Original Article

Correlates Related to Probable Common Mental Disorders among Ketamine Users: Cognitive and Urinary Impairments

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Abstract

Objective: In this study, we intended to determine the prevalence of common mental disorder (probable CMD) in ketamine users in Taiwan and identify whether factors including cognitive and urinary impairments developed over the course of ketamine use were correlated with probable CMD. **Methods:** Through a cross-sectional study design, 538 participants (115 women and 423 men) were recruited from reformatory educational classes in Taiwan. We used the 12-item Chinese Health Questionnaire to evaluate probable CMD. Furthermore, we designed a copy of questionnaire regarding ketamine use including questions related to age at first contact with ketamine, ketamine use expenses per month, intervals of use, route, concomitant substance use, legal problems, as well as cognitive and urinary impairments developed over the course of ketamine use. The relationships between ketamine use, physical health, concomitant substance use, cognitive impairments, urinary impairments, and probable CMD were examined using logistic regression analysis. **Results:** In this study, the prevalence of probable CMD among ketamine users in Taiwan was 19.7%. We found that poor physical health (from $p < 0.05$ to $p < 0.001$ for all kinds of severity), comorbid sedatives or hypnotic use ($p < 0.01$), and moderate cognitive impairments ($p < 0.05$) significantly developed after ketamine use were all independent factors correlated with probable CMD. But urinary impairments developed after ketamine use did not show any significant difference in regression analysis when considering other confounding factors. **Conclusion:** We suggest that an early survey of physical health, concomitant use of sedatives or hypnotics, and cognitive impairment can detect mental health problems among ketamine users.

Key words: ketamine use rating scale, physical health, the 12-item Chinese Health Questionnaire, sedative/hypnotic use
***Taiwanese Journal of Psychiatry* (Taipei) 2020; 34: 181-187**

Introduction

Common mental disorder (CMD), including nonpsychotic, depressive, and anxiety disorders, is the principal cause of psychiatric morbidity in the general population [1]. The prevalence of CMD is increasing in industrialized nations [2-5]. The upward trends in the prevalence of CMD may be related to increased public awareness of CMD [6], social stress and anxiety, as well as economic and employment changes related to industrialization [7]. Higher frequencies of CMD have been reported in individuals who are female, unemployed, unmarried, low in educational attainment, poor in physical health, or unstable economically [8-11]. But the prevalence and risk factors of CMD in ketamine users have not been examined.

Ketamine, first synthesized in the 1960s as a derivative of phencyclidine, has been used as an anesthetic medicine [12]. Ketamine has been reported to have antidepressant effects [13]. But the euphoria and dissociation from ketamine leads to its use as a popular recreational drug, especially among adolescents and young adults in Taiwan [14, 15] and throughout the world [16]. The euphoric and addictive effects of ketamine may be due to increased dopamine activity following ketamine use [17-19]. Compared to heroin or cocaine, ketamine is relatively cheap and easy to obtain. According to the Controlled Drugs Act in

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Received: Aug. 19, 2020 revised: Sep. 26, 2020 accepted: Sep. 28, 2020
date published: Dec. 17, 2020

Access this article online

Quick Response Code:

Website: www.e-tjp.org

DOI: 10.4103/TPSY.TPSY_36_20

How to cite this article: Wang CJ, Huang LL, Chang YS, Tsai CH, Wu YH, Lin YF, *et al*. Correlates Related to Probable Common Mental Disorders among Ketamine Users: Cognitive and Urinary Impairments. Taiwan J Psychiatry 2020;34:181-7.

Taiwan, ketamine was listed as a schedule III illicit drug in 2002 [20]. The use of pure ketamine has been classified as an offense and not as a crime. The Taiwanese juridical system has implemented a regulation program in which ketamine users must attend a reformatory educational class for 4–8 hours after being arrested by the police. The treatment of ketamine use is critical in Taiwan.

Chronic ketamine use has psychiatric risks including cognitive impairment, psychosis, anxiety, depression, and psychological cravings, leading to academic and occupational functional impairments [16, 21, 22], particularly in women [23]. Frequent ketamine use causes neurocognitive impairments, especially in working and episodic memory [24]. Image studies have revealed changes in cerebral structures, connectivity, and activation in chronic ketamine users [25]. Therefore, ketamine users may be at risk of developing CMD, warranting further study.

