ABSTRACT

Background*:** Both ketamine and methamphetamine (MA) have become very popular and have been abused worldwide over the past two decades. However, the relationship between dependence on ketamine or MA and psychiatric comorbidities is still unclear. Objectives: This study aimed to examine the frequency of co-morbid psychiatric disorders in patients dependent on ketamine or methamphetamine who were receiving treatment at three substance abuse treatment clinics (SACs) in Hong Kong. ***Methods: This was a retrospective chart review. The medical records of 183 patients (103 with ketamine and 80 with MA dependence) treated between January 2008 and August 2012 were retrieved. Patients' demographic data, patterns of substance abuse and comorbid psychiatric diagnoses were recorded. ***Results***: The mean age of onset and duration of substance abuse were 18.1 ± 4.7 and 9.2 ± 6.2 years for ketamine and 19.9 ± 8.8 and 10.5 ± 9.8 years for MA users, respectively. Psychotic disorders were more common in MA dependent users (76.2% vs. 28.2%, $p < 0.001$), whereas mood disorders were more common in ketamine dependent users (27.2% vs. 11.2%, $p = 0.008$). ***Conclusions***: Ketamine and MA dependence have a notably different profile of psychiatric co-morbidity. Compared with MA dependence, ketamine dependence is more likely to be associated with mood disorders and less likely with psychotic disorders.

Keywords co-morbidity, ketamine, methamphetamine, mood disorders, psychotic disorders

INTRODUCTION

Ketamine has become a mainstream club drug and is emerging as a major public health concern in many parts of the world, including East Asia and Hong Kong (Gahlinger, 2004; McCambridge, Winstock, Hunt, & Mitcheson, 2007; Narchotics Division, 2013). Chronic abuse of ketamine may cause serious neurological and psychiatric adverse effects (Morgan et al., 2010) and even permanent physical damage (Wong et al., 2014; Yee et al., 2015). Recently, there has been growing interest in evaluating the efficacy of short-term ketamine administration for the treatment of major depression (Browne & Lucki, 2013; Hasselmann, 2014; Lapidus et al., 2014; Yang & Hashimoto, 2014). In the United Kingdom, the percentage of ketamine users among nightclub goers rose from 25% to 40% between 1999 and 2003 (McCambridge, Winstock, Hunt, & Mitcheson, 2007). Ketamine has already surpassed other club drugs and even replaced heroin as the predominant drug of abuse in Hong Kong in the early 2000s (Cheung & Cheung, 2010). The proportion of ketamine users increased from 16.9% in 2002 to 31.5% in 2011 and ketamine has consistently ranked among the most commonly abused psychotropic substances for more than 10 years (Narcotics Division, 2011).

Methamphetamine (MA) became a popular prescription drug during the 1940s and 1950s for a variety of indications, such as to promote wakefulness, improve mood or attention, and lose weight. Due to its adverse effects and high addictive potential, MA was later withdrawn from most of the indications for medical use (Vearrier, Greenberg, Miller, Okaneku, & Haggerty, 2012). MA abuse has become a growing public health problem over the past 30 years (Durell, Kroutil, Crits-Christoph, Barchha, & Van Brunt, 2008; Maxwell & Rutkowski, 2008; McKetin, Kozel, Douglas, Ali, Vicknasingam, Lund, & Li, 2008). The United Nations Office on Drugs and

Crime (UNODC) estimates that there are approximately 34.4 million abusers of amphetamine-type stimulants worldwide, exceeding the number of cocaine (17 million) and heroin (33 million, prescription drugs not included) abusers (UNODC, 2014). The 2011 UNODC report describes the MA problem as a global epidemic, citing an unprecedented rise in MA use compared to other illicit substances (Misawa et al., 2011). MA use is particularly common among young people in the western regions of the US and Canada (Rawson, Anglin, & Ling, 2002). MA use is also very frequent in Hong Kong, where it ranks as the second most commonly abused psychotropic substance (Narcotics Division, 2011).

Ketamine causes N-Methyl-D-Aspartate (NMDA) hypofunction in the central nervous system (CNS) after repeated exposure mainly via acting as an NMDA receptor antagonist (Jentsch & Roth, 1999). The psychotomimetic effect of a ketamine analogue, phencyclidine (PCP), led to the NMDA hypofunction hypothesis of schizophrenia (Angrist & Gershon, 1970). Ketamine induces positive and negative psychotic symptoms by reducing glutamate transmission in the hippocampus (Tamminga, Lahti, Medoff, Gao, & Holcomb, 2003) and sensory cortex (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012), resulting in a dopaminergic deficit in several frontal regions and possibly leading to dopaminergic hyperactivity in the subcortical system (Jentsch & Roth, 1999).

