Substance abuse in adolescence in Taiwan Focus on Ketamine

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Abstract

Ketamine is an anesthetic and analgesic agent but has been identified to have abuse potential in recent years. Ketamine abuse is found to be rapidly increasing especially among adolescents and early adults for its relative low cost and lack of immediate severe side effects. Ketamine is a NMDA antagonist and has acute antidepressant effects from recent pharmacological research. The association between abuse potential and antidepressant effects is still uncertain. Though there are no obvious physical withdrawal symptoms of ketamine, strong cravings were noted from chronic ketamine abusers. On the other hand, ketamine can cause severe damage to the urinary system. "Ketamine-induced uropathy" was proposed in recent years, with presentation of severe lower tract urinary symptoms (LUTS; including frequency, urgency, dysuria and hematuria) and urinary system damage. Similar to patients with other substance abuse, ketamine abusers have higher incidence of co-morbid psychiatric diseases. Currently there is still lack of specific medical treatment for managing ketamine abuse, but psychosocial intervention plays an important role especially for adolescents. In this brief review, we hope to call more attention to this emerging problem.

Keywords : Adolescence, Ketamine, Substance abuse

Introduction

Ketamine, a derivative of phencyclidine that was developed in the 1960s for medical use, and is an anesthetic and analgesic with hallucinogenic effects. Ketamine abuse has been identified as a grave issue in public health in many Asian societies, when used alone and especially when combined with other designer drugs. The increase in illicit use prompted ketamine's placement in Schedule III of the United States Controlled Substance Act in August 1999 (Marshall, 1999). In the United Kingdom, it became labeled a Class C drug in 2006. In Canada, ketamine is classified as a Schedule I narcotic, since 2005 (Li et al., 2011). Although ketamine abuse has been observed in many parts of the world and the deleterious effects associated with nonmedical use are widely recognized, ketamine has not been scheduled as a controlled substance worldwide. Therefore, the situation of ketamine abuse may not be appropriately assessed. In Taiwan, ketamine is regulated as a schedule III drug in 2006 and individuals who use ketamine are subjects to a fine and 4 to 8 hours of drug education. The relatively lenient punishment and the lack of a policy to criminalize ketamine use have propelled ketamine to one of the most

commonly used or abused substances. Now there is a debate of whether ketamine should be re-scheduled to class II drug in Taiwan.

Long-term recreational use of ketamine can develop a psychological tolerance and dependence. Previous studies in humans and animals have documented the medical consequences of ketamine abuse, including effects on the urinary system (Winstock et al., 2012; Yeung et al., 2009), cardiotoxicity (Chan, Liang, Wai, Hung,., and Yew., 2011), and neurotoxicity (Morgan and Curran,, 2006) and addiction to the use of ketamine (Critchlow, 2006; Lim, 2003; Wolff and Winstock, 2006). This issue is particularly important, because ketamine use is most prevalent during adolescence and young adulthood, in which the development of brain is most vulnerable to the effects of substance of abuse (Lankenau et al., 2010; Lankenau and Sanders, 2007; Maxwell and Spence, 2005; McCambridge et al., 2007; Reynaud-Maurupt, Bello, Akoka and Toufik, 2007). In this brief review, we summarized recent studies on ketamine abuse, including the prevalence of ketamine abuse, the characteristics of ketamine abusers, the CNS effect and physical complications, psychiatric co-morbidities, and current management of ketamine abuse. However, there are not abundant studies focused on this field at present. Through this review, we hope to call for more attention to this emerging problem worldwide.

