RESEARCH ARTICLE

Risk factors affecting cognitive function in chronic metamfetamin users

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Camellia V, Irfani Fitri F, Aldiansyah D, Ichwan M, Khairunnisa K, Zulfendri. Risk factors affecting cognitive function in chronic metamfetamin users. J Child Adolesc Psychiatr. 2022; 6(4):53-56.

ABSTRACT

The high use of methamphetamine among adolescents of millennial age has an impact on the occurrence of dependence with chronic use and has an impact on the brain that has an impact on cognitive impairment, so researchers want to look at risk factors that affect cognitive function in methamphetamine use. This cross-sectional study took place at the Insyaf rehabilitation center in North Sumatera Province. Conducted with a period of March 2019 to November 2019 with a total sample of 101 people collected using the consecutive sampling method, willing to participate in the study, male 15 years to 40 years old, cooperative and understands Indonesian, history ofmethamphetamine use 1 year, meets criteria for methamphetamine use disorder, has abstinence 1 month, total WHO ASSIST questionnaire for methamphetamine. This study showed that as many as 57 people with chronic methamphetamine users had a cognitive decline and the factors affecting cognitive function in methamphetamine users were using ecstasy. They are at risk for impaired cognitive function with a risk value of 2,560. Individuals who use chronic methamphetamine together with ecstasy will be at risk of experiencing cognitive function impairment even though they have been abstinent for more than one month.

Key Words: *Chronic methamphetamine; Cognitive function;risk factors*

INTRODUCTION

Methamphetamine abuse is a global health problem, causing serious health and well-being problems in society. The increased use of methamphetamine in crystal form has increased public health concerns due to its high bioavailability, and higher levels of harm and dependence. This trend also results in higher demand for care and places an increasing burden on healthcare globally [1-3].

Data show that methamphetamine use is on the rise in East and Southeast Asia. All countries in the Greater Mekong Sub-region, except Thailand, reported an increase in the use of methamphetamine in tablet form in 2015. Similar to all countries in East and Southeast Asia, except for Indonesia and Japan, there was an increase in the use of crystal methamphetamine [4]. According to the most recent national drug use survey in 2015, approximately 0.6% of the general population between the ages of 10 and 59 is estimated to have used illegal drugs. Cannabis remains the most widely used illicit drug in the country with an annual prevalence of around 0.18%, followed by methamphetamine at 0.09%. Between 2008 and 2015, the number of methamphetamine-related arrests nearly tripled, from 8,685 in 2008 to 23,420 in 2015. In 2015, methamphetamine seizures were 4,420 kg, which is by far the largest number ever reported from Indonesia. This sharp increase was due to the seizure of several methamphetamine shipments containing hundreds of kilograms of the drug, originating from abroad. Specifically, the Aceh Province in Indonesia, located in North. Data from the Indonesian national narcotics agency states that drug abuse in people prone to exposure is those in the 15 years to 35 year range or the millennial generation. In a cross-sectional study of substance abuse from 6 rehabilitation centers in the city of Medan, it was found that the most common age was 21 years, namely, 69% (87 people), and the most widely used substance was methamphetamine [5-7].

Methamphetamine is a strong and highly addictive stimulant that affects the central nervous system. Also known as methamphetamine, blue, ice, and crystal, among many other terms, it is a white, odorless, bitter-tasting crystalline powder that readily dissolves in water or alcohol. Methamphetamine can be in several forms, it can be smoked, inhaled, injected, or ingested orally. Smoking or injecting methamphetamine delivers the substance very rapidly into the bloodstream and brain, causing an intense immediate "rush" and amplifying the potential for drug addiction and adverse health consequences.The rush, or "flash", only lasts a few minutes and is described as a lot of fun. Inhaling produces an effect of 3 mins to 5 mins or swallowing orally produces an effect within 15 mins to 20 mins, the effect that arises is euphoria. After intravenous injection or inhalation of MA, the euphoric effect appears within five minutes and lasts 8 hours to 12 hours [8]. From the background that the high use of methamphetamine among adolescents of millennial age has an impact on the occurrence of dependence with chronic use and has an impact on the brain that has an impact on cognitive impairment, the researchers wanted to look at the risk factors that affect cognitive function in the use of methamphetamine.

