COGNITIVE AND NEUROPSYCHOLOGICAL ASSESSMENTS FOR CO-OCCURRING OPIOID AND AMPHETAMINE-TYPE STIMULANT (COATS) DEPENDENT PATIENTS

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By

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TABLE OF CONTENTS

LIST OF FIGURE

Page

LIST OF TABLES

LIST OF ABBREVIATIONS

DDD	Dual Drug Dependence
HIV	Human Immunodeficiency Virus
ATS	Amphetamine Type Stimulants
UNODC	United Nation of Drug and Crime
MA	Methamphetamine
UNODC	United Nation on Drug and Crime
ROCF	Rey-Osterrieth Complex Figure
TMT	Trail Making Test
DST	Digit Span Test
SDT	Symbol Digit Test
VTA	Ventral Tegmental Area
DA	Dopamine
NAC	Nucleus Accumben
PFC	Prefrontal Cortex
NIDA	National Institute of Drug Abuse
CBT	Cognitive Behavioral Therapy

PENILAIAN KOGNITIF DAN NEUROPSIKOLOGIKAL DALAM KALANGAN PESAKIT YANG ADA DWI-KEBERGANTUNGAN TERHADAP OPIOID DAN PERANGSANG JENIS AMFETAMINA (COATS)

ABSTRAK

Kajian menunjukkan individu yang ada kebergantungan terhadap dadah mempunyai fungsi kognitif yang lebih rendah dalam domain fungsi eksekutif. Kajian yang melibatkan pengguna dadah yang menggunakan beberapa jenis dadah adalah terhad. Kajian ini direka bentuk untuk menilai skop dan corak spesifik masalah kefungsian kognitif dan neuropsikologikal dalam kalangan individu yang menyalahgunakan opioid dan ATS (dwi-kebergantungan (DDD)) dan memasuki rawatan bantuan ubatan di Hospital Universiti Sains Malaysia (HUSM), Kelantan. Sejumlah *n*=96 responden lelaki (*n*=56 pesakit dan *n*=40 kumpulan kawalan) telah diambil untuk kajian rentas ini. Ujian neuropsikologikal *Rey Osterrieth Complex Figure, Trail Making Test, Raven's Progressive Matrices, Digit Span Test, Digit Symbol Test, and Stroop Test* telah dilakukan. Keputusan kajian menunjukkan prestasi pesakit adalah lebih rendah daripada prestasi kumpulan kawalan dalam kelajuan persepsi motor dan imbasan visual yang diukur menggunakan *Trail Making Test Part A*, dalam fleksibiliti kognitif yang diukur menggunakan *Trail Making Test Part B* dan dalam kelajuan pemprosesan mental yang diukur menggunakan *Digit Symbol Test*. Keputusan menunjukkan ada sedikit gangguan dalam kelajuan persepsi motor, imbasan visual, fleksibiliti kognitif dan kelajuan pemprosesan mental dalam kalangan pesakit yang ada dwi-kebergantungan. Oleh itu, intervensi pencegahan dan rawatan yang baik perlu mengambil kira masalah kognitif dalam kalangan pesakit yang ada dwi-kebergantungan.

COGNITIVE AND NEUROPSYCHOLOGICAL ASSESSMENTS AMONG CO-OCCURRING OPIOID AND AMPHETAMINE-TYPE STIMULANT (COATS) DEPENDENT PATIENTS

ABSTRACT

Several studies have shown that individuals with drug dependence have poorer cognitive functions in the domain of executive functions. Studies investigating cognitive impairments in people with poly-drug use are limited. This study is designed to evaluate the scope and the specific patterns of deficits in cognitive and neuropsychological functioning among opiate and ATS (Dual Drug Dependence (DDD)) abusing individuals enrolled in a medication-assisted treatment in Hospital Universiti Sains Malaysia (HUSM), Kelantan. A total of *n*=96 male respondents (*n*=56 patients, and *n*=40 control group) were recruited for this cross-sectional study. Cognitive functions evaluated were Rey-Osterrieth Complex Figure, Trail Making Test, Raven's Progressive Matrices, Digit Span Test, Digit Symbol Test, and Stroop Test were administered. Results showed that patients performed significantly worse in perceptual motor speed and visual scanning measured by Trail Making Test Part A, cognitive flexibility measured by Trail Making Test Part B, and mental processing speed measured by Digit Symbol Test compared to those in the control group. Results suggest that there were slight impairments in perceptual motor speed, visual scanning, cognitive flexibility, and mental processing speed among patients with dual drug dependence. Therefore, proper prevention and treatment interventions should take into account the cognitive problems in patients who have dual dependency.