Methods

Finding and analysis

Prevalence of ketamine use in Taiwan

Recreational using or abusing ketamine is rapidly becoming a serious problem in Taiwan. In a 2003 study (Lua et al., 2003), by collecting samples from participants in a dancing club, the positive rates of common drugs of abuse detected were as follows: MDMA, 75.7%; ketamine, 47.0%; Methyl amphetamine, 41.6%; opiates, 0%. At that time methyl amphetamine was thought to be the leading drug of abuse among adolescents, however, it called to attention the rapidly rising incidence of ketamine abuse. In a following survey of school-attending adolescents in grades 7, 9, 10, and 12, aged 11–19 years, conducted in 2004, 2005, and 2006, the ecstasy and ketamine appeared as the first and second commonly used illegal drugs by lifetime prevalence and incidence. Among middle (grades 7 and 9) and high school students (grades 10 and 12) during the 3-year survey period, however, this order was reversed in the middle school-aged students starting in 2006. In another National Household Survey on Health and Substance Abuse on the population aged between 12 to 64 years in Taiwan in 2005, it found that ketamine abusers were ranked third (22.0%) following the amphetamine (49%) and MDMA (35%) among people who used illicit drugs. In recent surveys of school-attending adolescents, ketamine was overtaking amphetamine and MDMA as the leading drug of abuse in this population population (Chen et al., 2009). For example, Lee et al. randomly sampled 3,868 high school students and found out that 1.07% self-reported having used club drugs (Szu-Hsien, 2009). Of students who used drugs, 64.4% reported that they used ketamine, followed by ecstasy (50%) and amphetamine (29%). The average age at first drug use was 13.95 years old. In addition, ketamine is usually abused with other drugs. For example, “Trinity” is a description for a sequence of polydrug use at a club with MDMA first, followed by ketamine, and then marijuana (Leung et al., 2008). It showed an increasing trend of ketamine use/abuse, especially among young age groups.

Accordingly, as statistics compiled in 2011 by the Taiwan Ministry of Education (2011) shows (Table 1 and Figure 1), the number of school students who used or misused designer drugs such as amphetamine, MDMA and ketamine has increased for the past eight years, with the Schedule III drugs showing the most significant increase. This

increase in the use and abuse of club or designer drugs also mirrors the data reported by the Taiwan Department of Police (2012), which shows that young adults aged 18 to 24 years and adolescents 12 to 18 year-old each accounts for 39.15% and 16.26% of all Schedule III and IV drug use. The numbers of people arrested by police and tested positive for ketamine use were 8,633 and 9,632 for the years of 2010 and 2011, respectively.

Considering the global trends, ketamine abuse is seen across the world, but it appears to be more prevalent in East and South-East Asia (refers to table 2; adapted from (Wang et al., 2013). Ketamine is much cheaper than other recreational use drugs and lacks immediate side effects or withdrawal symptoms. These characteristics have created a rapid increase of ketamine use among young age groups and on the university campus. Global reports of ketamine seizure rose from negligible amounts in 1999 to over 11 metric tons in 2007, with nearly all of this in East and South-East Asia, where ketamine seizures exceeded that of heroin (APAIC, 2009; UNODC, 2010). Moreover, illicit manufacturing laboratories have now also been reported, particularly in China and South-East Asia (UNODC, 2010). These statistics suggest a widening of ketamine supply and clearly highlight the increasing prevalence of ketamine use in adolescents and young adults. It is important to monitor the trends of ketamine abuse and make policy to deal with it.

Table 1: Numbers and percentage of students with drug abuse in Taiwan (from 2004 to 2011; Data from Ministry of Education, Taiwan)

Year	Heroin	Amphetamine MDMA	Ketamine	Others	Total (100%)
2004	2 (1.48%)	85 (62.96%)	39 (28.89%)	9 (6.67%)	135 (100%)
2005	8 (5.84%)	88 (64.23%)	26 (18.98%)	8 (5.84%)	137 (100%) (100%)
2006	2 (0.87%)	98 (42.42%)	104 (45.02%)	26 (11.26%)	231 (100%)
2007	4 (1.36%)	55 (18.70%)	235 (79.93%)	0 (0.00%)	294 (100%)
2008	4 (0.49%)	107 (13.12%)	702 (86.31%)	2 (0.25%)	815 (100%)
2009	8 (0.61%)	151 (11.54%)	1,148 (87.76%)	1 (0.07%)	1,308 (100%) (100%) (100%)
2010	2 (0.13%)	282 (18.08%)	1,271 (81.52%)	4 (0.26%)	1,559 (100%)
2011	4 (0.22%)	257 (14.20%)	1,548 (85.52%)	1 (0.05%)	1,810 (100%)