Ketamine use can cause serious physical complications, including ulcerative cystitis, kidney dysfunction, and gastrointestinal dysfunction [26, 27]. Physical harm resulting from accidents and cardiac risks has also been reported [28]. Chronic ketamine users often develop urinary complications including increased urinary frequency and urgency, urgent incontinence, pelvic or bladder pain, as well as hematuria [29]. Smoking or concomitant MDMA use worsens lower urinary tract symptoms (LUTSs) [30]. Moreover, long-term ketamine use causes fibrosis of the bladder, resulting in the need for receiving a cystectomy [31]. The prevalence of psychiatric comorbidities has been reported to be 64.5% in patients with LUTSs [32]. Therefore, when suspecting probable CMD in ketamine users, urinary complications and comorbid substances should also be considered.

Ketamine use often precedes the use of other substances [33]. Ketamine users in Taiwan frequently show polysubstance use such as ecstasy (MDMA), marijuana, alcohol, and tobacco [14, 34, 35]. Marijuana users are at a higher risk of alcohol use disorder, nicotine dependence, and generalized anxiety disorder than nonusers [36]. Insomnia is also a critical issue among substance users. A study revealed that the level of tobacco, alcohol, and marijuana use is positively associated with the risk of insomnia [37]. Therefore, the effect of polysubstance use in patients with probable CMD and ketamine users should be considered together.

Treating the physical and psychological complications of ketamine use is costly. Therefore, understanding the risk factors of probable CMD in frequent ketamine users is essential for developing prevention, early detection, and intervention strategies. Moreover, identifying the risk factors for probable probable CMD among frequent ketamine users can improve our understanding of the potential pathogenic mechanisms in ketamine use.

In this study, we hypothesized that probable CMD would be related to factors including cognitive and urinary impairments developed over the course of ketamine use among ketamine users. Therefore, we recruited ketamine users from Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, where the reformatory education classes were sponsored, and studied the demographic data, behaviors, physical health, cognitive impairment, urinary impairment, as well as general issues such as age and gender of ketamine users. With a cross-sectional study and a logistic regression model, we intended to study the behaviors of ketamine users and the inter-relationships among urinary impairment, cognitive impairment, and probable CMD.

Methods

Study procedures and subjects

Ketamine users were recruited from January 2016 to December 2016 at Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, where the reformatory education classes were sponsored. Individuals who were arrested for ketamine use were placed on probation, receiving reformatory education, or detoxification. The inclusion criterion was an age of 20 years or older, because people aged 20 years or older are considered legally competent in Taiwan without the need of obtaining informed consent from a custodian. In our study, copies of self-report questionnaire were administered. After the reformatory educational class, the study doctor provided a comprehensive description of the questionnaire and explained to participants that their legal status would not be influenced by participation in the study. Participants were not required to identify themselves unless they wanted to leave their personal information for referral or contact. Written informed consent was obtained from all the participants before the assessment. Face-to-face interviews were given to participants. Those exhibiting any cognitive deficits (e.g., intellectual disability, intoxication, or deficits due to or withdrawal from substanceuse) that could have prevented them from understanding the study purpose or completing the questionnaire were excluded. The study was approved by the institutional review board of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital (IRB protocol number = KSPH-2015-12 and date of approval = January 5, 2016) with the requirement of obtaining informed consent from the study participants.

The 12-item Chinese Health Questionnaire

The self-administered 12-item Chinese Health Questionnaire (CHQ) is a modified version of the General Health Questionnaire assessing the severity of nonpsychotic symptoms in participants in the two preceding weeks [38]. This instrument has been applied in several studies to identify minor psychiatric disorders among patients in primary care or in a community setting. Each item was assessed on a four-point scale, ranging from 0 (not at all) to 3 (more than usual) [39]. A relatively high total score (0–12) indicates a more severe level of nonpsychotic symptoms than a relatively low total score. The internal reliability (Cronbach's α) of the CHQ for this study was 0.87. The total CHQ scores range from 0 to 12; participants with scores of 3 or higher were categorized into the probable CMD group. Individuals with CHQ scores of 0 to 2 are entered into the nonprobable CMD group [39].