CHAPTER 1

INTRODUCTION

1.1 Background Of The Study

Drug addiction continues to be a global rampant problem. According to National Institute of Drug Abuse (2014), addiction is a relapsing disease characterized by intense drug seeking behavior and use of drug accompanied by chemical changes in brain Malaysia is also no exception in this problem. In Malaysia, heroin continues to be the main drug used whereas amphetamine-type stimulants use is increasing (Singh, Chawarski, Schottenfeld, & Vicknasingam, 2013). The drug users that were detected between 1988 and 2006 were 300,241. It is also estimated that Malaysia has 170,000 injecting drug users who also have Human Immunodeficiency Virus (HIV) and the prevalence among drug users in the country ranges from 25% to 45% (Singh et al., 2013).

Recently, amphetamine-type stimulants (ATS), including crystal methamphetamine and various other methamphetamine and/or amphetamine-containing substances/pills, have been identified as a growing problem, not only in Malaysia but also throughout the Southeast Asia Region (Mcketin, Kozel, & Douglas, 2008). Although much research has been done on drug addiction in Malaysia, the cognitive and neuropsychological aspects of drug use remained scarce (Zamani, Nasir, Desa, Khairudin, & Yusooff, 2014).

1.2 Opioid

Opioid is usually used in medicine for pain relief. But misuse of opioid may lead to many withdrawal symptoms such as restlessness, weakness, chills, body and joint pain, social withdrawal and many more. There has been little study on neurocognitive effects by heroin pure users. Opioids, namely heroin and illicit morphine, continued to be the most widely used drugs in Malaysia (United Nation Office on Drugs and Crime, 2013). Heroin remains the primary drug used in Malaysia. In 2012, approximately 48% of all drug users had used heroin while 31% had used illicit morphine (Malaysia Country Report, 2013). A large portion of heroin seized in Malaysia is originated from Myanmar and is trafficked overland through Thailand (Malaysia Country Report, 2013). Malaysia has been involved in drug abuse problems since the 1970s, and the major driver of HIV transmission in Malaysia is causing by drug abuse (Chawarski, Vicknasingam, Mazlan, & Schottenfeld, 2012).

Heroin is extracted from the poppy plant. It is characterized as a white powder with a bitter taste. Pure heroin can be either smoked or inhaled. The short term effect of heroin is being in a pleasurable sensation due to the activation of brain reward system and this may last for a few hours, thus, individual must take it repeatedly and lead to addiction (National Institute of Drug Abuse, 2010). Long term effect and repeated use of heroin can change physiology and neuronal imbalance in brain and aid to physical dependence on this drug (NIDA, 2014)

Withdrawal symptoms such as muscle pain, insomnia, restlessness, bone pain, and many more occur when one stops using heroin. Addiction to heroin may bring the individual to put the use of this drug are main purpose of life. But, there are several medications that are recommended for detoxification from heroin such as Methadone

and Buprenorphine (Whelan & Remski, 2012). Also, some cognitive behavioral therapies (CBT) are recommended as part of treatment. CBT is the process of identifying negative pattern of thought which will influence one's behavior. The negative thought patterns always play a main role in development of addiction (Kimmel, 2015). Examples of CBT techniques used in addiction treatment include pleasant activity schedule which may help recovering addict to make a healthy weekly list including fun activities that may break up daily routines. This may help reduce negative automatic thoughts and the subsequent need to use drug. (Addiction Center, 2015).

Figure 1.1: Heroin Powder and Common Route of Administration Using Syringe

1.3 Amphetamine-Type-Stimulants

Amphetamine and methamphetamine are from the group of psycho-stimulants where the methamphetamine is a synthetic derivative of amphetamine. Because of the chemical structure of methamphetamine, it has high lipid solubility compared to amphetamine and thus, it has intense effect on central nervous system. ATS is a group of drugs whose principal members are amphetamine and MA. The use of ATS has

become a part of the mainstream culture in many countries and has become a worldwide problem in the recent years (United Nation of Drug and Crime, 2009). According to the United Nation on Drug and Crime (UNODC), ATS has become the world's second most widely abused drug type after cannabis (UNODC, 2011). The geographical spread is widening, but awareness of it is limited. There are urgent needs to study about ATS problem because the higher usage may increase the level of presentation of ATS psychosis to mental health service (World Health Organization, 2015)

The trafficking of ATS to Malaysia for both domestic use and as a transit location for international markets remains a problem (UNODC, 2013). ATS continued to be the most commonly used drug among new drug users and drug users arrested for the first time (UNODC, 2013). More recently, ATS including crystal methamphetamine and various other methamphetamine and/or amphetamine containing substances or pills, have been identified as a growing problem in Malaysia and throughout East and South-East Asia (McKetin et al., 2008; Sutcliffe et al., 2009; UNODC, 2011). UNODC's 2010 estimated that up to 20.7 million individuals in Asia and the Pacific have used ATS in the past years (Global SMART Programme, 2010). A study done by Vicknasingam et al., (2010) found that in many regions of Malaysia, most of opioid Injecting Drug Users individuals use ATS during their lifetime.

