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Co-morbid psychiatric symptoms and clinical outcomes for treatment – seeking opioiddependent patients prescribed methadone opioid substitution therapy (OST): A 7year prospective cohort study

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Abstract

Mental illness and opioid dependence are common comorbidities that may affect individuals' clinical outcomes on Opioid Substitution Therapy (OST) treatment. Though many associations have been described, the long-term impacts of common comorbid mental illnesses on OST treatment progress remain poorly understood. This is particularly relevant when there is a renewed drive to improve progress towards recovery in OST patients.

Aims: Using the scaled General Health Questionnaire (GHQ28) and other validated instruments, this prospective cohort study aimed to describe the prevalence of psychiatric caseness in a large representative cohort of methadone-prescribed substance misusers and to explore the relationships between these psychiatric comorbidities, clinical process and long-term outcomes over 7 years.

Design and Methods: A baseline cohort of 623 methadone OST patients was assessed using a range of validated instruments. Seven year follow up data were collected using casenote review and health informatics procedures.

Results: GHQ-derived psychiatric caseness was identified in 58.4% at baseline but showed no significant associations with clinical process or 7-year outcomes. Post-Traumatic Stress Disorder was more prevalent than previously described while ADHD was less prevalent. Significant associations were demonstrated between baseline psychiatric comorbidities and substance misuse risk behaviours, clinical processes and associated 7-year outcomes.

Conclusions and discussion: Psychiatric comorbidity is common though studies show considerable variation in prevalence. Common psychiatric comorbidities impact upon long term substance use outcomes in OST patients. The relationships, however, are complex. These relationships must be better understood to improve OST outcomes and opportunities for progress towards recovery.

Introduction

Opioid dependency is the dominant illicit drug problem worldwide, with an estimated annual prevalence in the general population of 0.3-0.5% [1]. It follows a chronic, relapsing clinical course and abstinence, if achieved, must be sustained for many years to promote continued recovery and reduce likelihood of relapse [2]. Traditionally, therapeutic intervention aims to reduce drug-related harms, typically using drug substitution strategies.

More recently, services have been encouraged to also deliver 'recovery' [3]. Opioid Substitution Therapy (OST) appears effective in terms of delivering harm-reduction outcomes [4]. The evidence base demonstrating the influence of OST on progress towards recovery, however, remains limited [5]. High levels of psychiatric comorbidity have been consistently identified in surveys of substance misusers [6]. Despite this, OST services often fail to diagnose or treat psychiatric comorbidities, potentially resulting in poorer short-term treatment outcomes [7]. Indeed, it has been proposed that screening for psychiatric symptoms, or "caseness" should be promoted in addiction services [8]. The study of the impact of psychiatric comorbidity on substance misuse outcomes is further complicated by the heterogeneity and relapsing-remitting course of both domains of disorder [6]. A recent systematic review considering the treatment of psychiatric comorbidity in substance users acknowledged the general paucity of the evidence base and the subsequent difficulty in evidencing the most effective treatments [9]. Some studies have considered the potential impact of comorbidity on the effectiveness of methadone OST itself. Many have been unable to demonstrate any significant effect of psychiatric comorbidity on treatment retention or substance misuse outcomes. In other studies, various psychiatric diagnoses – anxiety, depression, Post-Traumatic Stress Disorder (PTSD) and Attention Deficit Hyperactivity Disorder (ADHD) - have all been implicated in exerting negative effects

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on short term clinical outcomes, although causal relationships have not been established [10-19]. It has also been hypothesised that current psychiatric symptoms – rather than any formal syndromal psychiatric diagnosis - may be the key factor influencing treatment effectiveness in opioid-dependency [7,9].

Thus, despite the widespread acknowledgement that psychiatric comorbidity is common in opioid dependency, the effect on OST outcomes is poorly understood. As expectations for OST increase, there is a need to better understand the potential impact of comorbid mental illness. Therefore, the present study aimed:

1. To assess the prevalence of psychiatric caseness in a large representative cohort of OST patients; and
2. To consider the relationships between baseline indicators of psychiatric comorbidity and outcomes over 7 years.