Ketamine use

We designed a copy of questionnaire because we were not aware of any established or validated Chinese versions of questionnaire for ketamine use. Through the ketamine use questionnaire used in this study, we collected data regarding age at first ketamine use, ketamine use expenses per month, intervals of use, methods of ketamine use, polysubstance use, legal consequences, as well as complications including cognitive impairments developed over the course of ketamine use and urinary impairments developed over the course of ketamine use. This self-administered questionnaire categorized cognitive and urinary impairments into four levels of severity (none, mild, moderate, and severe). "None" indicated no cognitive or urinary impairments, "mild" slight cognitive or urinary impairments, "moderate" worse than slight cognitive or urinary impairments, and "severe" obvious signs of cognitive or urinary impairments.

Statistical analysis

Participants were invited to complete the CHQ and the ketamine use questionnaire. Differences in gender, age, physical health, and polysubstance use were examined in the probable and nonprobable CMD groups. A Chi-square test was used to evaluate categorical variables, the Mann–Whitney U-test was used for ordinal variables, and a *t*-test was used for continuous variables. If a significant group difference was determined in the Chi-square tests, the Bonferroni method was used for *post hoc* comparisons. The significant variables in the Chi-square test, Mann–Whitney U-test, and *t*-test were used for the logistic regression analysis to examine their relationships with probable CMD during the study period. Data were presented as odds ratios (ORs) and 95% confidence intervals (CIs).

All statistical analyses were done using the Statistical Package for the Social Science version 22.0 (SPSS Inc., Chicago, Illinois, USA). The differences between the groups were considered significant if $p < 0.05$.

Results

Totally 672 ketamine users were enrolled in the initial assessment, with 134 ketamine users not enrolled. Among the enrolled participants, 47 did not fit the inclusion criteria and 87 did not complete the copy of the questionnaire. Totally 538 participants (115 women and 423 men) participated in

Table 1. Comparisons of demographic characteristics and physical health between nonprobable common mental disorder group and probable common mental disorder group

	Nonprobable CMD (n = 432) n (%)	Probable CMD (n = 106) n (%)
Age, mean ± SD, years***	26.2 ± 5.4	28.3 ± 7.1
Gender†,**		
Female	82 (19.0)	33 (31.1)
Male	350 (81.0)	73 (68.9)
Education		
Illiterate	1 (0.2)	1 (0.9)
Junior high school	81 (18.8)	20 (18.9)
Senior high school	291 (67.4)	67 (63.2)
College	36 (8.3)	10 (9.4)
Graduate institute	23 (5.3)	8 (7.5)
Marital status†,*		
Single	175^{A} (40.5)	41^{A} (38.7)
Married	48^{A,B} (11.1)	12^{A,B} (11.3)
Cohabitated	184^{A} (42.6)	37^{A} (34.9)
Others	25^{B} (5.8)	16^{B} (15.1)
Income per month (NT$)		
0-30,000	215 (49.8)	57 (53.8)
30,001-60,000	195 (45.1)	36 (34.0)
60,001-90,000	14 (3.2)	6 (5.7)
> 90,000	8 (1.9)	7 (6.6)
Physical health***		
Very poor	4 (0.9)	12 (11.3)
Poor	29 (6.7)	29 (27.4)
Normal	235 (54.4)	58 (54.7)
Good	120 (27.8)	6 (5.7)
Very good	44 (10.2)	1 (0.9)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, using Chi-square or *t*-test when appropriate (n = 538).
†*Post hoc* analysis using the Bonferroni method.
US$1 = about NT$30.
SD, standard deviation; NT$, new Taiwan dollar; CMD, common mental disorder

the assessment. No significant differences in gender and age were found between those who completed the copy of the questionnaire and those who did not.

As shown in Table 1, the probable CMD group had significantly more women (31.1% vs. 19.0%, $p < 0.01$). The probable CMD group was also significantly older (28.3 ± 7.1 vs. 26.2 ± 5.4 years old, $p < 0.001$) and had a significantly higher percentage of individuals with a marital status other than single, married, or cohabitating (15.1% vs. 5.8%, $p < 0.05$). Those in the probable CMD group also had significantly worse physical health ($p < 0.001$) than those in the nonprobable CMD group. No significant difference in education and income was revealed between the groups. Overall, 85% of the participants had a lower income than the average income of the general population of Taiwan (about NT$60,000 per month).