Amphetamine also can affect the capacity of brain to stimulate neurogenesis (growth and development of nervous tissue) and this could cause the disruption of Blood-brain barrier (BBB) (Silva et al., 2010). The chronic effects of amphetamine (psychostimulatory effect) not only connected with reward and euphoria, but the effects are including impairment in attention and memory. Thus, this cognitive effect related to neurotoxic effect of drug and apoptosis (Krasnova, Ladenheim, & Cadet, 2005).

Amphetamine in acute phase may inhibit the reuptake of Dopamine, Norepinephrine, and Serotonin by membrane transporters and increase this level of this neurotransmitter in the brain and it will then result in depletion of dopamine transporter and this will give impairment in their neuropsychological functioning (Logan, 2002; Camí, & Farré, 2003; Nordahl, Salo, & Leamon, 2003; Fernández-Serrano, Pérez-Garcia, & Verdejo-Garcia, 2011).

Figure 1.2: ATS tablet that commonly used in Kelantan region

1.4 Co-Occurring Opioid and Amphetamine Type Stimulants (COATS)

The use of two or more substances at the same time and sequentially are considered as a poly-drug use. There are various patterns that can be seen, one of the patterns was different substances being taken together to have a cumulative or complementary effect (UNODC, 2014).

ATS is a stimulant whereas heroin is a depressant. The combination of these drugs have become more frequent and popular among drug users (Singh et al., 2013). A new trend of dual-dependence (Opioid and ATS) provides the baseline information regarding the need to implement the effective treatment approach (Singh et al, 2013). The effective treatments include medication therapy and psychological aspect such as

counseling. Cognition is the central of drug addiction thus, it is important to conduct research that evaluates cognition and one of the tests that can be used to measure it was neuropsychological assessment.

The simultaneous use of stimulants and opioids has, for over a century, have been reported to be a superior combination for pain relief. Besides, it is perceived that the endogenous endorphin-opioid receptor system is the only pain control mechanism in the central nervous system. In reality, multiple neurochemical systems are at play in pain relief. They include, among others, the serotonergic, gamma-amino-butyric acid (GABA-ergenic), and adrenergic (norepinephrine-dopamine) systems. Pain relief with stimulants appears to be primarily mediated by norepinephrine and not dopamine. It is the simultaneous triggering of the endorphin and adrenergic neurochemical systems that gives the combined administration of opioids and stimulants a pain-relieving effect much greater than either one alone.

1.5 Addiction and Cognition

Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. Chronic use of heroin and morphine may lead to various cognitive impairments (Spain & Newsom, 1991; Hauser, Houdi, Turbek, Elde, & Ili, 2000; Yin, Woodruff, Zhang, Whaley, Miao, & Ferslew, 2006). The consequence of damaging cognitive function will give the negative impact to their thinking and memory process that could lead to mental illness and ineffective treatment approach

There are widespread deficits in neuropsychological function associated with chronic use of psychoactive substance (Verdejo-Garcia et al, 2004; Ornstein, Iddon, Baldacchino, Sahakian, London, Everitt, & Robbins, 2000). From the neurological and

psychological perspectives, addiction may cause disorders or alteration in cognition. Drugs alter normal brain structure and function in regions that are responsible for controlling cognitive functions such as learning, attention, memory, and impulse control. This will promote continues of drug use and will hinder the treatment process that support sustained abstinence.

Numerous studies found that individuals who use drugs usually have alteration in the prefrontal cortex (Kelley, 2004; Kalivas & Volkow, 2005; and Lemoal & Koob, 2007). There are many factors that influence whether a particular person who takes and experiments with opioid drug will continue taking them for a longer time to become dependent or addicted. Opioid may provide intense feeling of pleasure.

Heroin or other opioid can cross the blood brain barrier and thus, travel through bloodstream in the brain. The chemical will then be attached to specialized proteins called mu receptors on the brain cell. Linkage between this chemical and receptor will trigger biochemical brain process and the reward system is activated and they feel pleasure. This opioid may activate brain circuit that we call mesolimbic (midbrain) reward system. This system then will generate the signal in a part of brain that we call ventral tegmental area (VTA) that will result the release of dopamine (DA) in another part of brain, the nucleus accumbens (NAc- brain key pleasure centre). The release of DA to NAc will cause the feeling of pleasure. The opioid stimulation of brain's reward system is the main reason why some people take drugs repeatedly. Repeated exposure of opioid drugs may induce brain mechanism of dependence and lead to daily drug use to alleviate withdrawal symptoms.

