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

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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.
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 pain 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.
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...
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.
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\(^\text{13}\), 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\(^\text{14}\); however, the
 corresponds to a rise in drug-related death, which began to emerge in the US around 2009, was not witnessed in the UK\textsuperscript{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\textsuperscript{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\textsuperscript{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.
Materials

A service-modified version of the 9-item Brief Pain Inventory – Short Form (BPI-SF)\textsuperscript{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\textsuperscript{18}.

The 28-item version of the General Health Questionnaire (GHQ-28)\textsuperscript{19} was designed as a screening tool to indicate psychiatric diagnostic status. The GHQ scoring method was used and a threshold of 23/24 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)\textsuperscript{20}. The reliability and validity of the GHQ-28 is well-documented in numerous clinical populations\textsuperscript{12-25}. Whilst acceptable levels of reliability and validity have been demonstrated for the GHQ-60 in substance misusers\textsuperscript{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)\textsuperscript{27} assesses the level of current psychological global distress. A threshold of $\geq 34$ was used to indicate clinical status\textsuperscript{28}. It has been validated in samples from the general population and in clinical samples\textsuperscript{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\textsuperscript{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
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’.
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.
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 (\( \sigma \)), 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.
**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\(^1\), 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
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
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
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. Bipolar disorder and chronic pain are common comorbidities, and substance dependence in patients with bipolar disorder is associated with a desire to manage the emotional and behavioral extremes that characterize this disorder. Faced with pre-existing 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. 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. It is not only patients with pain who minimize the role of psychological distress, however, but also clinicians and policymakers who
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\textsuperscript{13}. Persistent and debilitating pain can exacerbate ongoing anxiety or can induce pain-related anxiety or pain catastrophisation\textsuperscript{38}. This is a dynamic relationship which can, eventually, exacerbate both pain and anxiety in patients\textsuperscript{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\textsuperscript{40}; and inhibition of cytochrome P450 can lead to decreased clearance of these drugs, thereby increasing risk of overdose, respiratory depression and accidental death\textsuperscript{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.

\textit{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
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 have the ability to accurately detect diagnoses in accordance with the CIDI\textsuperscript{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.
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.

Acknowledgements 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).
References


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

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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.

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

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<td>( \sigma )</td>
<td>( \bar{x} )</td>
</tr>
<tr>
<td>GHQ-28: Social Dysfunction</td>
<td>8.27</td>
<td>3.24</td>
<td>7.62</td>
</tr>
<tr>
<td>GHQ-28: Somatic Symptoms</td>
<td>8.03</td>
<td>3.83</td>
<td>5.87</td>
</tr>
<tr>
<td>GHQ-28: Anxiety/Insomnia</td>
<td>8.81</td>
<td>4.86</td>
<td>7.22</td>
</tr>
<tr>
<td>GHQ-28: Severe Depression</td>
<td>5.07</td>
<td>4.87</td>
<td>4.03</td>
</tr>
<tr>
<td>CORE-OM: Subjective Wellbeing</td>
<td>7.39</td>
<td>4.48</td>
<td>6.47</td>
</tr>
<tr>
<td>CORE-OM: Problems/Symptoms</td>
<td>25.68</td>
<td>17.44</td>
<td>18.66</td>
</tr>
<tr>
<td>CORE-OM: Life Functioning</td>
<td>18.94</td>
<td>11.88</td>
<td>15.90</td>
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<tr>
<td>CORE-OM: Risk/Harm</td>
<td>2.55</td>
<td>3.67</td>
<td>1.83</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th></th>
<th>Direction</th>
<th>Mean difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiolytics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect of group</td>
<td>CP ↑ / NoP ↓</td>
<td>+1.53 prescriptions</td>
<td>0.025</td>
</tr>
<tr>
<td>Overall effect of time</td>
<td>Decrease</td>
<td>Described in text</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction effect</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect of group</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Overall effect of time</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Interaction effect</td>
<td>Described in text</td>
<td>Described in text</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Antimanics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect of group</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Overall effect of time</td>
<td>Increase</td>
<td>Described in text</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction effect</td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>
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.
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.
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.