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Sex differences amongst dependent heroin users: histories, clinical characteristics and predictors of other substance dependence

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Abstract

Introduction and aims—To examine differences in the characteristics and histories of male and female dependent heroin users, and in the clinical characteristics associated with multiple substance dependence diagnoses.

Design and methods—1513 heroin dependent participants underwent an interview covering substance use and dependence, psychiatric history, child maltreatment, family background, adult violence and criminal history. Family background, demographic and clinical characteristics were analysed by sex. Ordinal regression was used to test for a relationship between number of substance dependence diagnoses and other clinical variables.

Results—Women were more likely to experience most forms of child maltreatment, to first use heroin with a boyfriend or partner, to experience ongoing adult violence at the hands of a partner, and to have a poorer psychiatric history than men. Males had more prevalent lifetime substance dependence diagnoses and criminal histories and were more likely to meet criteria for ASPD. Predictors of multiple substance dependence diagnoses for both sexes were mental health variables, antisocial behaviour, childhood sexual abuse, victim of adult violence, younger age at first cannabis use and overdose. As the number of dependence diagnoses increased, clinical and behavioural problems increased. Childhood emotional neglect was related to increasing dependence diagnoses for females but not males, whereas PTSD was a significant predictor for males but not females.

Discussion and conclusions—Mental health problems, other substance dependence, childhood and adult trauma were common in this sample, with sex differences indicating different treatment needs and possible different pathways to heroin dependence for men and women.

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Keywords

opioid dependence; heroin dependence; opioid; polydrug use; polydrug dependence; substance use disorders

Introduction

Studies of heroin dependent persons have described a chronic disorder strongly associated with polydrug use, poor mental and physical health, an increased risk for mortality, and poor legal, social and economic outcomes (Bargarli, et al., 2006; Burns, et al., in press; Craddock, Rounds-Bryant, Flynn, & Hubbard, 1997; Degenhardt, et al., in press; Fischer, Firestone Cruz, & Rehm, 2006; Fischer, Manzoni, & Rehm, 2006; Gossop, et al., 1998; Hubbard, Craddock, & Anderson, 2003). Although it is a low prevalence disorder, the severity of problems associated with it makes it an important public health issue to understand. Further, within the heroin dependent population, important clinical differences may be manifest for different subpopulations including males and females.

There is some evidence of different characteristics for male and female dependent heroin users. Those studies that have reported sex differences found that females were younger (Chen, Shu, Liang, Hung, & Lin, 1998; Chiang, et al., 2007; Williamson, Darke, Ross, & Teesson, 2007) and had more suicide attempts and fewer completed suicides (Darke & Ross, 2002; Darke, Ross, Lynskey, & Teesson, 2004; Darke, Williamson, Ross, & Teesson, 2005); different injecting behaviours (Hoda, Kerr, Li, Montaner, & Wood, 2008); less education and employment (Chen, et al., 1998; Chiang, et al., 2007); a younger onset of heroin use (Chen, et al., 1998); more dysfunctional families and exposure to more unfavourable social factors (Chatham, Hiller, Rowan-Szal, Joe, & Simpson, 1999; Chiang, et al., 2007); greater health service utilization (Darke, Ross, Teesson, & Lynskey, 2003; Fletcher, Broome, Delany, Shields, & Flynn, 2003); higher standardised mortality ratios (Rehm, et al., 2005); more psychological problems (Chatham, et al., 1999; Mills, Teesson, Darke, Ross, & Lynskey, 2004); and were more likely to sustain abstinence after treatment (Darke, et al., 2007a) than men. The evidence regarding sex differences in polysubstance use and dependence amongst heroin users is mixed, with one study finding no differences in the number of current or lifetime diagnoses (Darke & Ross, 1997), another found higher levels of polydrug use amongst male heroin users (Darke & Hall, 1995) and another finding no sex differences in class memberships based on polysubstance use (Monga, et al., 2007).

Although general population studies consistently find that males have higher rates of substance use and dependence than females (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler, et al., 1994; Stinson, et al., 2005; Teesson, Hall, Lynskey, & Degenhardt, 2000; Warner, Kessler, Hughes, Anthony, & Nelson, 1995), these sex differences may be less marked amongst a sample distinguished by high levels of antisocial or externalising problems. There is evidence of a heritable liability for antisocial behaviour, and the polygenic multiple threshold model suggests that females may need a greater liability to express antisocial behaviour (Rhee, Waldman, Rhee, & Waldman, 2002). Therefore the women in the current sample may carry a higher genetic and/or environmental liability for antisocial behaviour (ASB) than the males. Greater environmental liability for females has already been noted in the form of more dysfunctional families and exposure to more unfavourable social factors (Chatham, et al., 1999; Chiang, et al., 2007). Alternatively, there may be sex differences in gene-environment interactions or gene-environment correlation (Rutter, et al., 2006).

Consistent with the existence of a general heritable liability to ASB, having one externalising disorder increases the risk of having other externalising disorders (Krueger, Markon, Patrick,

& Iacono, 2005). Use of several drug classes amongst dependent heroin users is common, and is associated with poorer mental health (Darke & Ross, 1997), increased fatal and non-fatal overdose (Darke, Ross, & Hall, 1996; Zador, Sunjic, & Darke, 1996) risky injecting behaviour (Klee, Faugier, Hayes, Boulton, & Morris, 1990) and poorer treatment outcomes (Marsden, et al., 2009). Amongst drug users in treatment, polydrug use is associated with adverse family histories, self-harm, aggression, psychoticism and impulsivity (Martinotti, et al., 2009). 'Polydrug use' is used in the research literature to describe the use of two or more drugs within a particular timeframe (concurrent, sequential, 30 day, 12-month or lifetime). The term 'polysubstance dependence' is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a substance use disorder where an individual uses at least three different classes of substances repeatedly within a 12-month period, but no single substance predominates (American Psychological Association, 1994). It has also been used to refer to multiple lifetime substance dependence diagnoses (Agrawal, Lynskey, Madden, Bucholz, & Heath, 2006b). In this paper, the term 'multiple substance dependence diagnoses' will be used to refer to meeting lifetime criteria for two or more substance dependence diagnoses, in order to avoid confusion with the DSM-IV definition of polysubstance dependence.

