ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PATIENTS ON METHADONE MAINTENANCE THERAPY

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CERTIFICATION

This is to certify that the candidate, Dr. Sharon Kaur Bhart, had carried out this research project, and to the best of my knowledge, this dissertation is entirely her work.

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ABSTRACT (ENGLISH)

BACKGROUND

There is a lack of local research regarding the prevalence of adult Attention Deficit Hyperactivity Disorder (ADHD) in patients on Methadone Maintenance Therapy (MMT). Given that current studies report a high prevalence of adult ADHD in these patients along with associated adverse outcomes, it would be useful to determine the factors associated with ADHD in patients on MMT and its impact on substance use related factors.

OBJECTIVE

This study primarily aims to determine the prevalence of adult ADHD in patients enrolled in the MMT program. In addition, it also aims to determine the association between ADHD and sociodemographic characteristics, substance use related factors, other psychiatric comorbidites, crime, HIV risk and quality of life in patients on MMT.

METHODS

This is a cross-sectional study conducted in the methadone clinic in Hospital Kuala Lumpur and Klinik Kesihatan Kuala Lumpur. A total of 145 patients with ADHD whose diagnosis were based on the M.I.N.I International Neuropsychiatric Interview-Plus (M.I.N.I.-Plus) (Adult ADHD version) were recruited. Substance use related factors, crime and HIV risk-taking behaviour were assessed with the Opiate Treatment Index (OTI). The presence of other psychiatric comorbidities was assessed using the M.I.N.I and M.I.N.I Plus. Finally, quality of life was assessed using the World Health Organisation Quality of Life BREF (WHOQOL-BREF).

RESULTS

The prevalence of adult ADHD in patients on MMT in this study was 19.3%. A diagnosis of ADHD in these patients was significantly associated with a lower education level and with unemployment. ADHD was also significantly associated with an early age of first drug use, an increase in the number of drugs used and also preferential use of heroin, cannabis and methamphetamines. These patients had a higher number of other psychiatric comorbidities and significantly higher prevalence of Major Depressive Disorder. Patients with comorbid ADHD had higher crime rates, a higher risk of acquiring HIV along with lower quality of life scores. These outcomes remained significant after accounting for a history of conduct disorder.

CONCLUSION

This study showed a substantial prevalence of adult ADHD in patients on MMT. A diagnosis of ADHD in these patients was associated with unfavourable outcomes in comparison to patients without ADHD. There is a need for the recognition and treatment of adult ADHD in patients enrolled in MMT.

ABSTRAK (BAHASA MELAYU)

LATAR BELAKANG

Terdapat kekurangan kajian tempatan mengenai kadar prevalen *Attention Deficit Hyperactivity Disorder* (ADHD) dewasa di kalangan pesakit yang mengambil rawatan terapi gantian Methadone. Kajian lain menunjukkan kadar prevalen ADHD yang tinggi di golongan pesakit ini beserta dengan hubungkait dengan faktor negatif. Memandangkan ini, wujudnya keperluan untuk mengenalpasti faktor yang berhubungkait dengan diagnosa ADHD di kalangan pesakit yang menjalani rawatan Methadone beserta dengan impak terhadap pengunaan bahan ketagihan.

OBJEKTIF

Objektif kajian ini adalah untuk mengenalpasti kadar prevalen ADHD dewasa di kalangan pesakit yang mengambil rawatan terapi gantian Methadone. Objektif kedua kajian ini adalah untuk menyelidik kaitan antara ADHD dengan faktor socio-demografi, faktor berkaitan dengan pengunaan bahan ketagihan, gejala psikiatri lain, jenayah, risiko *Human Immunodeficiency Virus* (HIV) dan qualiti kehidupan.

METODOLOGI

Kajian ini dijalankan di kinik Methadone di Hospital Kuala Lumpur dan Klinik Kesihatan Kuala Lumpur. Sejumlah 145 subjek yang diberi diagnosa ADHD selepas memenuhi kriteria berdasarkan *M.I.N.I International Neuropsychiatric Interview-Plus* (M.I.N.I.-Plus) (versi ADHD untuk dewasa) dimasukkan dalam kajian ini. Subjek seterusnya diwawancara untuk mengenalpasti faktor berkaitan dengan pengunaan dadah, jenayah dan risiko untuk HIV menerusi *Opiate Treatment Index* (OTI). M.I.N.I dan M.I.N.I-Plus digunakan untuk mengesan gejala psikiatri lain.

Kualiti kehidupan subjek dikenalpasti dengan *World Health Organisation Quality of Life BREF* (WHOQOL-BREF).

KEPUTUSAN

Kadar prevalan ADHD di kalangan pesakit yang mengambil rawatan gantian Methadone dalam kajian ini adalah 19.3%. Diagnosa ADHD didapati berkaitan dengan tahap pendidikan yang rendah dan pengangguran. ADHD juga mempunyai hubungkaitan rapat dengan pengunaan dadah pada umur yang lebih awal, pengunaan dadah yang lebih berserta keutamaan kepada pengunaan dadah jenis heroin, cannabis dan methamphetamine. Subjek dengan ADHD juga mempunyai lebih diagnosa gejala psikiatri lain, dan prevalen yang lebih tinggi untuk *Major Depressive Disorder*. Di samping itu, mereka juga mempunyai penglibataan yang lebih tinggi dalam jenayah, risiko HIV yang tinggi berserta dengan qualiti kehidupan yang rendah. Hubungkait yang rapat ini kekal selepas mengambil kira pengaruh conduct disorder.

KESIMPULAN

Kajian ini menunjukkan bahawa kadar prevalen ADHD dewasa di kalangan pesakit yang mengambil rawatan terapi gantian Methadone. Di samping itu, diagnosa ADHD di kalangan pesakit ini berkaitan dengan hasil yang negatif berbanding dengan pesakit tanpa diagnosis ADHD. Oleh itu, ada keperluan untuk mengenalpasti ADHD di golongan pesakit ini dan justeru itu memberi rawatan yang lebih awal dan khusus.

1.0 INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder with hallmark symptoms of pervasive and persistent deficits in attention, hyperactivity and impulsivity.[1] It is considered to originate in childhood and affects 4% to 12% of children who are school-aged.[2] A Malaysian study based on parent and teacher ratings of children aged 6 to 12 years yielded a prevalence rate of 1.6%, with a male to female ratio of 4:1.[3] ADHD persists into adulthood in 10% to 60% of cases.[2] In most of these adults, hyperactivity and impulsivity tend to abate while symptoms of attention deficit persist.

Prior attempts to determine the preponderance of adult hyperactivity were either based on extrapolation from childhood prevalence data combined with research evidence reporting the fraction of paediatric cases that persisted into adulthood,[4,5] or via direct assessment from small samples.[6,7] These studies reported adult ADHD prevalence rates of 1% to 6%. Although there is no global consensus, multiple imputation analyses indicate that the current global prevalence of ADHD among adults is 3.4%, with a range of 1.2% to 7.3%.[8]

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), there are nine criteria for attention deficit, which includes poor attention to details, challenges in maintaining attention, appearing distracted, failure to complete tasks, challenges in organisation, not listening when spoken to, forgetfulness, reluctance to participate in mentally challenging tasks, and frequently losing everyday required items.[9] The symptoms of hyperactivity and impulsivity include being fidgety, inability to remain seated, inability to conduct activities in a quiet manner, constantly on-the-go, restlessness, speaking in excess, inability to wait their turn including in conversations and interrupting others.[9] At least six symptoms each are required

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from both categories (only five symptoms from each category for individuals aged 17 years and above) for at least six months. A DSM-5 diagnosis of ADHD also requires the presence of some of the above symptoms to be present before the age of 12. In addition, the symptoms have to manifest in at least two different environmental settings. These disturbances must have resulted in deterioration in functioning in order to qualify as a disorder.[9]

DSM-5 further sub classifies ADHD into three categories the first being combined presentation where both the features of attention deficit and hyperactivity-impulsivity are seen.[9] The second category is predominantly inattentive presentation, where features of hyperactivity-impulsivity are not evidenced. Finally, there is predominantly hyperactive/impulsive presentation, in which features of attention deficit are not seen. In all three categories, the duration of time in which the symptoms are observed is six months.[9]

The aetiology of ADHD is both multifactorial and heterogenous; a complex interplay of biology, genes and the environment. Research on twin and adoption studies indicate that genetic factors confer a substantial portion to its aetiology with heritability ranging from 60% to 90%.[10] Neurological studies have demonstrated a deficit in connectivity as well as neurotransmitter function in significant regions of the brain, along with lack of inhibitory control and delay in brain maturation.[11]

ADHD is linked to dysfunctional interpersonal, academic and occupational functioning, elevated rates of substance dependence, with chronic neuropsychological deficits resulting in an overall heightened associated cost to society.[12] More specifically, adults with ADHD display

more psychological symptoms, higher substance use, poorer job performance and more marital discord than adults without ADHD.[13]

On the other hand, substance abuse is a global problem that has resulted in consequential detriment to individuals, their families and the community at large. The use of illicit drugs contributes to nearly 9% of the total global burden of disease.[14] Latest figures show that there are approximately 185 million substance users worldwide, with cannabis, amphetamines and opiates being the most frequently used drugs.[14] In Malaysia there are an estimated 300, 241 drug users between 1988 and 2006, and this represents 1.1% of the local population.[15] Furthermore, there are 170,000 intravenous drug users locally.[15]

There are nearly 14 million people abusing opioids worldwide.[16] Although this figure is lower than that of other drugs, individuals who abuse opioids make up a much larger percentage of substance abusers who seek treatment. The use of opioids is fraught with numerous complications. This includes contracting infections such as Hepatitis B and C and Human Immunodeficiency Virus (HIV), pulmonary, cardiac and hepatic complications as well as fatalities from drug overdose.[17]

The roots of opioid use in Malaysia can be traced as far back as the eighth century where it was predominantly used by Chinese immigrants.[18] The influx of opium into our local shores was facilitated by Malaysia's strategic location in the Golden Triangle. Opium use heightened during the British invasion and throughout the country's post-independence era.[18] In cognisance of the seriousness of opioid use, the Drug Dependents (Treatment and Rehabilitation) Act was enacted in 1983 whereby drug users were incarcerated for a maximum of two years.[19] The

mainstay of drug rehabilitation was the government funded "Pusat Serenti". Mounting evidence showing high rates of recidivism among previous addicts who underwent these programmes along with the rapid increase in the rates of HIV related to intravenous heroin use resulted in a paradigm shift in the form of harm reduction management, namely methadone.[19]

Methadone is a synthetic miu receptor agonist that possesses similar pharmacological properties to morphine.[20] It is well absorbed upon oral intake with onset of action detectable within 30 minutes and peak effects at four hours.[20] Methadone undergoes metabolisation in the liver and is later excreted in the urine and bile. It is orally active and long-acting, where one dose can inhibit symptoms of opioid withdrawal for up to 36 hours without producing euphoria, analgesia and drowsiness.[21] The optimum maintenance dose of methadone is the dose which serves to ameliorate withdrawals and reduce opioid cravings without resulting in unwanted side effects such as sedation or respiratory depression.[22] This maintenance dose can be reached within two to eight weeks of initiation of methadone. Stable doses of methadone are associated with better retention in the methadone program.[23] This allows patients to resume their daily functions of living without unwanted adverse effects.[21] In addition, methadone also inhibits craving for opioids.[21]

Methadone maintenance therapy (MMT) was first implemented as part of a nationwide government-financed project in Malaysia in 2005.[24] It has significantly reduced opioid and other drug use. It improves treatment retention and has a retention rate of 75%.[24] In addition, MMT has been shown to reduce criminal activity, HIV risk behaviours and transmission, opioid overdose and all-cause mortality. Research shows a reduction of urine opiate from 45% to 10% following a 12-month treatment period with MMT.[25] In 2011, there were a total of 674 MMT centres reaching out to 44,428 drug users.[25]

Research has long established an association between ADHD and substance dependence. The prevalence of hyperactive disorder is dramatically increased among the population of substance users.[26,27,28] Globally, this prevalence rate shows a wide variation with figures ranging from 2% to as high as 83%.[29,30] Not much light has been shed on the prevalence of ADHD in opioid users on methadone maintenance therapy. Of the few published studies, almost half were based on a retrospective diagnosis of childhood ADHD as opposed to its expression in adults.[31] Prevalence of 22% of childhood hyperactivity amongst patients on methadone therapy was found in one of the first studies highlighting this issue.[32] Later studies reported that up to 58% of patients in a methadone maintenance program reported experiencing one or more ADHD symptoms.[33] In summary, the prevalence rate of adult hyperactivity in substance abusers seeking methadone treatment range from 5% to 29% depending on the diagnostic criteria, sample population as well as treatment setting.[31] With regards to sociodemographic factors, drug users who have been diagnosed with ADHD tended to be in the younger age group with a lower educational attainment and employment status.[31,34,35]

There is a relatively high prevalence of substance use in adults with ADHD with estimates ranging from 10% to 24%.[36] When left untreated, patients with ADHD have a higher risk than those without ADHD of developing problematic substance use.[37] More specifically, hyperactive individuals start drug use at an earlier age earlier and progress more rapidly to drug abuse and dependence.[37] ADHD in patients with a substance use disorder is also associated with a more severe substance abuse with a poorer prognosis.[38] After controlling for conduct disorder, there were unique effects of ADHD on age of first substance use and number of substance use disorder diagnoses.[28]

There is conflicting evidence on the type of drug preferred by hyperactive drug abusers. Some studies show a higher prevalence of opioid use among these individuals,[39] whilst other research points to the preferential use of nicotine, cannabis or stimulants.[40,41,42] In contrast, there are contrasting studies that fail to show a significant difference in the drug of choice in this population.[43] In summary, evidence shows that the presence of ADHD is related to a more severe expression and complicated course of substance use.

Similarly, a growing body of literature also reports that ADHD is associated with a more severe manifestation of psychiatric disorders.[44,45] In addition, drug users with ADHD tend to have a higher number of psychiatric diagnoses in comparison to their counterparts. Interestingly, these associations remained significant even after adjusting for the presence of conduct disorder.[28]

The presence of a comorbid ADHD in the population of drug users also exerts a negative influence on other facets of life. For instance, studies point to a higher crime rate, with an earlier age of first arrest.[32] Furthermore, ADHD amplifies the risky behaviour associated with HIV among drug users, namely via a higher incidence of intravenous drug use combined with unsafe sexual practices.[46] This is a grave finding that bears further research, especially considering the fact that substance use itself confers a high risk of acquiring numerous blood borne infections. However, studies on the influence of ADHD on crime and HIV are sparse and bear further research. In congruence with the above findings, drug users diagnosed with hyperactivity also tend to have a poorer quality of life as well as reduced social functioning.[31,35]

The presence of comorbid ADHD in opioid users on MMT is characterised by greater addiction severity and a higher number of psychopathology.[31] These patients demonstrated more cognitive impairment than their counterparts without ADHD.[32] Patients with significant symptoms of ADHD achieved lower rates of abstinence from drug use and retention in the methadone program than those without significant symptoms.[47] It can thus be concluded from research evidence that the co-occurrence of hyperactivity in individuals seeking MMT tends to result in poor treatment outcome.[48]

In summary, methadone has been shown to be effective in reducing drug use, HIV rates and crime. However compliance to the methadone program may be hampered by ADHD, be it as a result of the symptoms of the illness or its sequelae. In addition, hyperactivity also has an adverse impact on substance use patterns as well as quality of life.[31] Currently, ADHD is not routinely assessed for in patients with opioid dependence seeking MMT in our local methadone clinics. The identification and treatment of these symptoms of ADHD has the potential to both improve the patient's functioning and quality of life as well as enhance compliance and retention rates in MMT.