Even at low doses, the acute administration of ketamine is associated with psychotic symptoms (Krystal et al., 1994; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004). PCP/ketamine can mimic the positive (e.g. thought disorder, delusions, hallucinations, excessive suspiciousness, etc.) and negative symptoms (e.g. emotional and social withdrawal and psychomotor retardation) of schizophrenia (Angrist & Gershon, 1970; Javitt & Zukin, 1991; Adell, Jimenez-Sanchez, Lopez-Gil, & Romon, 2012) in both healthy volunteers (Javitt & Zukin,

1991) and regular users (Malhotra et al., 1996; Curran & Morgan, 2000). Moreover, ketamine/PCP is unique in mimicking the functional deficits associated with schizophrenia (Javitt & Zukin, 1991). Frequent ketamine users show elevated scores on clinical assessments of psychosis-proneness (Morgan, Duffin, Hunt, Monaghan, Mason, & Curran, 2012; Stone et al., 2014) and self-reported depressive symptoms on the Beck Depression Inventory (Morgan, Muetzelfeldt, & Curran, 2009; Morgan, Duffin, Hunt, Monaghan, Mason, & Curran, 2012; Freeman, Morgan, Pepper, Howes, Stone, & Curran, 2013). However, there are limited data on the prevalence of psychotic and depressive symptoms according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (DSM) version III/IV/V* and *International Classification of Diseases (ICD) version 9/10* in chronic ketamine abusers. In a Hong Kong SAC, 44% and 24% of 133 ketamine users presented with substance-induced psychotic disorder or mood disorders (characterized by persistently depressed mood or loss of interest or pleasure for at least two weeks for depressive disorders, and persistently elevated, expansive or irritable mood and persistently increased goal-directed activity or energy at least one week for manic episode) (Tang, Liang, Ungvari, & Tang, 2011). In a Hong Kong female residential centre, 16% and 47% of 32 ketamine users were diagnosed with substance-induced psychotic disorder or mood disorder, respectively (Tang, Cheung, Liang, Ungvari, & Tang, 2011). In a community-based study, 28.3% ketamine users were diagnosed as at least one psychiatric disorder. Mood and psychotic disorders accounted for 80.4% and 7.8% of all co-morbid psychiatric diagnoses in ketamine abusers, respectively (Tang, Morgan, Lau, Liang,Tang, & Ungvari, 2014). However, it was not known how many patients in these two studies developed dependence and whether they were dependent on other drugs in addition to ketamine.

MA predominantly blocks dopamine reuptake and increases dopamine release by interacting with the dopamine transporter, thereby increasing dopamine levels in nerve terminals and the cytosol (Seiden, Sabol, & Ricaurte, 1993). The pharmacologic properties of MA explain why it induces psychotic symptoms. The prevalence of lifetime psychosis in MA-dependent users ranges between 26% and 46% (Shoptaw, Peck, Reback, & Rotheram-Fuller, 2003; Lin, Ball, Hsiao, Chiang, Ree, & Chen, 2004; Grant et al., 2012). The discrepancy between these figures is mainly due to differences in the sampling methods. MA users who are dependent are three times more likely to have psychotic symptoms than those who are non-dependent (McKetin, McLaren, Lubman, & Hides, 2006). In a survey of 1016 MA users using the Beck Depression Inventory, 34% of female and 24% of male participants reported depressive symptoms in the last 30 days (Zweben et al., 2004).

As both ketamine and MA have the potential to induce psychotic symptoms or other psychiatric symptoms in MA and ketamine abusers via different mechanisms. It would be interesting to know whether there are differences in the prevalence of psychotic or other psychiatric symptoms. We expect that ketamine dependent users have higher percentage of depressive disorder and equal psychotic disorder than methamphetamine dependent users. To the best of our knowledge, no such comparison has yet been performed. Thus, the aim of this study was to compare the psychiatric co-morbidities of ketamine- and MA-dependent users in a retrospective chart review in Hong Kong.

MATERIALS AND METHODS

Sample

The medical records of patients with ketamine or MA dependence diagnosed according to ICD-10 criteria who attended three **SAC**s in Hong Kong between January, 2008 and August, 2012 were reviewed. The three SACs serve the north-eastern region of Hong Kong with a population of approximately 1.2 million, which constitutes about one sixth of Hong Kong's population. SACs target patients with concurrent substance dependence and potentially other psychiatric disorders, and thus they differ from patients attending drug treatment or rehabilitation centers.