Methods

Detailed clinical data were collected from methadone OST patients (n=623), resident in a single Scottish region, in 2005. Four years later, follow-up data were collected by structured casenote review. These data were then linked, using unique identifiers, with validated health informatics datasets describing clinical contacts and outcomes from 2005-12. The resulting database contained detailed information on the baseline cohort over this 7-year period. Standard operating procedures at HIC Services, University of Dundee, were followed to ensure anonymisation of the dataset. HIC Services is a University of Dundee research support unit within the Tayside Medical Science Centre (TASC). It operates a secure "safe haven" environment with robust data governance for the provisioning of clinical data to academics for research (http://medicine.dundee.ac.uk/hic). Ethics Committee guidance was sought and full Ethics Committee approval was not required. NHS Caldicott Guardian agreement was obtained to cover all aspects of data handling and sharing. (Figure 1).

Identification of Baseline Cohort (2005)

In January 2005, all patients in receipt of methadone OST in Tayside region, Scotland were identified from NHS databases (n=817). Only methadone was used as OST in Tayside at this time. Only Tayside residents in a defined OST programme were included. Patients were provided with written information prior to review appointments. Interviews were conducted by experienced, trained, substance misuse nurses in NHS facilities. Every effort was taken to include all regional OST patients in the review. Non-attenders were offered further appointments at their convenience. Further non-attendance resulted in written communication through their community pharmacy to encourage participation.

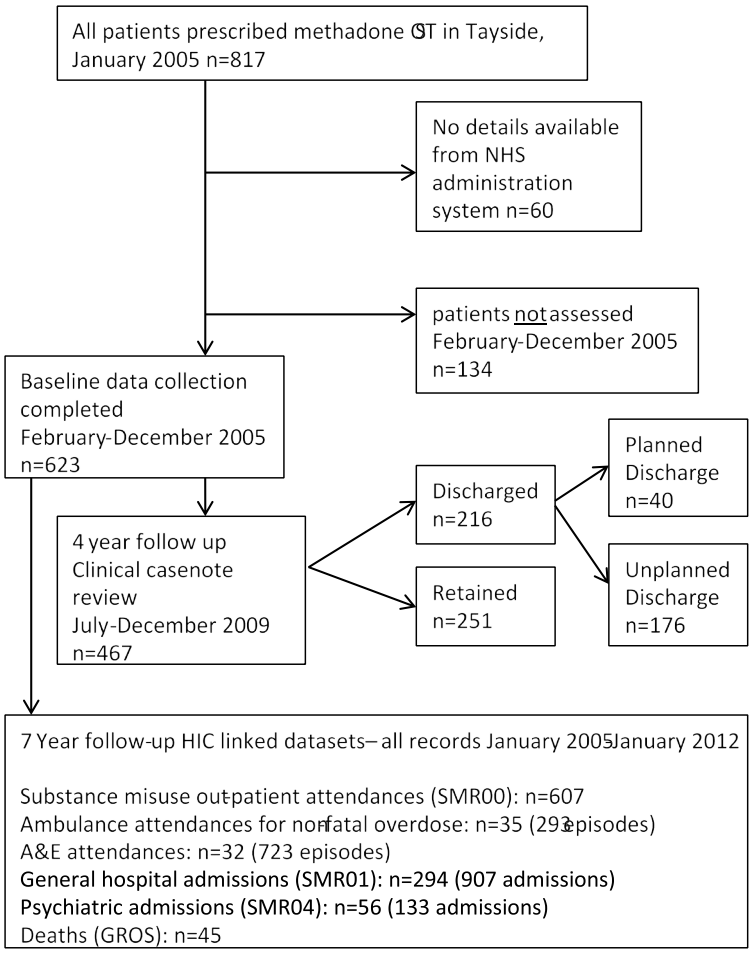

Figure 1. Study data collection

Baseline data collected and instruments used

Substance use status was assessed using the Maudsley Addiction Profile (MAP) [20],

Injection Risk Questionnaire (IRQ) [21] and Treatment Perception Questionnaire (TPQ) [22].