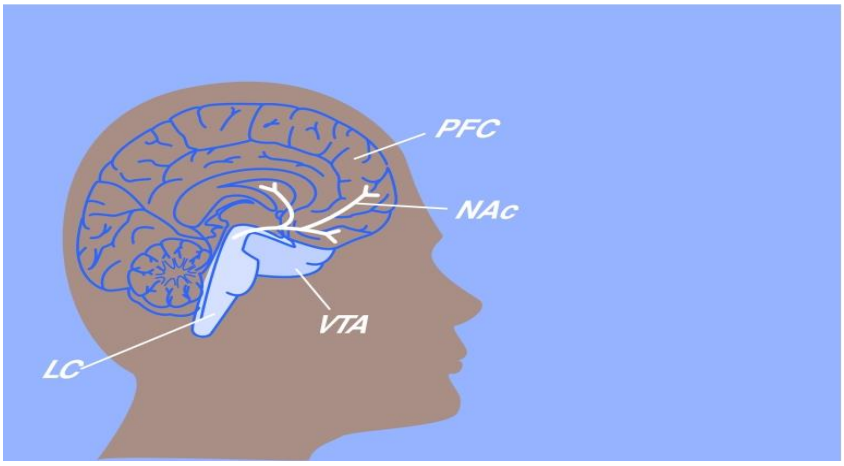

Figure 1.3: Mesolimbic Reward System (Kosten, & George, 2002)

1.6 Cognitive Deficit Model

This model states that a person who develops addictive disorder may have abnormalities in an area in brain called the prefrontal cortex (PFC). PFC is important for regulation of judgment, planning, and other executive functions. This model also proposes that PFC signals to mesolimbic reward system are compromised in individuals with addictive disorders and as a result, the ability to use judgments to restrain their impulses is reduced and leads to a predisposition to compulsive drug-taking behavior. Consistent with this model, stimulant drugs such as ATS is suggested to damage the fronto-striatal loop that carries inhibitory signal from PFC to mesolimbic reward system. (Kosten & George, 2002)

1.7 Amphetamine and Opioids Cognitive Deficit

Both amphetamine and opioid may activate dopamine system in midbrain which associated with positive reinforcing effect and have addictive potential. But, both pharmacological effects are different. There are studies on comparison of psycho-stimulant drug and opioids and most of the studies were conducted with participants in treatment settings (Fernández-Serrano, Pérez-García & Verdejo-García, 2011).

A study performed by Ornstein et al. (2000) that evaluated cognitive functions among amphetamine or heroin were compared, together with age- and IQ-matched control subjects showed deficit in a range of cognitive skills, including pattern recognition, planning and ability to shift attention from one frame of reference to another. This study suggested chronic drug use may lead to distinct patterns of cognitive impairment that may be associated with dysfunction of different components of cortico-striatal circuitry. Additionally, Ersche and colleague (2006) found that chronic drug users display neuropsychological impairment in executing function and memory also, if the impairment persist after several years, it may reflect neuropathology in frontal and temporal cortices.

The chronic effects of prolonged substance abuse may differ between opiate and amphetamine supported by a study of examination of post-mortem of brain indicate amphetamine users qualitatively obtain more severe neuropathology compared to opiate users (Kish et al., 2001). Even though there are neuropathology studies regarding effect of amphetamine and opioid users respectively, neuropsychological studies that directly compare the cognitive performance in both amphetamine and opiate users are still sparse (Ersche et al., 2006).

1.8 Problem Statement

Having stimulant and hallucinergic effects, ATS has a wide range of physical and psychological health impact. Long term of the use of both substances may lead to various cognitive impairments. Dependence on opioid and ATS frequently co-occur, and many studies showed that cognitive impairment as a result of using this drug (Pilowsky, 2011).

However, studies about cognitive function for drug user that use both drugs are scarce. Based on the study done by Dalleys et al. (2005), they found that most amphetamine users have deficit in cognitive especially in their attention. Other than that, one of the studies done by Hekmat et al. (2010) found that the addicted subject in performing heroin is worse in executive function measures such as speed of mental processing measured by digit symbol test. The trend of using this both drugs together are keep increasing, thus the cognitive measure may provide a clear picture and will aid in treatment programs for drug users.

Kelantan was experiencing serious problem with opioid, ATS and HIV compared to other state of Malaysia. The number of ATS-related arrests in Kelantan increased 5051 substantially from 2,900 in 2007 to 5,300 in 2010 and 9,413 in 2012 (Royal Malaysian Police 2013). According to AADK report, the statistic of a new drug users in Kelantan was increased from 1019 (7.49%) in 2014 to 1683 (8.30%) in 2015 (AADK, 2014, 2015). Besides, there was also increased in registered new drug users from 29 269 in 2014 to 31 257 in 2015 based on AADK current report.