Data collection

Demographic data including sex, age, education, marital status, employment and forensic records were extracted from the case notes. The history of ketamine and MA use and other substances and comorbid psychiatric diagnoses were recorded. Psychiatric disorders were diagnosed according to ICD-10 criteria. All subjects fullfilled the criteria of dependence syndrome under the category of "Mental and behaviour disorder due to psychiatric substance use" (code F1X.2). For a diagnosis of substance-induced mood disorder (F1x.8) and substance-induced psychotic disorder (F1X.5), the symptoms should occur after the substance use and should not persist for more than one month after cessasion of substance use; otherwise, the diagnosis is coded as F30-39 (Mood disorders) or F20-29 (Schizophrenia, Schizotypal and Delusional disorders).

Two of the co-authors (AT and FC) transferred the demographic and clinical data to the Data Collection Sheet. The study identification number replaced the name of the patient. Personal information such as the patient's phone numbers and home address was not recorded on the Data Collection Sheet. A research assistant transferred the data from the Data Collection Sheet onto a computer for statistical analysis. Data collection took place from January 1 to May 31, 2013.

Statistical analysis

The data were analysed using SPSS for Windows, Version 20.0. The patients' socio-demographic and clinical characteristics are presented as descriptive statistics. Continuous variables are described as mean ± standard deviation (SD), while categorical variables are reported as numbers and percentages. Chi-square tests and t-tests were also used as appropriate. Logistic regression was used to control for possible confounding variables (age, education, and employment status and lifetime use of cannabis, opiates and cough syrup) in the comparison of psychiatric co-morbidity between the two groups of patients.

Ethical considerations

The study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee as well as the participating substance abuse treatment clinics. Written informed consent was not required in this type of anonymous retrospective study, as the collection of such information was part of routine clinical care and would not breach confidentiality or pose any risk to patients.

RESULTS

Demographic and clinical characteristics and drug use patterns

The study sample consisted of 103 and 80 patients with ketamine and MA dependence, respectively. The demographic and clinical characteristics and lifetime use of other psychotropic substances of the two groups were shown in Table 1. Patients with ketamine dependence were younger, had a higher level of education and were less likely to be unemployed. Both groups

were similar in terms of age of onset and duration of substance use. The groups were also equally likely to be married and to have been involved in drug-related crime. Patients with MA dependence were significantly more likely to have ever used cannabis, opiates and cough syrup (Table 1). However, the groups did not differ in their lifetime use of MDMA (Ecstasy), benzodiazepines, cocaine, zopiclone/zolpidem, solvents or other drugs.

Frequency of co-morbid psychiatric disorders

Table 2 shows the frequency of co-morbid psychiatric disorders. Overall, patients with ketamine dependence had a lower rate (n = 64, 62.1%) of co-morbid psychiatric disorders than patients with MA dependence (n = 70, 87.5%), $p< 0.001$. Compared with MA, ketamine-dependent users had a higher rate of mood disorders (n = 28, 27.2% vs. n = 9, 11.2%; $p = 0.008$). The frequency of substance-induced mood disorders was similar between the ketamine and MA groups (n = 13, 12.6% vs. n = 6, 7.5%; $p = 0.260$), but the difference in the frequency of major depression was of borderline significance (n = 8, 7.8% vs. n = 1, 1.2%; $p = 0.080$). The ketamine group had a lower rate of substance-induced psychotic disorders (n = 29, 28.2% vs. n = 80, 76.2%; $p < 0.001$) than the MA group. These differences remained significant after adjusting for age, education, employment status, and lifetime use of cannabis, opiates and cough syrup.

DISCUSSION

To the best of our knowledge, this was the first study to compare the psychiatric co-morbidity between MA and ketamine dependence. The main finding is that the frequency of psychosis in MA dependence is significantly higher than that in ketamine dependence. Depression, however, is more likely to co-occur in ketamine dependence than in MA dependence.

The study sample was recruited from SACs, which target substance users with possible psychiatric disorders. This may explain why the prevalence of psychotic disorders was much higher in the MA-dependent users than the 26-46% lifetime frequency found in community samples or drug dependence treatment centers (Grant et al., 2012). Positive symptoms such as persecutory delusions, delusions of reference, auditory and visual hallucinations and thought broadcasting are frequently observed in MA dependence (Grant et al., 2012). Regular MA users living in the community are 11 times more likely to develop psychotic symptoms compared to the general population in Australia (McKetin, McLaren, Lubman, & Hides, 2006). Psychotic disorders were found in 13% of 100 adult volunteers with a diagnosis of MA dependence recruited from a drug treatment centre in South Africa (Akindipe, Wilson, & Stein, 2014), and in 13% of 292 patients with MA dependence recruited from a drug rehabilitation centre in Malaysia (Sulaiman et al., 2014). Psychotic symptoms were found in 75% of long-term MA users in Japan (Sato, 1992).