RESEARCH METHODOLOGY

This cross-sectional study took place at the Insyaf rehabilitation center in North Sumatera province. It was carried out for a period from March 2019 to November 2019 with total criteria:

- Willing to participate in research.
- Boys.
- Aged 15 years to 40 years.
- Cooperative and understanding Indonesian.
- History of methamphetamine use 1 year.
- Meets the diagnostic criteria for methamphetamine use disorders
- Has abstinence 1 month
- Total WHO ASSIST questionnaire for methamphetamine
- Exclusion Criteria:
- Unable to read and write;
- Suicidal ideation and history of head trauma. surgery.

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. MoCA is useful for detecting a mild cognitive decline in various conditions including Alzheimer's

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Received: 24-May-2021, Manuscript No. PULJCAP-22-4989; Editor assigned: 28-May-2022, Pre QC No. PULJCAP-22-4989 (PQ); Reviewed: 03-Jun-2021, QC No. PULJCAP-22-4989(Q); Revised: 10-Jun-2022, Manuscript No. PULJCAP-22-4989 (R); Published: 05-Jul-2022, DOI: No 10.37532/puljcap.2022.6(4)-53-56

disease, vascular cognitive impairment, Parkinson's disease, Lewy body, frontotemporal dementia, multiple sclerosis, huntington's disease, brain tumors, ALS, sleep apnea and heart failure. Heart disease, substance abuse, schizophrenia, HIV and head trauma [9].

The specificity of MoCA to exclude normal controls was quite good at 87% and the sensitivity of MoCA was estimated to be very good at 90% for detecting mild cognitive impairment, and much more sensitive than MMSE [10,11].

Respondents who meet the inclusion and exclusion criteria will be explained and asked to sign an agreement after the explanation given by the researcher. The researcher will conduct a history and structured interview and allow patients to fill out the HADS and MoCA-Ina questionnaires (assisted by the researcher), which only take about 5minutes to 15 minutes to complete. The research results will be collected interpreted and further processed. This research has been approved by the Health research ethical committee medical faculty of the University Sumatera Utara /H.Adam Malik General Hospital No.486/TGL/KEPK FK USU-RSUP HAM/2018.

RESULT

Levels of anxiety and depression were assessed using the HADS (Hospital Anxiety and Depression Scale). The results of the HADS measurement are shown in Table 2. The mean (SD) scores for anxiety and depression were 6.9 (4.18) and 6.84,3.48, respectively. By categorizing the anxiety scores, it can be seen that as many as 59 subjects (58.4%) are in the normal category followed by mild depression ion anxiety cases totaling 23 people (22.8%). Next, the categorizing depression scores showed as many as 57 subjects (56.4%) with normal results followed by mild cases totaling 30 people (29.7%).

Table 1

HADS Examination Results

HADS Check	n = 101
Anxiety Score, mean (SD)	6,9 (4,18)
Anxiety Category, n (%)	
Normal	59 (58,4)
light case	23 (22,8)
Medium case	16 (15,8)
heavy case	3 (3)
Depression Score, mean (SD)	6,84 (3,48)
Category Depression, n (%)	
Normal	57 (56,4)
light case	30 (29,7)
Medium case	13 (12,9)
heavy case	1 (1)

For cognitive assessment in this study using the MoCA-Ina instrument. The mean and SD values for each domain of cognitive function with the MoCA-Ina instrument are shown in Table 3. Using a cut of 26, it was obtained that 57 subjects (56.4%) had impaired cognitive function.

Table 2

Cognitive Function Examination Results

Cognitive Function	Renata (SD)	Min-mak
Visuospatial	3,82 (1,37)	0 – 5
Naming	2,81 (0,61)	0 – 3
memory	1,68 (0,56)	0 – 2
Attention	3,34 (0,89)	0 – 4
Language	2,41 (0,83)	0 – 3
Abstraction	1,24 (0,76)	0 – 2
Delayed Recall	3,07 (1,94)	0 – 5
Orientation	5,95 (0,22)	5 – 6
Total	24,32 (3,90)	12 – 30
Impaired cognitive function, n (%)	57 (56,4)	
Cognitive function is not impaired, n (%)	44 (43,6)	

Table 3 presents a bivariate analysis of all independent variables on the dependent variable, namely cognitive function which is grouped into two, namely the group of subjects with impaired cognitive function and the group of subjects with normal cognitive function. The results of the bivariate analysis showed that only two independent variables had a significant relationship ($p < 0.05$) with cognitive function, namely the education level variable ($p = 0.048$), and ecstasy users ($p = 0.028$).