2.0   LITERATURE REVIEW

2.1   THE PREVALENCE OF ADHD IN PATIENTS ON MMT

The occurrence of adult ADHD among individuals with SUD has consistently and persistently been overestimated.[26,27,28] Depending on the study methodology, the prevalence of hyperactivity in drug users range from 14% to 44%.[49,50] This is in stark comparison to the community prevalence of ADHD which is estimated at 2.5% to 4%.[51] There is a wide variation in the individual country prevalence of ADHD in patients with SUD, with a rate as low as 2% in Iceland up to 83% in Japan.[29,30] In India, up to 22% of patients with SUD were reported to have adult ADHD.[52] A meta analysis that included 12 studies of adult substance users engaged in treatment revealed a pooled ADHD prevalence of 23.3% with a range of 10% to 54% in each study. [53] Reasons for this large variation include distinctions in diagnostic criteria used, main drug of abuse, demographic factors and treatment variables.[50]

Changes in the diagnostic criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) were postulated to affect the prevalence of adult ADHD among patients with substance use.[50] More specifically, the increase in age criteria for the onset of ADHD symptoms along with a reduction in the number of symptoms required for an ADHD diagnosis may result in a higher prevalence of adult ADHD.[50] With respect to that, an international cross-sectional study utilising identical diagnostic criteria, assessment methods and instruments was recently conducted, revealing a prevalence rate of 5.4% to 31.3%.[50] This is indeed an increased rate in comparison to the 10% to 24% prevalence rate obtained by studies that utilised DSM-4 criteria.[54,55]

There is a paucity of studies of patients with ADHD who are enrolled in methadone therapy. In addition, many of them focused on a retrospective diagnosis of childhood ADHD as opposed to its adult manifestations.[31] In a study of 157 opioid users undergoing methadone

replacement, the prevalence of childhood ADHD was 22%.[32] However, assessment of adult ADHD symptoms was not performed. A more extensive study that encompassed both childhood and adult presentation of ADHD in a sample of 125 individuals enrolled in a methadone program revealed an adult ADHD prevalence of 16.7%.[55] In another study involving 687 patients registered to a methadone maintenance program in Minnesota, 19% of them revealed ADHD symptoms that impaired daily functioning.[33] In Italy, an ADHD prevalence rate of 19.4% was found amongst opioid abusers on substitution treatment.[40] A similar study of heroin users on methadone in Taiwan resulted in a 7.8% prevalence rate.[56] There is no local research with regards to the prevalence of ADHD amongst Malaysian opioid abusers or those seeking methadone treatment.

2.2   THE ASSOCIATION BETWEEN ADHD AND SOCIODEMOGRAPHIC CHARACTERISTICS

AGE

Research evidence for the association between ADHD and age in substance users is rather consistent. In the Netherlands study mentioned prior, the 48 patients on MMT diagnosed with ADHD were significantly younger than the group of patients on MMT without ADHD.[31] The mean age of the ADHD group was 37.8 whereas the mean age for the non-ADHD group was 41.8.[31] In Zurich, the age range of the opioid dependent inpatient sample was 18 to 48 years.[57] The subgroup with hyperactivity showed an average trend of being four years younger than the non-ADHD subgroup. However, this figure was not statistically significant.[57] In the earlier mentioned Connecticut study of patients with cocaine and opioid dependence, logistic GEE regression of the ADHD diagnosis on multiple sociodemographic criteria showed a significant difference for age with an earlier mean age of 32.56 years for the subgroup of ADHD compared to a mean of 38.54 years for the subgroup without.[28] Meanwhile, Eyre's study of childhood ADHD amongst heroin abusers failed to demonstrate a significant age difference.[32]

Overall the evidence shows that substance dependent individuals (including those enrolled in methadone replacement programs) diagnosed with ADHD tend to fall in the younger age group when compared to their non-ADHD counterparts. This is in congruence with research demonstrating an overall higher prevalence of ADHD in the younger age group as well as a tendency for the symptoms and severity of ADHD to diminish with age.[35]

GENDER

The majority of studies involving either treatment seeking or non treatment seeking opioid abusers with comorbid ADHD failed to report any gender differences.[31,32]. This may be explained by previous literature that reports different ratios for the prevalence of childhood ADHD and adult ADHD among males and females. In hyperactive children, the male to female ratios vary from 10:1 to 6:1 whereas the ratio in hyperactive adults declines to 1:1.[5]

MARITAL STATUS

The National Comorbidity Survey Replication in the United States reported that adult ADHD was significantly associated with being previously married.[51] However, there was no association with being married or never having married.[51] A community sample of Germans showed a higher prevalence of being divorced or never being married among those with ADHD.[58] However, these findings are not replicated in studies involving adult hyperactivity in substance abusers. One of the pioneering studies on ADHD in opioid users showed no difference in the marital status among the ADHD subgroup versus their counterparts.[32] Later studies echoed this finding in a sample of hyperactive methadone seeking individuals.[31] The earlier mentioned Swiss study on opioid abusers also failed to show a difference in marital status between the group with and without adult hyperactivity.[57]

EDUCATION

On average, hyperactive individuals had completed nearly 3 years less of schooling than the control group.[59] of those with ADHD had dropped out of school versus 2% in the latter group. These differences remained significant even after antisocial personality disorder was accounted for.[59] Nearly half of opioid addicts who reported symptoms of ADHD failed to complete school, whereas 82% of opioid dependents without symptoms of ADHD completed school.[60] However, rates with or without vocational training or university studies did not differ between the two groups.[60] There was no significant difference reported for years of education among opioid addicts with ADHD (mean of 11.48 years) versus opioid addicts without a diagnosis of ADHD (mean of 11.39 years).[28] In Connecticut, opioid addicts seeking treatment who who were diagnosed with ADHD were more likely to drop out of school at a younger age than their non-ADHD counterparts.[32] They were also more likely to be engaged in jobs that were semi-skilled or unskilled in comparison to those without ADHD.[32]

Overall, a diagnosis of ADHD in the population of substance users is independently associated with a lower level of academic attainment. There are numerous attributing factors which include the core symptoms of ADHD itself, neuro-cognitive deficits and school environments that are particularly not conducive to hyperactive pupils.[59] The evidence from these studies are also congruent with current knowledge of how ADHD symptoms are known to cause a decline in educational achievement and that is thought to play a role in the association between childhood hyperactivity and the subsequent onset of drug and alcohol related problems.[34]

EMPLOYMENT

Data from research shows that a diagnosis of ADHD is associated with occupational decline, namely impaired work performance and higher levels of unemployment.[28,51,58] For the individuals with ADHD who were gainfully employed, they tended to belong to the lower working class, with very few holding professional positions.[59] Opioid users with ADHD tended to work in positions that require minimal or no skills.[32] A study on treatment seeking drug abusers showed that there was no significant difference in employment status in the last three months from admission between those with and without ADHD.[57] However, the subgroup with hyperactivity had a significantly lower professional aptitude as reflected by lesser expert training and experience.[57] Although the Netherlands study on opioid dependent adults on methadone treatment did not show a statistically significant difference in employment rate among those with ADHD and without, this study is in the minority when taken into account the much larger proportion of research reporting poorer occupational functioning among SUD patients diagnosed with hyperactivity.[31]

2.3   THE PREVALENCE OF SUBSTANCE USE IN ADHD

Research has distinctly shown that the presence of ADHD influences the use of alcohol and illicit substances beginning in adolescence and into adulthood. Adults with both a history of hyperactivity and current adult hyperactivity are twice as likely to develop drug dependence compared to adults without ADHD.[28] Initial evidence for the role of ADHD in the genesis of substance abuse came from studies that showed an increased prevalence of childhood ADHD amongst individuals seeking treatment for various SUDs.[61] For instance, 22% of nearly 160 patients seeking treatment for opioid dependence fulfilled the criteria for childhood hyperactivity.[32] Further retrospective studies continue to show the impact of ADHD on substance dependence. For instance, out of 56 men and women with a DSM-III-R diagnosis for ADHD, 30% met the criteria for drug dependence and 34% met the criteria for alcohol

dependence.[62] However, the validity and accuracy of forming a diagnosis based on retrospective collection of hyperactivity symptoms has been challenged. There may be many distortions associated with long-term recall especially among drug dependent patients seeking treatment.[63] This suggests that it is preferable to obtain data from longitudinal prospective studies instead, whereby children are followed up through adolescence and adulthood and repeatedly tested for symptoms of ADHD and drug use at various intervals in time.[64]

The findings in prospective studies tend to echo those of the retrospective type. In one study spanning nine years, men who had a childhood diagnosis of ADHD carried a 19% rate of developing a substance or alcohol use disorder compared to the control group at 7%.[65] The authors further concluded that the persistence of ADHD was the most significant risk factor for the occurrence of drug abuse.[65] Another prospective study found that the lifetime prevalence rate for SUD for adults with ADHD was nearly twice as high as adults without ADHD.[66] It can thus be surmised that adults who fulfil the diagnostic criteria for ADHD possess a greater risk of developing a SUD that is characterised by more complex and severe patterns of drug use and abuse.

2.4   THE RELATIONSHIP BETWEEN ADHD AND SUBSTANCE USE

There are numerous factors that have been posited to explain the relationship between ADHD and substance abuse. One of them is the co-occurrence of a conduct disorder or antisocial personality disorder. A number of studies report that hyperactive children with comorbid conduct disorder and adults diagnosed with ADHD along with antisocial personality disorder had a greater risk of developing SUDs compared to the control group.[43,67] It has been postulated that in the absence of conduct disorder, the presence of ADHD alone does not heighten the risk of developing SUDs.[61] More specifically, a study on 109 treatment-seeking opioid addicts in Germany revealed that ADHD alone may not confer an increased risk of

developing opioid dependence.[60] But even though a diagnosis of conduct disorder has a strong relationship with the development of drug use in adolescents, research points that ADHD may be an independent risk for SUDs in adults, even after controlling for the presence of antisocial personality.[43] Thus, where conduct disorder is offered as an explanation for drug use among children and teenagers, ADHD is a greater predictor of drug abuse in the adult age group.

Another explanation for the apparent association between ADHD and substance use is related to the sequelae of ADHD. Severe and ongoing hyperactivity is known to lead to functional disability particularly in the domains of education, work and relationships. These deficits may result in poor self-image as well as depression, propelling the individual to resort to alcohol or illicit substances as a means of coping with the functional deficits.[68]

In relation to the above self-medication hypothesis, it has been theorised that stimulants are used by individuals with ADHD as a means of ameliorating the symptoms of ADHD. For instance, the use of cocaine as a treatment for attention deficit.[69] Nicotine has similar properties as methylphenidate and amphetamine, which are known medications for hyperactivity.[70] Nicotine indirectly reinforces dopamine and also stimulates acetylcholine, which enhances attention.[70] Considering the wide availability as well as legal status of cigarettes, it is likely that nicotine might be a sufficient option for hyperactive adults seeking to self-medicate. Nevertheless, hyperactive adults tend to abuse any substance that rewards them with instant relief from their debilitating symptoms rather than preferentially use substances that specifically reduce their inattention and hyperactivity.[69] This is reflected in studies that failed to show any difference in the drug of choice between ADHD adults and the control group.[43] Other research also fails to demonstrate preferential use of stimulants over other drugs in hyperactive drug dependent adults.[32]

Genetic explanations have also been brought forward to explain the association between ADHD and substance use. For instance family studies have demonstrated that relatives of ADHD probands carry a higher risk for SUDs, whether or not the proband has other psychiatric illnesses. [71,72] Pathology of the dopamine transporter has been cited to play a role in the association of ADHD with drug use.[73,74] It has been long recognised that the use of substances results in an outpouring of dopamine into the nucleus accumbens.[75] Thus it is said that drugs that increase this flow of dopamine would be utilised by individuals with hyperactivity as a means of self-medication.

A highly disputed theory for the relationship between ADHD and drug abuse is the use of stimulants. This hypothesis states that stimulant use by an individual (including the types prescribed in recommended dosages by healthcare professionals) heightens the chance of said individual using and/or misusing drugs and alcohol as adults.[69] There are two proposed mechanisms for this theory. Firstly, it is said to occur via behavioural sensitisation.[69] Secondly, it is attributed to the patient's erroneous belief that because they have been prescribed treatment in the form of psychostimulants, therefore the use of cocaine along with other stimulant agents can be done without the danger of dependence or abuse.[69] A study reported that adults who had been prescribed stimulants for ADHD in childhood had a higher likelihood of nicotine dependence than the group of individuals who had not been prescribed stimulants.[76LAMBERT42] However, numerous other studies failed to support this hypothesis. In fact, individuals who were not prescribed with stimulants to manage their ADHD had a four-fold higher risk of developing SUDs versus the treated group.[51] A later meta-analysis reinforced this study by reporting that medical treatment of paediatric hyperactivity decreases the risk of later drug and alcohol use.[77WILENS200376]

2.5   THE ASSOCIATION BETWEEN ADHD AND SUBSTANCE RELATED FACTORS

AGE OF FIRST SUBSTANCE USE

There was no significant relationship reported between ADHD and the age of onset of drug or alcohol use in a study done that involved both male and female treatment-seeking opioid addicts.[60] More specifically, it was reported that the age of first heroin consumption did not differ significantly among the addicts with ADHD versus those without.[60] However, subsequent studies have consistently showed that the presence of ADHD is associated with an earlier age of alcohol and drug use. In the study in Netherlands involving opioid abusers enrolled in a methadone maintenance program, the age of first substance use was found to be earlier in the subjects with ADHD versus those without ADHD.[31] Another study in Switzerland involving a similar sample of adults enrolled in a treatment program reported an earlier age of onset of substance use among the ADHD subgroup.[57] In addition, those with ADHD showed a younger age of first opioid use as well as first regular opioid use.[57] This echoes the earlier mentioned German study of opioid and cocaine dependent individuals which showed a difference in age of onset whereby the subgroup with ADHD had a mean onset age of 10.92 years compared to the subgroup with no ADHD which had a mean of 12.77 years.[28] In Sydney, a study involving 269 illicit drug users reported that nearly 45% of them fulfilled the diagnosis for ADHD.[34] This subgroup with ADHD showed a much younger age of first becoming intoxicated with drugs or alcohol as well as a younger age of first intravenous drug use.[34] In addition, they also commenced with regular use of illicit substances at a younger age than those without ADHD.[34] This included the use of alcohol, tobacco, cannabis and methamphetamine. In general, evidence seems to point towards an earlier age of first substance use among individuals with ADHD in comparison to their counterparts. This earlier age of onset has been attributed to the low levels of self-esteem experienced by individuals with ADHD, leading them to self-medicate with

substances.[68] It is also proposed that the higher levels impulsivity that is seen in ADHD may be responsible for the earlier onset of drug use.[69]