One study directly compared the effects of ketamine and amphetamine in 41 healthy individuals who all received an infusion of ketamine, amphetamine or placebo once a day for up to 4 days. Positive "psychotic"-like symptoms, negative symptoms and cognitive deficits were far more prominent in the ketamine group (Krystal et al., 2005). Another study comparing dependent users of ketamine, cocaine or cannabis with polydrug and non-using controls found higher prodromal "basic symptoms" (subtle, subclinical self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action (Klosterkotter et al., 2001)) in ketamine users compared to cocaine users (Morgan, Duffin, Hunt, Monaghan, Mason & Curran, 2012). However, that study did not assess psychiatric symptoms using DSM/ICD criteria, and our study is the first to compare the effects of chronic ketamine use with that of MA use.

Another remarkable difference in the psychiatric co-morbidity profiles between MA and ketamine dependence concerns the frequency of depression. The association between ketamine and depression is complex; a single dose of ketamine has an antidepressant effect (Berman et al., 2000; Zarate et al., 2006), while persistent depressive symptoms are consistently observed in chronic ketamine users (Curran & Morgan, 2000; Morgan, Muetzelfeldt, & Curran, 2009; Morgan, Huddy, Lipton, Curran, & Joyce, 2009; Tang, Liang, Lau, Tang, & Ungvari, 2013; Freeman, Morgan, Pepper, Howes, Stone, & Curran, 2013). Although increasingly more studies have focused on ketamine and its antidepressant property, the effects of long-term ketamine treatment on depression are largely unknown (Szymkowicz, Finnegan, & Dale, 2013). Intriguingly, when a group of 30 frequent ketamine users were monitored over one year in a longitudinal study, their depression scores went up, despite equal levels of ketamine exposure at follow up (Morgan, Muetzelfeldt, & Curran, 2010). Acute and repeated ketamine exposure generates different neurobiological changes. For example, glutamine and dopamine levels increase after acute (Moghaddam, Adams, Verma, & Daly, 1997) but decrease following repeated ketamine administration (Mouri, Noda, Enomoto, & Nabeshima, 2007). In this study, 27.2% of the patients dependent on ketamine had concurrent mood disorder, consistent with the result of a previous Hong Kong study that reported 22% (Tang, Liang, Ungvari, & Tang, 2011), but lower than the 47% found in another Hong Kong study (Tang, Cheung, Liang, Ungvari, & Tang, 2011). The latter study had a small sample size (n=32) and all of the subjects were females. The higher figure in the latter study is consistent with previous studies that suggested female with substance use disorders presents higher mood disorders than male (Zilberman et al., 2003; Ali et al., 2015).

There is evidence that MA abuse can induce depressive symptoms (McKetin, Lubman, Lee, Ross, & Slade, 2011). In the present study, 11.2% of patients with MA dependence were diagnosed with co-morbid mood disorder, which was slightly higher than the 12-month prevalence of 8.2% found in the general population of Hong Kong (Lee et al., 2010). The prevalence of co-morbid mood disorder in MA dependence is consistent with the literature. Slightly more than 10% of 189 MA-dependent American users had some form of mood disorder induced by amphetamines (Salo, Flower, Kie lstein, Leamon, Nordahl, & Galloway, 2011). At 3-year follow-up, 15% of 526 adults dependent on MA met the criteria for major depressive disorder (Glasner-Edwards et al., 2009).

Given that the terms "substance induced mood disorder and psychotic disorder" were used in this study, the causality of MA and ketamine use and the co-morbid psychiatric disorders was difficult to confirm. Schizophrenia and substance use disorder share vulnerabilities (Chambers, Krystal, & Self. 2001). It could be that substance dependence triggers psychotic symptoms or the vulnerability to schizophrenia increases the risk for substance dependence (Bramness et al., 2012). Receptor availability may also be involved in the connection between drug and psychotic symptoms. In MA dependent users, A1 allele carriers (indicating low dopamine 2 receptor availability in the striatum) are less likely to have psychotic symptoms whilst the141C Del allele (indicating high dopamine 2 receptor availability in the striatum) increases the risk of rapid onset psychosis after MA administration (Ujike et al., 2009). It will be of interest to verify whether such genetic variants underlie the different incidence of psychosis and depression found in MA and ketamine dependent users.