In sum, evidence suggests that there are at least some clinical and family background differences between male and female dependent heroin users; that polydrug use is problematic amongst this population; and that polysubstance dependent individuals have more adverse family backgrounds and self-harming behaviours than mono-substance dependent individuals. To our knowledge the relationship between sex, multiple substance dependence diagnoses, mental health and family background variables in a heroin dependent sample has not been tested in a comprehensive model. The current study is based on an extensive interview with a large sample of dependent heroin users recruited in Sydney, Australia. It provides a different focus from the previous Australian study of heroin users, the Australian Treatment Outcome Study (ATOS). ATOS was a longitudinal study of heroin users in treatment, with a sample size of 825 (Ross, et al., 2005). Its focus was on treatment and its outcomes. The current study explores the characteristics and family backgrounds of dependent heroin users, their other substance dependence, and their mental health problems. In sum, the current study allows us to test the strength of the relationships between several additional variables. Thus, this paper aims to:

1. Describe sex differences in the family history, socio-demographic and clinical characteristics of a heroin dependent sample. It is hypothesised that women will have higher rates of all mental disorders but not antisocial personality disorder (ASPD), higher rates of sexual abuse and family dysfunction, lower rates of incarceration, higher rates of suicidal behaviour and lower rates of other substance dependence, than men.
2. Identify clinically salient correlates of multiple substance dependence diagnoses for males and females. Separate models will be used for males and females, with number of lifetime substance dependence diagnoses (other than heroin) as the dependent variable in both models. It is expected that higher numbers of substance dependence diagnoses will be associated with poorer outcomes across most mental health and clinical variables, although there may be different associations by sex.

1. Method

2.1 Procedure

This study used data from the Comorbidity and Trauma Study, a retrospective case-control study examining genetic and environmental factors contributing to opioid dependence liability. The study was funded by the National Institute of Drug Abuse, and was run in collaboration

with Washington University, the Queensland Institute of Medical Research, and the National Drug and Alcohol Research Centre (NDARC), University of New South Wales. Participants were recruited from methadone clinics in the greater Sydney area, representing approximately one-quarter of the clinical population in that area. Written informed consent was obtained from all participants. Ethics approval was obtained from the ethics committees of the University of New South Wales, Washington University, the Queensland Institute of Medical Research, and the area health service ethics committees governing the participating clinics. Participants were reimbursed AU\$50.00 for out-of-pocket expenses.

2.2 Participants

Participants (n = 1513) were recruited from public and private opioid pharmacotherapy clinics in the greater Sydney region between November 2005 and March 2008. At a minimum, patients receiving opioid replacement therapy (ORT) in New South Wales undergo an assessment for opioid dependence and a medical review including testing for blood borne viruses. In ORT clinics, recent drug use for a range of drug classes is assessed, and a mental state examination is undertaken. Each ORT recipient must be assigned a case manager. The provision of mental health services, however, differs across services. Some, but not all, ORT clinics are part of a larger drug and alcohol service with access to psychiatrists, counsellors, and psychologists. Some general practitioners in private practice also prescribe ORT and the provision of services is different again in this setting.

Respondents were eligible if they were aged 18 years or over; had an adequate understanding of English (in order to provide informed consent and participate in a long interview); and had participated in pharmacotherapy maintenance treatment for heroin dependence. Individuals reporting recent suicidal intent or who were psychotic were excluded from participating in the study.

2.3 Structured interview

Each participant completed a 1.5 to 2.5 hour face-to-face structured interview. The diagnostic sections of the interview were based on the Semi-Structured Assessment of the Genetics of Alcoholism - Australia (SSAGA-OZ) and allowed for lifetime DSM-IV and/or DSM-III-R diagnoses to be made for heroin abuse and dependence, alcohol, cannabis, sedative, stimulants, and cocaine abuse and dependence, nicotine dependence, post-traumatic stress disorder (PTSD), major depressive episode, panic disorder and antisocial personality disorder (ASPD) (Bucholz, et al., 1994; Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999). A screener for borderline personality disorder (BPD) was adapted from the International Personality Disorder Examination (IPDE) (Loranger, et al., 1994). Sections of the Christchurch Health and Development Study interview were modified to assess for childhood trauma and adult victimization history (Fergusson, Horwood, Shannon, & Lawton, 1989). Sexual abuse included 10 items asking about non-contact, contact and penetrative sexual abuse, as well as items assessing onset and recency, and relationship of perpetrator to the participant. Physical abuse included 13 items asking about physical assault from a caregiver or injury arising from a caregiver's actions towards the participant. Conflict between parents included items to assess for verbal and physical conflict, frequency, and severity. Five items were used to assess physical, emotional and supervisory neglect. Emotional abuse was measured with one item assessing verbal insult. All items were reported to have occurred before the age of 18 years. Family history information was collected using the Family History Assessment Module (FHAM) and the Family History Screen (FHS) (Weissman, et al., 2000). This section assessed lifetime substance use problems and suicidality amongst immediate biological family members (parents, siblings and children).

The heroin overdose items assessed any lifetime non-fatal overdose due to heroin, and any lifetime overdose due to heroin requiring medical treatment (the variable used in this study). The suicide section assessed lifetime occurrence of suicidal thoughts, persistent suicidal thoughts (7 days or more in a row); suicide plans, suicide attempt, and number of suicide attempts. The criminality and incarceration items asked participants if they'd ever been in prison, the total length of time in prison, the longest period of time in prison, if they'd ever been arrested for anything other than traffic offences, if they'd ever committed a crime for which they hadn't been arrested, and the nature of the crime/s committed. The relapse variables included whether the participant had ever relapsed to heroin use after a period of abstinence, and the reason for the relapse. Adult violence (after age 18) assessed whether the participant had ever been the victim or perpetrator of various forms of assault (e.g. pushing, hitting, punching, kicking, strangling) or threats of violence (hitting, threatened with a weapon), or had experienced unwanted sexual activity through the use of violence, threats of violence, blackmail, or threats of relationship break-up.