Comorbid mental health caseness was determined using the General Health Questionnaire – Scaled version (GHQ - 28). The GHQ is a well-established self-administration screening instrument designed to detect probable psychiatric disorder, previously proposed as a screening tool in substance users [8]. The GHQ-28 is more convenient for patients and has been used in a wide range of clinical settings [23].

Screens for specific psychiatric conditions were also undertaken. A range of validated instruments, mainly self-completion questionnaires, were chosen to minimise administrative burden and to avoid disruption to clinical services. The Social Phobia Diagnostic Questionnaire (SPDQ) was used to screen for Social Phobia. This brief self-report questionnaire has been shown to be reliable and valid in a range of populations. It addresses the DSM IV diagnostic criteria for social phobia [24]. The Impact of Events Scale (IES) was used to screen for Post-Traumatic Stress Disorder (PTSD). The IES is a screen for traumatic experiences and can detect likely PTSD. It is recommended for use in a clinical setting and has been used as a screening tool in a range of general populations [25].

Attention Deficit Hyperactivity Disorder (ADHD) was screened using the Current Symptoms Scale (CSS). The CSS has been found to be a useful screening tool in a range of populations and was included as it was one of only a few briefs, validated self-completion questionnaires available [26].

A bespoke database was built using SPSS 16 (SPSS 2003). Data were input by experienced HIC Services data-entry staff with rigorous quality assurance through a comparison of 10% of database entries against the hard copy information.

Follow up data

In 2009, a follow up review of the 2005 cohort was undertaken. A bespoke proforma captured information from clinical records. All data (2005 baseline and 2009 casenote reviews) were lodged in HIC Services' "safe haven". In 2012, these data were linked with datasets that supplied information describing demographics (available through the NHS Scotland Community Health Index – CHI), use of NHS services (available through the Scottish Morbidity Records - SMR) and outcomes (e.g. deaths available from the Registrar General records). Once linked, HIC Services supplied each subject with a new unique identifier (or "ProCHI") making a fully anonymised dataset available for analysis through a secure IT portal. Table1. shows the data used in the analyses. All data were analysed using SPSS v18 (IBM 2010). (Table 1)

Statistical analysis

Descriptive analyses were used to describe the baseline sample, reported as number (percentage) for categorical variables and mean (SD) for continuous variables. Univariate associations between baseline and follow up data were assessed. Categorical data were compared using the chi-squared test. Testing of continuous data was determined by normality of distribution. Normally distributed data were subject to parametric tests with Bonferroni corrections applied to reduce the likelihood of Type 1 error. Effect sizes were calculated.

Table 1. Variables used in longitudinal analyses

Independent variable	Dependent variable (4 yr-casenote reviews)
Psychiatric caseness (GHQ28)	Process measures
GHQ 28 caseness	Retained on treatment - 4 years
GHQ 28 Total score	If discharged – positive or negative
Anxiety disorders	Methadone dose
Social phobia caseness (as SPDQ)	Diazepam dose
PTSD caseness (IES cut off 26)	Regular drug screen done
PTSD severity (IES total score)	Outcome measures
ADHD	Employment status
ADHD Symptoms (CSS)	Family stability (proxy - living with children)
ADHD type (CSS)	Any illicit drug use reported
ADHD impairment (CSS)	Heroin use reported
	Heroin use (days)
	Heroin use (route)
	Diazepam use reported
	Diazepam days
	Illicit methadone use reported
	Illicit methadone days
	Illicit painkiller (other opiate) use
	Illicit painkiller days
	Test positive opiates
	Test positive benzodiazepines
	Acute hospital admissions reported
	Psychiatric hospital admissions reported
	Incarceration reported
	Dependent Variables (7yr-HIC linked datasets)
	Process measures
	SMR00 (out-patient) sessions (number)
	Outcome measures
	SAS (Ambulance) attendances
	Naloxone administrations
	A&E attendances
	SMR01 admissions (acute) - All
	SMR01 duration (acute nights) - All
	SMR04 admissions (psychiatric)
	SMR04 (psych) emergency/routine
	SMR04 admissions - total days
	SMR04 admissions - longest stay
	GROS dead/alive