The findings of this study provide information that should alert clinicians to carefully screen for depressive symptoms in ketamine-dependent users and psychotic symptoms in amphetamine-dependent users.

Future studies should compare the symptom characteristics, treatment response and prognosis between ketamine- and amphetamine-induced psychiatric co-morbidity. Longitudinal studies should explore the causality between these substances and psychiatric co-morbidity.

Limitations

The findings of this study are subject to several limitations, mainly related to the retrospective study design. The first is the missing information about risk factors for developing psychiatric disorders, such as family history, premorbid personality, route of administration, severity of dependence and of pre-existing psychiatric symptoms, and social factors such as stressful life events, which could not be reliably ascertained from the medical files (Darke, Kaye, McKetin, & Duflou, 2008; McKetin, Lubman, Lee, Ross, & Slade, 2011). The lack of important variables limited the evaluation of differences between ketamine and MA dependence and the psychiatric disorders associated with dependence on the two substances. Finally, as the sample was drawn from a psychiatric clinic, the findings may not be generalizable to other populations of MA and ketamine users.

CONCLUSIONS

Patients with ketamine dependence were more likely to have mood disorders and less likely to suffer from psychotic disorder than patients with methamphetamine dependence. Future prospective studies comparing the differences between these two substances on premorbid traits,

symptom presentation and prognosis would help to understand the link between clinical presentation and the neurobiological mechanisms underlying psychosis associated with ketamine and MA dependence, and could also provide clues to the pathophysiology of psychosis and mood disorders in general.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

Adell, A., Jimenez-Sanchez, L., Lopez-Gil, X., & Romon, T. (2012). Is the acute NMDA receptor hypofunction a valid model of schizophrenia? *Schizophrenia Bulletin, 38*(1), 9-14.

Akindipe, T., Wilson, D., & Stein, D. J. (2014). Psychiatric disorders in individuals with methamphetamine dependence: prevalence and risk factors. *Metablic Brain Disease, 29*(2), 351-357.

Ali, B., Seitz-Brown, C. J., & Daughters, S. B. (2015). The interacting effect of depressive symptoms, gender, and distress tolerance on substance use problems among residential treatment-seeking substance users. *Drug and Alcohol Dependence*, 148, 21-26.

Angrist, B. M., & Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biological Psychiatry, 2*(2), 95-107.

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., et al. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry, 47*(4), 351-354.

Bramness, J. G., Gundersen, Ø.H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E. M., et al. (2012). Amphetamine-induced psychosis
a separate diagnostic entity or primary psychosis triggered in thevulnerable?
***BioMed Central Psychiatry, 12*, 221.**

Browne, C. A., & Lucki, I. (2013). Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. *Frontiers in Pharmacology, 4*, 161.

Chambers, R. A., Krystal, J. H., & Self, D. W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biological Psychiatry*, *50*(2), 71-83.

Cheung, Y., & Cheung, N. (2010). Drug policy in Hong Kong: changes and challenges. Paper presented at the Anti-Drug International Conference, Taipei, Taiwan.

Curran, H. V., & Morgan, C. (2000). Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction, 95*(4), 575-590.

Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review, 27*(3), 253-262.

Durell, T. M., Kroutil, L. A., Crits-Christoph, P., Barchha, N., & Van Brunt, D. L. (2008). Prevalence of nonmedical methamphetamine use in the United States. *Substance Abuse Treatment, Prevention, and Policy, 3*, 19.

Freeman, T. P., Morgan, C. J., Pepper, F., Howes, O. D., Stone, J. M., & Curran, H. V. (2013). Associative blocking to reward-predicting cues is attenuated in ketamine users but can be modulated by images associated with drug use. *Psychopharmacology (Berl), 225*(1), 41-50.

Gahlinger, P. M. (2004). Club drugs: MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine. *American Family Physician, 69*(11), 2619-2626.

Glasner-Edwards, S., Marinelli-Casey, P., Hillhouse, M., Ang, A., Mooney, L. J., Rawson, R., et al. (2009). Depression among methamphetamine users: association with outcomes from the Methamphetamine Treatment Project at 3-year follow-up. *The Journal of Nervous and Mental Disease, 197*(4), 225-231.

Grant, K. M., LeVan, T. D., Wells, S. M., Li, M., Stoltenberg, S. F., Gendelman, H. E., et al. (2012). Methamphetamine-associated psychosis. *Journal of Neuroimmune Pharmacology, 7*(1), 113-139.

Hasselmann, H. (2014). Ketamine as antidepressant? Current state and future perspectives. *Current Neuropharmacology, 12*(1), 57-70.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *American Journal of Psychiatry, 148*(10), 1301-1308.