2.4 Scales

Participants completed two measures of social anxiety: the Social Interaction Anxiety Scale (SIAS), which corresponds to Generalised Social Phobia in DSM-III-R (Mattick & Clarke, 1998), and the Social Phobia Scale (SPS), which corresponds to the criteria for Circumscribed Social Phobia in DSM-III-R (Mattick & Clarke, 1998). The SIAS measures fear of social interaction. The SPS assesses fear of being scrutinized during routine activities such as eating, drinking, and writing. The Barratt Impulsivity Scale version 11 (BIS-11), a paper based 30-item self-report scale, was administered to all participants. Participants rate their frequency on impulsive behaviours and traits or non impulsive behaviours and traits (Patton, Stanford, & Barratt, 1995). The BIS is the most frequently used self report measure of impulsivity (Dougherty, Mathias, Marsh, Moeller, & Swann, 2004), and has good validity and reliability (Moeller, et al., 2002; Patton, et al., 1995).

2.5 Statistical analysis

T-tests were used to test for differences in age by sex, with the mean and standard deviation reported (SD). Chi square tests (χ^2) were conducted to determine whether an association existed between categorical variables. In the case of odds ratios, 95% confidence intervals have been reported. Not all variables reported by sex were included in the ordinal regression analysis.

Ordinal regression was used to test for associations between the dependent variable, number of lifetime other substance dependence diagnoses (zero through to five dependence diagnoses: alcohol, cannabis, sedatives, stimulants and cocaine) and the independent variables. Ordinal regression assumes that the slope coefficients in the model are the same across response categories (and lines of the same slope are parallel: the proportional odds model). Since the ordered logit model estimates one equation over all levels of the response variable, the test of parallel lines assesses whether the one-equation model is valid. If the null hypothesis is not rejected, it can be concluded that the proportional odds assumption holds. For both males and females, the test of parallel lines was non-significant (males χ^2 60.70, df 48, $p=0.10$; females χ^2 22.26, df 52, $p=1.00$), indicating that the slope coefficients in the model were the same across number of dependence diagnoses.

The following independent variables were first entered univariately: socio-demographic variables (age at interview, unemployment, educational attainment, marital status, time in prison ever); substance use variables (age of first regular drinking, age at first cannabis use, age at first heroin use, length of heroin career, heroin use per day during period of heaviest use, ever relapsed to heroin use, overdose requiring medical treatment); mental health variables (lifetime panic disorder, PTSD, ASPD, BPD, depression, suicide attempt); family background

variables (physical abuse, physical neglect, emotional abuse, emotional neglect, sexual abuse, violence between parents, early separation from one or both parents, problematic parental substance use); treatment variables (ever tried methadone maintenance treatment, supervised detoxification, outpatient counseling, residential rehabilitation, or unsupervised detoxification) and adult violence (victim of adult violence, perpetrator of adult violence, experienced unwanted sexual activity). A significance threshold of $p < 0.10$ was used as a cutoff for determining which variables were included in one of six second stage models that were differentiated on conceptual grounds: demographic characteristics, mental health diagnoses, substance use variables, treatment history, family background and adult violence. Any variables that remained significant at $p < 0.05$ at this second stage were entered into the final regression model. Separate models were run for males and females; age and employment status were controlled for in both models. Some variables (onset heroin use, panic disorder, emotional abuse, and physical abuse) were removed due to non-significance. Participants with five other substance dependence diagnoses were used as the reference group. All analyses were carried out using SPSS for Windows, version 15.0.

2. Results

3.1 Demographics and substance use/dependence

Males constituted 60.3% of the sample (599 females, 914 males). The median age of the sample was 36 years. Females were younger on average than males, more likely to be married, and to be receiving a government benefit than males, however there were no sex differences in unemployment rates or level of education (Table 1).

Sixty three per cent of participants were diagnosed with two or more lifetime dependence diagnoses. Six percent met criteria for all five other lifetime dependence diagnoses, as well as heroin dependence. Use of more than one drug in any one session was common, with 73 per cent using two or more drugs concurrently. Cannabis was most commonly used concurrently with heroin (63.1%), followed by sedatives (41.2%), stimulants (33.2%) and cocaine (30.8%). Males were more likely than females to receive a lifetime diagnosis for cannabis, stimulant or alcohol dependence (Table 1). There were no sex differences in the prevalence of sedative, cocaine or nicotine dependence. Nicotine and cannabis dependence were particularly prevalent, with almost two thirds receiving a lifetime diagnosis for nicotine dependence and more than half for cannabis. Cocaine dependence had the lowest lifetime prevalence with just under one third of participants receiving a lifetime diagnosis.

3.2 Onset and duration of heroin and other substance use

The most common introduction to heroin and its use was through a friend (Table 2). However women were more likely than men to be introduced to heroin by a partner, boyfriend or spouse, whereas men were more likely than women to be introduced to heroin by a friend. There were no sex differences in age of initiation to drug or alcohol use, or in onset of heroin dependence. On average, females sought treatment for heroin dependence at a younger age than males (Table 1). Onset of cannabis use and first alcohol intoxication occurred, on average, at about the same age (~14 years, Table 1).

3.3 Family background and child maltreatment

Males were more likely than females to be raised by both biological parents until age 16 (Table 3). For participants who were separated from one or both parents, the mean age of separation was 10.7 years (SD 6.0). Females were more likely than males to have had a poor relationship with their mother during childhood and adolescence, and to experience problematic parental substance use, childhood sexual abuse, emotional abuse, and emotional neglect (Table 3). Males were more likely to have experienced childhood physical punishment. Forty percent of

participants had ever received injuries as a result of physical punishment from a parent or another adult member of the family or household.

Half of the participants reported that one or both parents had a drug and/or alcohol problem. Three quarters reported verbal or physical conflict between their parents. Sexual abuse, emotional abuse and neglect were also common. For a more detailed description and analysis of child maltreatment and family background factors in this sample, see Conroy et al (2009) (Conroy, Degenhardt, Mattick, & Nelson, 2009).