Results

Representativeness of samples

At baseline, 817 Tayside patients were in receipt of methadone OST, of which 623 (76.2%) were assessed. Means and standard deviations of selected descriptive variables – age, gender and methadone dose - were collected in order to assess representativeness of this baseline sample compared with the known total OST population. In the assessed participants, males were over-represented (Chi-squared test; $\chi^2(1) = 7.064$; p=0.008), mean age was older (t-test; t=3.4; p=0.001), and methadone dose lower (t-test; t=2.3; df=752; p=0.022) than in the total treatment population. At 4-year follow-up, clinical records were accessed for 467 subjects (75% of those assessed at baseline). Comparisons with those not reviewed were made regarding variables including age, gender, residence, educational attainment, employment status and living circumstances. No significant differences were found, confirming that the casenote follow-up sample was generally representative of the baseline assessment sample. For informatics follow-up data, all data-linked records were available for all clinical episodes for all individuals from 2005-2012.

Demographics and personal circumstances at baseline

Four hundred and twenty four of the cohort were male (68.4%). Three hundred and eighty two (61.6%) lived in an inner city area and 483 (77.9%) within the 2 most deprived quintiles as assessed using the Scottish Index of Multiple Deprivation (SIMD) [27]. The majority (443 participants - 75.7%) were parents with at least one child. Over half (370 participants - 55.5%) reported that they were living with a partner though the mean contact frequency was 15/30 days (SD 14.4). Educational attainment was poor with 312 (52.6%) having gained no qualifications and 61% of those with any qualifications having achieved elementary qualifications only. Only 63 (13%) were in paid employment, working a mean of only 2 days per month.

Substance misuse treatment at baseline

Five hundred and eighty-eight participants (97%) were found to be in receipt of a methadone prescription as, having been identified at the inception date, some had completed detoxification, or ceased to be prescribed methadone for some other reason. Mean dose was 49.5mg (SD 25.3), range 0-170mg and mode 50mg. One hundred and seventy-eight (29%) were also prescribed diazepam. Mean dose was 6.8mg (SD 13.6, range 0-85mg; mode 20mg). OST was being delivered in three settings: NHS specialist service – 298 subjects (47.4%); Criminal Justice services – 93 subjects (14.8%); General Practice Shared-Care – 156 subjects (24.8%).

Drug use, injecting risks, general health and support (MAP)

Two hundred and eighty nine (54%) of participants' urine drug screens tested positive for heroin at their baseline review appointment while 314 (58.9%) tested positive for diazepam. Only 178 (29%) were prescribed diazepam. Only 87(16.2%) reported any injecting. Of those who injected, the mean number of injecting days within the last 30 was 1.9 (range 0-30 days; SD 6.1). Mean frequency of daily injecting was 0.3 injections/day (range 0-5 injections; SD 0.7). Four hundred and fifty (83.8%) stated they never shared injecting equipment, while of the 82 who reported any sharing, 4 (4.9%) stated they shared "frequently". Regarding general health, 580 participants (93.5%) were registered with a GP. Two hundred and ninety three (51.7%) reported having physical health problems for which 177 (60%) were receiving treatment. Mean MAP physical health score was 14.2 (SD 7.98) suggesting that physical health problems were mild/moderate. Two hundred and sixty five (49.7%) reported mental health problems for which 184 (69%) were being treated. Mean MAP psychological health score was 15.73 (SD 9.22) suggesting that mental health problems were mild/moderate. Only 152 (30%) were receiving additional support from non-NHS agencies.

Mental health Co-morbidity

The results of the mental health screens are shown in Table 2.