Co-occurring ATS and Opioid are quite concerning in Kelantan. Both types of drugs are highly addictive, and it overlapping effect on brain reward system and circulatory that regulating motivation, emotional and executive function including impulse control (Ersche & Sahakian 2007; Trujillo, Smith & Guaderrama 2011). Other than that, the person that using both drug (ATS and Opioids) usually having high level of psychiatric co-morbidity and require more intensive clinical management (Pilowsky et al. 2011).

1.9 Objectives of the Study

To evaluate the scope and the specific patterns of deficits in cognitive and neuropsychological functioning among opiate and ATS (Dual Drug Dependence (DDD)) abusing individuals enrolled in a medication-assisted treatment in Hospital Universiti Sains Malaysia (HUSM) with a healthy control group in Kelantan. Cognitive functions evaluated were:

1. Visuo-constructional, visuo-perceptual ability, incidental visual memory and attention - Rey-Osterrieth Complex Figure (ROCF).
2. Perceptual Motor Speed, Visual Scanning and Cognitive Flexibility - Trail Making Test Part A and B
3. Reasoning Skills - Raven's Progressive Matrices.
4. Short-term Memory and Working Memory - Digit Span Test Forward and Backward (DST).
5. Speed of Mental Processing - Symbol Digit Test (SDT).
6. Response Inhibition - Stroop test.

1.10 Hypotheses

1. H_0 - There is no significant mean difference in visuo-constructional, visuo-perceptual ability, incidental visual memory and attention between Dual Drug Dependence (DDD) patients and control group measured by Rey-Osterrieth Complex Figure (ROCF).

   H_1–There is a significant mean difference in visuo-constructional, visuo-perceptual ability, incidental visual memory and attention between (DDD) patients and control group measured by Rey-Osterrieth Complex Figure (ROCF).

2. H_0 - There is no significant mean difference in Perceptual Motor Speed, Visual Scanning and Cognitive Flexibility between DDD patients and control group measured by Trail Making Test Part A and B.

   H_1 – There is a significant mean difference in Perceptual Motor Speed, Visual Scanning and Cognitive Flexibility between DDD patients and control group measured by Trail Making Test Part A and B.

3. H_0 - There is no significant mean difference in reasoning skills, between DDD patients and control group measured by Raven's Progressive Matrices.

   H_1 - There is a significant mean difference in reasoning skills, between DDD patients and control group measured by Raven's Progressive Matrices.

4. H_0 - There is no significant mean difference in short-term memory and working memory between DDD patients and control group measured by Digit Span Test Forward and Backward (DST).

   H_1 - There are significant mean differences in short-term memory and working memory between DDD patients and control group measured by Digit Span Test Forward and Backward (DST).

5. H_0 - There is no significant mean difference in speed of mental processing between DDD patients and control group measured by Symbol Digit Test (SDT).

H_1 - There are significant mean differences in speed of mental processing between DDD patients and control group measured by Symbol Digit Test (SDT).

6. H_0 - There is no significant mean difference in response inhibition between DDD patients and control group measured by Stroop test.

   H_1 - There are significant mean differences in response inhibition between DDD patients and control group measured by Stroop test.

1.11 Significance of the Study

This study is about cognitive and neuropsychological functioning of opioid and ATS use and it provides cognitive profile (executive functions) with the emphasis on visuo-perceptual, visuo-constructional ability, incidental visual memory, attention, perceptual motor speed, visual scanning, cognitive flexibility, reasoning skills, short term memory, working memory, speed of mental processing and response inhibition. This study is expected to provide an insight about possible cognitive impairments related to the use of both drugs since this is the first known study to measure cognitive function among drug addicts that use both drugs in Malaysia. Besides, this study also provides data on cognitive function of heroin and ATS users.

It is important in considering the present cognitive function when treating patient with addiction. This could enable clinicians to help patients to master adaptive strategies in overcoming patient relapse when patient return to the environments related with their prior use of drug. Besides, cognitive deficit may hinder patient's ability to maximize benefits from counseling session and other psycho-social treatments in aiding the patient to stay abstinent from drug use by learning or incorporating sustaining

strategies in their daily routine (Gould, 2010). Evidence showed that cognitive impairment in drug use has negative impact especially in treatment engagement (Ersche & Sahakian, 2007).

1.12 Scope of the Study

This study was carried out in Kelantan (Kota Bharu) because heroin and ATS dependence are highly prevalent and frequently co-occur (Singh et al., 2013). This region has high concentrated amount of individuals who use drugs and the trend of using both drugs is increasing. Also, Kelantan has the highest number of HIV case in Malaysia (Utusan Malaysia, 2015). The study focus on cognitive function that may impair DDD patients by using selected neuropsychological test.

Neuropsychological tests are used to study a range of cognitive skills in different areas. Neuropsychological testing is a crucial part of assessment and treatment of patients especially patients with brain problem and it is also beneficial to investigate substance use effects on brain functioning (Barry & Carson-DeWitt, 2005). This test is used for screening to know if diagnostic assessments are needed or not.