TYPE OF SUBSTANCE USED

Individuals with ADHD had a higher risk of developing drug dependence as opposed to alcohol dependence or abuse.[43] In addition, there was a higher prevalence of ADHD in patients with a drug use disorder as opposed to alcohol use disorder.[50] This corresponds with previous evidence that hyperactivity and drug use disorders share a genetic relation that ADHD and alcohol use disorders do not. [77] The penchant for drugs over alcohol is also said to be in line with the theory of ADHD patients using drugs to self-medicate.[41]

In Italy, opioid addicts on substitution treatment who smoked heavily (more than 20 cigarettes daily) had double the odds of having symptoms of hyperactivity versus the non-smoking opioid addicts.[40] In addition, hyperactive adults diagnosed with nicotine addiction are more resistant to quitting smoking in comparison to nicotine dependent individuals without ADHD.[78] Individuals with nicotine use disorders tend to consistently report enhanced attention levels upon smoking, which corresponds to literature evidence on the effects of nicotine on acetylcholine receptors.[79]

An earlier study of treatment seeking drug users showed that the subjects had used various types of substances. However, opioids were the preferred drug amongst the subjects with ADHD (71%) compared to those without ADHD (49%).[80]

Subsequent research on adults with ADHD reported higher rates of SUDs, particularly of the psychostimulant variety and have attributed it to attempts to self-medicate.[37,42] But this theory has been disputed by further research that failed to find a significant difference in the

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preferred drug between adults with ADHD and the control group.[32,81] Furthermore, studies involving opioid abusers enrolled in methadone programmes report that there was no significant difference in prevalence of each individual drug use or SUD, with cannabis tending to have the highest prevalence for both subgroups with and without ADHD.[28,31,32]

In general, drug users with ADHD appear to be highly similar to their non-ADHD counterparts in terms of classification of substance use.[43] As opposed to anecdotal studies, systematic evidence points to the fact that stimulant and cocaine use is not over-represented in hyperactive patients. Cannabis remains as the most frequently used drug amongst individuals with ADHD but the figures are not significantly higher than non-ADHD drug users.[43]

SEVERITY AND NUMBER OF SUBSTANCES USED

Research consistently shows that the presence of ADHD has an adverse effect on substance use, reflected by more severe drug dependence as well as a greater number of substance used. In opioid users with symptoms of ADHD in childhood, there is a shift towards heavier drug use.[32] Further support for this is demonstrated by findings that opioid addicts on methadone who have ADHD tend to be hospitalised more frequently for substance related issues compared to their counterparts without ADHD.[28] (ARIAS) They also had a higher number of comorbid SUDs.[31] The association between ADHD and severity of drug use remained substantial even after controlling for conduct disorder in patients seeking methadone therapy.[31,55]

Substance using adults with ADHD present with more complex and chronic patterns of drug addiction.[82] This is further complicated with problems such as a lack of resources for rehabilitation, unemployment, comorbid psychological illnesses and nicotine addiction.[40] Reduced treatment compliance, slower remission of SUD and higher likelihood of relapse are problems that further contribute to a more severe pattern of drug use in these individuals.[83] In

addition, these individuals with ADHD who had more serious drug dependence had a higher chance of being prescribed psychotropics highlighting the fact that these patients necessitate more rigorous and complex management regime.[40]

In line with these findings, it has been theorised that the presence of ADHD results in a more severe phenotypic manifestation of SUD whereby these patients dabble in drugs at a younger age and undergo a more morbid course of substance abuse and dependance.[28] More specifically, traits of poor impulse control along with novelty seeking in these hyperactive individuals are said to be responsible for this.[28]

2.6   THE ASSOCIATION BETWEEN ADHD AND OTHER PSYCHIATRIC DIAGNOSES

ADHD is reported to result in a more severe manifestation of psychiatric illnesses.[44,45] The co-occurence of substance use further augments this risk. Substance users with a diagnosis of ADHD were more likely to have other comorbid psychiatric illness compared to their counterparts.[28,31] However, this risk did not extend to include psychotic disorders. Arias showed that ADHD was significantly associated with bipolar I disorder, post traumatic stress disorder, conduct disorder and antisocial personality disorder.[28] Furthermore, these individuals had a higher number of hospital admissions for psychiatric illness.[28] A separate study on treatment seeking opioid abusers showed a higher prevalence of mood and anxiety disorder in the subgroup with ADHD.[55] Interestingly, Carpentier's sample of patients on methadone showed a significant association between ADHD and the occurrence of post traumatic stress disorder.[31] Even after controlling for the presence of conduct disorder, the risk for developing comorbid mental illnesses remained significant.[31]

THE ASSOCIATION BETWEEN ADHD AND CONDUCT DISORDER IN SUBSTANCE
USE

The relationship between ADHD, conduct disorder (CD) and substance dependence is highly complex and current research shows conflicting evidence. A retropsective diagnosis of conduct disorder (CD) in patients with ADHD and SUD is highly prevalent. Schubiner reported a conduct disorder prevalence of nearly 40% among individuals seeking treatment for substance addiction with 34 of those participants having comorbid ADHD.[54] A conduct disorder prevalence as high as 93% was reported among hyperactive opioid abusers seeking treatment.[37] The presence of ADHD itself is a risk factor for the development of conduct disorder. Research has consistently shown that individuals with hyperactivity had an earlier onset of conduct disorder and displayed a greater number of conduct disorder symptomatology versus those without hyperactivity.[57]

It has been argued that conduct disorder exerts a more powerful influence on drug dependence behaviours than ADHD. This is evidenced by the significance of ADHD disappearing or reducing in samples where there is a high comorbidity of hyperactivity and conduct disorder.[84,85] Supporting this theory is research that reports ADHD and conduct disorder as two distinct entities, and that it is sociopathy and not ADHD that predicts future substance abuse.[86] However, evidence from other studies shows that the persistence of hyperactivity is responsible for substance addiction as well as the genesis of antisocial personality disorder.[87] More specifically, the presence of ADHD is significantly associated with a younger age of drug use onset as well as an increase the number of substances abused.[28] This influence remains even after controlling for the presence of conduct disorder.[28] Regardless of the conflicting findings, it appears that the the presence of both ADHD and sociopathy result in an interaction that heightens the risk of substance dependency more than either entity by itself. [88]

2.7 THE ASSOCIATION BETWEEN ADHD AND CRIME

ADHD is related to a myriad of issues that confer an increased risk for criminal behaviour. These include neurological deficiencies, reduced scholastic and cognitive capacities, psychological issues, disinhibition, poor impulse control and aggression.[89] The concept of "low self-control" was introduced in 1990 and has been associated with a higher risk of involvement in crime.[90] This has remained one of the principal hypotheses in the field of criminology. This led to the focus on ADHD and one of its overarching features of reduced self-control. This was supported by a study of nearly 2500 schooling youth which showed that children who were receiving medication for hyperactivity demonstrated reduced levels of self-control. This remained significant after adjusting for factors such as parenting.[91]

In the Netherlands study prior mentioned, the opioid dependent subjects with ADHD had higher scores for problem severity in terms of legal status. However, after controlling for the presence of conduct disorder, the high scores in legal status was no longer statistically significant.[31] But these findings were disputed by the the earlier-mentioned German study of opioid users on treatment which showed that opioid dependent women with ADHD tend to have a higher crime rate compared to the opioid dependent women without ADHD. The crime record was tabulated using police registration and youth penalties. The same study did not find a statistically significant difference in criminal record among the males.[60] Furthermore, opioid addicts with ADHD showed a younger age of first arrest for crime at 15.8 years of age compared to their counterparts with a mean of 17.4 years.[32]

There is numerous literature linking ADHD with increased crime rates. There are not many published studies that specifically examine crime among individuals with ADHD who are also abusing substances. However, the evidence currently available points to an association between ADHD and criminal activity in treatment seeking substance users.

2.8 THE ASSOCIATION BETWEEN ADHD AND HIV RISK-TAKING BEHAVIOUR

In a study done on adult males with ADHD in India, individuals diagnosed with ADHD exhibited a higher incidence of unsafe sexual practices in comparison to their counterparts without hyperactivity (p<0.0001).[92] A theory has been put forth that there are numerous interplaying factors that have resulted in ADHD carrying a risk for these behaviours.[92] Among these factors include interpersonal relationships, the influence of peers, the role of the family and most crucially, the fundamental symptoms of ADHD which include impulsiveness.[92] The average duration of HIV illness among these patients was almost 8 months. In the prior month, a significant proportion had engaged in risky sexual practices despite being aware of their HIV diagnosis. This would suggest that hyperactivity plays a significant contributing role for perpetuating risky sexual practices. There is limited research on the association between ADHD and HIV risk-taking behaviour in drug users. An Australian study examining this possible link involved treatment seeking drug users with ADHD. The group with ADHD were found to have a significantly higher rate of intravenous drug use or sexual risk-taking when compared to the group without ADHD.[46] However, there is a limitation to this study where only risky behaviour that occurred in the preceding month was accounted for.[46]

In summation, individuals who engage in substance dependence and abuse show a high prevalence of risky practices that predispose to HIV. A co-occurring diagnosis of hyperactivity appears to amplify these risky practices.[46]

2.9 THE ASSOCIATION BETWEEN ADHD AND QUALITY OF LIFE

In the Netherlands study of opioid dependent patients on MMT, the EuroQOL-5 was used to assess the participant's health-related quality of life. Subjects with ADHD scored

significantly lower in numerous domains including self-care, usual activities, anxiety/depression, health and visual analog scale.[31] Controlling for conduct disorder in this group of patients did not influence the score, leading to the conclusion that a diagnosis of ADHD in patients on MMT was significantly associated with a reduced quality of life.[31] This study also had a small group of 19 subjects with a childhood history of hyperactivity symptoms but an absence of ADHD features in adulthood. The quality of life scores in this group was not significantly different from the group of patients without ADHD. The rationale for this finding was that the symptoms and severity of ADHD tended to diminish with age, thus resulting in a corresponding reduction in ADHD related sequelae associated with life domains such as health, social status and relationships.[31]

In Eyre's study of opioid addicts in Connecticut, the subgroup with ADHD did not differ significantly from those without ADHD in terms of current social functioning as measured by the Social Adjustment Scale - Self Report (SAS-SR).[32] However, hyperactive addicts scored significantly lower on the Social Assets Scale which assessed lifetime range of social advantages and disabilities. When social class was assessed using Hollingshead's criteria, more hyperactive addicts were found to be in the lower classes IV and V versus the non-hyperactive group.[32] Based on research findings, it can be deduced that substance use and dependence itself contibutes significantly to a decline in quality of life. However, the presence of comorbid ADHD has an additive effect to this decline. This supports the literature that pervasively shows that ongoing and untreated ADHD results in functional decline, thus leading to an overall deterioration in the experienced standard of living.[35]

3.0   RATIONALE OF STUDY

Although the persistence of ADHD in adulthood has become increasingly highlighted over the last few years, little attention had been devoted to this issue in our local setting. ADHD prevalence studies are lacking and have been limited to school-going children in Malaysia. Substance use disorders have been on the rise both locally and internationally. Over the years, a growing body of research has been demonstrating an association between ADHD and SUDs. It can be summarised that ADHD worsens the phenotypic expression of substance use. In addition, hyperactivity in this group of drug users is associated with a decline in many aspects of quality of life, including crime rates, social functioning and HIV-related behaviours. Worryingly, a diagnosis of ADHD has been found to result in a poorer outcome of methadone treatment. However, there is no local data to support these findings.

In view of this, a study was done to determine the prevalence of adult ADHD among patients on methadone maintenance therapy. This study also examined the relationship between ADHD and other associated factors (as documented in the objectives) among this group of treatment seeking drug users. By determining and understanding the association and the impact that ADHD plays on substance users, it will aid local clinicians in the recognition and management of the specific factors. This in turn, may result in improvement in substance dependent behaviour as well as compliance to methadone treatment.

4.0   OBJECTIVES

PRIMARY OBJECTIVE

To determine the prevalence of ADHD in individuals on MMT.

SECONDARY OBJECTIVES

To determine the association between ADHD and sociodemographic factors (including gender, age, ethnicity, marital status, education and employment) in patients on MMT.

The determine the association between ADHD and substance-related factors in patients on MMT. These factors include:

- Age of first substance use

- Type of substance used

- Number of substances used

- Severity of substance use

To determine the association between ADHD and other psychiatric disorders.

To determine the association between ADHD and crime in individuals on MMT.

To determine the association between ADHD and HIV risk-taking behaviours in individuals on MMT.

To determine the association between ADHD and quality of life in individuals on MMT.

5.0   METHODOLOGY

5.1   BACKGROUND OF STUDY AREA

The methadone clinics in Hospital Kuala Lumpur and Klinik Kesihatan Kuala Lumpur are among the largest government run centres located in Kuala Lumpur. They serve approximately 170 and 110 patients respectively. The clinics operate from Monday to Friday from 8am to 5pm. These clinics were chosen because they were able to provide the large sample size that this study required. In addition, they were chosen for logistic convenience as the researcher is a trainee in Hospital Kuala Lumpur.

5.2   STUDY DESIGN

This is a cross sectional observational study to assess the prevalence of ADHD among patients enrolled in the methadone maintenance program in the Hospital Kuala Lumpur and Klinik Keishatan Kuala Lumpur methadone clinic. This study also aims to assess the socio-demographic characteristics, drug dependency features, presence of other psychiatric comorbidities as well as the quality of life among these patients on methadone maintenance who have been diagnosed with ADHD.

5.3   POPULATION, STUDY POPULATION AND SETTING OF STUDY

• DURATION OF STUDY

This study took place from August 2017 to November 2017.

• STUDY POPULATION

All patients who are enrolled in the methadone replacement programme and who are eligible in accordance with the study inclusion and exclusion criteria.

• SETTING OF STUDY

     Methadone clinic in Hospital Kuala Lumpur and Klinik Kesihatan Kuala Lumpur.

5.4   **SAMPLING METHOD**

• SAMPLING

     This study utilised universal sampling. Therefore all patients enrolled under the methadone program in the Hospital Kuala Lumpur and Klinik Kesihatan Kuala Lumpur methadone clinic who attended the clinic were recruited. These patients were deemed eligible according to the study inclusion and inclusion criteria and only recruited if they provided consent.