3.4 Adult violence and unwanted sexual activity

Females were more than four times more likely than males to have experienced unwanted sexual activity after the age of 18, either through the use of physical violence, threats of physical violence, blackmail, or the threat of relationship break-up (Table 3). Most commonly the perpetrator of the unwanted sexual activity against females was a partner, boyfriend or husband (39.8%) followed by a stranger (24.7%) or a friend (21.4%). Of those who reported any unwanted sexual activity, females reported a higher number of events than males (Table 3). Women were also more likely to be victims of adult violence (pushing, grabbing, shoving, slapping, hitting, kicking, punching, choking, strangling) or threats of violence (hitting, threatened with a weapon), whilst males were more likely to be perpetrators of violence (Table 3).

3.5 Mental Health and suicidal behaviours

Females were more likely than males to experience all mental health problems except ASPD. Females had higher mean scores than males on the Social Interaction Anxiety Scale but not the Social Phobia Scale (Table 3). Females also had a higher prevalence of suicidal thoughts and behaviours than males (Table 3). A more detailed analysis of suicidal behaviours and associated characteristics amongst this sample is reported elsewhere (Maloney, Degenhardt, Darke, Mattick, & Nelson, 2007).

3.6 Non-fatal heroin overdose

Non-fatal heroin overdose had been experienced by more 58% of participants, with 46% experiencing an overdose that required medical treatment. One quarter had experienced three or more overdoses requiring medical treatment. Slightly more males than females had experienced an heroin overdose requiring medical treatment. There were no sex differences in the experience of multiple overdoses (Table 3).

3.7 Treatment and relapse

Relapse to heroin use after a period of abstinence from heroin was reported by 83.4% of participants, with males slightly more likely than females to have ever relapsed. Most participants were in treatment at the time of interview. Males had been in treatment for less time and sought treatment at an older age than females (Table 4). There were no sex differences in type of treatment received (Table 4).

3.8 Incarceration and criminal activity

Eighty per cent of participants had ever been arrested. Males had a longer total time in prison and longer sentences than females. Males had a higher risk of incarceration, criminal activity and arrest, and committed different types of crime than females (Table 4).

3.9 Associations with other drug dependence

With the exception of demographic variables, unadjusted odds ratios were significant for almost all variables tested and confirmed that for both sexes, more substance dependence

diagnoses were associated with a higher risk of mental health problems, antisocial behaviour, suicide attempts and heroin overdose (Tables 5 and 6). In the adjusted model, a younger onset of cannabis use, screening BPD+, depression, heroin overdose, sexual abuse, experiencing adult violence and having spent time in prison were associated with a greater number of substance dependence diagnoses for males (Table 5) and females (Table 6). For males, more heroin use per day, ASPD and PTSD were also associated with multiple substance dependence diagnoses. For females, childhood emotional neglect, suicide attempt/s and antisocial behaviour (ASB) were associated with increasing substance dependence diagnoses. Although the differences in ASPD for females across number of substance dependence diagnoses were significant in the univariate analysis, in the adjusted model these differences were better accounted for by prison time. A diagnosis of PTSD was not associated with increased dependence diagnoses for females (Tables 5). In sum, increasing substance dependence diagnoses were associated with poorer mental health, greater harms (overdose and suicide attempt) and child maltreatment for both sexes; however sex differences emerged with respect to type of psychiatric disorder and child maltreatment.

3. Discussion

An estimated one quarter of patients participating in opioid replacement therapy in the greater Sydney area participated in this study of heroin dependence. The study has enabled a more complete understanding of the childhood and adult experiences of this population. Participants had experienced high levels of childhood maltreatment, parental substance use, and parental conflict. Unsurprisingly, mental health problems, early substance use, criminal activity, and multiple dependence diagnoses were also highly prevalent. It has also highlighted key differences between males and females, and identified clinically relevant correlates of multiple substance dependence for both sexes. The inclusion of demographic, child maltreatment and clinical variables presents, to our knowledge, the most comprehensive modelling of multiple substance dependence amongst dependent heroin users to date. Of note for *both* sexes was the increase in clinical and other problems as the number of dependence diagnoses increased, whereas earlier onset of cannabis use was associated with higher numbers of dependence diagnoses.

Striking differences emerged in the childhood and adult histories of females and males. Although overall levels of childhood trauma were high, females were more likely than males to experience a range of problems in childhood. These difficulties for women were more likely to continue after the age of 18 in the form of unwanted sexual activity and violence as adults, frequently from a partner or boyfriend. Their introduction to heroin use was also more likely to be through a partner or boyfriend. In addition, women had a higher prevalence of most adult psychiatric disorders, suicidal thoughts, persistent suicidal thoughts, and suicide attempts (Chatham, et al., 1999; Chiang, et al., 2007). Evidence of a more dysfunctional family background for female participants confirms earlier studies identifying these family background factors as strongly associated with the development of both substance use disorders and mental illness in females (Graeven & Schaefer, 1978; Hyman, Garcia, & Sinha, 2006). Women were likely to have sought treatment at a younger age and to remain in treatment for longer (Chatham, et al., 1999). Whether earlier treatment seeking is due to the higher rates of psychiatric problems, dysfunctional family background and adult violence experienced by women is unclear.

Conversely, males had higher prevalence of most dependence diagnoses and were more likely to be involved in antisocial behaviours. Males and females had similar lifetime prevalence of sedative and cocaine dependence. In general population studies, prescribed sedative use is often higher amongst females (Goodwin & Hasin, 2002) but this pattern may not extend to sedative dependence amongst heroin users (Darke & Ross, 1997). However, female heroin users have

been shown to obtain more benzodiazepine prescriptions than male heroin users (Darke, et al., 2003). Overall, males appeared to have a higher prevalence of externalising problems, whereas females were more at risk of internalising disorders.