Six neuropsychological test was used in this study to the COATS patient and control healthy group. For the population, this study focus on two group, which are DDD patient who dependence on ATS and Opioid and one control healthy group. This study was conducted to determine the cognitive status of COATS patient and comparing with control group. COATS patient that was recruited in this study was from medication assisted treatment (treatment that combine medication and psychological aspect) in HUSM. The aspects looked into were the neurocognitive functioning among COATS patient. For the control group, the test was similar used by COATS patients and also the place of assessment also the same. The problem was identified to provide

better treatment by recognizing their impairment comparing with the normal control group who did not use any illegal drug and identifying the proposed solution to the problem. The location of the study was at HUSM.

1.13 Study Limitations

There were some unavoidable limitations. For this study, it was conducted in only one state in Malaysia (Kelantan), and thus should not be generalized to the whole issue of drug use in the country. It was important to do this study in every part of Malaysia to see the clear picture on drug addiction cognitive profiles crucially. Thus, in the future, these types of study can be done in every part of the state in Malaysia with the convenient drug detoxification facility to address their cognitive deficit.

Other limitation was the number of COATS patient was small. In order to get better result higher number of patient are required. The problem encountered was, the COATS patients was a hidden population, hard to get reach to their area. But with the amount of COATS patient we get are enough to run the analysis. In future, getting more participant may give concrete result. Nevertheless, for the control group, easy to get the involved in this study because easy recruiting them because they was not a hidden population.

1.14 Definition of Terms

1.14.1 Opioid

Opioid are mainly used to relieve pain. It will reduce the intensity of the pain when the signal of pain reaching the brain and it will diminished the painful effects stimulus (NIDA, 2014). Opioids are chemically interacted with opioid receptors in the nerve cells especially in the body and brain. Misuse of opioid may lead to euphoria instead of pain relievers. Misuse of opioid also can lead to drug dependence and fatal if overdose (NIDA, 2014).

1.14.2 Amphetamine-Type Stimulants

Amphetamine-type stimulants (ATS) refer to a group of drugs whose principal members include amphetamine and methamphetamine. However, a range of other substances also fall into this group, such as methcathinone, fenetylline, ephedrine, pseudoephedrine, methylphenidate and MDMA or 'Ecstasy' – an amphetamine-type derivative with hallucinogenic properties (WHO, 2016).

1.14.3 Co-Occurring Opioid and ATS

Co-occurring define as a 'to appear together'. In this context, co-occurring refer to person that take both opioid and ATS simultaneously to get pleasurable effect. The use of this both drug will increased the pleasurable effect uniquely such as reduce anxiety, that was experienced by ATS or reduces sedation which experienced by opioid, compared if using it alone (Leri, Bruneau & Stewart 2003; Trujillo, Smith & Guaderrama 2011).

1.14.4 Cognitive Psychology

This is one of the branches of the psychology that concerned with mental processes such as thinking, learning, perception and memory especially with the internal event that happen between the sensory stimulation and overt expression of behavior (Merriam-Webster, 2016). The cognitive psychology will look into how our mental processing information will influences the behavior.

1.14.5 Neuropsychological Assessment

Neuropsychological assessment is a performance-based method to assess cognitive functioning. This method is used to examine the cognitive consequences of brain damage, brain disease, and severe mental illness (Harvey, 2012). Typically, neuropsychological assessment is performed with a battery approach, which involves tests of a variety of cognitive ability areas, with more than one test per ability area. These ability areas include skills such as memory, attention, processing speed, reasoning, judgment, and problem-solving, spatial, and language functions.

1.14.6 Memory

Memory is essential to all our lives. Memory is commonly described as the process of maintaining information over time (Matlin, 2005). Without a memory of the past we cannot operate in the present or think about the future. We would not be able to remember what we did yesterday, what we have done today or what we plan to do tomorrow. Without memory we could not learn anything (Mcleod, 2007). Memory is when one's draw the past experience in order to use the information at present (Sternberg, 1999).

1.14.7 Attention

Attention is the concentration of awareness on some phenomenon to the exclusion of other stimuli. Attention is the behavioral and cognitive process of selectively concentrating on a discrete aspect of information, whether deemed subjective or objective, while ignoring other perceivable information (Anderson & John, 2004).

1.14.8 Visual Scanning

Visual Scanning is the ability to actively find relevant information in our surroundings quickly and efficiently (Cognifit, 2016). Examples of visual scanning are spotting certain person in a crowded place such as at the party or the other example was finding a specific location in a map. Slow speed and the accuracy of the reaction and responses may indicate lack of visual scanning. Example when driving, lack of visual scanning may cause an accident and dangerous.