Figure 1: Percentage of students with drug abuse in Taiwan from 2004 to 2011

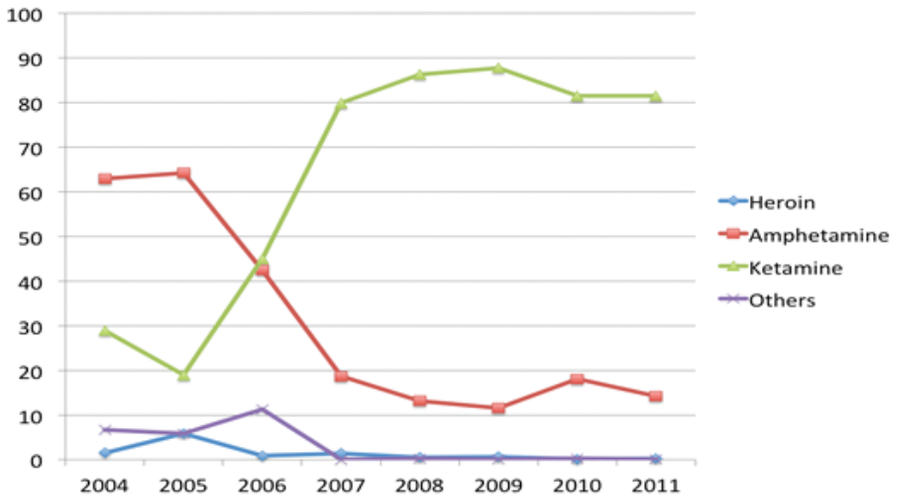

Table 2: Ketamine use from population survey (adapted and modified from (Wang et al., 2013)

Country, year	% Lifetime ketamine use	% Ketamine use in the past year	% Ketamine among students with drug abuse	Age range
Australia, 2007	1.1	0.2	-	14 to 40+
Canada, 2009	2.2	1.6	-	12-18
United Kingdom, 2010	2.0	0.5	-	16-59
United States, 2011[1]		~1.7%	-	18
Hong Kong, 2009[2]	-	-	>80%	Students
Indonesia, 2009[3]	-	-	1.8%	Students
Taiwan, 2009, 2012	0.7[4]	0.7[5]	>80%	12-18

1. Monitor the future study (2011)
2. Central Registry of Drug abuse, Hong Kong Government
3. (Li et al., 2011)
4. (Szu-Hsien, 2009)
5. (Lee et al., 2012)

The characteristics of ketamine users

Some studies were conducted to analyze the characteristics of ketamine users in Taiwan. Yen et al. randomly selected 9860 adolescents from high school in Southern Taiwan during 2004, they showed that ketamine users were more likely to have low paternal and maternal educational levels, not live with their parents, use marijuana, have peers using illicit drugs, and interact with friends more actively than ketamine non-users. In addition, it reported that ketamine users had a lower negative outcome expectancy for using ketamine, drank alcohol and used tobacco more frequently, and were more depressed than ketamine non-users (Lee et al., 2012). In 2007, they reported a study of poly-substance use and its correlates in adolescent ecstasy users in Taiwan. Most of them were MDMA, amphetamine and ketamine users. Those who were male, were older, had been employed, had dropped out of school, had higher novelty seeking traits, had higher psychopathology, actively interacted with peers more, and whose father's education level less than 9 years were more likely to be poly-substance users (Yen, Hsu and Cheng, 2007). Meanwhile, those who perceived less severe family conflicts, had more family monitoring, and had fewer substance-using peers were less likely to be poly-substance users. In the survey of attending school students who used ecstasy and ketamine from 2004 to 2006, reported having a sexual experience, tobacco and betel nut use which were contributing factors consistently associated with the onset of illegal substance use across years (Chen et al., 2009). During the adolescent period, they are eager to build up their self-image and identity. Adolescents need peer group identification and the feeling of belonging. Therefore, the environment influences them easily. The data showed ketamine users seem to interact with others more actively, which might come from the biological effect of ketamine, namely feeling good, relaxed...etc. (please refer to the CNS effect of ketamine below). On the other hand, the psychosocial meaning of the "behavior" of ketamine use might also play a part. It is similar to social media to link everybody together, to share experiences, to know friends, and to get group support. Thus, the "characteristics" of the abusers might reveal some parts of the "benefits" of ketamine abuse. This data demonstrates that during this high-risk adolescent period, it is important to have a strong and supportive school and family environment to reduce the potential allure of substance-using peers.