The most consistent predictors of multiple substance dependence diagnoses for both sexes were mental health variables, antisocial behaviours, childhood sexual abuse, younger age at first cannabis use and heroin overdose. The relationship between multiple dependence diagnoses and poorer mental health has been demonstrated previously, as has the risk for overdose and suicide attempts (Darke & Ross, 1997; Darke, et al., 1996; Darke, et al., 2007b). The link between early onset and frequent cannabis use and subsequent other illicit drug use has been demonstrated in other studies and populations (Agrawal, et al., 2006a; Fergusson, Boden, & Horwood, 2008; Lynskey, et al., 2003), and may be partially but not wholly explained by shared genetic and environmental risks (Hall & Lynskey, 2005; Lynskey, et al., 2003; Lynskey, Vink, & Boomsma, 2006). Sexual abuse has also been linked to greater drug related problems and poorer psychosocial functioning amongst women entering opioid replacement treatment (Bartholomew, Courtney, Rowan-Szal, & Simpson, 2005). More generally, childhood sexual abuse has been demonstrated to increase the risk of substance use disorders and early onset drug user over and above the risk conferred by genetic and familial factors (Nelson, et al., 2006). Some evidence suggests that women may be more at risk of increased severity of substance abuse following childhood emotional neglect than males (Hyman, et al., 2006).

For males, there was a consistently positive relationship between dependence diagnoses and all mental health diagnoses assessed except panic disorder. Females with more substance dependence diagnoses were also at increased risk for depression, BPD but not PTSD or ASPD. The relationship between substance dependence diagnoses and PTSD for males may be externally mediated: exposure to trauma may increase as drug use increases; however there was no evidence of lower rates of trauma for females.

The relationship between ASPD and substance use disorders is entirely consistent with the existence of a spectrum of externalising disorders. This relationship held true for males and was partially supported for females. Work by Krueger and colleagues has placed heroin and other drug dependence in the context of a broader externalising spectrum, albeit closely linked to internalising disorders (Krueger & Markon, 2006; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Krueger, et al., 2005). In the current study, there was an increase in other externalising problems (antisocial behaviour/ASPD, prison time) as the number of dependence diagnoses increased, whereas internalising disorders were less consistently linked to greater substance dependence.

The aetiology of such comorbidity has been the topic of extensive research. Many theories have focused on the co-occurrence of two disorders. Some argue for a direct causal relationship whereby a mental illness causes substance use problems. A subset of this theory is the self-medication hypothesis. An alternative explanation is that substance use problems cause a mental illness, such as the case put forward for alcohol causing secondary depression (Fergusson et al., 2009), or cannabis triggering psychosis in vulnerable individuals (Degenhardt et al., 2003b, Muller-Vahl & Emrich, 2008, McGrath et al., 2010). There are other feasible explanations for comorbidity, such as an indirect causal relationship whereby the presence of one disorder affects a third variable, which in turn increases the risk for the development of a second disorder. Early-onset substance use disorders decrease the likelihood of completing school and other education, and increase the likelihood of teenage parenthood and marriage breakdown (Kessler et al., 1995, Kessler et al., 1997a, Kessler et al., 1998). This may in turn lead to difficulties establishing stable relationships and earning an income, which could increase the likelihood of depression and other disorders. There is also the common factor theory which proposes that there are genetic, intrapersonal, environmental or social factors or

an interaction between all of these factors that underpin the co-occurrence of disorders (Kendler et al., 2003b). Whilst this study cannot be interpreted as support for any of the theories of comorbidity, the levels of comorbidity observed in this sample argue against one unidirectional theory. It is more likely that the comorbidity between substance use disorders and psychiatric disorders seen here is the result of a combination of direct causal relationships and common genetic and environmental risk factors. There is evidence that externalising disorders such as substance use disorders and ASPD can be represented as a spectrum of severity or liability, and internalising disorders form a separate but related severity spectrum (Krueger etc). The idea behind these models is that it is these latent severity spectra that give rise to comorbidity across numerous mental disorders.

Implications

Several clinical and public health implications arise from these findings. Most simply, those with greater substance use and dependence are more at risk for mental health disorders, personality disorders, suicide and overdose. However even those with no other dependence diagnoses had relatively high rates of these problems. Although a lack of other substance dependence does not preclude these problems, there may be a rationale for more intensive interventions for those with a greater number of dependence diagnoses. There is also a case for shifting the emphasis when assessing and addressing risks for males and females: males may be more at risk of criminal reoffending and other substance dependence, particularly alcohol dependence which has implications for liver disease given the high prevalence of the Hepatitis C virus amongst injecting drug users (Day & Dolan, 2006). Females in this population appear to be more at risk of problems related to sex work, adult violence and sexual assault, childhood trauma, internalising disorders and suicidality. Additionally, the prevalence of these problems for women with multiple substance dependence diagnoses is exceptionally high.

The risk for women (and to some extent men) of ongoing assault and violence needs to be addressed to ensure their physical safety, and to prevent further trauma. When the clinical profile is complicated by other substance dependence diagnoses and ongoing trauma it is likely that opioid replacement therapy alone, whilst effective in reducing many of the problems associated with heroin dependence (Cacciola, Alterman, Rutherford, McKay, & Mulvaney, 2001), is insufficient for these more complex cases (Sacks, McKendrick, & Banks, 2008). Where there is a history of childhood trauma, treatment may require a concurrent focus on substance use, mental health and trauma issues, with some evidence suggesting that such an approach is more effective than standard intervention (Cocozza, et al., 2005; Morrissey, et al., 2005). In addition, the presence of a mood disorder has been found to predict treatment dropout and poor treatment outcome across several domains more strongly than the presence of Axis II disorders amongst dependent opioid users (Kokkevi, Stefanis, Anastasopoulou, & Kostogianni, 1998; Teesson, et al., 2007). Hence, greater focus on the treatment of mood disorders may lead to better outcomes across the board.

