higgins, Cassie; Smith, Blair H.; Matthews, Keith

Published in:
Addiction

DOI:
10.1111/add.14768

Publication date:
2020

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
Higgins, C., Smith, B. H., & Matthews, K. (2020). Comparison of psychiatric comorbidity in treatment-seeking, opioid-dependent patients with versus without chronic pain. *Addiction*, *115*(2), 249-258. https://doi.org/10.1111/add.14768

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 06. Dec. 2023

Higgins Cassie (Orcid ID: 0000-0002-5506-324X)

FULL TITLE: Comparison of psychiatric co-morbidity in treatment-seeking, opioid dependent patients with versus without chronic pain

RUNNING TITLE: Psychiatric morbidity in OAT patients with pain

AUTHORS: Cassie Higgins[a], Blair H Smith[b], Keith Matthews[a]

[a] Division of Neuroscience, University of Dundee, Mailbox 6, Level 6, Laboratories Block, Ninewells Hospital and Medical School, Dundee, DD1 9SY. Tel: +44 (0)1382 383025.

[b] Division of Population Health Sciences, University of Dundee, Mackenzie Building, Kirsty Semple Way, Ninewells Hospital and Medical School, Dundee, DD2 4RB. Tel: +44 (0)1382 383728.

Corresponding author: Cassie Higgins

Cassie Higgins, PhD. ORCID: 0000-0002-5506-324X Email: c.z.higgins@dundee.ac.uk

Blair H Smith, PhD. ORCID: 0000-0002-5362-9430. Email: b.h.smith@dundee.ac.uk

Keith Matthews, PhD. ORCID: 0000-0002-4478-5888. Email: k.matthews@dundee.ac.uk

KEYWORDS: None.

WORD COUNT: 3694

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/add.14768

This article is protected by copyright. All rights reserved.

Accepted Article

CONFLICTS OF INTEREST: Professor Blair H Smith has received funding from Pfizer, on behalf of his institution, for research into the genetics of pain. He is National Lead Clinician for Chronic Pain (Scottish Government). Professor Keith Matthews has chaired advisory boards for studies of Deep Brain Stimulation for Obsessive-Compulsive Disorder sponsored by Medtronic. He has received educational grants from Cyberonics Inc. & Schering Plough, and has received research project funding from Merck Serono, Lundbeck, Reckitt Benckiser, St Jude Medical and Indivior. He has received travel and accommodation support from Medtronic and St Jude Medical to attend scientific meetings. Cassie Higgins was in receipt of funding from TENOVUS Scotland, within the past 36 months, for research into the impact of prescribing on opioid-related mortality.

Accepted Article

This article is protected by copyright. All rights reserved.

Abstract

Aim: To compare psychiatric morbidity in treatment-seeking, opioid-dependent patients with versus without chronic pain.

Design: A retrospective comparative cohort design was used involving record linkage from routinely-collected, nationally-held datasets. Data were managed within a Scottish Government-certified *Safe Haven*.

Setting and participants: Participants comprised all patients of an NHS Substance Misuse Service in the East of Scotland (N=521) who were in treatment during the calendar year 2005 and had been in treatment for varying lengths of time. Their mean age at study inception was 35.0 years in the chronic pain group and 32.1 years; 32.2% of the chronic pain group and 26.4% of the no pain group were female.

Measurements: The outcomes were a) psychiatric co-morbidity assessed at study inception using the 28-item General Health Questionnaire and the Clinical Outcomes in Routine Evaluation – Outcome Measure, and b) receipt of at least one prescription for a psychiatric condition over a 5-year period following study inception. The independent variable was chronic pain measured at study inception using the Brief Pain Inventory – Short Form.

Findings: 246 (52.7%) reported chronic pain and 221 (47.3%) did not. A higher proportion of patients with chronic pain had at least one psychiatric morbidity (62.4% versus 46.3%, $p<0.001$). At the study inception a higher proportion of patients with chronic pan were prescribed anxiolytics (49.0% versus 39.1%, $p=0.015$) and antimanic drugs (9.9% compared with 4.9%, $p=0.015$).

Conclusions: Patients of opioid treatment services in Scotland who report chronic pain may have a higher prevalence of psychiatric co-morbidity than those who do not.

Accepted Article

This article is protected by copyright. All rights reserved.

Introduction

It is estimated that pain affects up to 80% of opioid-dependent people treated with opioid agonist therapy (OAT)[1], and severe chronic pain is reported in up to 61%[2]. The prevalence of psychiatric morbidity is substantial in patients treated in OAT (76%) and, in particular, depressive disorders and anxiety disorders[3]. Furthermore, the presence of psychiatric morbidity and moderate to severe chronic pain can indicate an increased risk of opioid dependence in patients exposed to chronic opioid analgesic therapy[4,5,6,7]. Additional comorbidities can often complicate treatment, including the delivery of psychotropic medication and effective analgesia[8].

A small number of studies have examined psychiatric morbidity in treatment-seeking, opioid-dependent patients with and without chronic pain. They found that the presence of chronic pain was associated with a higher prevalence of depressive disorders[9], anxiety disorders[10] or both[11]. Barry and colleagues[12] examined a range of psychiatric morbidities in 150 methadone-maintained patients, divided into three groups: chronic severe pain (CSP) lasting at least 6 months; some pain (SP) in the past week; and no pain (NP). They found that, compared with the NP group, both the CSP and the SP groups demonstrated a significantly higher prevalence of depression, somatization and anxiety, along with significantly higher Global Severity Index (GSI) scores. Furthermore, the CSP group was found to have a significantly higher prevalence of somatization and significantly higher GSI scores than the SP group.