Physical complications of ketamine use

The first reported ketamine related cystitis was in 2007 by Shahani who studied nine patients in Canada with daily ketamine use and presented with severe dysuria, frequency, urgency, and gross hematuria hematuria (Shahani, Streutker, Dickson and Stewart , 2007). By the same time, Chu et al in Hong Kong also reported of ten young ketamine abusers who presented with lower urinary tract symptoms at two regional hospitals (Chu et al., 2007). From June 2008 to July 2011, Hong Kong Poison Information Centre managed 188 and 96 cases of acute and chronic ketamine poisoning, respectively, which reflect its acute and chronic toxicity pattern (Yiu-Cheung, 2012). Demographically, there is a male predominance, and the majority is between the ages of 10–39. For the acute cases, 48 % presented with neurological features such as confusion, drowsiness, or transient losses of consciousness that usually subside with supportive care in a few hours. For the chronic cases, 92 % of them presented with features of ketamine cystitis while about 66 % presented with chronic abdominal pain. For the 96 chronic cases, their mean and median duration of ketamine abuse is 8.6 years (SD, 4.1 years) and 4 years, respectively. Majority (88.92 %) of them presented with features of ketamine cystitis such as dysuria, urgency, and frequency while 63 (66 %), 40 (42 %), and 15 (16 %)

of them presented with chronic abdominal pain, nasal problems (including three cases of septal perforation) and psychiatric features, respectively. As early as 2004, in a local annual meeting of Taiwan Urology, Tsai et al. reported a case report of interstitial cystitis which mimicked a bladder tumor due to ketamine use (Tsai, 2004). Chiew et al. also had a case report of ketamine related ulcerative cystitis in 2009 (Chiew and Yang, 2009). Chen et al reported of 4 cases of ketamine-related cystitis in 2011 (Chen et al., 2012). Bladder ulceration with severe diffuse hemorrhage and low bladder capacity were noted under anesthetized cystoscopic examination. Transurethral bladder mucosa biopsy was consistent with chronic cystitis. With the recent growing awareness of the severity and prevalence of ketamine cystitis, there is some research in Taiwan focused on pathophysiology and management. Meng E et al. used an animal model to explore the etiology of ketamine-related cystitis (Meng et al., 2011). They reported that at 8 weeks mice treated with ketamine showed increased voiding frequency and decreased bladder capacity, the same symptoms that develop in human ketamine abusers. Enhanced noncholinergic contractions and P2X1 receptor expression in the ketamine bladder indicate that dysregulation of purinergic neurotransmission may underlie detrusor overactivity in cases of ketamine induced bladder dysfunction. Chung SM et al. examined a ketamine treated rats and proposed that ketamine treatment affected bladder tissues by enhancing interstitial fibrosis and accelerating macrophages infiltration. Ketamine also initiated the up-regulations of COX-2 and iNOS and eNOS expressions (Chuang et al., 2013). These up-regulated enzymes might play an important role in contributing to ketamine-induced alterations in micturition patterns and ulcerative cystitis (Chen et al., 2011). In 2013, Lee et al. further investigate the suburothelial inflammation and urothelial dysfunction that occurs among ketamine-related cystitis, interstitial cystitis and bladder pain syndrome, respectively. It showed the three groups had bladder tissues showing defective junction protein, increased suburothelial inflammation and increased urothelial cell apoptosis. Decreased expression of E-cadherin and increased apoptosis were more severe in ketamine-related cystitis bladder and these findings were associated with the clinical symptoms of all three groups (Lee et al., 2013).