• SAMPLE SIZE

     Size of the sample was determined by the following formula:

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

$$= 1.96^2 \times 0.078 \, (1-0.078) / 0.05^2$$

$$= 3.8416 \times 0.078 \times (0.922) / 0.0025$$

$$= 0.2762 / 0.0025$$

$$= 110.48$$

$$\approx 110$$

Description:

n = required sample size

t = confidence level at 95% (standard value of 1.96)

p = estimated prevalence of substance use disorder in the area*

m = margin of error at 5% (standard value of 0.05)

∗ Latest prevalence study of adult ADHD in patients enrolled in an MMT program yielded a

prevalence rate of 7.8% (Liao, Y. T., Chen, C. Y., Ng, M. H., Huang, K. Y., Shao, W. C., Lin,

T. Y., ... & Gossop, M. (2017). Depression and severity of substance dependence among

heroin dependent patients with ADHD symptoms. *The American journal on addictions*, *26*(1),

26-33.)

Therefore the expected sample size is 110.

5.5   FLOW DIAGRAM

Enrollment

Patients enrolled in the MMT Program were seen. (n=150)

Excluded (n=5)
- Not meeting inclusion criteria (n=0)
- Declined to participate (n=5)

Assessment

Assessment (n=145)

Mini International Neuropsychiatric Interview Plus (M.I.N.I.-Plus)
Adult ADHD
Conduct disorder

Mini International Neuropsychiatric Interview (M.I.N.I.)

Opiate Treatment Index (OTI)

WHOQOL-BREF

Analysis

Analysed (n=145)

5.6 SELECTION CRITERIA

INCLUSION CRITERIA

• Patients enrolled in the methadone maintenance program.

• Have been retained in the methadone program for at least two months.

• Ages of 18 years and above.

• Able to read and understand Malay or English.

• Diagnosis of opioid dependence at start of methadone treatment.

The methadone maintenance program in our local setting recruits patients who are aged 18 and above.[20] This is because of the potential side effects of methadone and issues associated with informed consent in the adolescent/paediatric age group. In addition, this study involves the prevalence of adult ADHD, in which the cut off age is 18. Thus, the inclusion criteria of patients aged 18 and above is included in this study.

As elaborated in the literature review above, stable doses of methadone can only be reached within two to eight weeks of initiation of methadone. In view of this evidence, this study will only include patients who have been retained in the program for two months in order to eliminate confounders such as opioid withdrawal symptoms resulting from insufficient doses of methadone (such as restlessness, agitation) that might affect the diagnosis of ADHD.

EXCLUSION CRITERIA

• Below 18 years of age.

• Not proficient in English or Malay.

• Patients who do not consent to participate.

• Cognitive impairment or intellectual impairment.

• Presence of major mental illness.

5.7   ETHICAL APPROVAL

Approval from The Medical Research and Ethics Committee (MREC) was obtained prior to the study being conducted. The ethics approval form is included in the appendix.

5.8   INFORMED CONSENT

Patients were informed of the study during their usual Methadone Clinic visits. Those who expressed interest were then given the Patient Information Sheet (PIS) and consent form in the Methadone Clinic. When required, an appointment was made where PIS and consent form was provided and explained to them. Any queries the patient had regarding these forms were answered by the investigator. Only patients who fulfilled the inclusion criteria and who had consented were recruited into the study. If required, the patients were allowed to take the PIS home to consult with their family members and arrange another day for obtaining consent. Upon signing the consent form, the selected patients were then interviewed in the methadone clinic.

5.9   INSTRUMENTS

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (MINI) AND MINI-PLUS

A diagnosis of ADHD among the participants was determined using the ADHD portion of the MINI-Plus. Despite the high prevalence of ADHD among children and adults, ADHD as a disorder is not included in the standard structured psychiatric interview, such as the Structured Clinical Interview for DSM disorders (SCID). The Mini-International Neuropsychiatric Interview (MINI) is the collaborative effort of North American and European clinicians and psychiatrists designed for clinical practice, research in psychiatric, primary care settings and epidemiological surveys.[93] It is a short and structured diagnostic clinician rated scale

designed for the Diagnostic and Statistical Manual for Mental Disorders: Fourth Edition (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) psychiatric disorders.[93]

The MINI-Plus is an extended version of the MINI that contains 23 mental disorders which include, major depressive disorder, dysthymic disorder, manic disorder, panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalised anxiety disorder, alcohol dependence, drug dependence and drug abuse, psychotic disorders, suicidality, anorexia nervosa, bulimia, post-traumatic stress disorder, antisocial personality disorder, conduct disorder, somatisation disorder, attention deficit hyperactivity disorder, adjustment disorder, premenstrual dysphoric disorder and mixed anxiety-depressive disorder.[93]

The portion for ADHD has questions related to both child and adult features of the condition.[94] It has a shorter administration time of 15 minutes and is easier to use in comparison to the SCID.[93] In addition, the separate ADHD module in the MINI-Plus allows for a methodical assessment of ADHD symptoms along with criterion for diagnosis. The questions resemble those found in the DSM-IV and ICD-10 and encompass the domains of hyperactivity/restlessness, inattention and impulsivity.[94] First part consists of 10 questions pertaining to childhood symptoms of ADHD. A score of six and above requires patient to answer the second part which consists of 14 questions pertaining to adult symptoms of ADHD.[94] A score of nine and above along with the symptoms having caused impairment results in a diagnosis of adult ADHD.[94]

The MINI-Plus was the preferred instrument to diagnose adult ADHD in this study as the MINI-Plus addresses symptoms in childhood and then moves on to address

symptoms of ADHD in adulthood. It is therefore longitudinal in nature and comprehensive. The Conner's Adult ADHD Scale requires at least a sixth grade level of education and also requires 20 to 30 minutes for assessment. The Adult ADHD Self-Report Scale (ASRS) is cross sectional over the last six months and does not take into account the presence of ADHD symptoms in childhood. The limitations of these two instruments thus render the MINI-Plus as the instrument of choice in diagnosing adult ADHD in this study.

MINI was also utilised to diagnose the other psychiatric comorbidities which includes Major Depressive Disorder, Dysthymia, Bipolar Disorder, Panic Disorder, Agoraphobia, Social Anxiety Disorder, Obsessive Compulsive Disorder, Post Traumatic Stress Disorder, Psychosis, Generalised Anxiety Disorder and Antisocial Personality Disorder. Conduct Disorder was assessed using the MINI-Plus.

The MINI has demonstrated good validity in a multi centre European study comparing the diagnoses obtained by medical practitioners utilising the MINI with the diagnoses obtained by psychiatrists utilising non-structured interviews.[93] MINI has been compared to the Structured Clinical Interview for DSM-III—R Patients (SCID-P) and has been found to have comparable validity and reliability.[95] MINI has also been compared to the Composite International Diagnostic Interview (CIDI) and found to have good kappa coefficient, sensitivity, specificity as well as inter-rater and test-retest reliability.[96] Furthermore, it has been validated against expert opinion in a large sample in four European countries including France, United Kingdom, Italy and Spain and in Asian countries such as Japan.[93,97] There are over 100 studies as well as 20 medical specialities that utilise the MINI (together with its extension, the MINI-Plus) with the interview being translated and back-translated in over 30 languages.[93] In addition, the Malay version of the MINI for Major Depressive Disorder shows good inter-rater reliability and adjustment to the local setting.[98]

OPIATE TREATMENT INDEX (OTI)

The OTI is a structured interview-rated scale designed to assess the outcome of opioid treatment.[99] The index measures six outcome domains which include drug use, HIV-risk taking behaviour, social functioning, criminality, health status and psychological functioning.[99] The higher the score obtained in each domain, the greater the level of dysfunction.[99] Discounting the Social Functioning section (which encompasses behaviour over the preceding six months), all questions refer to behaviour in the last month before the day of interview. This time frame was chosen to obtain an estimate of the participant's current behaviour and to optimise the reliability of recall.

Section I consists of the demographics/treatment history. This includes socio-demographic information such as sex, age, number of completed school years, courses completed after school and employment status. Data regarding treatment history includes duration and type of current treatment and past treatment.[99]

Section II is concerned with drug use. The drug categories include heroin, other opiates, alcohol, cannabis, amphetamines, cocaine, tranquilisers, barbiturates, hallucinogens, inhalants and tobacco.[99] For each drug category, subject is asked when their three latest days of drug use occurred along with how much was used on the last two days. The gap between days of substance use become an estimate of frequency of use. The number of drug use episodes on the last two days of drug use is an estimate of quantity of drug use. Thus, a quantity/frequency estimate in the form of a Q score can be made on the grounds of how much drugs are being taken, and how often they are being taken.[99] A Q score of zero indicates abstinence, a Q score range from 0.01-0.13 indicates quantity/frequency of once a week or less, a Q score range from 0.14-0.99 indicates a quantity/frequency score of more than once a week, a Q score of 1.00-1.99 indicates a quantity/frequency score of daily use and a Q score of 2.00 and above indicates drug

use that is more than once a day.[99] The time frame for drug use is one month. If a subject has not used a particular drug in the last month, the Q score is given as zero.[99] This is in view of the fact that the OTI is a reflection of current drug-related behaviour and thus past behaviour is not measured.[99] The poly drug score is then tabulated using the total Q score for each drug.

Section III examines HIV-risk taking behaviour. This consists of practices and behaviour employed by drug users that enhance the risk of both contracting and spreading HIV and other blood borne infections such as Hepatitis B and C.[99] The two subsections are injecting drug use and sexual behaviour. These take into consideration not only the risk these users pose to themselves, but also the risk to others. Section IV is related to social functioning.[99] It assesses issues such as employment, residential stability, interpersonal difficulties as well as degree of social support. The index further examines the participation of the individual in substance sub-culture through questions asking how many of their friends are current drug users and whether they are living with current users.[99] Scores for each question rate from zero to four.

Section V is concerned with crime. It consists of four questions related to property crime, drug dealing, fraud and violent crimes.[99] As in the previous section, scores for each question rate from zero to four. Section VI is related to health. It touches on general health, injection related problems, cardio/respiratory, genito-urinary, gynaecological, musculo-skeletal, neurological and gastrointestinal symptoms.[99] Questions concern symptoms experienced over the last one month and every "yes" given by patient is scored as one. Section VII assesses psychological adjustment. It utilises the general health questionnaire with 28 questions related to anxiety, depression, somatic symptoms and social dysfunction. [99]

The OTI possesses excellent psychometric properties and has been validated in the United Kingdom, Australia and New Zealand.[99] It provides a valid and reliable instrument

for assessing opiate treatment outcome across a broad range of drug related problems.[19] The index also shows good agreement with the well established Addiction Severity Index (ASI). The validity and reliability of the OTI has not been tested in the local population. However, there are local studies that have been published which utilised the OTI in a sample population that is identical to this proposed study i.e. patients on methadone maintenance therapy.[100] In addition, the OTI is used as the primary tool for assessing the level of opioid dependence in the recruitment of patients into local methadone maintenance programs including centres such as University Malaya Medical Centre.[19]

For this study the OTI was utilised as a means of evaluating opiate treatment in the sample participants. Therefore, only Sections I, II, III, IV and V of the OTI were utilised in accordance with the study's objectives. In many studies utilising the OTI, only selected components of the index was implemented and in this study, the sections on health and psychological adjustment were not used.

WORLD HEALTH ORGANISATION QUALITY OF LIFE-BREF (WHOQOL-BREF)

The WHO Quality of Life plan of action was launched in 1991. This program aimed to develop a global, culturally transcending index for the assessment of quality of life. The WHOQOL-100 was thus borne out of a worldwide collaboration of numerous centres and has been widely tested. It evaluates the individual's observation and appraisal in the context of their culture, their personalised targets, aspirations and concerns. Given its lengthiness, there may be circumstances in which the WHOQOL-100 may not be suitable for use. This gave rise to the WHOQOL-BREF, a condensed version of the former index. It contains 26 questions, with one item from each of the 24 subgroups in the WHOQOL-100 were included. There are an additional two items from the Overall Quality of Life and General Health subgroup which has

also been incorporated. The 24 elements are clustered into four domains which include physical health, psychological, social relationships and environment.[101]

The physical health domain includes questions related to activities of daily living, dependence on medicinal substances and medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest and work capacity.[101] The psychological domain is concerned with bodily image and appearance, negative feelings, positive feelings, self-esteem, spirituality/religion/personal beliefs and thinking, learning, memory and concentration.[101] The social relationship domain examines personal relationships, social support and sexual activity.[101] Finally, the environment domain is concerned with financial resources, freedom, physical safety and security, health and social care, home environment, chances to acquire new skills and information, recreation and leisure activities, physical environment and transport.[101]

Each item is rated on a Likert scale ranging from one to five where lower scores indicate a poorer quality of life.[101] The average score of items within each domain is used to obtain the domain score. The average scores are then multiplied by four to render the domain scores comparable with the scores utilised in the WHOQOL-100.[101] The WHOQOL-BREF is available in 19 different languages. It can be self-administered should the participant possess adequate ability, otherwise it can be administered by the interviewer. The Malay version has been validated and is shown to have good internal consistency, reliability and validity.[102]

5.10   STATISTICAL ANALYSES

All the statistical analyses were performed the IBM SPSS Statistics Software version 20.0.

Descriptive statistics were used to present the baseline characteristics (gender, age, marital status, race, education level, employment status) of the study subjects presented as either frequencies (%) or mean with SD values.

Normality tests were run for all numerical continuous variables. Appropriate analyses was made based on values for asymmetry and kurtosis. Values between -2 and +2 were considered acceptable for normal univariate distribution.

Individual QoL raw scores were calculated manually following the WHOQOL-BREF assessment form. These raw scores were then converted to two forms of transformed scores (1) range between 4-20, comparable with the WHOQOL-100; (2) raw scores converted to domain scores on a 0-100 scale. Total QoL scores and Domain scores were computed following the instructions given by the WHOQOL-BREF manual on scoring. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life). The mean score of items within each domain is used to calculate the domain scores.

The ADHD patients were compared with the non-ADHD patients on age of first drug use, HIV Risk-Taking behaviour, Social Functioning, Crime, Severity of drug use, Total QoL scores and domain scores using independent samples t-tests and Mann-Whitney tests. Chi-squared tests for independence were conducted to analyse associations between ADHD diagnosis and race, number of drugs used, psychiatric comorbidity. Binary logistic regression analyses were conducted to determine the effect of ADHD diagnosis on the likelihood (Odds Ratio) of binary

categorical variables models were adjusted for age, age of first drug use, education level and employment status since other demographic variables (gender, marital status and race) were found not statistically significantly associated with ADHD ($p>0.05$).

To differentiate the influence of ADHD and conduct disorder on drug use, crime, HIV and quality of life, linear and binary logistic regressions were carried out with ADHD and conduct disorder as the independent variables. The corresponding standardised coefficients and odds ratios were estimated.

An α-level of $p < 0.05$, two-tailed, was adopted.

6.0   RESULTS

6.1   SOCIODEMOGRAPHIC DATA

A total of 150 patients were approached in the Methadone Clinic for the duration of the study period. Five patients were not keen to participate. The remaining 145 patients fulfilled both the inclusion and exclusion criteria and gave consent to be included in the study. Thus 145 patients were enrolled. Table 1 on the following page shows the sociodemographic characteristics of the subjects.

GENDER

93.8% of the participants were males while 6.2% were females.