Table 3.

Risk Factors for Impaired Cognitive Function based on the MoCA-Ina. Instrument

Cognitive Function Risk Factors	Cognitive Function Risk Factors		Cognitive Function Risk Factors
	Disturbed Normal	Disturbed Normal	
Age, mean (SD), years	27,07 (7,47)	25,18 (6,08)	0,256[a]
Education, n (%)			
junior high school	28 (71,8)	11 (28,2)	0,048[b]
senior High School	26 (46,4)	30 (53,6)	
College	3 (50)	3 (50)	
Marital Status, n (%)			
Not married yet	37 (52,9)	33 (47,1)	0,417[b]
Marry	16 (61,5)	10 (38,5)	
Widower	4 (80)	1 (20)	
Occupation, n (%)			
Yes	36 (56,3)	28 (43,8)	0,961[c]
Not	21 (56,8)	16 (43,2)	
Income, n (%)			
No income	17 (51,5)	16 (48,5)	0,485[b]
< Rp. 1 million	13 (61,9)	8 (38,1)	
IDR 1 – 5 million	26 (60,5)	17 (39,5)	
IDR 5 – 10 million	1 (25)	3 (75)	
Cigarette Consumption, n (%)			
Light	5 (62,5)	3 (37,5)	0,533[b]
Currently	46 (58,2)	33 (41,8)	
Heavy	6 (42,9)	8 (57,1)	
Abstinence duration, mean (SD), months	5,33 (2,93)	4,61 (2,73)	0,242[a]
Duration of methamphetamine consumption, mean (SD), years	6,61 (5,46)	6,25 (4,31)	0,767[a]
Marijuana Users, n (%)			
Yes	26 (59,1)	18 (40,9)	0,636[c]
Not	31 (54,4)	26 (45,6)	
Ecstasy Users, n (%)			
Yes	14 (41,2)	20 (58,8)	0,028[c]
Not	43 (64,2)	24 (35,8)	
Anxiety, mean (SD)	6,84 (4,04)	6,91 (4,36)	0,937[d]
Depression, mean (SD)	7 (3,40)	6,70 (3,61)	0,680
Tobacco WHO Assist, n (%)			
Intensive treatment	20 (58,8)	14 (41,2)	0,505[b]
Short intervention	37 (56,1)	29 (43,9)	
No intervention	0	1 (100)	
WHO Assist cannabis, n (%)			
Intensive treatment	9 (56,3)	7 (43,8)	0,880[c]
Short intervention	22 (53,7)	19 (46,3)	
No intervention	26 (59,1)	18 (40,9)	
WHO Assist methamphetamine, n(%)	34 (59,6)	23 (40,4)	0,459[c]
Intensive treatment	23 (52,3)	21 (47,7)	

By using the multivariate test, it can be obtained that the most dominant variable affects cognitive function. The independent variable that is eligible to be included in the multivariate analysis is the independent variable that has a value <0.25 from the bivariate analysis. Based on the results of the bivariate analysis presented in Table 4. It is known that the independent variables included in the multivariate analysis were the education variable

(p=0.048), the length of abstinence (p=0.242), and the ecstasy user variable (p=0.028).

By using multiple logistic regression analysis with the enter method, it was found that only one independent variable affected cognitive function, namely ecstasy users. However, in this study, subjects who used ecstasy were at risk of experiencing cognitive dysfunction with a risk value of 2,560 (Table 4).

Table 4

Multivariate Analysis of Risk Factors for Cognitive Functional Disorders based on the MoCA-Ina. Instrument

	B	P	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Select 1					
Abstinence duration	0,078	0,315	1,081	0,929	1,259
Ecstasy Users	0,958	0,040	2,606	1,045	6,499
Education		0,093			
Education (1)	-0,988	0,031	0,372	0,151	0,916
Education (2)	-0,320	0,738	0,726	0,111	4,755
constant	-0,167	0,798	0,846		
Selection 2					
Abstinence duration	0,099	0,202	1,104	0,948	1,284
Ecstasy Users	0,959	0,028	2,609	1,110	6,132
constant	-0,857	0,105	0,424		
Selection 3					
Ecstasy Users	0,940	0,029	2,560	1,098	5,965
constant	-0,357	0,306	0,700		