Patients with chronic pain and coexisting opioid dependence disorders present with complex illnesses that are difficult to treat together effectively. Psychiatric morbidity is prevalent in both of these conditions and further compounds the complexities impacting on treatment. The development of effective treatment strategies for patients with chronic pain and coexisting

This article is protected by copyright. All rights reserved.

Accepted Article

opioid dependence is dependent upon also understanding the prevalence and pattern of psychiatric morbidity in this clinical population.

Aims and objectives

Based on the findings of the previous studies noted above, our main hypothesis was that OAT patients with chronic pain, compared with those with no pain, would have a higher prevalence of psychiatric morbidity. We also hypothesised that there would be group differences concerning psychotropic prescribing; however, the direction of these differences could not be anticipated by prior evidence.

The aim of the present study was therefore to compare psychiatric morbidity (and, specifically, depressive disorders, anxiety disorders and bipolar disorder) in treatment-seeking, opioid-dependent patients with and without chronic pain who were attending a substance misuse service in the East of Scotland. The specific study objectives were:

1) To compare sociodemographic characteristics by group (i.e. those with chronic pain versus those with no pain);
2) To compare the proportion of each group meeting clinical thresholds for general psychiatric morbidity (using both the GHQ-28 and CORE-OM), and to compare subscale scores derived from both instruments at study inception;
3) To examine rates of psychotropic drug prescribing (antidepressants, anxiolytics and antimanics) at study inception and during the 5-year follow-up period, and to compare these between groups.

Accepted Article

This article is protected by copyright. All rights reserved.

Our rationale was to either substantiate, or challenge the currently limited evidence base in this area of study, thereby improving our understanding of the cluster of opioid dependence, chronic pain and general psychiatric morbidity.

Previous work

In a recent publication[13], by the authors of the present study, illicit drug use was described in these two groups, using the same clinical population. This previous study reported that, compared with those with no pain, a significantly higher proportion of those with chronic pain were engaged in abuse of benzodiazepines and cannabinoids, both at study inception and during the 5-year follow-up period.

Methods

Design

The present cohort study employed the use of a health informatics approach to link and interrogate routinely-collected data held by the Scottish Government. This was considered the most cost-effective means of responding to the research aim of the present study. The study inception data were collected during the calendar year 2005, and 5-year follow-up data spanned 2005-2010. The protocol was developed in 2016 and took advantage of a service audit that had been undertaken during the calendar year 2005, as detailed above. The present study also took advantage of the historical nature of the Scottish-Government health datasets, to ensure that an accurate 5-year observation period was included for each participant.

These data are now several years old; however, the relevance of the findings is likely to apply in many current contexts. The increase in opioid analgesic prescribing, generally considered to have contributed to the 'opioid crisis' was witnessed in the UK[14]; however, the

This article is protected by copyright. All rights reserved.

Accepted Article

corresponding rise in drug-related death, which began to emerge in the US around 2009, was not witnessed in the UK[15]. Whilst there is a literature suggesting cautionary lessons, which could be extrapolated from US data, the 'opioid crisis' has had little impact on prescribing practices in the UK to date, and current papers continue to call for policy changes aimed at reducing high-dose prescribing practices[14].

Participants

Participants comprised all methadone-maintained patients attending a National Health Service (NHS) substance misuse service in the East of Scotland, UK. Overall, relative to Scotland, this Health Board is generally characterized by high socioeconomic deprivation and relatively poor health. The Scottish Office for National Statistics (ONS) has reported this as a consistent finding for the past several decades. All participants were clinically-diagnosed as being dependent upon opioids – primarily heroin – on entry to treatment, and many were also engaged in polysubstance abuse. A case-control design was employed: cases were treatment-seeking, opioid-dependent patients with comorbid chronic pain and controls were treatment-seeking, opioid-dependent patients with no pain. In previous studies, three temporal thresholds have been established to identify chronic pain: 3 months; 6 months; and 12 months[16]. In the present study the chronicity threshold was set at 12 months; the rationale for employing this threshold was that, in a clinical population familiar with persistent, debilitating conditions, the highest conventional threshold was considered to facilitate the best comparison between truly 'chronic' pain and no pain. Patients reporting pain that had been present for less than 12 months were excluded, since these patients may not have formed a sufficiently-homogenous group to justify inclusion in the present study.

Accepted Article

This article is protected by copyright. All rights reserved.

Materials

A service-modified version of the 9-item Brief Pain Inventory – Short Form (BPI-SF)[17] was designed to assess the sensory and reactive dimensions of pain. The BPI-SF has been validated in a number of clinical populations, including patients in receipt of methadone maintenance therapy for the treatment of opioid dependence[18].

The 28-item version of the General Health Questionnaire (GHQ-28)[19] was designed as a screening tool to indicate psychiatric diagnostic status. The GHQ scoring method was used and a threshold of23/24 was applied to indicate clinical status. It has been shown to have the ability to accurately detect diagnoses in accordance with the Composite International Diagnostic Interview (CIDI)[20]. The reliability and validity of the GHQ-28 is well-documented in numerous clinical populations[12-25]. Whilst acceptable levels of reliability and validity have been demonstrated for the GHQ-60 in substance misusers[26], the psychometric properties of the GHQ-28 have not yet been assessed in opioid-dependent clinical populations.