AGE

The mean age of the subjects was 48.03 years with a standard deviation of 10.38.

ETHNICITY

79.3% of the study participants were Malays. 12.4% were Indians and 8.3% were Chinese. This ethnic distribution did not accurately reflect the true local racial composition.

MARITAL STATUS

More than half of the subjects (51%) were single. 33.8% were married. 10.3% of the subjects were either divorced or separated and 4.8% were widowed.

EDUCATION LEVEL

26.9% sat for the Ujian Penilaian Sekolah Rendah (UPSR) and completed their primary school education. 44.8% had an education level up until Penilaian Menengah Rendah (PMR) and thus did not complete secondary school. The remaining 28.3% sat for the Sijil Pelajaran Malaysia (SPM) and thus completed secondary school. None of the subjects had received tertiary education.

EMPLOYMENT STATUS

More than half (54.5%) of the subjects were presently employed. 41.4% were unemployed and a further 4.1% were retired.

Table 1. Sociodemographic characteristics of the entire sample

Characteristics	N	(%)
Gender		
Male	136	93.8
Female	9	6.2
Age		
18-30	7	4.8
31-40	35	24.1
41-50	41	28.3
51-60	41	28.3
61 and above	21	14.5
Mean age (24-68)	48.03±10.38	
Ethnicity	115	79.3
Malay	12	8.3
Chinese	18	12.4
Indian		
Marital Status		
Single	74	51.0
Married	49	33.8
Divorced/Separated	15	10.3
Widowed	7	4.8
Educational Level		
Primary school (UPSR)	39	26.9
PMR	65	44.8
SPM	41	28.3
Employment Status		
Currently employed	79	54.5
Retired	6	4.1
Unemployed	60	41.4

6.2   PREVALENCE OF ADHD AMONG PATIENTS ON METHADONE MAINTENANCE THERAPY

Out of the 145 patients who were recruited, 28 subjects (19.3%) reported ADHD symptoms in childhood and adulthood. Out of the remaining 80.7% of subjects who were not diagnosed with ADHD, two subjects (1.7%) reported childhood symptoms of ADHD which remitted in adulthood, whereas the remaining 115 subjects (98.3%) did not report ADHD symptoms in either childhood or adulthood. Since a diagnosis of adult ADHD requires the persistence of childhood symptoms into adulthood, therefore subjects that did not report the requisite number of ADHD symptoms in adulthood were not considered to have a diagnosis of ADHD.

Table 2. Prevalence of ADHD among patients on MMT

ADHD Diagnosis	N	%
Yes	28	19.3
No	117	80.7

6.3   SOCIODEMOGRAPHIC CHARACTERISTICS OF MMT PATIENTS WITH COMORBID ADHD

There were a total of 28 MMT patients who were diagnosed with ADHD. Table 3 details the sociodemographic characteristics of this group of patients.

GENDER

Among the subgroup of patients on MMT that were diagnosed with ADHD, the majority of

them were male (92.9%). The remaining 7.1% were female.

AGE

The mean age was 37.39 years with a standard deviation of 7.26.

ETHNICITY

78.6 % of the participants were Malay. The number of Chinese and Indian subjects were similar at 10.7% each.

MARITAL STATUS

The majority of the ADHD subjects were single (64.3%). 21.4% were married. 10.7% of the subjects with ADHD were divorced or separated and 3.6% were widowed.

EDUCATION LEVEL

46.4% of the subjects with ADHD completed primary school. 39.3% completed schooling up until Form Three while 14.3% completed SPM.

EMPLOYMENT SATUS

More than half of the subjects with ADHD were unemployed (64.3%) while 35.7% of them are currently working.

Table 3. Sociodemographic characteristics of MMT patients with comorbid ADHD

Characteristic	N	%
Gender		
Male	26	92.9
Female	2	7.1
Age Group		
18-30	5	17.9
31-40	15	53.6
41-50	6	21.4
51-60	2	7.1
61 and above		
Mean age	37.39± 7.26	
Ethnicity		
Malay	22	78.6
Chinese	3	10.7
Indian	3	10.7
Marital status		
Single	18	64.3
Married	6	21.4
Divorced/Separated	3	10.7
Widowed	1	3.6
Education Level		
Primary school (UPSR)	13	46.4
Secondary school (PMR)	11	39.3
Secondary school (SPM)	4	14.3
Employment Status		
Employed	10	35.7
Unemployed/Retired	18	64.3

6.4 ASSOCIATION BETWEEN ADHD AND SOCIODEMOGRAPHIC CHARACTERISTICS

All 145 of the study subjects were divided into two subgroups: with ADHD and without ADHD for the purpose of comparison.

The socio-demographic variables between the non-ADHD and ADHD group were compared using two models. Firstly, binary logistic regression was conducted using ADHD diagnosis as an independent variable and the sociodemographic characteristics of gender, ethnicity, marital status, education level and employment status as the dependent variables. The results of this comparison are illustrated in Table 4.

Educational level shows a significant difference between the non-ADHD and ADHD groups among the patients on MMT. Patients on MMT who were diagnosed with ADHD were three times more likely to have a lower education level with an odds ratio of 3.033 (p = 0.012). In addition, a diagnosis of ADHD was also associated with a significantly higher risk of being unemployed where the odds ratio is 2.591 (p = 0.03).

There was no significant difference between the non-ADHD and ADHD group for gender, marital status and race (p > 0.05).

Table 4. Comparison between non-ADHD and ADHD group: sociodemographic characteristics (gender, ethnicity, marital status, education level and employment status)

Variables	Non-ADHD N =117	ADHD N = 28	OR	95%CI	P
Gender Male Female	110 7	26 2	1.21	0.237 to 6.161	0.819
Marital Status Single/Divorced/Separated Widowed Married	74 43	22 6	2.13	0.801 to 5.660	0.129
Ethnicity Malay Chinese/Indian/Others	93 24	22 6	1.057	0.386 to 2.896	0.914
Educational Level Primary Secondary	26 91	13 15	3.033	1.282 to 7.176	0.012*
Employment Status Unemployed/Retired Currently employed	48 69	18 10	2.591	1.099 to 6.092	0.030*

*p < 0.05, **p < 0.01

OR = Odds Ratio

CI = Confidence Interval

Secondly, for the sociodemographic variable age, an independent samples t-test was conducted to compare the age between the non-ADHD and ADHD groups. The results are illustrated in table 5.

There was a significant difference in age for the non ADHD group (M = 50.57, SD = 9.35) and the ADHD group (M = 37.39, SD 7.26); $t(143) = 8.123$, $p < 0.001$. The magnitude for the differences in the means (mean difference = 13.180, 95% CI: 9.92 to 16.44).

Thus it can be concluded that a diagnosis of ADHD among MMT patients is significantly associated with a younger age ($p < 0.001$).

Table 5. Comparison between non-ADHD and ADHD group: age

Variables	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	*P*
Age *Mean (years)*	50.57±9.35	37.39±7.26	13.180	9.922 to 16.437	<0.001**

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.5   ASSOCIATION BETWEEN ADHD AND AGE OF FIRST SUBSTANCE USE

An independent-samples t-test was conducted to compare age (of first substance use) between the non-ADHD and ADHD groups. There was a significant difference in age for the

non-ADHD group (M = 15.76, SD = 1.38) and the ADHD group (M = 14.11, SD 1.81); t(143) = 5.338, p < 0.001. The magnitude for the differences in the means (mean difference = 1.654, 95% CI: 1.041 to 2.26). The results are as shown in Table 6.

Thus it can be concluded that a diagnosis of ADHD is significantly associated with an earlier age of first substance use (p < 0.001).

Table 6. Comparison between non-ADHD and ADHD group: age of first substance use

Variable	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	P
Age of first substance use	15.76±1.381	14.11±1.81	1.654	1.041 to 2.266	<0.001**

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.6   ASSOCIATION BETWEEN ADHD AND TYPE OF SUBSTANCE USED

The association between ADHD and the type of substance used was determined using binary logistic regression. In conducting this regression model, a diagnosis of ADHD was used as the independent variable and the 11 individual substances (heroin, other opiates, alcohol, cannabis, amphetamines, cocaine, tranquilisers, barbiturates, hallucinogens, inhalants and tobacco) were the dependent variables. The results of this model is as shown in Table 7.

A diagnosis of ADHD was significantly associated with a higher likelihood of using heroin with an odds ratio of 3.320 (p = 0.010). In addition, MMT patients who were diagnosed with ADHD were nearly 13 times more likely to abuse cannabis with an odds ratio of 12.955 (p < 0.001). ADHD was also significantly associated with a higher likelihood (odds ratio: 7.923) of using amphetamines (p < 0.001).

There was no significant difference between the ADHD and non-ADHD group for the other drugs.

Table 7. Comparison between non-ADHD and ADHD group: type of substance used

	Non-ADHD N =117	ADHD N = 28	OR	95%CI	*P*
Heroin	32 (27.4%)	15 (55.6%)	3.320	1.404 - 7.855	0.010*
Other Opiates	6 (5.1%)	2 (7.1%)	1.423	0.272 - 7.457	0.675
Alcohol	14 (12.0%)	4 (14.8%)	1.280	0.386 - 4.246	0.936
Cannabis	22 (18.8%)	21 (75%)	12.955	4.896 - 34.276	<0.001**
Amphetamines	14 (12.0%)	14 (51.9%)	7.923	3.098 - 20.261	<0.001**
Cocaine	0	0	-	-	-
Tranquilisers	10 (8.5%)	4 (14.3%)	1.783	0.515 - 6.170	0.570
Barbiturates	0	0	-	-	-
Hallucinogens	0	0	-	-	-
Inhalants	0	0	-	-	-
Tobacco	110	26	0.827	0.162 - 4.216	0.819

*p < 0.05, **p < 0.01

CI = Confidence Interval

OR = Odds Ratio

6.7   ASSOCIATION BETWEEN ADHD AND SEVERITY OF SUBSTANCE USE (Q SCORE)

The severity of substance use between the non-ADHD and the ADHD group were compared. The Q score (frequency/severity) in the OTI was used as an indicator of the severity of substance use.

Firstly, the severity of each individual drug use (heroin, other opiates, alcohol, cannabis, amphetamines, cocaine, tranquilisers, barbiturates, hallucinogens, inhalants and tobacco) was compared using the Mann-Whitney U test. The results are as shown in Table 8.

The ADHD group had a more significantly severe use of heroin ($p < 0.001$), cannabis ($p < 0.001$) and amphetamines ($p < 0.001$).

There were no significant differences in the use of other drugs such as other opiates, alcohol, cocaine, tranquilisers, barbiturates, hallucinogens, inhalants and tobacco.

Table 8. Comparison between non-ADHD and ADHD group: severity of individual substance use (individual Q score)

Substance	Non-ADHD N =117	ADHD N = 28	*P*
Heroin	0.0829±0.336	0.7604±1.099	<0.001**
Other Opiates	0.0067±0.030	0.0067±0.025	0.675
Alcohol	0.254±0.823	0.2707±0.799	0.760
Cannabis	0.0691±0.323	0.870±1.184	<0.001**
Amphetamines	0.0778±0.431	0.5814±1.026	<0.001**
Cocaine	0.000	0.000	1
Tranquilisers	0.0518±0.293	0.0636±0.283	0.358
Barbiturates	0.000	0.000	1
Hallucinogens	0.000	0.000	1
Inhalants	0.000	0.000	1
Tobacco	10.658±5.301	13.000±7.318	0.141

*p < 0.05, **p < 0.01

Next, the total severity of substance use (total Q score) for all 11 substances were compared between the ADHD and non-ADHD group using an independent t-test. The results are as shown in Table 9.

There was a significant difference in overall severity of substance use for the non-ADHD group (M = 11.200, SD = 5.414) and the ADHD group (M = 15.552, SD = 8.534), p = 0.015. The magnitude for the difference in the means (mean difference = -4.352, 95% CI: -6.900 to -1.804).

Therefore, a diagnosis of ADHD in MMT patients is significantly associated with a higher severity of overall substance use (p = 0.015).

Table 9. Comparison between non-ADHD and ADHD group: overall severity of drug use (total Q score)

Variable	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	*P*
Total Q score	11.200±5.414	15.552±8.534	-4.352	-6.900 to -1.804	0.015*

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.8   ASSOCIATION BETWEEN ADHD AND NUMBER OF SUBSTANCES USED

A comparison of the number of substances used between the non-ADHD and ADHD group was made using a Chi-square test. The results are shown in Table 10.

A Chi-square test for independence indicated a significant association between ADHD and the number of drugs used in combination, χ^2 (5, n = 145) = 34.45, p < 0.001.

Thus, a diagnosis of ADHD in MMT patients is significantly associated with the use of more substances (p < 0.001).

Table 10. Comparison between non-ADHD and ADHD group: number of substances used

Number of substances used	Non ADHD (N = 117)	ADHD (N = 28)	Chi Square	p
No substance	7 (6.0%)	2 (7.1%)		
1 substance used	57 (48.7%)	2 (7.1%)		
2 substances	24 (20.5%)	4 (14.3%)	34.45	<0.001
3 substances	14 (12.0%)	8 (28.6%)		
4 substances	15 (12.8%)	8 (28.6%)		
5 substances	0	4 (14.3%)		

*p < 0.05, **p < 0.01

6.9 PREVALENCE OF PSYCHIATRIC DISORDERS AMONG PATIENTS ON MMT

Table 11 shows the prevalence of psychiatric disorders for the entire sample of MMT patients in the study. Conduct disorder has the highest prevalence (48.3%) followed by Major Depressive Disorder (13.8%).

Table 11. Prevalence of psychiatric disorders within sample (N = 145)

Psychiatric Disorders	N (%)
Major Depressive Disorder	20 (13.8)
Dysthymia	15 (10.3)
Bipolar Disorder	10 (6.9)
Panic Disorder	8 (5.5)
Agoraphobia	5 (3.4)
Social Anxiety Disorder	3 (2.1)
Obsessive Compulsive Disorder	2 (1.4)
Post Traumatic Stress Disorder	9 (6.2)
Psychosis	15 (10.3)
Generalized Anxiety Disorder	6 (4.1)
Antisocial Personality Disorder	23 (15.9)
Conduct Disorder	70 (48.3)

6.10 ASSOCIATION BETWEEN ADHD AND OTHER PSYCHIATRIC DISORDERS

The association between ADHD and other psychiatric disorders was determined using binary logistic regression. In this model, a diagnosis of ADHD was used as the independent variable and the 12 psychiatric disorders (Major Depressive Disorder, Dysthymia, Bipolar Disorder, Panic Disorder, Agoraphobia, Social Anxiety Disorder, Obsessive Compulsive Disorder, PTSD, Psychosis, Generalised Anxiety Disorder, Antisocial Personality Disorder and Conduct Disorder) were the dependent variables. The results of this model is shown in Table 12.

The ADHD group had a higher prevalence for all the other psychiatric disorders compared to the non-ADHD group, with the exception of psychosis. A diagnosis of ADHD was significantly associated with a higher likelihood of acquiring Major Depressive Disorder with an

odds ratio of 3.5 (p = 0.026). There was also a higher likelihood of Conduct Disorder in the ADHD group with an odds ratio of 2.732 (p = 0.036).