Table 2 presents age at first ketamine use, expenses, intervals between uses, methods, polysubstance use, and cognitive and urinary impairments developed over the course of ketamine use in both the groups. Compared with those in the nonprobable CMD group, those in the probable CMD group were generally significantly older when they first used ketamine (21.3 ± 5.1 vs. 22.9 ± 7.8 years old, $p < 0.001$) and had significantly more expensive (NT$5,232.8 vs. NT$8,328.2, $p < 0.01$). Regarding polysubstance uses, the probable CMD group had significantly higher percentages for the use of sedatives and hypnotics (21.7% vs. 3.7%, $p < 0.001$), amphetamine (13.2% vs. 6.7%, $p < 0.05$), marijuana (7.5% vs. 2.1%, $p < 0.01$), and heroin (3.8% vs. 0%, $p < 0.001$) than the nonprobable CMD group. Compared with the nonprobable CMD group, the probable CMD group had significantly more severe cognitive (59.3% vs. 77.4%, $p < 0.001$) and urinary (47.5% vs. 63.2%, $p < 0.01$) impairments developed over the course of ketamine use. No significant differences were observed

Table 2. Comparisons of ketamine use between nonprobable common mental disorder group and probable common mental disorder group

	Nonprobable CMD (n = 432) n (%)	Probable CMD (n = 106) n (%)
Age at first ketamine use, mean ± SD, years***	21.3 ± 5.1	22.9 ± 7.8
Ketamine use expenses per month, mean ± SD, NTD**	5232.8 ± 10973.6	8328.2 ± 5058.0
Intervals of uses, mean ± SD, days	14.0 ± 30.3	12.0 ± 37.0
Being arrested	179 (41.4)	40 (37.7)
Methods of ketamine use		
Oral	11 (2.5)	3 (2.8)
Intravenous	0 (0)	0 (0)
Intramuscular	0 (0)	0 (0)
Snorting	49 (11.3)	11 (10.4)
Mixed with tobacco	400 (92.6)	97 (91.5)
Others	5 (1.2)	2 (1.9)
Being caught by the police	179 (41.4)	40 (37.7)
Polysubstance use		
No*	75 (17.4)	9 (8.5)
Cigarette	322 (74.5)	85 (80.2)
Alcohol	169 (39.1)	46 (43.4)
Betel nut	149 (34.5)	36 (34.0)
Sedatives/hypnotics***	16 (3.7)	23 (21.7)
MDMA	49 (11.3)	18 (17.0)
Amphetamine*	29 (6.7)	14 (13.2)
Marijuana**	9 (2.1)	8 (7.5)
Heroin**	0 (0)	4 (3.8)
Glue	0 (0)	0 (0)
Cognitive impairment developed over the course of ketamine use***		
Nil	176 (40.7)	24 (22.6)
Mild	206 (47.7)	56 (52.8)
Moderate	26 (6.0)	17 (16.0)
Severe	24 (5.6)	9 (8.5)
Urinary impairment developed over the course of ketamine use**		
Nil	227 (52.5)	39 (36.8)
Mild	157 (36.3)	48 (45.3)
Moderate	27 (6.2)	12 (11.3)
Severe	21 (4.9)	7 (6.6)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; using Chi-square test or t-test when appropriate (n = 538).
CMD, common mental disorder; SD, standard deviation; NTD, new Taiwan dollar

Table 3. Risk factors for probable common mental disorder of ketamine users:Logistic regression analysis

	OR (95% CI)
Gender (male as reference)	0.99 (0.50-1.95)
Age	0.99 (0.93-1.08)
Marital status	
Single (reference)	1.00
Married	1.23 (0.50-3.04)
Cohabitated	0.67 (0.37-1.19)
Others	1.40 (0.50-3.92)
Income per month, in NT$	
0-30,000 (reference)	1.00
30001-60,000	0.61 (0.35-1.06)
60,001-90,000	1.06 (0.31-3.65)
> 90,000	2.74 (0.68-11.01)
Physical health	
Normal (reference)	1.00
Very poor	11.41 (2.60-50.05)**
Poor	3.49 (1.75-6.98)***
Good	0.23 (0.09-0.56)**
Very good	0.11 (0.01-0.82)*
Age at first ketamine use	
Ketamine use expenses per month	1.1 (0.96-1.10)
Polysubstance use	1.0 (1.00-1.00)
Sedatives/hypnotics	3.83 (1.53-9.62)**
Amphetamine	0.96 (0.38-2.46)
Marijuana	1.59 (0.37-6.87)
Complications	
Cognitive impairment developed over the course of ketamine use	
Nil (reference)	1.0
Mild	1.12 (0.51-2.46)
Moderate	4.26 (1.17-15.52)*
Severe	4.32 (0.64-29.23)
Urinary impairment developed over the course of ketamine use	
Nil (reference)	1.0
Mild	1.64 (0.78-3.48)
Moderate	0.54 (0.14-2.12)
Severe	0.27 (0.03-2.49)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
US$1 = about NT$30.
CI, confidence interval; OR, odds ratio, NT$, new Taiwanese dollar

in the intervals between uses and methods of ketamine use between the groups.