The 34-item Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM)[27] assesses the level of current psychological global distress. A threshold of ≥34 was used to indicate clinical status[28]. It has been validated in samples from the general population and in clinical samples[27,29]. Its validity is yet to be assessed in opioid-dependent populations, and the CORE-OM is yet to be compared with 'gold standard' diagnostic instruments, such as the Composite International Diagnostic Interview (CIDI); however, it is shown to have a strong positive correlation (0.75) with the GHQ[30].

An electronic regional extract of the nationally-held prescribing data was obtained from the Prescribing Information System (PIS), National Services Scotland (NSS). These data include

This article is protected by copyright. All rights reserved.

Accepted Article

a record of every prescription dispensed. Within this dataset exists a field documenting the clinical indication for which the medication was prescribed, recorded as British National Formulary (BNF) sub-section codes. Prescribing data relating to individuals are identified by a person-specific unique code, the Community Health Index (CHI) number, which is held by every individual registered with the NHS in Scotland. The CHI number is also included in every record of every NHS transaction, and can be used for linkage of data between services.

Procedure

The study was incepted on 1 January 2005, and the BPI-SF, GHQ-28 and CORE-OM were completed at routine weekly clinic appointments, with specialist addiction nurses, for each participant at an arbitrary point during that calendar year. Time spent in treatment prior to study inception was unknown for study participants. Five-year follow-up prescribing data were obtained spanning 01/01/05-12/12/10. The BNF codes used to identify anxiety disorders, depression and bipolar disorder were: '4.1.2 Anxiolytics'; '4.3 Antidepressant drugs'; and '4.2.3 Drugs for mania and hypomania'. It should be noted that the patient population in receipt of drugs for mania and hypomania is likely to be relatively heterogeneous since these medications includes anticonvulsants, lithium and antipsychotic medication. Without extreme rigour in this process, misclassification could result in a spuriously higher prevalence of bipolar disorder. [BNF can be accessed at http://gmmmg.nhs.uk/html/formulary_bnf_chapters.html] Prescribing was used as a proxy indicator of clinically-significant psychiatric morbidity; however, it should be noted that this does not include patients with psychiatric morbidity being treated solely with non-pharmaceutical interventions. Participants were excluded from the study if no BPI-SF was completed or if duration of pain at study inception was not recorded, since it was not possible to determine if their pain was 'chronic'.

This article is protected by copyright. All rights reserved.

Data from study inception were transferred to the Health Informatics Centre (HIC) Services, one of the Scottish government-certified electronic *Safe Havens*, based at the University of Dundee. These data were then linked within a secure virtual environment, using the CHI numbers, and anonymized prior to release to the research team for analysis via a secure web link.

Terminology

The term, 'psychiatric morbidity' is used throughout the present manuscript, for consistency and clarity; however, it should be noted that the GHQ-28 and CORE-OM subscales are not designed to assess clinical status concerning specific psychiatric morbidities, but rather to assess overall symptom severity.

Statistical considerations

The Statistical Package for Social Scientists (SPSS v22) was used to undertake statistical testing. Chi square testing was used in all examinations of group associations where both the dependent and independent variables were categorical (i.e. nominal). This included analyses by: gender; deprivation status; presence of psychiatric morbidity; and receipt of prescription drugs. Comparison of the proportions of each group in receipt of prescribed medication at study inception and 5-year follow-up was also undertaken using Chi square testing since repeated measures analyses of these binary outcomes for individuals (in receipt or not in receipt of medication) was not regarded as clinically meaningful. Descriptive summary data are presented as number of events (n) and percentage of group (%), and the p-value is reported.

Accepted Article

This article is protected by copyright. All rights reserved.

Univariate analysis of variance (ANOVA) was used in all examinations of group differences where the dependent variables were continuous and the independent variables were categorical (i.e. nominal). This included analyses by age, GHQ-28 subscales and CORE-OM subscales. Descriptive summary data are presented as mean value ($\bar{x}$) and standard deviation around the mean (σ), and the p-value is reported.

Repeated measures ANOVA was used to assess group changes over time in the mean number of prescriptions dispensed each year during the observation period. Repeated measures ANOVA statistics are reported in the same way as univariate ANOVA findings. In addition, the repeated measures ANOVA computes: main effect of group (overall group differences during the entire observation period); main effect of time (changes over time in the entire treatment population irrespective of group); and the interaction effect (between group and time). Sphericity exists in ANOVA testing when the variance of the difference between all possible pairs of within-subject conditions are equal. The violation of sphericity results in an increase in the Type I error rate (i.e. false positive results). The Mauchley Sphericity Test was used to identify violations of sphericity and, where present, to identify the appropriate method of adjustment. A Bonferroni correction was applied in the repeated measures ANOVA procedure to compensate for multiple comparisons. As a result of the small number of participants available for repeated measures analyses (i.e. the number prescribed medication during each of the 5 years in the observation period), participants were included in the graphs on the right side of each figure if they received relevant prescribed medication at any point during the observation period.

Accepted Article

This article is protected by copyright. All rights reserved.

Ethical approval

Ethical approval was not required for the present study, since all data were anonymized and accessed via a national *Safe Haven*; however, a favorable ethical opinion was obtained from the East of Scotland Research Ethics Committee (EoSREC).

Results

The study sample after exclusions was demographically similar to the cohort before exclusions[13], and the reasons for exclusion are also reported in this previous manuscript. ***Table 1*** shows the sociodemographic characteristics of the chronic pain (CP) group and the no pain (NoP) group.

Indications of psychiatric morbidity in patients with and without chronic pain at study inception (assessed using the GHQ-28 and the CORE-OM)

The proportion of each group meeting clinical thresholds, and the subscale scores on the GHQ-28 and the CORE-OM are shown in ***Table 2***.