1.14.9 Mental Processing Speed

Mental processing speeds refer to ability to solve easy task in the restricted amount of time (Doebler & Holling, 2015). Processing Speed is one of the measures of cognitive efficiency or cognitive proficiency. It involves the ability to automatically and fluently perform relatively easy or over-learned cognitive tasks, especially when high mental efficiency is required.

1.14.10 Working Memory

Working memory refers to a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning (Baddeley, 1992). Often known as short-term memory, working memory is just like a brain task. As the information coming into the brain, it will process and simultaneously, storing it. It is important to learn, reasoning, and remember. Example when doing a mathematical, one's have to store the number temporary while at the same time they have to solve the problem. In general, keeping the information temporarily and process it at the same time is a working memory (Psychology Glossary, 1998).

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

In this chapter, theories and past studies that are relevant to the focus of the present study are described and reviewed. The conceptual and theoretical frameworks for the study are also explained.

2.1 Drug Addiction

The word drug was originality from a French word “drogue” which means “a dry substance” and during that time, the dried herbs were widely used to prepare most of the pharmaceuticals (Abadinsky, 2010).

Drug addiction is a chronic, often relapsing brain disease that causes compulsive drug seeking and use, despite harmful consequences to the drug addict and those around them. Drug addiction is a brain disease because the abuse of drugs leads to changes in the structure and function of the brain. Drugs are chemicals that tap into the brain's communication system and disrupt the way nerve cells normally send, receive, and process information. There are at least two ways that drugs are able to do this: by imitating the brain's natural chemical messengers, and/or over stimulating the "reward circuit" of the brain. In 2014, the Malaysian National Anti-Drug Agency (NADA) reported that there were 387,144 individuals registered as using drugs; however, the true number of individuals using illicit psychoactive substances is likely to be higher. Based on the NADA statistics, opioid use continues to dominate among newly registered drug using individuals, with ~67% registered as using opioids and ~20% registered as using ATS (NADA 2015). Most individuals using opioids inject the

drug; 25-30% of people who inject drugs (PWID) are infected with HIV; and injection drug use accounts for 70% of HIV infections in Malaysia (101,672 registered HIV+ between 1986 and 2013).

Co-occurring ATS use among people who use opioids has also emerged as a major problem in Malaysia. In recent surveys of people who inject heroin or other opioids, 75% reported lifetime ATS use (and 21% reported injecting ATS), and lifetime ATS use was significantly associated with HIV infection (Chawarski et al. 2012). Some additional recently reported trends include rising rates of individuals under the age of 20 using drugs (NADA 2015; Hamudin 2015), growing attention on women who use drugs (Mohd Nasarrudin et al. 2015; Rahman et al. 2015; Wickersham et al. 2016), and continued research focus on relationships between substance use and infectious diseases, particularly HIV and Hepatitis C (Bachireddy et al. 2011; Choo et al. 2015).

Addiction is associated with impairments in prefrontal cortex (PFC) dependent cognitive functions; it is thought that these impairments promote compulsive drug use and relapse (Volkow & Fowler, 2000). Opiate addicts and psychostimulant addicts share some deficits in memory, cognitive flexibility and decision making (Bechara, 2005). Studies using laboratory animals have shown that repeated exposure to cocaine or heroin impairs spatial memory (Tramullas, 2008). There are some fundamental differences between opiates and psychostimulants. For example, cocaine and amphetamine addicts are more impulsive and show more pronounced deficits in attention and cognitive flexibility than heroin addicts (Lundqvist, 2005).

2.2 Opioid

Opioids act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, gastrointestinal tract, and other organs in the body. When these drugs attach to their receptors, they reduce the perception of pain. Opioids can also produce drowsiness, mental confusion, nausea, constipation, and, depending upon the amount of drug taken, can depress respiration. Some people experience a euphoric response to opioid medications, since these drugs also affect the brain regions involved in reward. Heroin addiction is defined as a chronic relapsing condition that, for many, is an unrelenting, lifelong illness with severe effects. This is particularly relative to short life expectancies and high rates of morbidity Hser et al. (2004). Ninety percent of the world's heroin supply is directly from opium grown in Afghanistan. Heroin that is produced from Afghan poppies is shipped worldwide (UNODC, 2010).

2.3 Amphetamine Type Stimulants

ATS or commonly known as 'Ya Ba' (crazy medicine) in Thailand and 'pil kuda' or buah (street name) in Malaysia. Yaba is a combination of methamphetamine (a powerfuland addictive stimulant) and caffeine. Yaba, which means crazy medicine in Thai, is produced in Southeast and East Asia. The drug is popular in Asian communities in the United States and increasingly is available at raves and techno parties. Yaba is sold as tablets. These tablets are generally no larger than a pencil eraser. They are brightly colored, usually reddish-orange or green. Yaba tablets typically bear one of a variety of logos; R and WY are common logos. Yaba tablets typically are consumed orally. The tablets sometimes are flavored like candy (grape, orange, or vanilla). Another common method is called chasing the dragon. Users place the yaba tablet on aluminum foil and heat it from below. As the tablet melts, vapors rise and are

inhaled. The drug also may be administered by crushing the tablets into powder, which is then snorted or mixed with a solvent and injected.