Finally, although this was a cross-sectional study and firm conclusions about causal pathways are not possible, the results suggest that the path to heroin and multiple substance dependence may be different for males and females. A meta-analysis of studies examining genetic and environmental influences on antisocial behaviour (ASB) concluded that the heritable liability was the same for both sexes (Rhee, et al., 2002). The polygenic multiple threshold model suggests that females may need a greater liability to *express* antisocial behaviour, thus explaining the lower prevalence of ASB amongst females (Rhee, et al., 2002). Other studies have found that there are genetic effects on an individual's tendency to seek out deviant peers and high risk environments (McGue, Iacono, & Krueger, 2006; Rowe & Rodgers, 1984). This is referred to as active gene-environment correlation, where it is the child's genes which influence their liability to seek out particular environmental circumstances (Rutter, et al.,

2006). This study's results are consistent with a more passive gene-environment correlation for females than for males. Passive gene-environment correlation refers to the parents' genetic liability for ASB which in turn shapes the home environment. Thus, for the women in this study we may be observing greater parental ASB resulting in a more hostile home environment which in turn leads to greater negative peer affiliations. The finding that women were more likely to experience most forms of child maltreatment, to first use heroin with a boyfriend or partner, and to experience ongoing adult violence at the hands of a partner suggests a series of poor relationships and maltreatment that began in early childhood. For the men, there may be a more active gene-environment correlation whereby they are actively selecting more problematic environments and peers during adolescence.

Limitations

The participants in this study may not be representative of dependent heroin users who have never sought treatment, as most of our participants are at the severe end of the heroin dependence spectrum. However, non-treatment samples in Australia have been found to have similar characteristics to treatment samples (Ross, et al., 2005). A further limitation is that the participants were predominantly heroin dependent, not opioid analgesic dependent. Differences between these two groups may mean that different associations exist and so the results of this study may not generalize to dependent opioid analgesic users (Subramaniam & Stitzer, 2009). The study was also cross-sectional and retrospective. Although studies have shown that adult recall of child abuse can be inconsistent, the bias is towards false negatives rather than false positives (Fergusson, Horwood, & Woodward, 2000; Hardt & Rutter, 2004). There is also evidence that self-reported drug use amongst heroin users is reliable in research settings (Darke, 1998; Ross, et al., 2003). However, it is difficult to draw firm conclusions about pathways and causal relationships from a cross-sectional study. Finally, lifetime diagnoses were used so it is not possible to distinguish between those with concurrent and non-concurrent substance dependence diagnoses.

Conclusions

Dependent heroin users are not a homogeneous group, with some having no other lifetime substance dependence diagnoses whilst others had five other dependence diagnoses. These differences in substance use were reflected in other problems, which increased as the number of other substance dependence diagnoses increases. In addition, clinically important differences between males and females emerged with regard to childhood and adult trauma, antisocial behaviours, mental health disorders, dependence diagnoses and variables associated with a higher number of dependence diagnoses. Despite these differences, the treatment options for heroin dependence are somewhat limited and do not account for the often clinically complex profiles amongst this population.

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Table 1Demographic characteristics and substance use/dependence by sex^a

Variables	Males n=914	Females n=599	Total n=1513	Statistic (95% CI)
Age at interview yrs (SD)	37.2 (8.4)	35.3 (8.6)	36.4 (8.5)	t=-4.35, df 1511 ***
Marital status (%)	62.0	70.3	65.3	OR 0.69 (0.55–0.86) *
Unemployed (%)	81.8	83.7	82.5	OR 0.85 (0.65–1.12)
Government benefit (%)	89	92.5	90.4	OR 0.64 (0.44–0.92) *
School education only (%)	70.6	70.3	70.5	OR 1.00 (0.80–1.25)
Cannabis dependence (%)	57.8	50.0	55.5	OR 1.26 (1.02–1.55) *
Stimulant dependence (%)	52.2	45.8	49.8	OR 1.30 (1.05–1.59) *
Sedative dependence (%)	35.4	37.6	36.3	OR 0.91 (0.74–1.13)
Cocaine dependence (%)	32.6	30.7	31.9	OR 1.09 (0.87–1.36)
Alcohol dependence (%)	43.0	34.7	39.8	OR 1.42 (1.15–1.76) ***
Nicotine dependence (%)	64.0	64.7	64.3	OR 0.97 (0.78–1.20)
Onset heroin use yrs (SD)	19.6 (5.6)	19.4 (5.6)	19.5 (5.6)	t=-0.77, df 1511
Onset heroin dependence yrs (SD)	23.3 (6.4)	22.6 (6.7)	23.0 (6.5)	t=-1.78, df 1476
Duration heroin dependence yrs (SD)	10.6 (7.5)	9.0 (7.1)	9.9 (7.3)	t=-4.24, df 1489 ***
Onset regular drinking yrs (SD)	16.7 (4.8)	16.4 (5.0)	16.6 (4.7)	t=-0.85, df 1175
Onset alcohol intoxication yrs (SD)	14.5 (3.0)	14.2 (3.2)	14.3 (3.1)	t=-1.67, df 1431
Onset cannabis use yrs (SD)	14.3 (2.9)	14.2 (3.1)	14.2 (3.0)	t=-0.34, df 1490

^a odds ratios obtained by cross tabulations, differences in means obtained by independent t-tests*
p<0.05**
p<0.01***
p<0.001

Table 2Introduction to heroin use by sex^a

Variable	Males	Females	Total	OR (95% CI)
<i>First offered heroin by:</i>				
Partner, spouse, boyfriend, girlfriend	5.6	28.4	14.4	0.15 (0.11–0.21) ***
Friend	67.0	46.7	59.1	2.33 (1.87–2.90) ***
Acquaintance	16.4	15.0	15.8	1.11 (0.83–1.49)
<i>First used heroin with:</i>				
Partner, spouse, boyfriend, girlfriend	9.1	36.3	19.8	0.18 (0.13–0.24) ***
Friend	69.6	43.5	59.5	2.94 (2.36–3.67) ***
Acquaintance	12.1	12.3	12.1	0.99 (0.71–1.36)