Table 2 shows that a significantly higher proportion of people in the CP group were identified as having psychiatric morbidity compared with the NoP group, using both the GHQ-28 and the CORE-OM assessment instruments. It further shows that the CP group had significantly higher mean scores on all of the GHQ-28 and CORE-OM subscales.

Prescribing characteristics indicative of clinically-significant psychiatric morbidity during the 5-year follow-up period

Figures 1 to 3 show the proportion of participants in receipt of the psychotropic medication at any point during each of the years during the observation period (on the left of each figure) and

This article is protected by copyright. All rights reserved.

Accepted Article

the mean number of prescriptions dispensed during each of these years (on the right of each figure). The statistics from the repeated measures ANOVA are shown in ***Table 3***.

Figure 1 shows that a significantly higher proportion of the CP group was prescribed anxiolytics at inception ($\chi^2(1)=5.090$; $p=0.015$; $\omega=0.104$); however, there was no group difference at 5-year follow-up. ***Table 3*** shows that the CP group was in receipt of a higher overall mean number of anxiolytic prescriptions per person during the observation period. There was a main effect of time, whereby the mean number of prescriptions decreased over time, and pairwise comparison determined a significant difference between 2005 and 2007 (-1.93; $p=0.001$), between 2005 and 2008 (-1.88; $p=0.002$), between 2005 and 2009 (-2.20; $p<0.001$) and between 2005 and 2010 (-2.37; $p<0.001$). There were no other differences on pairwise comparison.

Figure 2 shows that the proportion of each group in receipt of prescribed antidepressant drugs was relatively similar; there was no significant group difference at study inception or at 5-year follow-up. ***Table 3*** shows no overall effect of group or time. There was a significant interaction effect between group and time. Whilst the mean number of prescriptions remained relatively consistent over time in the CP group (4.99 mean prescriptions per person in 2005 and 5.14 mean prescriptions per person in 2010), there was a steady increase in the number within the NoP group (ranging from 2.99 in 2005 to 4.87 in 2010).

Figure 3 shows that a significantly higher proportion of the CP group was in receipt of prescribed antimanic drugs at study inception ($\chi^2(1)=5.337$; $p=0.015$; $\omega=0.107$); however, there was no significant group difference at 5-year follow-up. ***Table 3*** shows that there was a significant main effect of time. Pairwise comparison revealed a significant difference between

This article is protected by copyright. All rights reserved.

Accepted Article

2005 and 2009 (+3.26; p=0.002) and between 2005 and 2010 (+4.13; p<0.001). There was no significant interaction effect between group and time.

Discussion

This study aimed to compare psychiatric morbidity (and, specifically, depressive disorders, anxiety disorders and bipolar disorder) in treatment-seeking, opioid-dependent patients with and without chronic pain. At study inception, based on the GHQ-28 and the CORE-OM, a significantly higher proportion of the chronic pain group reported higher anxiety- and mood-related symptom severity, poorer overall wellbeing and life functioning, and increased risk of harm. During the observation period, a significantly higher proportion of the chronic pain group was in receipt of prescribed medication for the treatment of anxiety disorders and bipolar disorder but, despite a higher proportion reporting mood-related symptoms, there was no significant group difference in prescription drugs used to treat depressive disorders.

Higher prevalence of depressive symptoms in the chronic pain group is consistent with the findings of other studies[9,11,12,31]. Jamison and colleagues[2] reported that antidepressant medication was prescribed to 28% of the chronic pain group compared with 15% of methadone-maintained patients with no pain. These figures are lower than the findings of the present study, where substantially more than a third of each group was prescribed antidepressant medication at any point during the observation period. The disparity in findings between the studies may reflect ease of access to treatment in these two populations. Jamison and colleagues undertook their study in a US population and indicated that almost three quarters of their study cohort were in receipt of financial aid (and, presumably, eligible for Medicaid/Medicare), whereas, the present cohort utilized NHS treatment resources in the UK. Prior authorization and financial reimbursement requirements associated with US

This article is protected by copyright. All rights reserved.

Accepted Article

governmental health insurance may mean that access to specific treatments is limited compared with NHS treatment access in the UK. The higher prevalence of depressive symptoms in those with chronic pain and the absence of group differences concerning receipt of prescription drugs for the treatment of depression may reflect unrecognized psychiatric morbidity, particularly in the chronic pain group and, again, highlights the importance of psychiatric assessment in clinical populations at risk of psychiatric morbidity.

The relatively high prevalence of treatment for bipolar disorder in the chronic pain group may reflect the more 'chaotic' symptoms associated with this condition[32]. Bipolar disorder and chronic pain are common comorbidities[33,34,35], and substance dependence in patients with bipolar disorder is associated with a desire to manage the emotional and behavioral extremes that characterize this disorder[36]. Faced with pre-exisitng substance misuse, clinicians are likely to find pain management difficult to achieve due to the risk of exacerbating substance misuse problems. Effective treatment of this dynamic comorbidity cluster necessitates collaborative approaches between addiction psychiatrists, general psychiatrists and pain specialists.

The significantly higher prevalence of anxiety-related symptoms in the chronic pain group is consistent with the findings of other studies[9,11,12,31]. Given the high prevalence of anxiety-related symptoms in the present cohort (based on the GHQ-28 and the CORE-OM) – particularly in the chronic pain group – and the relatively small proportion in receipt of anxiolytic treatment, this may indicate undertreatment of anxiety in both groups. This may reflect a patient reluctance to seek help for psychological distress. Indeed, it has been suggested that patients with chronic pain often minimize their psychological distress, fearing that their pain symptoms may be dismissed as mental disorders[37]. It is not only patients with pain who minimize the role of psychological distress, however, but also clinicians and policymakers who

This article is protected by copyright. All rights reserved.