Javitt, D. C., Zukin, S. R., Heresco-Levy, U., & Umbricht, D. (2012). Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophrenia Bulletin, 38*(5), 958-966.

Jentsch, J. D., & Roth, R. H. (1999). The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology, 20*(3), 201-225.

Klosterkotter, J. , Hellmich, M., Steinmeyer, E. M., & Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase . *Arch Gen Psychiatry, 58*(2), 158-164.

Krystal, J., Perry, E., Gueorguieva, R., Belger, A., Madonich, S., Abi-Dargham, A., et al. (2005). Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Archives of General Psychiatry, 62*(9), 985-995.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., et al. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry, 51*(3), 199-214.

346 Lapidus, K. A., Levitch, C. F., Perez, A.M., Brallier, J.W., Parides, M.K., Soleimani, L., et al.
347 (2014). A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive
348 Disorder. *Biological Psychiatry, pii*, S0006-3223(14) 00227-00223.
349 Lee, S., Guo, W., Tsang, A., Mak, A., Wu, J., Ng, K., et al. (2010). Evidence for the 2008
350 economic crisis exacerbating depression in Hong Kong. *Journal of Affective Disorders,*
351 *126*(1-2), 125-133.
352 Malhotra, A. K., Pinals, D. A., Weingartner, H., Sirocco, K., Missar, C. D., Pickar, D., et al.
353 (1996). NMDA Receptor Function and Human Cognition: The Effects of Ketamine in
354 Healthy Volunteers. *Neuropsychopharmacology, 14*(5), 301-307.
355 Maxwell, J., & Rutkowski, B. (2008). The prevalence of methamphetamine and amphetamine
356 abuse in North America: a review of the indicators, 1992–2007. *Drug and Alcohol*
357 *Review, 27*(3), 229-235.
358 McCambridge, J., Winstock, A., Hunt, N., & Mitcheson, L. (2007). 5-Year trends in use of
359 hallucinogens and other adjunct drugs among UK dance drug users. *European Addiction*
360 *Research, 13*(1), 57-64.
361 McKetin, R., Kozel, N., Douglas, J., Ali, R., Vicknasingam, B., Lund, J., & Li, J. H. (2008). The
362 rise of methamphetamine in Southeast and East Asia. *Drug and Alcohol Review, 27*(3),
363 220-228.
364 McKetin, R., Lubman, D., Lee, N., Ross, J., & Slade, T. (2011). Major depression among
365 methamphetamine users entering drug treatment programs. *The Medical Journal of*
366 *Australia, 195*(3), S51-55.
367 McKetin, R., McLaren, J., Lubman, D. I., & Hides, L. (2006). The prevalence of psychotic
368 symptoms among methamphetamine users. *Addiction, 101*(10), 1473-1478.

Misawa, F., Shimizu, K., Fujii, Y., Miyata, R., Koshiishi, F., Kobayashi, M., . . . Kashima, H. (2011). Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects? A cross-sectional study. *BioMed Central Psychiatry, 11*, 118.

Moghaddam, B., Adams, B., Verma, A., & Daly, D. (1997). Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *Journal of Neuroscience, 17*(8), 2921-2927.

Morgan, C. J., Duffin, S., Hunt, S., Monaghan, L., Mason, O., & Curran, H. V. (2012). Neurocognitive function and schizophrenia-proneness in individuals dependent on ketamine, on high potency cannabis ('skunk') or on cocaine. *Pharmacopsychiatry, 45*(7), 269-274.

Morgan, C. J., Muetzelfeldt, L., & Curran, H. V. (2010). Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction, 105*(1), 121-133.

Morgan, C. J. A., Mofeez, A., Brandner, B., Bromley, L., & Curran, H. V. (2004). Acute Effects of Ketamine on Memory Systems and Psychotic Symptoms in Healthy Volunteers. *Neuropsychopharmacology, 29*(1), 208-218.

Morgan, C. J. A., Muetzelfeldt, L., & Curran, H. V. (2009). Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. *Addiction*(1), *104*, 77-87.

Morgan, C. J., Huddy, V., Lipton, M., Curran, H. V., & Joyce, E. M. (2009). Is persistent ketamine use a valid model of the cognitive and oculomotor deficits in schizophrenia? *Biological Psychiatry, 65*(12), 1099-1102.

Mouri, A., Noda, Y., Enomoto, T., & Nabeshima, T. (2007). Phencyclidine animal models of schizophrenia: approaches from abnormality of glutamatergic neurotransmission and neurodevelopment. *Neurochemistry International, 51*(2-4), 173-184.