DISCUSSION

This study found 57 respondents who experienced impaired cognitive function, consistent with research conducted by Hagen et al in 2019 where 34.6% were found to have impaired cognitive function. Hagen et al. also stated that MoCA is a time-efficient measuring tool in assessing impaired cognitive function in substance use [12, 13]. This study is also consistent with research conducted by Hagen et al. in which psychiatric disorders were found to be higher in polydrug use, and respondents reported symptoms of anxiety and depression, which increased the risk of suicide, decreased quality of life, and impaired social functioning [14]. Many individuals with substance use disorders are also diagnosed with mental disorders and vice versa. Although there is little research on comorbidity at a young age, research supports that adolescents with substance use disorders have a high rate of comorbid mental disorders. Approximately 60% of adolescents in community-based substance use treatment programs also meet mental disorder diagnosis criteria. Because of genetic susceptibility, the influence of epigenetic mechanism, and the environment can cause long-term genetic adaptation, involvement of brain areas, stress and childhood trauma experiences [14-16].

The methamphetamine molecule is structurally similar to amphetamine and to the neurotransmitter dopamine, a chemical in the brain that plays an important role in behavior. Methamphetamine has a longer duration of metabolic action, and a larger percentage of the drug remains unchanged in the body. Therefore, methamphetamine stays in the brain longer, which in turn causes a prolonged stimulant effect. At low doses, methamphetamine also blocks the reuptake of dopamine, but it also increases dopamine release, leading to much higher concentrations at the synapse (gaps between neurons), which can be toxic to nerve terminals [17,18].

The exact mechanism by which drugs such as methamphetamine produce euphoria (high pleasure) is still poorly understood. But along with the euphoria, methamphetamine use releases very high levels of the neurotransmitter dopamine in the reward circuit, which "teaches" the brain to repeat pleasurable activities while taking the drug. Dopamine is involved in motivation and motor function and its release in the reward circuit is a hallmark of addictive drugs [19]. The increased release of dopamine produced by methamphetamine is also thought to contribute to the drug's damaging effects on nerve terminals in the brain. Long-term methamphetamine abuse has many negative consequences, including addiction. Addiction is a chronic, relapsing disease, characterized by compulsive substance seeking and use and accompanied by functional and molecular changes in the brain. In addition to addiction, people who use methamphetamine long-term may develop symptoms that can include significant anxiety, confusion, insomnia, mood disorders and violent behavior [20]. Although drugs are effective in treating some substance use disorders, there is currently no drug that can counteract the specific effects of methamphetamine or that can prolong abstinence and reduce methamphetamine abuse.

Chronic methamphetamine use is also associated with cognitive problems, such as impaired decision-making and behavioral inhibition disorders. Given the important role, catecholamine's play in frontal lobe function, it is not surprising to observe that chronic methamphetamine use can impair executive function and working memory. The main factor to consider when assessing cognitive effects is the duration of abstinence from the last use [21].

Some literature suggests that the cognitive processes most affected by this abuse are learning, memory, and cognitive flexibility. Cognition is the ability to acquire, store, retrieve and use knowledge. In this case, drug use and abuse alter the nervous system, affecting cognitive function. Among these functions, learning is defined as a relatively permanent change in behavior; knowledge, strategies, skills, beliefs, and attitudes are implied in the definition. On the other hand, memory is the capacity of the CNS to encode, store, organize, or retrieve information. The so-called executive functions are the most complex functions performed by humans. In general, the prefrontal cortex facilitates human adaptation to new situations. In this sense, cognitive flexibility is the ability to change the criteria in the monitoring strategy to perform a task. Executive function is the most sensitive function to disorders caused by substance abuse. Loss of executive function in the prefrontal cortex will have a detrimental effect, namely impulsivity, and compulsive behavior, this occurs in individuals who have experienced addiction.

In vitro and in vivo studies have shown that METH and ecstasy can exert toxic effects on peripheral organs, as well as in brain regions that regulate movement and/or superior brain function. In addition, clinical studies have shown that METH and ecstasy can cause brain abnormalities in users. In addition, ecstasy users may develop serotonin syndrome, a potentially lethal condition that requires immediate treatment, the symptoms of which include agitation, hyperthermia, sweating, tremors, increased reflexes, dilated pupils, and diarrhea. Finally, ecstasy users may exhibit signs of neurologic toxicity (i.e, ataxia), sleep disturbances, psychiatric disturbances and neurocognitive deficits that persist even after discontinuation of the drug. However, the relationship between ecstasy use and the manifestation of neurocognitive deficits has recently been questioned. Several neuroimaging studies have shown that heavy ecstasy users may exhibit decreased serotonin transporter levels, increased cortical excitability, or altered cortical serotonergic signaling. Finally, other meta-analyses have shown that ecstasy users may display deficits in executive function, such as access to semantic memory, mental shifting, and information updating. Because the executive function is regulated by serotonin-rich prefrontal cortical areas, deficits in this function may explain the behavioral correlation of the possible serotonergic damage induced by ecstasy.