Accepted Article

oppose opioid use for chronic pain management on the basis of individual harms such as dependence or abuse.

Potential undertreatment of anxiety may be associated with the substantial illicit benzodiazepine use reported previously in both groups[13]. Persistent and debilitating pain can exacerbate ongoing anxiety or can induce pain-related anxiety or pain catastrophisation[38]. This is a dynamic relationship which can, eventually, exacerbate both pain and anxiety in patients[39]. There was, however, a reduction in the proportion of each group treated with anxiolytics during the follow-up period, but particularly in the chronic pain group. These reductions may be driven by concern for patients since benzodiazepines are known to enhance the euphoric effect of opioids and may potentiate substance misuse[40]; and inhibition of cytochrome P450 can lead to decreased clearance of these drugs, thereby increasing risk of overdose, respiratory depression and accidental death[40,41]. This renders general psychiatric intervention of key importance in ensuring that benzodiazepine requirements are recognized, and consumption is controlled and monitored.

The finding that psychiatric morbidity is more prevalent – rather than less prevalent – in those with chronic pain, is important in understanding the patient pathways into substance use disorders. Effective pain management could reduce the prevalence of psychiatric morbidity in this dynamic morbidity cluster and could potentially result a reduction in substance misuse in these patients.

Limitations

A key limitation of this study is that psychiatric assessment instruments were used at study inception only. Whilst psychiatric morbidity is generally chronic, this may have resulted in a

This article is protected by copyright. All rights reserved.

Accepted Article

degree of misclassification during the observation period, since some patients may have developed psychiatric morbidity and, indeed, some may have recovered. It should be noted that, when comparing psychiatric assessments (which were undertaken at study inception only) with psychiatric prescribing, any evidence of undertreatment may be a result of recovery. Furthermore, it should be noted that the GHQ-28 and CORE-OM were not designed to be used as diagnostic instruments; however, the GHQ-28 is shown to to have the ability to accurately detect diagnoses in accordance with the CIDI[20].

A further limitation is the use of prescribed medication to indicate psychiatric morbidity; however, it is likely to indicate relatively severe and chronic psychopathology. This may also have resulted in a degree of misclassification since this would not have included those that were treated solely using non-pharmacological interventions.

Additionally, the process of assigning BNF codes in the prescribing dataset has not undergone psychometric assessment. This particular technique for identifying clinical diagnoses could be strengthened by validation of the BNF code selection process used in that particular data field.

Finally, the present study was unable to consider the role of patient pathways to substance abuse, and this may be an important consideration when examining differences between patients with chronic pain and with no pain. There is a need of further work in this area, identifying initial exposure (prescription opioids or 'street' opioids) and examining the impact that this route of exposure has on treatment outcomes.

Accepted Article

This article is protected by copyright. All rights reserved.

Conclusions

There is a high prevalence of psychiatric morbidity – specifically mood- and anxiety-related disorders – in opioid-dependent patients, particularly those with chronic pain; however, not all patients who exhibit psychiatric morbidity are treated with medication. General psychiatric intervention, in collaboration with addiction psychiatrists, may assume a pivotal role in addressing the complex and challenging health problems in these clinical populations.

Details of authors' contributions

Conception and design was undertaken by all three authors (CH, BHS, KM). Data acquisition and analysis were undertaken by CH. All three authors (CH, BHS, KM) contributed to interpretation of data, critical evaluation of intellectual content and final approval of the published version.

Acknowlegements and funding

Whilst the present study received no funding, the data used in its preparation were obtained from a previously-conducted study. The funding for that study was obtained from Scottish Government monies that had been ring-fenced for the improvement of substance misuse services, directed by the regional Alcohol and Drug Partnerships (ADPs).

Accepted Article

This article is protected by copyright. All rights reserved.

References

[1] Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK (2003) Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA*, 289(18):2370-8.

[2] Jamison RN, Kauffman J, Katz NP (2000) Characteristics of Methadone Maintenance Patients with Chronic Pain. *J Pain Symptom Manage*, 19(1):53-62.

[3] Callaly T, Trauer T, Munro L, Whelan G (2001) Prevalence of psychiatric disorder in a methadone maintenance population. *Aust N Z J Psychiatry*, 35(5):601-5.

[4] Sehgal N, Manchikanti L, Smith HS (2012). Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician*, 15(3 Suppl):ES67-92.

[5] Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD (2010) Risk for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP Study. *Drug Alcohol Depend*, 112(1-2):90-98.

[6] Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN (2007) Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *The Clin J Pain*, 23(4):307-315.

[7] Schieffer BM, Pham Q, Labus J, Baria A, Van Vort W, Davis P *et al.* (2005) Pain medication beliefs and medication misuse in chronic pain. *J Pain*, 6(9):620-629.

This article is protected by copyright. All rights reserved.

Accepted Article

[8] Gureje O (2008) Comorbidity of pain and anxiety disorders. *Curr Psychiatry Rep*, 10(4):318-322.

[9] Dhingra L, Masson C, Perlman DC, Seewald RM, Katz J, McKnight C *et al.* (2013) Epidemiology of pain among outpatients in methadone maintenance treatment programs. *Drug Alcohol Depend*, 128:161-165.

[10] Morasco BJ, Gritzner S, Lewis L, Oldham R, Turk DC, Dobscha SK (2011) Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain*, 152(3):488-497.