^a odds ratios obtained by cross tabulations***
p<0.001

Table 3Child maltreatment, adult trauma and mental health variables by sex^a

Variable	Males % n=914	Females % n=599	Total % n=1513	Statistic (95% CI)
Close to mother	69.8	54.5	63.7	OR 1.28 (1.18–1.39) ***
Close to father	42.1	39.5	41.0	OR 1.11 (0.90–1.37)
Raised by both biological parents to age 16	45.9	34.1	41.2	OR 1.66 (1.34–2.06) ***
Parental substance problem	46.5	56.4	50.5	OR 0.67 (0.54–0.83) ***
Parental conflict (violent)	72.9	76.4	74.3	OR 0.84 (0.66–1.06)
Physical punishment (any)	86.7	81.8	84.7	OR 1.06 (1.01–1.11) **
Physical punishment resulting in injury	38.9	42.8	40.4	OR 0.86 (0.69–1.05)
Sexual abuse (contact only)	6.9	11.0	8.5	OR 0.60 (0.42–0.86) **
Sexual abuse penetrative	21.3	53.8	34.1	OR 0.24 (0.19–0.30) ***
Emotional abuse	48.2	60.7	53.1	OR 0.60 (0.48–0.77) ***
Emotional neglect	69.0	78.9	72.9	OR 0.60 (0.47–0.77) ***
Physical neglect	12.6	16.2	14.1	OR 0.76 (0.56–1.02)
Supervisory neglect	34.1	43.7	37.9	OR 0.67 (0.54–0.82) ***
Unwanted sexual activity (adult)	10.7	47.7	25.3	OR 0.13 (0.10–0.17) ***
No. of unwanted sexual acts (SD)	6.9 (15.8)	14.5 (43.9)	11.9 (36.9)	t=2.43, df 347 *
Victim of violence (adult)	21.6	35.7	27.2	OR 0.50 (0.40–0.62) ***
Perpetrator of violence (adult)	15.8	7.5	12.5	OR 2.30 (1.62–3.28) ***
Panic disorder	20.0	31.2	24.4	OR 0.55 (0.43–0.69) ***
PTSD ^b	42.7	58.5	49.6	OR 0.45 (0.37–0.56) ***
Major Depressive Episode	56.3	70.5	62.0	OR 0.53 (0.43–0.66) ***
ASPD ^b	50.8	38.7	46.0	OR 1.65 (1.34–2.04) ***
BPD screener ^b	54.6	64.0	58.3	OR 0.68 (0.55–0.84) ***
SIAS score ^b	25.6 (14.2)	27.4 (15.5)	25.7 (14.5)	t=-2.42, df 1112 *
SPS score ^b	19.1 (15.9)	21.3 (17.1)	20.1 (17.0)	t=-2.25, df 1101
12 month suicide attempt	3.3	5.8	4.3	OR 0.55 (0.33–0.90) *
Lifetime suicide attempt	26.6	40.7	32.2	OR 0.53 (0.42–0.66) ***
Multiple suicide attempts	19.9	30.6	25.2	OR 0.57 (0.37–0.86) **
Suicidal thoughts	64.6	70.3	66.8	OR 0.77 (0.62–0.96) *
Persistent suicidal thoughts	20.7	27.2	23.3	OR 0.70 (0.55–0.89) **
Overdose (heroin) - medical treatment	48.6	43.4	46.5	OR 1.23 (1.00–1.52) *
Multiple heroin overdoses	25.2	21.0	23.5	OR 1.26 (0.99–1.62)

^a odds ratios obtained by cross tabulations, differences in means obtained by independent t-tests

* p<0.05

** p<0.01

p<0.001

^b PTSD=post traumatic stress disorder; ASPD=antisocial personality disorder; BPD=borderline personality disorder; SIAS=Social Anxiety Interaction Scale; SPS=Social Phobia Scale

Table 4Treatment, relapse and criminal activity variables by sex^a

Variable	Males n=914	Females n=599	Total n=1513	Statistic (95% CI)
In treatment at interview (%)	85.4	87.2	86.1	OR 0.87 (0.66–1.47)
Age treatment 1 st sought yrs (SD)	26.0 (7.1)	24.3 (6.5)	25.3 (7.0)	t = -4.92, df 1474 ***
Treatment duration yrs (SD)	3.0 (4.3)	3.6 (4.6)	3.2 (4.4)	t = -2.46, df 1511 *
Received methadone MT (%)	98.8	98.3	98.6	OR 1.38 (0.56–3.41)
Supervised detoxification (%)	87.7	86.4	87.2	OR 1.12 (0.82–1.52)
Cold turkey (unsupervised detox) (%)	68.9	66.8	67.9	OR 1.10 (0.89–1.38)
Outpatient counselling alone (%)	29.8	28.1	29.1	OR 1.09 (0.87–1.37)
Residential rehabilitation (%)	6.9	7.0	7.0	OR 0.98 (0.66–1.47)
Relapse to heroin use (%)	85.1	80.9	83.4	OR 1.34 (1.02–1.77) *
Ever in prison (%)	65.8	39.5	55.4	OR 1.67 (1.49–1.86) ***
Ever arrested (%)	83.6	73.8	79.7	OR 1.13 (1.07–1.20) ***
Illegal activity, not arrested (%)	53.8	47.2	51.2	OR 1.14 (1.03–1.27) **
Been paid for sex (%)	14.3	48.1	27.7	OR 0.18 (0.14–0.23) ***
Found customers for sex workers (%)	12.8	16.4	14.2	OR 0.75 (0.56–1.00)
Bought or sold stolen goods (%)	85.3	79.1	82.9	OR 1.08 (1.03–1.13) **
Total time in prison yrs (SD)	4.8 (5.2)	2.5 (3.3)	4.1 (4.8)	t = -7.74, df 671 ***
Longest prison sentence yrs (SD)	2.0 (2.1)	1.1 (1.5)	1.8 (2.0)	t = -6.41, df 599 ***

^a odds ratios obtained by cross tabulations, differences in means obtained by independent t-tests

* p<0.05

** p<0.01

*** p<0.001

Table 5

characteristics for males by number of substance dependence diagnoses (in addition to heroin dependence)^a