Dopamine agonist treatment; methamphetamine targets the dopamine system, so several stimulant drugs that activate dopamine receptors (agonists) and that are often used to treat Attention-Deficit Hyperactivity Disorder (ADHD) are being investigated as potential drugs for treating methamphetamine use disorders. Other monoamine targets (serotonin, norepinephrine, dopamine); methamphetamine withdrawal symptoms are similar to those of depression, leading researchers to investigate the use of antidepressants that act on the serotonin and norepinephrine systems for methamphetamine use disorders. Substance use, including substance use cessation, can also cause mental disorders. Substance-induced mental disorders may be transient and subside rapidly (usually within 1 month of abstinence). However, some substance-induced mental disorders are of long duration and subside only with prolonged abstinence. Antipsychotic drugs also act on the dopamine system and may hold promise for ameliorating the effects of chronic methamphetamine use. Opioid system; the euphoric effects of addictive substances most likely involve the opioid system. Drug candidates in this category include the opioid antagonist naltrexone (currently being studied in combination with the antidepressant bupropion) and the partial opioid agonist buprenorphine. GABA and glutamate system; several drugs that target excitatory and inhibitory balance disorders (mediated by the neurotransmitters GABA and glutamate) are also being investigated to treat methamphetamine use disorders. The hormones cholecystokinin-8 and oxytocin have shown promise in reducing the efficacy of methamphetamine in animals

Treating someone who uses methamphetamine with other types concurrently requires special care. Many programs take an intensive approach to treatment, particularly for polydrug abuse. Detox is the most important part of treatment, and medical monitoring may be necessary to manage the onset of bothersome withdrawal symptoms. In some

cases, residential or inpatient addiction rehabilitation programs can offer the most intensive level of care to polydrug users who are struggling to recover. For people who are far from the hospital, an outpatient program is a good option. This allows people in addiction treatment to continue to stay at home, only needing to fulfill their obligations while attending scheduled therapy sessions several times a week. There are currently no government-approved drugs to treat methamphetamine and polydrug addiction, so treatment focuses heavily on behavioral therapy. Types of therapy that have been found to help with methamphetamine and polydrug addiction include Cognitive behavioral therapy. This method helps people understand their substance abuse better by examining why they abuse drugs, how they can overcome cravings, and how to fight relapses. Contingency management, this method provides an incentive to maintain composure to increase one's motivation. The matrix model, an intensive 16 week program that combines: knowledge of substances and addictions. Behavioral therapy, blood drug testing to confirm abstinence, counseling, self-help group support, and promotion of non-drug activities. The treatment process for dealing with methamphetamine addiction is sometimes challenging and uncomfortable.

The merits of this study have attempted to analyze the many factors associated with individual methamphetamine use disorders, including socio-economic, demographic factors, psychological conditions and substance use patterns. The limitations of this study were that it did not measure the level of dependence on ecstasy use using WHO-ASSIST and could not measure the amount of methamphetamine and ecstasy used

CONCLUSION

This study was successful in showing that a factor that plays an important role in impaired cognitive function in people with chronic methamphetamine use is the concurrent use of ecstasy. Impaired cognitive function in people with chronic methamphetamine use was found in all cognitive domains and found that there were psychological disorders in the form of anxiety and depression. This condition needs to be noticed that even though it has been abstinence for more than 1 month, there are still cognitive disorders, symptoms of depression, and anxiety. This condition needs to be watched out for and concerned in the rehabilitation of individual methamphetamine users so that intensive examinations and specific interventions are needed to assist recovery. This is also a possible high-risk factor for falling back into methamphetamine abuse after completion of inpatient rehabilitation. Further research is needed with a longitudinal study, to see the rate of recurrence and risk factors for recurrence of chronic methamphetamine use disorders after completion of rehabilitation.

ACKNOWLEDGMENT

This research received funding from the Ministry of Research, Technology, and Higher Education (DRPM) and Universities Sumatera Utara.

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