[11] Trafton JA, Oliva EM, Horst DA, Minkel JD, Humphreys K (2004) Treatment needs associated with pain in substance use disorder patients: implications for concurrent treatment. *Drug Alcohol Depend*, 73(1):23–31.

[12] Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS (2009) Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. *J Clin Psychiatry*, 70(9):1213-1218.

[13] Higgins C, Smith BH, Matthews K (2018) Substance misuse in patients who have comorbid chronic pain in a clinical population receiving methadone maintenance therapy for the treatment of opioid dependence. *Drug Alcohol Depend*, 193:131-136.

Accepted Article

This article is protected by copyright. All rights reserved.

[14] Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B (2019) Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *Lancet Psychiatry*, 6(2):140-150, February 01, 2019

[15] Weisberg DF, Becker WC, Fiellin DA, Stannard C (2014) Prescription opioid misuse in the United States and the United Kingdom: Cautionary lessons. *Int J Drug Policy*, 25(6):1124-30.

[16] Smith BH, Torrance N. "Epidemiology of Chronic Pain", in McQuay HJ, Kalso E, Moore RA (eds): Systematic Reviews in Pain Research: Methodology Refined. Seattle: IASP Press 2008, pp247 – 273.

[17] Cleeland CS, Ryan KM (1994) Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*, 23(2):129-138.

[18] Dennis BD, Roshanov PS, Bawor M, Paul J, Varenbut M, Daiter J *et al.* (2016) Usefulness of the Brief Pain Inventory in Patients with Opioid Addiction Receiving Methadone Maintenance Treatment. *Pain Physician*. 19:E181-E195.

[19] Goldberg DP, Hillier VF (1979) A scaled version of the General health Questionnaire. *Psychol Med*, 9:139-145.

[20] Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O *et al.* (1997) The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med*, 27:191-197.

This article is protected by copyright. All rights reserved.

Accepted Article

[21] Failde I, Ramos I, Fernandez-Palacín F (2000) Comparison between the GHQ-28 and SF-36 (MH 1-5) for the Assessment of Mental Health in Patients with Ischaemic Heart Disease. *European Journal of Epidemiology*, 16:311-316.

[22] Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, Rutter C (1997) The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med*, 27:191-197.

[23] Robinson R, Price T (1982) Post-stroke depressive disorders: a follow-up study of 103 patients. *Stroke*, 13(5):635-641.

[24] Sakakibara BM, Miller WC, Orenczuk SG, Wolfe DL (2009) A systematic review of depression and anxiety measures used with individuals with spinal cord injury. *Spinal Cord*, 47(12):841-851.

[25] Wernecke U, Goldberg DP, Yalcin I, Ustun TB, (2000) The stability of the factor structure of the General Health Questionnaire. *Psychol Med*, 30:823-829.

[26] Ross HE, and Glaser FB (1989) Psychiatric screening of alcohol and drug patients: The validity of the GHQ-60. *American Journal of Drug and Alcohol Abuse*, 15:429-442.

[27] Evans C, Mellor-Clark J, Margison F, Barkham M, Audin K, Connell J *et al.* (2000) CORE: Clinical Outcomes in Routine Evaluation. *J Ment Health*, 9(3):247-255.

Accepted Article

This article is protected by copyright. All rights reserved.

[28] Barkham M, Mellor-Clark J, Connell J, Cahill J (2006) A core approach to practice-based evidence: A brief history of the origins and applications of the CORE-OM and CORE System. *Couns Psychother Res*, 6:3-15.

[29] Skre I, Friborg O, Elgarøy S, Evans C, Myklebust LH, Lillevoll K *et al.* (2013) The factor structure and psychometric properties of the Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM) in Norwegian clinical and non-clinical samples. *BMC Psychiatry*, 13:99-112.

[30] Evans C, Connell J, Barkham M, Margison F, McGrath G, Mellor-Clark J, Audin K (2002) Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM. *Br J Psychiatry*, 180:51-60.

[31] Stevenson E, Cole J (2015) Associations between chronic non-cancer pain and medication assisted treatment outcomes for opiate addiction. *Am J Addict*, 24(2):138-143.

[32] Anderson IM, Haddad P, Scott J (2012) Bipolar disorder. *BMJ*, 345:e8508.

[33] Stubbs B, Eggermont L, Mitchell AJ, De Hert M, Correll CU, Soundy A *et al.* (2015) The prevalence of pain in bipolar disorder: a systematic review and large-scale meta-analysis. *Acta Psychiatr Scand*, 131(2):75-88.

[34] Birgenheir DG, Ilgen MA, Bohnert AS, Abraham KM, Bowersox NW, Austin K *et al.* (2013) Pain conditions among veterans with schizophrenia or bipolar disorder. *Gen Hosp Psychiatry*, 35(5):480-484.

This article is protected by copyright. All rights reserved.

Accepted Article

[35] Vornik LA, Hirschfeld RM (2005) Bipolar disorder: quality of life and the impact of atypical antipsychotics. *Am J Manag Care*, 11(9 Suppl):S275-80.

[36] Bizzarri JV, Rucci P, Sbrana A, Miniati M, Raimondi F, Ravani L *et al.* (2009) Substance use in severe mental illness: self-medication and vulnerability factors. *Psychiatry Res*, 165:88-95.

[37] Cheatle MD, Gallagher RM (2006) Chronic Pain and Comorbid Mood and Substance Use Disorders: A Biopsychosocial Treatment Approach. *Curr Psychiatry Rep*, 371-376.

[38] Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N *et al.* (2013) Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *Gen Hosp Psychiatry*, 35(4):359-65.