Variable/no of SUDS	0 (n=112)	1 (n=210)	2 (n=290)	3 (n=109)	4 (n=131)	5 (n=62)	Total (n=914)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age in yrs	40.0	37.1	36.3	35.7	37.8	38.3	37.2	0.99 (0.99–1.00)	1.00 (0.99–1.01)
Unemployed (%)	85.7	79.0	77.9	78.9	89.0	90.3	81.7	0.88 (0.74–1.05)	1.01 (0.83–1.20)
Cannabis age onset in yrs	15.7	14.8	14.0	13.8	13.7	13.3	14.3	0.92 (0.90–0.94)***	0.95 (0.93–0.98)***
Times per day (heroin)	1.9	1.9	1.9	2.1	2.1	2.2	2.0	1.33 (1.17–1.51)***	1.21 (1.06–1.38)**
ASPD (%)	25.9	39.5	55.2	51.4	70.2	71.0	50.8	0.57 (0.50–0.65)***	1.28 (1.10–1.42)***
BPD screener (%)	25.0	43.3	59.9	67.0	67.2	79.0	54.7	0.53 (0.46–0.61)***	1.42 (1.21–1.65)***
Depression (%)	36.6	47.1	55.9	58.7	67.2	75.8	54.8	0.64 (0.56–0.74)***	1.25 (1.08–1.46)**
PTSD (%)	15.2	19.0	30.7	41.3	40.5	56.5	30.5	0.57 (0.49–0.66)***	1.26 (1.08–1.48)***
Panic disorder (%)	11.6	13.3	22.8	20.2	27.5	22.6	19.6	0.74 (0.63–0.88)***	-
Suicide attempt/s (%)	12.6	20.2	24.0	40.4	38.5	37.1	26.6	0.64 (0.54–0.74)***	1.38 (0.98–1.36)
Heroin overdose (%)	37.5	44.3	45.5	55.0	59.5	62.9	48.6	0.74 (0.54–0.84)***	1.19 (1.03–1.37)*
Emotional abuse (%)	27.7	39.5	46.9	45.9	55.7	62.9	45.1	0.69 (0.60–0.79)***	-
Emotional neglect (%)	56.4	66.8	71.6	62.6	75.2	82.8	69.0	0.77 (0.66–0.89)***	-
Sexual abuse (%) [#]	14.3	12.4	20.3	27.5	27.5	38.7	20.9	0.62 (0.53–0.72)***	1.27 (1.07–1.50)**
Physical abuse (%)	23.2	33.3	39.0	45.0	49.6	48.4	38.6	0.71 (0.62–0.82)***	-
Victim adult violence (%)	11.6	12.0	21.4	28.7	29.8	43.5	21.6	0.40 (0.30–0.53)***	1.38 (1.16–1.65)***
Prison time (%)	58.0	59.0	64.8	70.6	72.5	83.9	65.8	0.73 (0.63–0.84)***	1.18 (1.01–1.37)*

^aUnadjusted odds ratios obtained with univariate ordinal regression, with 5 other drug dependence diagnoses as the reference group. Adjusted odds ratios obtained with multivariate ordinal regression, with 5 other drug dependence diagnoses as the reference group.

* p < 0.05

** p < 0.01

*** p < 0.001

[#] contact + penetrative sexual abuse for males

Table 6

characteristics for females by number of substance dependence diagnoses (in addition to heroin dependence)^a

Variable/no of SUDS	0 (n=82)	1 (n=157)	2 (n=183)	3 (n=90)	4 (n=59)	5 (n=28)	Total (n=599)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age in yrs	36.7	35.7	35.0	34.5	34.5	34.6	35.3	0.98 (0.97–1.00)	** 1.00 (0.93–1.01)
Unemployed (%)	78.0	84.1	83.1	86.7	91.5	82.1	84.0	0.72 (0.48–1.05)	1.11 (0.70–1.16)
Cannabis age onset in yrs	15.4	14.2	14.7	13.9	12.7	12.3	14.2	0.89 (0.84–0.93)	*** 0.96 (0.93–0.99)
ASPD (%)	14.6	34.3	41.5	41.1	50.8	75.0	38.4	0.42 (0.32–0.58)	*** -
Antisocial behaviour (%)	76.8	93.6	97.3	95.6	100	100	93.7	0.15 (0.08–0.28)	*** 1.87 (1.20–2.89)
BPD screener (%)	35.4	58.0	63.9	81.1	83.1	89.3	64.1	0.31 (0.23–0.42)	*** 1.43 (1.16–1.77)
Depression (%)	57.3	63.7	71.0	82.2	72.9	82.9	69.6	0.53 (0.39–0.73)	*** 1.28 (1.04–1.58)
PTSD (%)	37.8	42.0	47.5	60.0	61.0	75.0	49.2	0.51 (0.38–0.69)	*** 0.98 (0.81–1.19)
Panic disorder (%)	20.7	25.5	32.8	44.4	27.1	42.9	30.9	0.76 (0.63–0.91)	** -
Suicide attempt (%)	22.0	33.1	43.1	44.9	60.3	67.9	40.7	0.43 (0.32–0.58)	*** 1.22 (1.00–1.49)
Heroin overdose (%)	31.7	38.2	43.7	55.6	49.2	53.6	43.4	0.60 (0.45–0.80)	*** 1.22 (1.01–1.47)
Emotional abuse (%)	42.7	47.8	55.2	64.4	71.2	89.3	56.1	0.46 (0.34–0.62)	*** -
Emotional neglect (%)	59.5	74.5	78.6	87.2	96.2	96.3	78.7	0.34 (0.23–0.49)	*** 1.47 (1.16–1.86)
Sexual abuse (%) [#]	37.8	39.5	55.2	63.3	72.9	71.4	52.4	0.41 (0.33–0.55)	*** 1.32 (1.09–1.59)
Physical abuse (%)	26.8	39.5	41.0	43.3	59.3	75.0	42.2	0.52 (0.38–0.69)	*** -
Victim adult violence (%)	22.0	20.5	40.1	50.0	52.5	50.0	35.7	0.38 (0.28–0.52)	*** 1.33 (1.09–1.61)
Prison time (%)	30.5	31.8	41.5	51.1	50.8	35.7	39.6	0.61 (0.45–0.81)	*** 1.30 (1.07–1.57)

^aUnadjusted odds ratios obtained with univariate ordinal regression, with 5 other drug dependence diagnoses as the reference group. Adjusted odds ratios obtained with multivariate ordinal regression, with 5 other drug dependence diagnoses as the reference group.

* p < 0.05

** p < 0.01

*** p < 0.001

[#] penetrative sexual abuse for females