There was no significant difference between the ADHD and non-ADHD group for the other psychiatric diagnoses.

Table 12. Comparison between non-ADHD and ADHD group: types of psychiatric disorders

	Non-ADHD N =117	ADHD N = 28	OR	95%CI	P
Major Depressive Disorder	12 (10.3%)	8 (28.6%)	3.5	1.269 - 9.652	0.026
Dysthymia	11 (9.4%)	4 (14.3%)	1.606	0.471 - 5.479	0.677
Bipolar Disorder	7 (6.0%)	3 (10.7%)	1.886	0.456 - 7.805	0.637
Panic Disorder	5 (4.3%)	3 (10.7%)	2.688	0.602 - 11.994	0.379
Agoraphobia	3 (2.6%)	2 (7.1%)	2.923	0.465 - 18.391	0.538
Social Anxiety Disorder	2 (1.7%)	1 (3.6%)	2.130	0.186 - 24.355	0.534
Obsessive Compulsive Disorder	1 (0.9%)	1 (3.6%)	4.296	0.260 - 70.882	0.837
Post Traumatic Stress Disorder	6 (5.1%)	3 (10.7%)	2.220	0.520 - 9.485	0.506
Psychosis	13 (11.1%)	2 (7.1%)	0.615	0.131 - 2.898	0.784
Generalized Anxiety Disorder	4 (3.4%)	2 (7.1%)	2.173	0.378 - 12.506	0.718
Antisocial Personality Disorder	17 (14.5%)	6 (21.4%)	1.604	0.568 - 4.534	0.542
Conduct Disorder	51 (43.6%)	19 (67.9%)	2.732	1.141 - 6.542	0.036

*p < 0.05, **p < 0.01

CI = Confidence Interval

OR = Odds Ratio

6.11 ASSOCIATION BETWEEN ADHD AND NUMBER OF PSYCHIATRIC DISORDERS

A comparison of the number of other psychiatric diagnosis between the non-ADHD and ADHD group was made using a Chi-square test. The results are shown in Table 13.

A Chi-square test for independence indicated a statistically significant association between number of psychiatric disorders and ADHD status, χ^2 (6, 145) = 24.612, p <0.001, phi = 0.412.

Therefore, a diagnosis of ADHD in MMT patients is significantly associated with a higher number of other psychiatric comorbidities (p < 0.001).

Table 13. Comparison between non-ADHD and ADHD group: number of psychiatric disorders

Number of psychiatric disorders	Non-ADHD N =117	ADHD N = 28	Chi Square χ^2	p
None	47(40.2%)	5 (17.9%)		
1 disorder	29 (24.8%)	8 (28.6%)		
2 disorders	23 (19.7%)	9 (32.1%)		
3 disorders	15 (12.8%)	0 (0%)	24.612	<0.001
4 disorders	3 (2.6%)	3 (10.7%)		
5 disorders	0 (0%)	2 (7.1%)		
6 disorders	0 (0%)	1 (3.6%)		

6.12   ASSOCIATION BETWEEN ADHD AND CRIME

The total crime scores between the non-ADHD and ADHD group were compared using an independent t-test. The components of crime included property crime, dealing, fraud and crimes involving violence. The results are tabulated in Table 14.

There was a significant difference in criminal activity for between the non-ADHD group (M = 0.103, SD = 0.358) and the ADHD group (M = 0.714, SD = 0.976) , p = 0.003. The magnitude for the difference in means (mean difference = -0.611, 95% CI: -0.944 to -0.227).

Therefore, a diagnosis of ADHD in MMT patients is significantly associated with higher crime rates (p = 0.003).

Table 14. Comparison between non-ADHD and ADHD group: crime

Variables	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	*P*
Crime	0.103±0.358	0.714±0.976	-0.611	-0.994 to -0.227	0.003**

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.13 ASSOCIATION BETWEEN ADHD AND HIV RISK-TAKING BEHAVIOUR

The total HIV risk-taking behaviour scores between the non-ADHD and ADHD group were compared using an independent t-test. The components of HIV risk-taking behaviour included intravenous drug use and sexual behaviour. The results are tabulated in Table 15.

There was a significant difference in HIV risk-taking behaviour between the non-ADHD group (M = 1.778, SD = 2.446) and the ADHD group (M = 3.535, SD = 4.290) , p = 0.045. The magnitude for the difference in means (mean difference = -1.757, 95% CI: -2.958 to -0.557).

Therefore, a diagnosis of ADHD in MMT patients is significantly associated with higher HIV risk-taking behaviours (p = 0.045).

Table 15. Comparison between non-ADHD and ADHD group: HIV risk-taking behaviour

Variables	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	*P*
HIV risk-taking behaviour	1.778±2.446	3.535±4.290	-1.757	-2.958 to -0.557	0.045*

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.14   ASSOCIATION BETWEEN ADHD AND QUALITY OF LIFE

The quality of life scores between the non-ADHD and the ADHD group were compared using an independent t-test. The results are as shown in Table 16.

There was a significant difference in domain 1 (physical health) scores between the non-ADHD group (M = 13.128, SD = 3.097) and the ADHD group (M = 10.898, SD = 1.030), p < 0.001. The magnitude for the difference in the means (mean difference = 2.230, 95% CI: 1.055 to 3.405). Thus, a diagnosis of ADHD in MMT patients is significantly associated with lower physical health scores (p < 0.001).

There was a significant difference in domain 2 (psychological) scores between the non-ADHD group (M = 13.271, SD = 1.988) and the ADHD group (M = 10.898, SD = 1.626), p < 0.001. The magnitude for the difference in the means (mean difference = 2.342, 95% CI: 1.541 to 3.142). Thus, a diagnosis of ADHD in MMT patients is significantly associated with lower psychological scores (p < 0.001).

There was a significant difference in domain 3 (social relationships) scores between the non-ADHD group (M = 11.829, SD = 2.704) and the ADHD group (M = 10.048, SD = 2.393), p < 0.001. The magnitude for the difference in the means (mean difference = 1.781, 95% CI: 0.680 to 2.883). Thus, a diagnosis of ADHD in MMT patients is significantly associated with lower social relationships scores (p < 0.001).

There was a significant difference in domain 4 (environment) scores between the non-ADHD group (M = 13.214, SD = 2.202) and the ADHD group (M = 11.054, SD = 1.612), p <

0.001. The magnitude for the difference in the means (mean difference = 2.160, 95% CI: 1.285 to 3.035). Thus, a diagnosis of ADHD in MMT patients is significantly associated with lower environment scores (p < 0.001).

There was a significant difference in the total QOL score between the non-ADHD group (M = 85.248, SD =13.324) and the ADHD group (M = 70.607, SD = 8.354), p < 0.001. The magnitude for the difference in the means (mean difference = 14.641, 95% CI: 10.640 to 18.641). Thus, a diagnosis of ADHD in MMT patients is significantly associated with lower overall quality of life.

In conclusion, a diagnosis of ADHD in MMT patients is significantly associated with lower quality of life scores in all domains (p < 0.001).

Table 16. Comparison between non-ADHD and ADHD group: QOL scores for domain 1, 2, 3 and 4 and total QOL score

Variables	Non-ADHD N =117	ADHD N = 28	Mean Difference	95%CI	*P*
Total QOL score (0-100)	85.248±13.324	70.607±8.354	14.641	10.640 to 18.641	<0.001**
Domain 1 Physical Health (4-20)	13.128±3.097	10.898±1.030	2.230	1.055 to 3.405	<0.001**
Domain 2 Psychological (4-20)	13.271±1.988	10.928±1.626	2.342	1.541 to 3.142	<0.001**
Domain 3 Social Relationships (4-20)	11.829±2.704	10.048±2.393	1.781	0.680 to 2.883	<0.001**
Domain 4 Environment (4-20)	13.214±2.202	11.054±1.612	2.160	1.285 to 3.035	<0.001**

*p < 0.05, **p < 0.01

CI = Confidence Interval

6.15   INFLUENCE OF CONDUCT DISORDER ON AGE OF FIRST SUBSTANCE USE AND SEVERITY OF SUBSTANCE USE

To determine the influence of conduct disorder on age of first substance use and severity of substance use, **t**he mean number $\pm$ SD of age of first substance use and severity of substance use for the non-ADHD and ADHD groups were evaluated with hierarchical linear regression modelling using ADHD and conduct disorder diagnoses. The results are as shown in Table 17.

A diagnosis of ADHD was significantly associated with an earlier age of first substance use. In Step I, the R2 change indicates that ADHD explains 16.6% (F = 28.498, p < 0.001) of the variance in age of first substance use. In Step II, the R2 change indicates that conduct disorder explains only an additional 0.4% (F = 0.615, p = 0.434) and is not significant. The association with diagnosis of ADHD remained significant even after accounting for the presence of conduct disorder in the final model, as the beta value for ADHD (beta = -0.396, p < 0.001) in the final model is significant while the beta for conduct disorder (beta = -0.061, p = 0.434) is not significant. Therefore, ADHD is an independent risk factor for earlier age of first substance use.

Similar to age of first substance use, ADHD was shown to be significantly associated with increased severity of substance use. In Step I, the R2 change indicates that ADHD explains 7.4% (F = 11.401, p = 0.001) of the variance in severity of substance use. However, this significance diminished after conduct disorder was accounted for. In Step II, the R2 change indicates that conduct disorder explains an additional 5.5% (F = 9.013, p = 0.003) and is also significant. Looking at the final model, the beta value for conduct disorder (beta = 0.24, p < 0.003) has a larger magnitude and is more significant than the beta value for ADHD (beta = 0.226, p = 0.005). Therefore, although both ADHD and conduct disorder are significantly associated with increased severity of substance use, conduct disorder exerts a greater influence than ADHD.

Table 17. Mean number ± SD of age of first substance use and severity of substance use for non-ADHD and ADHD group, combined with hierarchical linear regression modelling using ADHD and conduct disorder diagnoses*

	Non ADHD (n = 117)	ADHD (n = 28)	Step I: ADHD			Step II: Conduct Disorder			β(p) n full model		Prop. Variance Explained
			R^2 change	F change	*P*	R^2 change	F change	*P*	ADHD	Conduct Disorder	
Age of first substance use	15.76±1.381	14.11±1.812	0.166	28.498	<0.001	0.004	0.615	0.434	-0.396 (<0.001)	-0.061 (0.434)	0.170
Severity of substance use	11.200±5.415	15.553±8.531	0.074	11.402	0.001	0.055	9.013	0.003	0.226 (0.005)	0.24 (<0.003)	0.129

* Significant at p < 0.05.

6.16   INFLUENCE OF CONDUCT DISORDER ON NUMBER OF SUBSTANCES USED

The influence of conduct disorder on the number of substance used was determined using the odds ratio of number of substances used for non-ADHD and ADHD group, combined with hierarchical logistical regression modelling using ADHD and conduct disorder diagnoses. Results are shown in Table 18.

The number of substances used by patients with ADHD is more likely to be influenced by a diagnosis of ADHD than by a history of conduct disorder. When accounting for ADHD in Step II, the OR of 6.985 ($p < 0.001$) is significant versus when including conduct disorder in Step II which gives an OR of 1.518 ($p = 0.280$) which is not significant. Therefore ADHD is an independent risk factor for higher number of substances used.

Table 18. Odds ratio of number of substances used for non-ADHD and ADHD group, combined with hierarchical logistical regression modelling using ADHD and conduct disorder diagnoses*

	Non ADHD (n = 117)	ADHD (n = 28)	OR	95%CI	Adj. OR	95%CI	P	Adj. OR	95%CI	P	Prop. Variance Explained
				Step I	**Step II: ADHD**			**Step II: Conduct Disorder**			**Prop. Variance Explained**
No. of substances used ≤2 substances	88 (75.2%)	8 (28.6%)	7.586	3.020-19.056	6.985	2.75-17.741	<0.001	1.518	0.712-3.235	0.280	0.196
≥3 substances	29 (24.8%)	20 (71.4%)									

∗ Significant at p < 0.05.

6.17   INFLUENCE OF CONDUCT DISORDER ON TYPE OF SUBSTANCE USED

The influence of conduct disorder on the type of substance used was determined using the odds ratio for type of substance used for non-ADHD and ADHD group, combined with hierarchical logistical regression modelling using ADHD and conduct disorder diagnoses. The results are tabulated in Table 19.

ADHD was significantly associated with a preferential use of heroin, cannabis and amphetamines. This significance persisted after a comorbid diagnosis of conduct disorder was adjusted for.

For heroin use, when accounting for ADHD in Step II, the OR of 3.215 (p =0.009) is significant versus when including conduct disorder in Step II which gives an OR of 1.157 (p = 0.695) which is not significant. For cannabis use, when accounting for ADHD in Step II, the OR of 11.564 (p < 0.001) is significant versus when including conduct disorder in Step II which gives an OR of 2.516 (p = 0.031) which is also significant but less than ADHD. For amphetamine use, when accounting for ADHD in Step II, the OR of 7.169 (p < 0.001) is significant versus when including conduct disorder in Step II which gives an OR of 1.757 (p = 0.232) which is not significant. Therefore, ADHD is an independent risk factor for the use of heroin and amphetamines and exerts greater influence on cannabis use than conduct disorder.

Table 19. Odds ratio of type of substance used for non-ADHD and ADHD group, combined with hierarchical logistical regression modelling using ADHD and conduct disorder diagnoses

Type of substance used	Non ADHD (n = 117)	ADHD (n = 28)	Step I		Step II: ADHD		Step II: Conduct Disorder		Prop. Variance Explained[a]
			OR (p-value)	95%CI	Adj. OR (p-value)	95%CI	Adj. OR (p-value)	95%CI	
Heroin	32 (27.4%)	15 (55.6%)	3.320 (0.006)* **	1.404 - 7.855	3.215 (0.009)* **	1.340 - 7.715	1.157 (0.695)	0.558 - 2.397	0.072
Cannabis	22 (18.8%)	21 (75%)	12.955 (<0.001)* **	4.896 - 34.276	11.564 (<0.001)* **	4.290 - 31.171	2.516 (0.031)*	1.087 - 5.828	0.316
Amphetamines	14 (12.0%)	14 (51.9%)	7.923 (<0.001)* **	3.098 - 20.261	7.169 (<0.001)* **	2.765 - 18.590	1.757 (0.232)	0.698 - 4.425	0.209

* Significant at $p < 0.05$. ** Significant at $p < 0.01$

[a] Nagelkerke R^2

6.18 INFLUENCE OF CONDUCT DISORDER ON CRIME, HIV RISK-TAKING BEHAVIOUR AND QUALITY OF LIFE

The influence of conduct disorder on crime, HIV risk-taking behaviour and quality of life was determined using the mean score ± SD of crime, HIV risk-taking behaviour and QOL (Domains 1-4 and Total QOL) scores for non-ADHD and ADHD group, combined with hierarchical linear regression modelling using ADHD and conduct disorder diagnoses. The results are as shown in Table 20.