ATS or psycho-stimulants will cause an individual who taking it to feeling euphoria, alertness, increased concentration and motor activity. They will increase blood pressure and pulse rate and the long term use may cause effect such as violent and irrational behavior and psychosis (Camí & Farré, 2003; Paci, 2008). Amphetamine was derived from methamphetamine which have high lipid solubility comparing with amphetamine and produce more intense effects on central nervous system (Barr et al., 2006). In acute phase, amphetamine inhibit reuptake of dopamine, norepinephrine and serotonin from membrane transporters and it will increase the level of these neurotransmitter in the brain. This will give decrease of dopamine transporter which associated with impaired neuropsychological functioning (Camí & Farré, 2003: Logan, 2002; Nordahl, Salo & Leamon, 2003; Scott et al., 2007).

2.4 Co-occurring Opioid and ATS Use

Co-occurring opioid and ATS use in Malaysia and Kelantan is increasing although pharmacological effect on opioid and ATS in human body and brain are different (Koob & Bloom 1988), the combination of an opioid and a psychostimulant (e.g., amphetamine, methamphetamine, or cocaine) is also known as a “speedball. The combination between Opioids and ATS may lead to addiction with overlapping effects in reward circuitary system in the brain that is important for regulation of executive function, motivation, affective or emotional response (Ersche & Sahakian 2007; Trujillo, Smith & Guaderrama 2011). People who use this combination of drug report that, it produces increased or unique pleasurable effects compared if taking a drug alone or reduces the adverse effects of one of the drugs (e.g., reduces anxiety experienced

with psychostimulants or reduces sedation experienced with opioids) (Leri, Bruneau & Stewart 2003; Trujillo, Smith & Guaderrama 2011).

While co-occurring use of opioids and ATS has recently become popular and ambigious across Asia, including in Malaysia (McKetin et al. 2008; Pilowsky et al. 2011; UNODC 2012). The double effects and increased toxicity of the combination of ATS and opioids has not been broadly evaluated in humans. However, the synergistic behavioral effects of ATS and opioids and raised toxicity associated with the combination have been found in laboratory studies in rats (Funahashi et al., 1988; Ginawi, Al-Shabanah & Bakheet 1997; Namiki et al. 2005; Trujillo, Smith & Guaderrama 2011).

Additionally, the combined use of these two classes of drugs may aggravate the disease progression and is likely to greatly hindered with recovery efforts (Volkow, Koob & McLellan 2016), as supported by exploratory findings among opioid dependent patients in Malaysia showing that co-occurring ATS and opioid use is associated with higher rates of HIV infection and poor treatment outcomes (Chawarski, Mazlan, & Schottenfeld 2012). Individuals using both opioids and ATS also exhibit increased levels of medical and psychiatric co-morbidity and often require more intensive clinical management (Pilowsky et al. 2011).

There is finited evidence supporting the efficacy of specific pharmacological or behavioral treatments for ATS use disorder (Brensilver et al., 2013; Harada et al., 2014), and currently there are no specific interventions provided to individuals with ATS use problems by the government, NGO's, or treatment providers in Malaysia. Individuals who are found with evidence of ATS use or possession can be detained by the police or by the National Anti Drug Agency, charged in court under section 15 (1)

of the Dangerous Drug Act 1952, and fined or placed under community supervision with the National Anti Drug Agency for a period of 2 years.

2.5 Neuronal Structure

Neuronal structure consists of central nervous system and peripheral nervous system. Central nervous system contains the majority of nervous system and consists of brain and spinal cord. The core components of nervous system are neurons which can be sensory or motor neurons.

2.5.1 Brain

Nervous system in human are important in receiving information from the environment, process the information and respond to it. The central nervous system (CNS) consists of brain and spinal cord. Brain act as a body's control center. Its weight around 1.2 kilogram and estimated to have around one hundred billion of nerve cells (O'Shea, 2005). The brain contains three main parts which is cerebrum, cerebellum and brain stem (Figure 2.2). The brain is divided into four lobes (Frontal, Parietal, Temporal, and Occipital) and each lobe handles specific functions (Table 2.1).

The brain is divided into two hemispheres. Even though the two hemispheres work together, each hemisphere related to specific functions. The right hemisphere controls muscles for the left side and analyses nonverbal information. The left hemispheres control the right side of the body and its responsible for logical abilities and languages. The different part of the brain are responsible for coordinating and performing specific functions. As we already know, drugs will alter some brain areas that are vital for life-sustaining functions and can drive the compulsive drug abuse that will mark to addiction.