Three hundred participants (58.4% of 514 screened) scored above the recommended threshold for caseness on the GHQ-28 [23]. Two hundred and fifteen (40% of 539 screened) met criteria for a diagnosis of Social Phobia [24]. Using the Impact of Events Scale, 280 subjects (48% of the 601 screened) had a high likelihood of having a form of Post -Traumatic Stress Disorder [25]. Only 368 subjects were specifically screened for ADHD at baseline. Of these, 59 (16%) were shown to have any symptoms of ADHD with the majority falling into the "inattentive" sub-group [26].

Associations – psychiatric comorbidity and 4-7-year outcomes

The associations between baseline screening results and outcomes are shown in Table 3.

Table 2. Baseline screens for mental health comorbidity

	N	%	Mean	median	Mode	Min-max	SD
General Health Questionnaire (GHQ28)							
Total score (514)			28.11	26	21	1-78	13.609
Likert threshold for caseness*: 23/24 (514)*							
Yes - caseness	300	58.4					
No - caseness	214	41.6					
Social Phobia Diagnostic Questionnaire (SPDQ)							
Total score (539)			6.88	0	0	0-27	8.587
Likert threshold for social phobia*: 21/22*							
Yes - caseness	215	40%					
No - caseness	323	60%					
Impact of Events Scale (IES)							
Total score (601)			23.90	19	0	0-75	24.981
Likert threshold for caseness*: 26*							
Yes - caseness	280	48%					
No - caseness	299	52%					
Avoidance score			14.04	14.00	0	0-65	13.390
Intrusion score			13.06	13.00	0	0-35	12.383
Current Symptoms Scale (CSS)							
Presence/type of ADHD			N			%	
Any ADHD? (n=368)							
No ADHD			309				
ADHD present			59			16%	
Type of ADHD (59)							
Inattentive			31			52.5%	
Hyperactive/impulsive			8			13.6%	
Combined			20			33.9%	

Table 3. Associations baseline comorbidity screens on process, service utilization and outcomes

4 year follow up results (case note review)		
Independent variable	Dependent variable	Statistics
GHQ caseness	All	NSD
GHQ total score	Illicit diazepam use	LDA $X^2(1)$ =6.686; p=0.010 Higher score=more likely use Cohen's d = 0.367 R=0.180 *Small effect size*
	Illicit methadone days	LRA $X^2(3)$ = 13.755; p=0.003 Higher score=more days use/30 Partial η^2 = 0.118 *Medium effect size*
SPDQ caseness	All	NSD
PTSD caseness 601 total scores of whom 271 scored zero. 280 show PTSD "caseness" based on cut off of 26 on scale. 321 no PTSD.	Family stability	Chi square $X^2(2)$ =6.648; p=0.036 PTSD caseness=less stability Cramer's V=0.122 p=0.036 *Relevant effect*
	Methadone dose	KWH $X^2(1)$ =5.009; p=0.025 PTSD caseness =higher dose Partial η^2 = 0.001 *Small effect size*
PTSD severity score Of cases, severity scale shows 175 "severe" and 105 "moderate"	Methadone dose	QRA t (1) =-2.674; p=0.008 Higher Score=higher dose Partial η^2 =0.003 *Small effect size*
ADHD symptoms present/type	All	NSD
7 year follow up results (data-linkage)		
GHQ caseness	All	NSD
GHQ total score	Psychiatric admissions (SMR04)	LRA t (1) =2.643; p=0.011 Higher score = more IP days Partial η^2 = 0.995 *Large effect size*
SPDQ caseness	All	NSD
PTSD caseness	Ambulance callouts (OD)	MWU=349.500; p=0.050 PTSD=more call outs Partial η^2 = 0.021 *Small effect size*
PTSD severity score	All	NSD
ADHD symptoms	Naloxone administrations	MWU=20.500; p=0.031 ADHD = more naloxone events Partial η^2 = 0.235 *Large effect size*
ADHD type	Out-patient attendance	KWH(2)=7.009; p=0.030 Hyperactive=more attendances Partial η^2 = 0.070 *Medium effect size*

Four year follow up – casenote reviews

Few associations were found between the baseline comorbidity screens and 4-year outcomes. GHQ-28 caseness showed no significant associations with these measures. A higher GHQ-28 total score was associated with more illicit drug use (diazepam use; illicit methadone days used). No associations were found between baseline Social phobia and 4-year outcomes. PTSD caseness was associated with a higher prescribed methadone dose and less family stability while severity of PTSD symptoms (IES total score) was also associated with a higher prescribed methadone dose. There were no significant associations found between baseline ADHD and 4-year outcomes.