Narcotics Division, Security Bureau. (2013). *Central Registry of Drug Abuse, drug abusers for 2002-2011*. Hong Kong: the Government of Hong Kong SAR. Retrieved from http://www.nd.gov.hk/en/statistics_list. htm

Narcotics Division, Security Bureau. (2011). *Central Registry of Drug Abuse Sixty-first Report*. Hong Kong: the Government of Hong Kong SAR. Retrieved from http://www.nd.gov.hk/pdf/report/ crda_61st/crda_61st_full_report.pdf

Rawson, R., Anglin, M., & Ling, W. (2002). Will the methamphetamine problem go away? *Journal of Addictive Diseases, 21*(1), 5-19.

Salo, R., Flower, K., Kielstein, A., Leamon, M. H., Nordahl, T. E., & Galloway, G. P. (2011). Psychiatric co-morbidity in methamphetamine dependence. *Psychiatry Research, 186*(2-3), 356-361.

Sato, M. (1992). A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Annals of the New York Academy of Sciences, 654*, 160-170.

Seiden, L. S., Sabol, K. E., & Ricaurte, G. A. (1993). Amphetamine: effects on catecholamine systems and behavior. *Annual Review of Pharmacology and Toxicology, 33*, 639-677.

411 Stone, J. M., Pepper, F., Fam, J., Furby, H., Hughes, E., Morgan, C., et al. (2014). Glutamate, N-
412 acetyl aspartate and psychotic symptoms in chronic ketamine users. *Psychopharmacology*
413 *(Berl), 231*(10)*, 2107-2116*.
414 Sulaiman, A. H., Said, M. A., Habil, M. H., Rashid, R., Siddiq, A., Guan, N. C., et al. (2014).
415 The risk and associated factors of methamphetamine psychosis in methamphetamine-
416 dependent patients in Malaysia. *Comprehensive Psychiatry, 55 Suppl 1*, S89-94.
417 Szymkowicz, S., Finnegan, N., & Dale, R. (2013). A 12-month naturalistic observation of three
418 patients receiving repeat intravenous ketamine infusions for their treatment-resistant
419 depression. *Journal of Affective Disorders, 147*(1-3), 416-420.
420 Tamminga, C. A., Lahti, A. C., Medoff, D. R., Gao, X. M., & Holcomb, H. H. (2003).
421 Evaluating glutamatergic transmission in schizophrenia. *Annals of the New York*
422 *Academy Sciences, 1003*, 113-118.
423 Tang, A., Liang, H. J., Ungvari, G. S., & Tang, W. K. (2011). Referral patterns and clinical
424 characteristics of subjects referred to substance abuse clinic of a regional hospital in
425 Hong Kong. *East Asian Archives of Psychiatry, 21*(1), 22-27.
426 Tang, A., Cheung, R. Y., Liang, H. J., Ungvari, G. S., & Tang, W. K. (2011). Psychiatric
427 morbidity at a female residential drug treatment centre in Hong Kong. *East Asian*
428 *Archives of Psychiatry, 21*(1), 28-31.
429 Tang, W. K., Liang, H. J., Lau, C. G., Tang, A., & Ungvari, G. S. (2013). Relationship between
430 cognitive impairment and depressive symptoms in current ketamine users. *Journal of*
431 *Studies on Alcohol and Drugs, 74*(3), 460-468.

Tang, W. K., Morgan, C. J., Lau, G. C., Liang, H. J., Tang, A., Ungvari, G.S. *(2015).* Psychiatric morbidity in ketamine users attending counselling and youth outreach services. *Substance Abuse,* 36(1), 67-74.

UNODC. World drug report 2014. (201). Vienna, United Nations.

Ujike, H., Katsu, T., Okahisa, Y., Takaki, M., Kodama, M., Inada, T., et al. (2009). Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset andpoor prognosis of methamphetamine psychosis. *Progress in Neuro-psychopharmacology and Biological Psychiatry,33*(4), 625-629.

Vearrier, D., Greenberg, M., Miller, S., Okaneku, J., & Haggerty, D. (2012). Methamphetamine: History, Pathophysiology, Adverse Health Effects, Current Trends, and Hazards Associated with the Clandestine Manufacture of Methamphetamine. *Disease-a- Month, 58*(2), 38-39.

Wong, G. L., Tam, Y. H., Ng, C. F., Chan, A. W., Choi, P. C., Chu, W. C., et al. (2014). Liver injury is common among chronic abusers of ketamine. *Clinical Gastroenterology and Hepatology, 12*(10),1759-1762.