ADHD was found to be significantly associated with increased criminal activity, with this significance remaining even after adjusting for the presence of conduct disorder. In Step I, the R2 change indicates that ADHD explains 17.2% (F = 29.528, p < 0.001) of the variance in criminal activity. In Step II, the R2 change indicates that conduct disorder explains an additional 3.0% (F = 5.333, p = 0.022) and is significant. The association with diagnosis of ADHD remained significant even after accounting for the presence of conduct disorder in the final model, as the beta value for ADHD (beta = 0.381, p < 0.001) has a higher magnitude and significance than the beta for conduct disorder (beta = 0.177, p = 0.022).

Similarly in HIV risk-taking behaviour, the ADHD exerted a greater influence as evidenced by the persistence of the significant association between ADHD in the presence of conduct disorder. In Step I, the R2 change indicates that ADHD explains 5.5% (F = 8.382, p = 0.004) of the variance in HIV risk. In Step II, the R2 change indicates that conduct disorder explains only an additional 2.4% (F = 3.624, p = 0.059) and is not significant. The association with diagnosis of ADHD remained significant even after accounting for the presence of conduct disorder in the final model, as the beta value for ADHD (beta = 0.205, p = 0.013) in the final

model is significant while the beta for conduct disorder (beta = 0.156, p = 0.059) is not significant.

Poor quality of life scores are more likely to be influenced by ADHD and conduct disorder. This is evidenced by ADHD continuing to display a significant relationship with total QOL scores after conduct disorder was accounted for. The inclusion of conduct disorder as an independent variable in this model had only a minor impact on this difference. In Step I, the R2 change indicates that ADHD explains 17.7% (F = 30.806, p < 0.001) of the variance in total QOL score. In Step II, the R2 change indicates that conduct disorder explains only an additional 0.3% (F = 0.574, p = 0.450) and is not significant. The association with diagnosis of ADHD remained significant even after accounting for the presence of conduct disorder in the final model, as the beta value for ADHD (beta = -0.410, p < 0.001) in the final model is significant while the beta for conduct disorder (beta = -0.059, p = 0.450) is not significant.

Therefore, ADHD is significantly associated with crime, HIV risk-taking behaviour and poor quality of life, independent of conduct disorder.

Table 20. Mean score ± SD of Crime, HIV risk-taking behaviour, Total QOL score for non-ADHD and ADHD group, combined with hierarchical linear regression modelling using ADHD and conduct disorder diagnoses*

	Non ADHD (n = 117)	ADHD (n = 28)	Step I: ADHD			Step II: Conduct disorder			β(p) n full model		Prop. Variance Explained
			R^2 change	F change	*P*	R^2 change	F change	*P*	ADHD	conduct disorder	
Crime score	0.1034± 0.358	0.7143±0.976	0.172	29.528	<0.001	0.030	5.333	0.022	0.381 (<0.001)	0.177 (0.022)	0.202
HIV Risk	1.778±2.446	3.536±4.290	0.055	8.382	0.004	0.024	3.624	0.059	0.205 (0.013)	0.156 (0.059)	0.079
Total QOL	85.248±13.325	70.607±8.355	0.177	30.806	<0.001	0.003	0.574	0.450	-0.410 (<0.001)	-0.059 (0.451)	0.180

* Significant at p < 0.05.

7.0   DISCUSSION

7.1   PREVALENCE OF ADHD IN MMT PATIENTS

This study found a substantial ADHD prevalence rate of 19.3% among the population of patients on methadone therapy. There is a slight variation in the global prevalence of adult hyperactivity. However, current research estimates this figure to be 3.4%.[51] In accordance with this, the 19.3% rate found in this study is nearly six times higher than the prevalence of ADHD in the general adult population. This finding is consistent with numerous other studies showing that the prevalence of hyperactivity in adults is overrepresented in the population of substance users. This includes a prevalence rate of 34% in alcohol dependents, 35% in cocaine users and 15% in polysubstance users.[36,37,62]

In addition, the prevalence data in this study also corresponds to that of other studies involving treatment seeking opioid users. Eyre's pioneering study found a childhood ADHD prevalence rate of 22% in their sample of methadone-treated individuals.[32] More than a decade later, King reported a prevalence of 19% in a similar sample.[55] Subsequent research on this patient demographic continue to report comparable prevalence rates, ranging from 29% to 11% despite differing diagnostic and methodological assessments.[33,57,60] However, Arias reported a significantly lower prevalence rate of nearly 6%.[28] This can be explained by the fact that Arias' sample consisted of individuals from the community as opposed to the other studies which sought out treatment-seeking patients. In addition, Arias' study excluded individuals who presented with a diagnosis of either schizophrenia or schizoaffective disorder. This may have resulted in a sample population with a lower incidence of psychiatric illnesses, including a reduction in the number of participants with adult hyperactivity.[28]

Overall, there appears to be a bi-directional overrepresentation of both ADHD and substance use. This is evidenced by the elevated rates of hyperactivity in drug dependence and

of drug dependency in hyperactivity. There are several factors that may be responsible for this overrepresentation. Firstly, the sample population itself consists of individuals with SUDs. Literature has consistently reported a significant association between a diagnosis of ADHD and subsequent drug use, thus one would expect to find a higher hyperactivity prevalence rate in this group of patients. Secondly, this study sample consists exclusively of treatment seeking drug users, resulting in a propensity for Berkson's bias. This is an example of a selection bias, which arises when a study sample is taken from a subpopulation, rather than the general community.[103] In this phenomenon, individuals who have both diseases are more likely to seek treatment that people who only have one.[103] In relation to this study, individuals afflicted with SUD along with a comorbid ADHD may be more likely to seek treatment as they may be more ill. Therefore it can be surmised that in a sample consisting of treatment seeking drug users, there is a higher probability of a comorbid ADHD as opposed to their non-treatment seeking counterparts.This is evidenced by the prior mentioned study conducted by Arias' whereby a sample that was recruited purely from the community resulted in a significantly lower prevalence rate in comparison to the various other studies that involved substance users that were enrolled in therapy.

Despite the variations in diagnostic assessment, methodology, treatment setting and socio-demographic elements, the findings of the majority of studies investigating the prevalence of ADHD in substance users, and more specifically those on methadone are fairly similar. The reported figures are substantial and highlight the significance of adult hyperactivity in this particular strata of society.

7.2 THE ASSOCIATION BETWEEN ADHD AND SOCIODEMOGRAPHIC CHARACTERISTICS

AGE

In this study, a few sociodemographic characteristics were found to be associated with ADHD. Firstly, a diagnosis of ADHD was significantly associated with a younger age (p < 0.001). This finding echoes that of several other studies showing that treatment seeking drug users diagnosed with ADHD were younger than their counterparts.[28,31,57] Literature studying the co-relates of ADHD have consistently demonstrated higher prevalence rates of hyperactivity among those in the younger age bracket.[5,8,51] This is also consistent with current knowledge that the symptoms of hyperactivity show a proclivity to decline with age, resulting in a lower prevalence among those in the older age group.[35]

ETHNICITY

The ethnic distribution in this study consists of a majority of Malay subjects (79.3%) followed by Indians (12.4%) and Chinese (8.3%). This ethnic distribution is not in congruence with the local ethnic distribution whereby Malays, Chinese and Indians comprise 50.1%, 22.6% and 6.7% respectively. This can be explained by the ethnic distribution of Malaysian patients in the methadone clinics whereby a much larger majority are Malay, with the rest being Chinese and Malay. Thus we would expect a higher proportion of Malay patients in our sample as compared to the general population. Ethnicity was not significantly associated with a diagnosis of ADHD in this study (p = 0.914). As of the current date, this is the only study of its kind in South East Asia, and therefore, comparisons with the results of other similar studies in terms of ethnicity is not possible.

EDUCATION

This study found a significant association between hyperactivity and lower educational attainment (p = 0.012). This is in congruence with the majority of studies implying that hyperactive substance users tended to perform poorly in school in comparison to their counterparts.[32,59,60] Hyperactivity and attention deficit are significantly correlated with poorer education outcomes, even if their levels are sub-threshold for a diagnosis of ADHD.[104] In addition, academic achievement is also a product of IQ and it has been demonstrated that individuals afflicted with ADHD have reduced IQ scores in comparison to their counterparts.[105] The presence of comorbid conduct disorders and substance use further exacerbate the academic challenges faced by these individuals. It has even been postulated that it is the cognitive impediments of ADHD and not conduct disorder that are the causative factor for lower education levels.[106]

EMPLOYMENT

Similarly, this study reported that ADHD is significantly correlated with being unemployed (p = 0.03). There is a plethora of studies that echo these findings.[28,58] Even among the hyperactive substance users who were employed, they had a preponderance towards menial or unskilled jobs with a dearth of those occupying higher ranking professions.[32,59] This was corroborated by this study that showed the majority of ADHD subjects who were employed worked as security guards, parking lot attendants and shop assistants. The association between ADHD in methadone users and occupational dysfunction may likely be mediated by the poorer educational attainment in this group of individuals as explored above.

7.3   THE ASSOCIATION BETWEEN ADHD AND SUBSTANCE RELATED FACTORS

AGE OF FIRST SUBSTANCE USE, TYPE OF SUBSTANCES USED, NUMBER AND SEVERITY OF SUBSTANCE USE

This study reported that a diagnosis of ADHD in substance users on MMT is significantly associated with an earlier age of substance use ($p < 0.001$). Furthermore, this significance remained even after adjusting for the presence of conduct disorder.(TABLE 17) This is in agreement with other studies on treatment seeking drug users with hyperactivity.[28,31,107]

As previously hypothesised, the younger age of drug use may be a reflection of the poor self-esteem and negative self-perception held by this group of individuals. As a result, they choose to self-medicate with drugs.[68] The symptomatology of ADHD itself may confer a risk for earlier drug use, notably features of poor impulse control coupled with a higher propensity for novelty seeking.[28,69] It has been postulated that it is early onset of alcohol use in hyperactive individuals that resulted in subsequent drug use.[108] This hypothesis cannot be confirmed in this study as the subjects were assessed for first age of substance use in general without enquiring as to the exact type of substance which was first used. Further studies looking into this matter are needed to clarify this theory.

Further lending weight to the self-medication hypothesis is the finding that hyperactive methadone users in this study showed a significant tendency towards heroin ($p < 0.001$), cannabis ($p < 0.001$) and amphetamines ($p < 0.001$) use compared to their counterparts. Amphetamines share a number of pharmacological properties with the stimulants conventionally prescribed for the treatment of ADHD.[37,42] It is thus possible that these individuals have a preferential use of stimulant drugs in an effort to self-medicate the incapacitating symptoms of

hyperactivity. This theory was initially posited to explain the elevated rates of ADHD among cocaine users.[37] The data from this study fails to show evidence of cocaine use among the local population of methadone users. However, this can be attributed to the fact that the prevalence of cocaine use in Malaysia itself is low.[109] In addition, the highly prohibitive cost of cocaine in comparison to similar stimulants such as amphetamines further adds to its unpopularity especially among the patients in this study who belong to the lower socio-economic strata.

On a related note, the highly prevalent use of marijuana found in this study can also be attributed to an attempt to obtain short-term relief for the hyperactivity resulting from ADHD. This is supported by the frequent reporting by hyperactive substance users that smoking cannabis produces a calming sensation against the restlessness brought about by the disorder.[41] Both the sedating and stimulating (working paradoxically) effects of cannabis ameliorate the affective lability and agitation that characterise ADHD.[41]

The theory can be further extended to the increased use of heroin among this study sample. Similar to cannabis, they are capable of producing a tranquillising effect that counteracts the inner restlessness and intense episodes of rage experienced by these patients.[41] However, since this study population comprises exclusively of opioid dependent patients enrolled in methadone we would expect to find higher rates of heroin use in this study. In addition, local data reveals that heroin is the most widely misused substance in Malaysia.[110] Therefore, the self-medication hypothesis may not fully explain the preferential use of heroin here.

In line with nicotine's hypothesised ability to regulate attention and concentration, prior studies had demonstrated heavier smoking rates in the subgroup of opioid users on treatment.[40] This study did not report a significant difference in nicotine use. This could be attributed to the much higher general prevalence of smoking, which predominates the use of all other drugs with

this prevalence further escalating to 90% in drug users.[111] Therefore, because more drug users overall are smoking, it may be more difficult to establish significant differences in nicotine use between the two groups.

The hyperactive patients on MMT in this study significantly demonstrated a higher overall severity of substance use ($p = 0.015$) than their counterparts, specifically involving heroin ($p < 0.001$), cannabis ($p < 0.001$) and amphetamines ($p < 0.001$). Although conduct disorder exerts a bigger influence on severity of drug use (beta = 0.24, $p < 0.003$) as seen in Table 17, the influence of ADHD cannot be negated as it is also significant, although reduced in magnitude (beta = 0.226, $p = 0.005$). The subjects with ADHD also used a significantly higher number of substances ($p < 0.001$). This corresponds to studies involving similar sample populations in which those with ADHD show a proclivity for heavier drug use.[28,32]

Self-medication may only partly contribute to the pattern of drug use seen in this group of hyperactive patients. The high co-occurence of ADHD with substance misuse suggests that these two disorders may actually share similar underlying vulnerabilities. The findings in this study correspond to evidence that individuals with ADHD have a tendency towards drug use as opposed to alcohol use.[43,50] This lends strength to the hypothesis that ADHD and substance use disorders arise from a common genetic factor that is separate from alcohol use.[77] ADHD and SUD also have the neurotransmitter dopamine in common. It has thus been suggested that neurological dysfunction of the brain's reward processing in conjunction with impairment of the dopaminergic system confers a collective risk to overactivity, inattention and poor impulse control along with a predisposition to SUDs.[112,113] It has also been theorised that since the occurrence of ADHD precedes that of substance use, the symptoms of ADHD (such as hyperactivity and impulsivity) interact with the sequelae of this disorder (such as reduced education and impaired employment), thus setting the stage for an increased likelihood of

developing substance dependence.[114] This is supported by evidence that effective pharmacological treatment of ADHD in youth reduces the likelihood of later substance misuse.[115]

As a whole, the results of this study confirm the widely held view that a diagnosis of ADHD in substance users, including those seeking treatment with methadone is associated with a more complex and serious pattern of substance use. Although conduct disorder may account for the severity of drug use, ADHD appears to be an independent risk factor for an earlier age of first substance use as well as an increase in the number of substances abused. This is in support of previous evidence that ADHD has a more powerful influence on substance use than conduct disorder.[28,65] However, the comorbidity of ADHD with conduct disorder appears to have an additive effect on the risk of substance use.[88] In consideration of the fact that conduct disorder is a precursor of ADHD, its significance in drug and drug-related behaviour thus cannot be negated.