[39] Arola HM, Nicholls E, Mallen C, Thomas E (2010) Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: Can a temporal relationship be determined? *Eur J Pain*, 14(9):966-971.

[40] Gudin JA, Mogali S, Jones JD, Comer SD (2013) Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med*, 125(4):115-30.

[41] Jones JD, Mogali S, Comer SD (2012) Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend*, 125(1-2):8-18.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 1: *Group comparison of sociodemographic characteristics at study inception.*

	N	**%**	**N**	**%**	
Male	155	68	148	74	0.120
Socioeconomic deprivation †					0.087
SIMD Quintile 1	163	68	124	58	
SIMD Quintile 2	59	24	60	28	
SIMD Quintile 3	13	5	18	8	
SIMD Quintile 2	2	1	8	4	
SIMD Quintile 5	5	2	4	2	
Geographical area					0.396
Angus	49	22	54	27	
Dundee	171	75	139	69	
Perth & Kinross	8	3	8	4	
Urban-rurality					0.460
Large urban areas	176	73	147	69	
Other urban areas	46	19	49	23	
Accessible small towns	9	4	13	6	
Remote small towns	1	1	0	0	
Accessible rural	7	3	4	2	
Remote rural					

Accepted Article

This article is protected by copyright. All rights reserved.

	CP		NoP		p-value
	$\bar{x}$	σ	$\bar{x}$	σ	
Age (years)	34.97	7.49	32.10	7.86	<0.001

[†] The Scottish Index of Multiple deprivation was used in assessing socioeconomic deprivation, whereby, quintile 1 represents the greatest deprivation and quintile 5 represents the greatest affluence.

Accepted Article

This article is protected by copyright. All rights reserved.

***Table 2**: Indicators of psychiatric morbidity at study inception: clinical thresholds and subscale scores on the GHQ-28 and the CORE-OM*

	CP		**NoP**		**p-value**
	N	**%**	**N**	**%**	
Above 'clinical' threshold [GHQ-28]	126	62	84	46	0.001
Above 'clinical' threshold [CORE-OM]	175	74	127	58	<0.001
Subscales	**CP**		**NoP**		**p-value**
	$\bar{x}$	σ	$\bar{x}$	σ	
GHQ-28: Social Dysfunction	8.27	3.24	7.62	2.95	0.026
GHQ-28: Somatic Symptoms	8.03	3.83	5.87	3.52	<0.001
GHQ-28: Anxiety/Insomnia	8.81	4.86	7.22	4.38	<0.001
GHQ-28: Severe Depression	5.07	4.87	4.03	4.09	0.015
CORE-OM: Subjective Wellbeing	7.39	4.48	6.47	3.85	0.020
CORE-OM: Problems/Symptoms	25.68	17.44	18.66	10.68	<0.001
CORE-OM: Life Functioning	18.94	11.88	15.90	9.47	0.003
CORE-OM: Risk/Harm	2.55	3.67	1.83	3.07	0.024

NOTES: The range of the GHQ-28 subscales is 0-21; the range of the CORE subjective wellbeing subscale score is 0-16; the range of the CORE problems/symptoms and life functioning subscale scores is 0-48; the range of the CORE risk/harm subscale score is 0-24. The Subjective Wellbeing and Life Functioning CORE subscales are negatively scored, therefore, a higher score is indicative of greater symptom severity.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 3: *Overview of findings of repeated measures ANOVA examining the number of anxiolytic, antidepressant and antimanic prescriptions dispensed during the 5-year follow-up period*

	Direction	**Mean difference**	**p-value**
Anxiolytics			
Overall effect of group	CP ↑ / NoP ↓	+1.53 prescriptions	0.025
Overall effect of time	Decrease	Described in text	<0.001
Interaction effect	----------	----------	NS
Antidepressants			
Overall effect of group	----------	----------	NS
Overall effect of time	----------	----------	NS
Interaction effect	Described in text	Described in text	0.012
Antimanics			
Overall effect of group	----------	----------	NS
Overall effect of time	Increase	Described in text	<0.001
Interaction effect	----------	----------	NS

Accepted Article

This article is protected by copyright. All rights reserved.