Yang, C., & Hashimoto, K. (2014). Rapid antidepressant effects and abuse liability of ketamine. *Psychopharmacology (Berl), 231*(9), 2041-2042.

Yee, C. H., Lai, P. T., Lee, W. M., Tam, Y. H., & Ng, C. F. (2015). Clinical Outcome of a Prospective Case Series of Patients With Ketamine Cystitis Who Underwent Standardized Treatment Protocol. *Urology, 86*(2):236-243.

Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., et al. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry, 63*(8), 856-864.

Zilberman, M. L., Tavares, H., Blume, S. B., & el-Guebaly, N. (2003). Substance use disorders: sex differences and psychiatric comorbidities. *Canadian Journal of Psychiatry, 48*(1), 5-13.

Zweben, J. E., Cohen, J. B., Christian, D., Galloway, G. P., Salinardi, M., & Parent, D., Methamphetamine Treatment Project. (2004). Psychiatric symptoms in methamphetamine users. *The American Journal on Addiction, 13*(2), 181-190.

TABLE 1. Socio-demographic and clinical characteristics of ketamine and methamphetamine dependent patients

Variables	Ketamine (n=103; n, % / mean ± SD)	Methamphetamine (n=80; n, % / mean ± SD)	*p*
Age (years)	24.4 ± 6.4	28.7 ± 10.6	0.002[a]
Female	47 (45.6)	35 (43.8)	0.800[b]
Education (MG 4 or above)	52 (50.5)	20 (25.0)	<0.001[b]
Married	13 (12.6)	16 (20.0)	0.175[b]
Unemployed	47 (45.6)	53 (67.1)	0.004[b]
Drug-related crime	62 (61.4)	43 (53.8)	0.301[b]
Onset of substance abuse	18.1 ± 4.7	19.9 ± 8.8	0.217[a]
Duration of substance abuse	9.2 ± 6.2	10.5 ± 9.8	0.435[a]
Lifetime use of other substances			
Ketamine	-	43 (53.8)	-
Methamphetamine	23 (22.3)	-	-
Cannabis	23 (22.3)	29 (36.2)	0.038[b]
MDMA (Ecstasy)	26 (25.2)	26 (32.5)	0.280[b]
Benzodiazepines	33 (32.0)	23 (28.7)	0.632[b]
Cocaine	31 (30.1)	19 (23.8)	0.339[b]
Opiates	8 (7.8)	17 (21.2)	0.008[b]
Zopiclone/Zolpidem	13 (12.6)	17 (21.2)	0.118[b]
Cough syrup	7 (6.8)	13 (16.2)	0.042[b]
Others	5 (4.9)	6 (6.2)	0.750[c]
Solvent	1 (1.0)	4 (5.0)	0.170[c]

Notes: SD = standard deviation; MG4 = middle school grade 4.

[a] t-test; [b] Chi-square test; [c] Fisher's exact test.

TABLE 2. Psychiatric co-morbidity of ketamine and methamphetamine dependent patients

Variables	Ketamine (n = 103; n, %)	Methamphetamine (n = 80; n, %)	p^a	p^b
Any psychiatric co-morbidity	64 (62.1)	70 (87.5)	<0.001[a]	<0.001
Psychotic disorders	29 (28.2)	61 (76.2)	<0.001[a]	<0.001
Substance-induced psychotic disorder	28 (27.2)	59 (73.8)	<0.001[a]	<0.001
Schizophrenia	2 (1.9)	3 (3.8)	0.655[b]	
Mood disorders	28 (27.2)	9 (11.2)	0.008[a]	0.003
Substance-induced mood disorder (with depressive features)	13 (12.6)	6 (7.5)	0.260[a]	
Major depression	8 (7.8)	1 (1.2)	0.080[b]	
Dysthymia	2 (1.9)	0	0.505[b]	
Adjustment disorder with depressed mood	4 (3.9)	2 (2.5)	0.697[b]	
Bipolar affective disorder	1 (1.0)	0 (0.0)	1.000[b]	
Anxiety disorders	4 (3.9)	1 (1.2)	0.388[b]	
Generalized anxiety disorder	2 (1.9)	1 (1.2)	1.000[b]	
Panic disorder/ Agoraphobia	1 (1.0)	1 (1.2)	1.000[b]	

Posttraumatic stress disorder	1(1.0)	0 (0.0)	1.000[b]

Notes: [a] Chi-square test; [b] Fisher's exact test.

p [a] unadjusted; *p* [b] adjusted for age, education, employment status and lifetime use of cannabis, opiates and cough syrup by logistic regression