Seven-year follow-up – HIC linked datasets

At 7-year review, GHQ-28 caseness status showed no significant associations with *any* outcomes. Higher GHQ-28 total scores, however, were associated with more psychiatric admissions. No associations were found between baseline Social Phobia and 7-year outcomes. PTSD caseness was associated with an increased likelihood of emergency ambulance call-outs during the follow up period. Presence of any type of ADHD at baseline was associated with an increased likelihood of administration of naloxone to treat overdose during an emergency ambulance call-out. Those found to have the hyperactive type of ADHD were likely to be offered more outpatient clinic appointments over the seven year follow up period than other subjects.

Discussion

Strengths and limitations

We conducted a detailed assessment of a large representative sample of an OST treatment population within a defined geographical area. The demographic characteristics of this sample show them to be very similar to those described in previous large UK cohort studies [28,29]. The subjects were screened for the presence of comorbid psychiatric conditions using validated instruments. We have collected follow up data on clinical processes, service utilisation and outcomes on over 600 subjects over 7 years, allowing assessment of the long term impact of psychiatric comorbidity on OST effectiveness.

Missing data

This study also has a number of shortcomings, however. Subjects were already in treatment at baseline – and information about previous treatment was unavailable. This study has focused on the relationship between outcomes and presence or absence of psychiatric comorbidity. Other patient characteristics– relating to previous drug history, presence of physical comorbidity (e.g. chronic pain) or social factors - may be important influences. It would also have been useful to have access to more objective measures of harm reduction effectiveness – such as blood-borne virus sero-conversion. These data were not available at the time of this study.

Representativeness of samples

Statistical evaluation, at all stages of data collection, determined whether the samples were representative. Though the baseline sample represented 76% of all methadone OST patients in the region, the subjects assessed did show significant differences when compared to the total population. This may reflect the review process – which was part of a clinical service review, was time limited and invited individuals to attend. There may be both positive and negative reasons that this sub-group –younger females taking higher OST doses - were less likely to present for assessment. This is a weakness of the study – despite the large sample. The 4 year follow up sample represented 75% of the baseline cohort. No significant differences were found when comparing the follow-up sample with the population of interest.

Stability of sample at baseline

The baseline urine drug screens found over half (54%) to be positive for illicit opiate use while 314 subjects (58.9%) tested positive for use of benzodiazepines. Only 178 (29%) were prescribed benzodiazepines, suggesting considerable illicit benzodiazepine use in this sample. These treatment services traditionally delivered a harm-reduction orientated model of care. In such services it is not unusual for patients not to be completely abstinent and one-off testing is seen as a poor indicator of stability [30]. Data which would allow objective assessment of frequency of use - such as repeated urine drug screens - were unavailable. However, though illicit use was prevalent, reported risk-taking was low. Only a small proportion of those assessed - 87 subjects (16%) - were injecting at baseline with very few sharing injecting equipment.

Instruments

The main instruments were chosen because of their relevance from previous published research. The MAP has been a standard assessment tool for substance use studies [28-30]. The GHQ-28 was introduced to screen for psychiatric caseness. This instrument has been validated in a number of clinical settings and has been proposed as a useful screener for psychiatric comorbidity in substance users [8,23]. Some of the additional instruments used to screen for psychiatric comorbidity at baseline, however, may limit this study. They were chosen as the baseline data collection process was carried out in a clinical service where specific instruments were already being used and time limitations were in place, making use of self-completion questionnaires, with no added cost to services, preferable.