Table 3 summarizes the results of our logistic regression analysis, to calculate the ORs of probable CMD among ketamine users. Heroin was not included in the logistic regression models because of small sample sizes. Poor (OR = 3.49, CI = 1.75–6.98, $p < 0.001$) and very poor physical health (OR = 11.41, CI = 2.60–50.05, $p < 0.01$), moderate cognitive impairment developed after ketamine use (OR = 4.26, CI = 1.17–15.52, $p < 0.05$), and comorbid sedatives or hypnotic use (OR = 3.83, CI = 1.53–9.62, $p < 0.01$) were significantly correlated with probable CMD among ketamine users. Good (OR = 0.23, CI = 0.09–0.56, $p < 0.01$) and very good physical health (OR = 0.11, CI = 0.01–0.82, $p < 0.05$) were significantly protective factors against probable CMD. But gender, age, marital status, income, the age at first ketamine use, ketamine use expenses, concomitant use of amphetamine and marijuana, and urinary impairments developed over the course of ketamine use were not associated with probable CMD in the logistic regression analysis.

Discussion

In this study, we compared that ketamine users with a characteristic of poor or very poor physical health between the nonprobable and probable CMD groups (Table 1). We also found that ketamine users with moderate cognitive impairment developed over the course of ketamine use ($p < 0.001$), and concomitant use of sedatives or hypnotics ($p < 0.001$) were significantly associated with probable CMD (Table 2).

In this study, the prevalence of probable CMD among ketamine users was 19.7%. This finding is not higher than that in the general population (11.5%–23.8%), contrary to previous reports [40]. But the prevalence of probable CMD was different in men and women. We identified a gender difference in probable CMD prevalence among ketamine users, with a higher risk of probable CMD in women than in men (28.7% vs. 17.3%), which is in agreement with previous studies of the Taiwanese population [23, 40]. The increased risk of probable CMD may be because women are more vulnerable than men to psychological complications [23]. Those results indicate that probable CMD warrants greater attention among ketamine users, especially female users, in Taiwan.

In our study, the mean age at first ketamine use was more than 20 years of age in both groups (21.3 ± 5.1 and 22.9 ± 7.8 years of age, respectively), which was older than a previous study in a hospital setting (17.7 ± 4.4 years of age) [41]. The finding indicates that the ketamine use was less severe in this group than in users who have been hospitalized. But we suggest that this group may not seek medical help or receive treatment.

We studied polysubstance use, including the use of cigarettes, alcohol, sedatives or hypnotics, MDMA, and amphetamine (Table 2). The findings were in agreement with what has been reported elsewhere [41]. We also studied concomitant betel nut use. But betel nut use did not affect probable CMD incidence in either group. The majority of the participants reported normal to good physical health, but cognitive and urinary impairments developed over the course of ketamine use, which were worse in the probable CMD group. Comparing to the nonprobable CMD group, patients in the probable CMD group reported higher use of polysubstance, including sedatives and hypnotics. Insomnia has been suggested a marker of anxiety and depression disorders [42]. We showed a relationship between ketamine and insomnia. But further study is required to elucidate this causal relationship.

Cognitive impairments have also been identified in studies in the domains of mental and motor speed, visual and verbal memory, and executive functions [22]. In our study (Table 2), over half of the ketamine users in both the groups had developed cognitive impairment developed over the course of ketamine

use, with worse significantly cognitive impairments identified in the probable CMD group than in the nonprobable CMD group ($p < 0.001$). Depressive symptoms are frequently identified in ketamine users and have been correlated with cognitive impairments [41, 43]. We demonstrated that in the anxiety and worrying, somatic symptoms, depression, poor family relations, and sleep categories, the probable CMD group scored less favorably than the nonprobable CMD group. A study suggested that frequent ketamine users may have reduced psychological well-being [44]. Contrariwise, patients with CMD are correlated with social stress and anxiety which may increase the risk of substance use [7]. Therefore, the cognitive impairment may precede ketamine use or is worsened by underlying CMD.