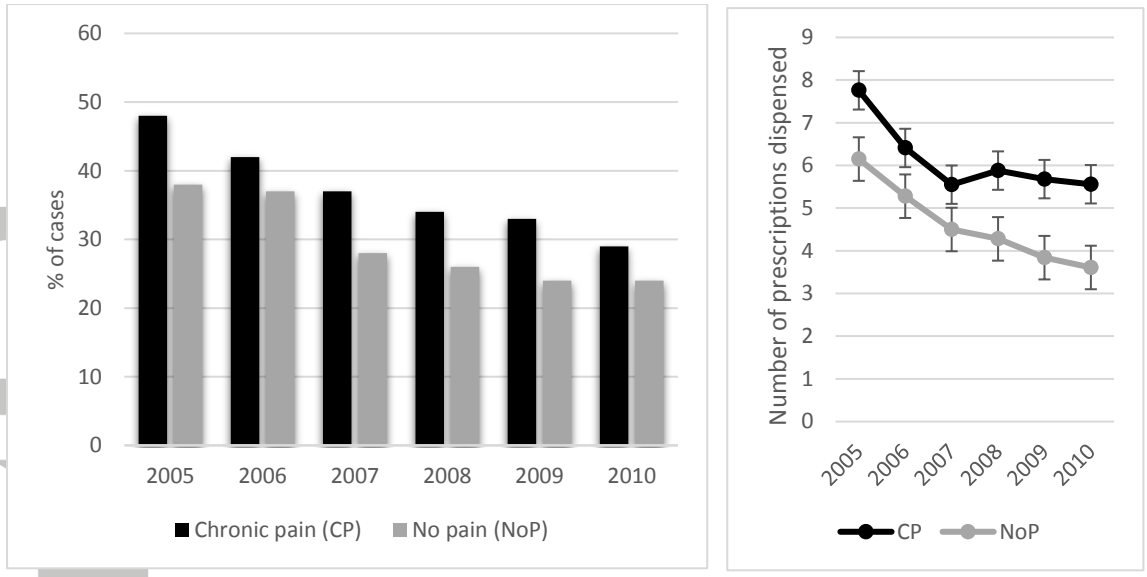

Figure 1: *Percentage of the cohort prescribed anxiolytics (n=168; 36% of the cohort), and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Accepted Article

This article is protected by copyright. All rights reserved.

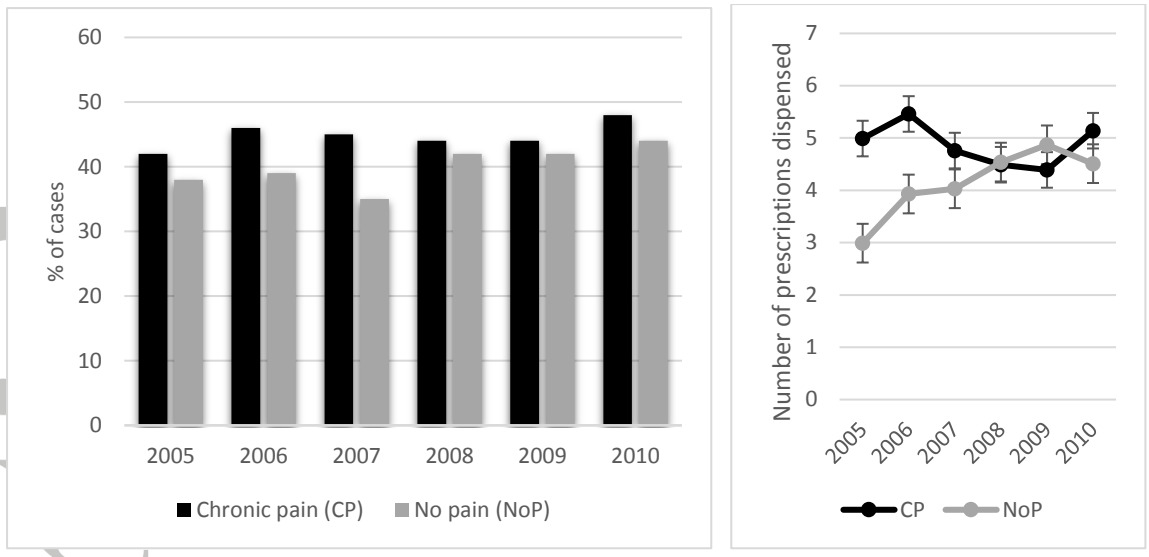

Figure 2: *Percentage of the cohort prescribed antidepressant drugs (n=307; 66% of the cohort), and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Accepted Article

This article is protected by copyright. All rights reserved.

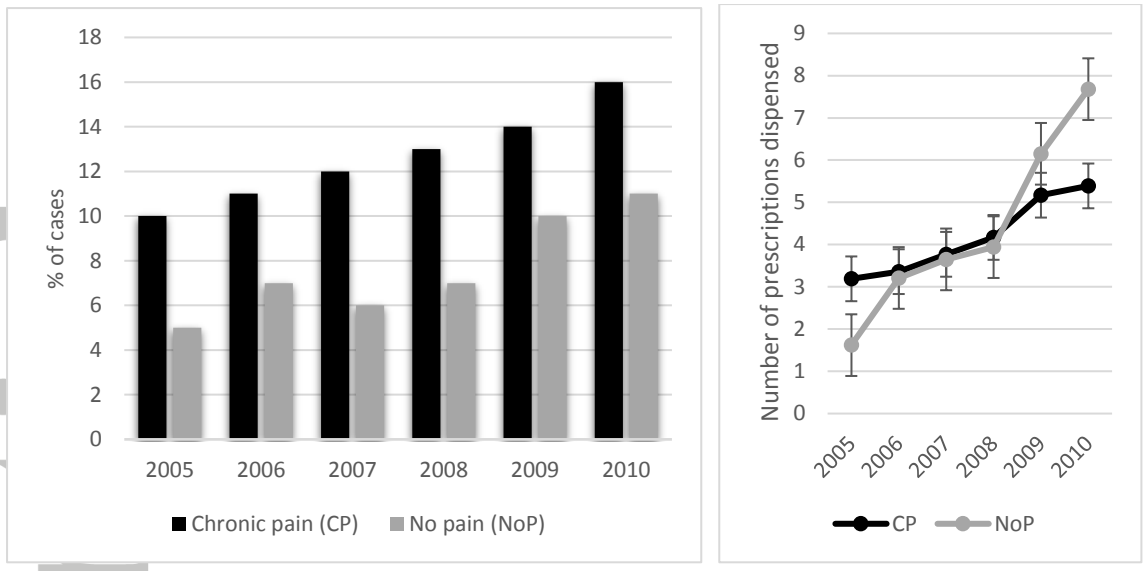

Figure 3: *Percentage of the cohort prescribed antimanic drugs (n=65; 14% of the cohort), and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Accepted Article

This article is protected by copyright. All rights reserved.