Prevalence of psychiatric comorbidity

We found that 58.4% of those screened met the GHQ-28 criteria for psychiatric caseness, confirming a high prevalence of psychiatric symptoms in this treatment population. It has been suggested that anxiety disorders are common in substance users and may be up to twice as common in this population when compared to the general public [31]. Forty percent of those who were assessed met the threshold criterion for Social Phobia caseness while 48% met the criteria for PTSD caseness. This is a much higher rate than of the 28% previously reported in opioid dependent subjects [18]. Findings were very different for ADHD, however, with only 16% of those screened showing symptoms suggestive of ADHD using the CSS. This figure is low in comparison to previously published work that has suggested prevalence levels as high as 58% [19]. We are unable to determine whether these findings reflect varying levels of comorbidity over time in this population or the choice of screening tool.

Impact on outcomes

Although a range of medical treatments are available to manage opioid dependence, methadone OST is the prominent treatment of choice in many countries [4]. Previous research has given conflicting results regarding the potential impact of various psychiatric comorbidities on OST effectiveness, with some studies unable to demonstrate any effect on retention or clinical outcomes while other studies have proposed negative effects on outcome associated with the presence of anxiety, depression, PTSD or ADHD [4,10-19,32] Meanwhile, some researchers have argued that undiagnosed psychiatric comorbidity is a risk factor for poorer retention in treatment [33]. These conflicting findings may reflect the methods used in these studies – which have focused on specific psychiatric diagnoses and have generally reported only short term OST outcomes. Some authorities have proposed that current symptoms or levels of distress may have more effect on substance use outcomes than formal DSM IV diagnoses. The limitations of the evidence base on comorbidity to date are well described [7-9]. As the expectations OST increase, it is important that these relationships are better understood.

In this study we have evaluated multiple measures of treatment process and clinical outcomes in a large representative sample from a regional NHS treatment service over 7 years and considered whether the presence/absence of psychiatric comorbidity at baseline is associated with poorer outcomes. Like the evidence base to date, our findings are inconsistent. We found that meeting the psychiatric caseness threshold on the GHQ-28 did not correlate with either poorer engagement with the treatment process, nor clinical outcomes. Anxiety disorders are common in substance misusers [31]. We screened for the presence of Social Phobia and found a prevalence of 40%. We found this, however, to have no associations with clinical processes or outcomes over the 7 year follow up period. Previous research has suggested that PTSD is associated with the development of more severe drug dependency/addictive behaviours, is associated with more disability and poorer work prospects and is harder to treat successfully with OST (requiring more intensive psychosocial inputs and higher methadone doses to achieve positive outcomes) [18,32]. We screened for PTSD and found 48% of those screened to have PTSD caseness – a higher level than previously reported. We demonstrated that, at 4 year follow up, both PTSD symptoms (total score) and caseness were associated with higher doses of prescribed methadone – perhaps reinforcing these previous studies' findings. Clinical outcomes assessed in this study were not, however, significantly associated with PTSD status at baseline. PTSD cases were less likely to show evidence of family stability at 4 years. Over 7 years PTSD cases were more likely to have required emergency ambulance callouts – perhaps suggesting higher levels of risk-taking. ADHD has previously been reported as having a high prevalence and the presence of ADHD has been shown to be associated with much poorer short term outcomes than those with no ADHD diagnosis [19]. In the

current study, only 16% were found to have symptoms suggestive of ADHD. We did not find ADHD was associated with substance misuse outcomes in general but did find that those with any ADHD symptoms were more likely to have required naloxone treatment administration than those without over the 7 year follow up period, suggesting this group may be more likely to be involved in risky behaviour than their peers. In terms of the treatment process, perhaps reflecting assessment of risk, those with symptoms suggestive of the hyperactive subtype ADHD received significantly more out-patient appointments during the 7 year follow up period than others.

There is a drive to improve the outcomes achieved in OST. Psychiatric comorbidities are common and may be an important factor which, if not addressed, has the potential to reduce treatment effectiveness – both in terms of poorer harm reduction outcomes and recovery.

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Declarations of interest

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