In contrast with a previous study reporting that more than 50% of the ketamine abusers have complications of LUTSs [30], we found that more patients (Table 2) in the probable CMD group developed urinary impairment developed over the course of ketamine use than in the nonprobable CMD group (63.2% vs. 47.5%, $p < 0.01$). Furthermore, the probable CMD group had more severe urinary impairment than the nonprobable CMD group (mild: 45.3% vs. 36.3%, moderate: 11.3% vs. 6.2%, and severe: 6.6% vs. 4.9%, respectively). Therefore, even ketamine users with only mild urinary impairments developed after ketamine use were vulnerable to probable CMD. But urinary impairments failed to show a correlation with probable CMD in our study.

The present study revealed that younger ketamine users were at a higher risk of developing probable CMD. But young age was not a significant factor in the logistic regression model (Table 3). Those findings suggested that the effects of age and gender on probable CMD were related to physical health, polysubstance use, and cognitive impairments. Relatively young age may indicate a relatively short duration of ketamine use, which, in turn, may increase the possibility of remission from ketamine use, less severe cognitive impairment, fewer comorbid substances, and better physical health. Adolescents are more vulnerable to drug use than adults and start with readily available and cheap substances such as ketamine [16]. Ketamine users are in earlier stages of substance use than users of methamphetamine or MDMA, which may facilitate abstinence [45]. Therefore, the risk of probable CMD may be because ketamine affects academic and social function, especially in younger users [25, 26]. Furthermore, people with mental health problems may use substances earlier than those without such problems. The causal relationship between probable CMD and ketamine use warrants further study.

Educational attainment is a confounder of cognitive performance. As shown in Table 3, gender, age, marriage, income, and urinary impairments were not significantly associated with probable CMD development, but the effects of physical health (from $p < 0.05$ to $p < 0.001$), concomitant use of sedatives and hypnotics ($p < 0.01$), and cognitive impairment developed over the course of ketamine use ($p < 0.05$) were considered significantly associated with probable CMD in the logistic regression analysis.

Those results suggested that clinicians should survey cognition, comorbid sedative/hypnotic use, and physical health for probable CMD in ketamine users. Following a recent publication on diagnostic issue of urinary screening for ketamine in quetiapine-medicated patients [46], we are pleased to add more wisdom in clinical management in treating patients with ketamine use disorder in Taiwan.

Study limitations

The readers are cautioned not to overinterpret the study results because our study had five limitations.

- The participants were recruited from reformatory educational classes. Ketamine users who did not come to reformatory educational classes would not have the opportunity to join this study.
- Data were drawn from self-reported questionnaire, which may have resulted in shared method variance. We did not obtain collateral information from other sources on participants' levels of ketamine use, physical illness, and psychiatric illness. Psychiatric disorders such as depression and schizophrenia are correlated with cognitive impairments. The physical, cognitive, and urinary impairments were collected by self-reported data which are subject to measurement bias. Multiple data collecting methods and longitudinal approach should be used in further research.
- We used CHQ rather than other structured or semi-structured diagnostic instruments to define patients with probable CMD in ketamine users. The CHQ was designed for mental health disorder screening in community settings. This questionnaire measures nonpsychotic symptoms, and psychotic symptoms are not assessed. The validity of CHQ in ketamine users was also not validated.
- Other risk or protective factors of mental health may be present among ketamine users who were not examined in the present study, such as psychotherapy and family support. Education level was another confounder for cognitive performance.
- Sedatives/hypnotics may be prescribed for preexisting CMD in ketamine users. We used a cross-sectional design, which did not allow us to make any casual statements about the relationships between the variables investigated.

Study summary

Poor physical health, concomitant use of sedatives or hypnotics, and cognitive impairment developed over the course of ketamine use should be the focus of CMD prevention and treatment strategies when targeting ketamine users. We propose that an early survey of physical health, concomitant use of sedatives or hypnotics, and cognitive impairment is pertinent for detecting mental health problems among ketamine users. Our results may help mental health organizations design suitable CMD prevention and intervention programs aimed at ketamine users.

Acknowledgments

We thank the Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Department of Health, Kaohsiung City Government, and other collaborating partners participating in the project.

Financial Supports and Sponsorship

We received no external funding in this study.

Conflicts of Interest

The authors declare no conflict of interest in writing this report.

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