7.4 THE ASSOCIATION BETWEEN ADHD AND OTHER PSYCHIATRIC DISORDERS

A diagnosis of ADHD in MMT patients increases the likelihood of psychiatric comorbidity.[28,31] Furthermore, individuals with a combination of hyperactivity and substance dependence have an amplified risk for developing other mental illnesses compared to either condition by itself.[41] The findings of this study is in agreement with these postulations whereby the group of MMT patients with hyperactivity have an increased prevalence of OCD, PTSD, mood and anxiety disorders than their counterparts. They also had an increased number of psychiatric disorders ($p < 0.001$). In addition the hyperactive group have a significantly higher prevalence of major depressive disorder ($p = 0.026$). This finding echoes that of other studies involving a similar study sample, including a recent extensive multisite one.[53,56] A diagnosis of

ADHD was also found to be significantly associated with comorbid conduct disorder (p = 0.036). Given that ADHD is an established precursor for the occurrence and development of conduct disorder, we would expect to find a higher prevalence of conduct disorder in a subset of ADHD patients versus those without.[37,54]

That other psychiatric comorbidities so frequently appear in the population of substance users with ADHD suggests that they may share a similar predisposition or vulnerability.[53] Research from prior studies have reported that the occurrence of ADHD predates that of many other comorbid psychiatric illnesses, thus inferring that prompt treatment of hyperactivity might hinder the later development and progression of those comorbidities.[58] This is especially relevant in light of evidence suggesting that the occurrence of other psychiatric comorbidities in ADHD patients with substance dependence is characterised by poorer treatment outcomes.[37,50] This highlights the need for an integrated treatment approach for these group of patients which combines psychiatric management with therapy for addiction.[116]

7.5 THE ASSOCIATION BETWEEN ADHD AND CRIME

The significant association between ADHD and criminal activity in this study (p = 0.003) confirms the findings made by previous researchers on this issue.[32,60] Substance use itself has been consistently correlated with lawbreaking.[117,118] ADHD and conduct disorder are both independent as well as additive risk factors associated with criminality.[119] More specifically, it has been postulated that it is the combination of overactivity and poor impulse control, but not attention deficit that confers this risk and that this contribution extends beyond the influence of conduct disorder alone.[119] This tallies with the results of this study where although a co-existing diagnosis of conduct disorder also heightens the risk for criminal behaviour, the role played by ADHD is more substantial (Table 20).

It can thus be concluded that a comorbidity of hyperactivity in treatment seeking substance users magnifies the risk of criminal activity. This risk is further heightened in the presence of conduct disorder. The ADHD rating instrument utilised in this study did not separate symptoms of hyperactivity, impulsivity and inattention, making it difficult to attribute a specific symptom to the risk of crime. Future studies implementing ADHD scales that make this symptom distinction could be helpful in researching this matter.

7.6   THE ASSOCIATION BETWEEN ADHD AND HIV RISK-TAKING BEHAVIOUR

A similar pattern of association plays out for HIV risk-related behaviour in this study where MMT patients with ADHD have a significantly higher risk of HIV ($p = 0.045$), with this risk retaining its significance even after accounting for conduct disorder (Table 20). It has been established that substance dependency is associated with numerous factors that heighten the risk for HIV; including unsafe sexual practices and indiscriminate sharing of needles.[120,121] In turn, interpersonal elements, parental behaviours, peer influence and impulsivity are among the attributes said to account for the relationship between hyperactivity and risk of acquiring HIV.[88] More worryingly, hyperactive individuals with HIV showed poorer compliance to Antiretroviral Therapy (ART) as opposed to their non-hyperactive counterparts.[92] Compounding to this concern is evidence that a majority of these individuals continued to engage in unprotected sex even after being updated on their positive HIV status.[92] Therefore, when a diagnosis of ADHD is added into the mix of treatment seeking substance abusers as found in this study, it is hardly surprising that the rates of HIV are amplified. This is an important element that bears further appraisement in upcoming studies. This also highlights the fact that early detection and treatment of ADHD has the propensity to alleviate the chances of later drug use and conversely reduce the risk of acquiring HIV.

7.7   THE ASSOCIATION BETWEEN ADHD AND QUALITY OF LIFE

Patients with substance dependency on methadone frequently report diminished scores in most facets of their lives.[122,123] A diagnosis of ADHD appears to exacerbate the deterioration of QOL in these group of patients.[31,32,56] The findings of poor quality of life outcomes in this study is consistent with the above research. Even after accounting for the effects of conduct disorder, ADHD remained a significant associating factor in this study (Table 20).

Social alliances, positive relationships and holding a job are among the key elements associated with improved living standards among hyperactive MMT patients.[123] Opioid dependent subjects who reported experiencing support from their family also show improved scores.[124] In this study a diagnosis of ADHD was significantly associated with unemployment. In addition, there was a high prevalence of unmarried and divorced patients in the ADHD subgroup, thus conferring some explanation for the lower scores in the relationship and environment domains. The poor scores reported in the psychological domain of the WHOQOL-BREF in this study are not surprising, given the high prevalence of psychiatric disorders among our MMT patients with ADHD. This is in line with evidence that these patients had even poorer life quality scores than individuals with major mental illnesses such as schizophrenia and depression.[125,126]

The persistence of ADHD causes impairment in multiple facets of life, including educational, occupational and psychological deterioration.[54] This pervasive impairment in functioning is what results in an overall decline in the experienced standard of living.[35] This finding warrants attention as poor quality of life is one of the factors associated with non-compliance to MMT, thus resulting in a poor treatment outcome.[127]

In summary, the significant prevalence rate found in this study highlights the importance of recognition, identification and treatment of ADHD among substance users enrolled in MMT. Methadone clinics should consider screening all potential patients to detect the presence of ADHD.

The finding that ADHD exerts a negative influence on SUD-related factors necessitates the planning and implementation of a treatment regime that incorporates both these disorders. This is especially crucial given that research reports a poorer treatment outcome for substance users with comorbid ADHD, including a lower likelihood of attaining drug abstinence as well as reduced compliance to methadone.[33] Due to the complex nature of SUDs combined with ADHD, conventional treatment regimes may not suffice.[31] Research on the use of psychostimulants in the treatment of ADHD with comorbid SUDs have reported mostly negative results, although some studies do demonstrate an improvement in secondary outcome measures.[128,129,130] This further emphasises the complexity of treating this group of patients. Non-pharmacological modalities such as Cognitive Behavioural Therapy (CBT) have shown to be efficacious in patients with ADHD[131,132,133] and research is currently underway to determine the potential benefits it may confer in treatment seeking SUD patients with ADHD.[134] This includes the use of learning to strategies to improve areas of cognition such as memory and attention, techniques that aid in emotional mastery and the acquisition of social skills.[133] For now, these are relatively uncomplicated techniques that can easily be implemented and do not place a restrain on healthcare resources.

This study also underscores the increased risk of psychiatric comorbidity in adult hyperactive patients with SUDs. Currently, dual-diagnosis patients tend to be given isolated treatment for their respective disorders. There should a shift towards integrated treatment that

addresses and incorporates ADHD, SUDs and psychiatric comorbidities respectively. This has the potential to enhance the quality of life as well as treatment outcomes of these patients. In addition, evidence has consistently shown that early and efficacious treatment of children and adolescents with ADHD has the potential to reduce later substance use and dependency.[76,135,136] Therefore, more effort should be undertaken to identify and treat this group of individuals as a potential strategy for mitigating the risk of developing SUDs and its associated sequelae, including elevated risks for crime, HIV as well as poorer quality of life as evidenced in this study.

This also includes adequate public literacy regarding ADHD. Campaigns regarding childhood ADHD should be held at national levels and target kindergartens, primary schools and secondary schools. Teachers and parents need to be educated on the symptoms of ADHD, its sequelae and the treatment modalities available and where to get them. Part of the educational campaigns include dispelling some of the myths surrounding ADHD and the treatment, including the erroneous belief that stimulant treatment will result in substance abuse. School counsellors should undergo training sessions that will equip them with skills on picking up cases of ADHD in their respective schools and referring them to child and adolescent psychiatrists. Psychiatrists along with clinical psychologists can implement programs where they go school-to-school, giving talks to raise awareness about ADHD as well as screen school children for the potential disorder.

There also needs to be more awareness as well as the use of diagnostic instruments among psychiatrists in diagnosing adult ADHD in general and specifically in the population of substance users. This can be attained by seminars, courses and workshops regarding adult ADHD targeted towards the mental health professionals. This is of importance as research points to an underdiagnosis of cases of adult ADHD.[137] The ability to accurately detect cases of ADHD

prior to or upon enrolment of patients into MMT will allow therapists to identify the at-risk patients, thus initiating more intensive and integrated management which has the potential to result in better MMT treatment outcomes.

7.8   LIMITATIONS & STRENGTHS

There were several limitations in this study. Firstly, this study was cross-sectional in nature. Therefore, we are unable to make any causal inferences regarding the possible predictive factors for substance abusers who were diagnosed with ADHD. We are only able to conclude that there is a significant association between a diagnosis of ADHD and substance use patterns, psychiatric comorbidity, criminal activity as well as HIV risk and poor quality of life. Thus, a longitudinal study, namely of the cohort variety may be preferable.

The study sample comprised exclusively of treatment seeking drug users, i.e. patients on methadone. As mentioned earlier, substance users who seek treatment tend to be more ill in comparison to their non treatment seeking counterparts.[60] This limits the study's generalisability to the community. In addition, the study was conducted in government funded methadone clinics. Patients attending these clinics tend to be at a socio-economic disadvantage in comparison to patients enrolled in private or semi-privatised methadone centres. These differences make it difficult to generalise the study findings to that of other populations such as psychiatric institutions, inpatient treatment seekers and privatised substance treatment centres. Future research should extend the sample population to include these individuals.

There is currently no Malay version of the OTI, M.I.N.I (except for a Malay version for Major Depressive Disorder) and M.I.N.I Plus instruments. A considerable amount of the patients spoke Malay and thus required translation. Cultural as well as language nuances would have an impact on the inter-rater reliability as well as the validity of these assessments. However, there was a Malay version of the WHOQOL-BREF which was utilised to measure quality of life.

Another limitation of the study is the use of a retrospective diagnostic method. This was especially pertinent in the diagnosis of ADHD and conduct disorder. Complete reliance on

information recalled from the past may not always lead to accurate data and may adversely affect the validity of the study results.[138] There is evidence that retrospective recall often results in exaggerated ADHD prevalence rates.[139] However, the positive predictive value of retrospective recall improves as the rate of expected cases increases.[140] Thus given that the sample population of this study consists of treatment seeking substance users (in which we expect a higher incidence of ADHD), this might minimise a portion of the false positives associated with retrospective recall.

On a related note, the establishment of diagnoses was primarily based on self-reporting. Exclusive dependence on self-report may lead to doubts about the veracity of the information provided by the participants. Substance users have a tendency to minimise their drug use and this could lead to an underestimation of the severity of the SUDs. This was partially countered by examining the patient's treatment records and obtaining collateral information (when possible). Future studies should include rapid urine toxicology to add strength to the self-report. However, this does not completely eliminate report bias as there are certain substances such as inhalants that cannot be tested for via urine samples. In addition, the OTI has a component that assess HIV risk by asking questions related to sexual practices. Patients might have been reluctant to disclose intimate information especially in our cultural context where such topics are considered taboo.

The absence of collateral history may also have an impact on the validity of the diagnosis of ADHD and conduct disorder. The diagnosis of these two disorders was established based on symptoms that originally manifested in childhood. Evidence suggests that prevalence rates are lower when a diagnosis of ADHD is made solely based on self-report versus parent reports.[141] For an overwhelming majority of our patients, there were no family members present to substantiate the information provided by the participants. Future research should look into

obtaining contemporaneous information from sources including family members, caregivers as academic transcripts and criminal records.

The accurate distinguishing of the symptoms of ADHD from that of substance intoxication or withdrawal is another limitation. This is because both these conditions may present with symptoms that resemble each other. Symptoms of either withdrawal or intoxication may have been taken to be that of ADHD while pre-existing ADHD symptoms may have been exacerbated by recent withdrawal or intoxication.[114] In view of this, patients were asked if the positive symptoms elicited were associated with their substance use or whether they were characteristic of patient's usual longitudinal behaviour.

Nonetheless, this study possessed a few strengths. Standardised interview criteria for the diagnosis of ADHD and all other psychiatric disorders was utilised throughout the study. Despite the unavailability of local versions of the M.I.N.I and OTI, these two instruments have had their validity and reliability established globally. There is a validated Malay version of the WHOQOL-BREF and M.I.N.I for Major Depressive Disorder which was used in this study. This study included patients on methadone, a subgroup of individuals who are generally associated with some of the most challenging patterns of substance use. This study thus enabled us to assess this complex subset of individuals and substantiate the significant prevalence of ADHD and its impact on substance use and other facets of life. As of the present time, this is the first local study to examine ADHD in the population of methadone seekers. This may thus lay the foundation for more extensive local research pertaining to this subject matter in the future.

7.9   CONCLUSION

In conclusion, this study was able to achieve its intended objectives. The prevalence of adult ADHD among patients enrolled in the methadone clinic in Hospital Kuala Lumpur and Klinik Kesihatan Kuala Lumpur stands at a substantial rate of 19.3%. A diagnosis of ADHD is associated with a younger age, lower education level and unemployment. ADHD results in a severe and complicated course of substance use characterised by early age of first substance use, the use of more number of drugs and more specifically, the use of heroin, cannabis and amphetamines. This may be the product of an interplay of genetic factors, alterations in dopamine function and attempts to self-medicate. In addition, MMT patients with ADHD have a higher number of other psychiatric comorbidities with a significant association with Major Depressive Disorder and Conduct Disorder.

A diagnosis of ADHD is further associated with crime, increased HIV risk-taking behaviour and lower quality of life scores which arise both as a result of the symptoms of ADHD itself and the sequelae of the illness. Although conduct disorder is highly comorbid with ADHD, ADHD remains an independent risk factor for the above outcomes. However, the additive influence of conduct disorder cannot be negated.

These adverse outcomes associated with a diagnosis of ADHD has the potential to affect MMT treatment outcome. In addition, treatment of ADHD comorbid with SUD appears to be complex. In view of this, there needs to be increased awareness and recognition of the concept of ADHD. This awareness needs to be generated in all strata including the parents, teachers, counsellors and health workers. In addition, clinicians need to detect and appropriately initiate treatment of ADHD in these group of patients. The treatment regime needs to be integrated, taking into account the multiple psychiatric comorbidities that may be present with an emphasis on CBT-based techniques to specifically target the core symptoms of inattention, hyperactivity and poor impulse control. Although the use of psychostimulants have not resulted in statistically

significant improvement, some studies have shown an improvement in secondary outcome measures. Timely and integrated treatment approach has the potential to improve treatment outcomes in MMT programs as well as exert a positive influence on other facets such as psychiatric comorbidity, crime, HIV risk and quality of life.

Currently, this is the first local study on adult ADHD in the population of MMT patients. However, the findings are substantial enough to necessitate further research on the subject. Future longitudinal studies, with a larger sample size, utilising biological investigations such as rapid urine toxicology and assessing the effects of ADHD on MMT treatment outcome might be helpful in further gleaning information on the exact relationship and consequences of adult ADHD in patients on MMT.

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