Considering about the irreversibility of ketamine-related bladder injury, Chung et al. performed augmentation enterocystoplasty for severe bladder pain associated with chronic ketamine cystitis on 14 patients (Chung et al., 2013). Every patient had been treated conservatively with medication or cystoscopic hydro-distention for at least 1 year before they had received surgical intervention. After receiving augmentation enterocustoplasty for 3-6 months, all patients reported marked improvement in Patient Perception of Bladder Condition scale from 6.0 to 1.4 ± 0.89 ($P < 0.0001$). All hydronephrosis disappeared and vesicoureteral reflux was resolved in five patients after enterocustoplasty with ureteral reimplantation. This pilot study demonstrated that augmentation enterocustoplasty is effective in relieving refractory ketamine-related bladder pain and lower urinary tract symptoms. Ketamine abusers, especially adolescents, are usually concerned more about genitourinary tract symptoms than CNS effects or problems of addiction. To motivate them to have abstinence, comprehensive assessment including cognitive and urinary dynamic examination might be helpful to make ketamine abusers aware of the complications. Also, physicians have to increase the awareness of the physical complications of ketamine and could provide appropriate management and suggestions about it.

Ketamine effect of central nervous system (CNS)

Besides its high abusing potential with obvious psychological craving, the short-term and long-term ketamine effects were not understood well. There are some research reports of the central nervous system effect of ketamine from animal studies. Chronic ketamine treatment causes damage on the CNS including neuronal loss, synaptic changes, formation of untreated tau protein in neurons, GABA receptors and dopaminergic neurons change (Tan et al., 2012; Tan et al., 2011), and induced changes of apoptotic markers in the prefrontal cortex (Sun et al., 2011; Yeung et al., 2010; Yu et al., 2012). Functional MRI studies showed hyperactivity on entorhinal cortex, striatum regions, but hypo activity in the midbrain and visual cortex (Yu et al., 2012). Research also reported a phenotype of chronic ketamine treatment as schizophrenia-like behavior, pain alternations (Becker et al., 2006; Becker et al., 2003), and abnormal behavior in movement, walking, jumping and climbing (Sun et al., 2011).

However, it's not easy to evaluate the long-term CNS effects of ketamine abuse in humans. With recent advanced imaging analysis techniques, we may have more opportunities to see the structural and functional changes in the brain under the effects of ketamine. A recent paper described for the first time via employing magnetic resonance imaging (MRI) the changes in ketamine addicts of 0.5–12 years and illustrated the possible brain regions susceptible to ketamine abuse (Wang et al., 2013). Twenty-one ketamine addicts were recruited and the results showed that the lesions in the brains of ketamine addicts were located in many regions that appeared 2–4 years after ketamine addiction. Cortical atrophy was usually evident in the frontal, parietal or occipital cortices of addicts. Such a study confirmed that many brain regions in the human were susceptible to chronic ketamine injury and presented a diffuse effect of ketamine on the brain that might differ from other central nervous system drugs, such as cocaine, heroin, and methamphetamine (Szu-Hsien, 2009; UNODC, 2010; Wang et al., 2013). A recent MRI study using voxel-based morphology showed structural deficits in the frontal cortex for ketamine-dependent patients compared to normal control subjects (Liao et al., 2011). Their results revealed significant decreases in gray matter volume in the bilateral frontal cortex of ketamine users. Besides brain structural changes, chronic ketamine use leads to neurocognitive impairments, including deficits in working memory, structures, and executive functions (De La Torre, 2010; Morgan et al., 2004; Morgan et al., 2009, 2010). Further brain functional assessment by other MRI modalities and neuropsychological testing could be carried out to obtain further information about ketamine effects. It should be noted that since many people using ketamine are poly-drug users, the drug-drug interaction between illegal substances may also be worth further study to know how the combined effects of drugs influence brain and human behavior.

Ketamine uses and co-morbid psychiatric disease

Besides causing physical complications, ketamine binds to a variety of receptors, principally acts at the NMDA receptors in human brains. There is convergent genetic and molecular evidence point to NMDA receptors hypofunction in psychotic disorders. In recent years, there has been a great advance in pathophysiology research of schizophrenia showing that the glutaminergic system might play an important role. In a subtle review of a ketamine model of schizophrenia by Frohlich J et al. recently, it proposed that the glutamate hypothesis can explain negative and cognitive symptoms of schizophrenia better than the dopamine hypothesis, and has the potential to explain dopamine dysfunction itself

(Frohlich and Van Horn, 2013). Furthermore, NMDA receptor hypofunction can explain connectional and oscillatory abnormalities in schizophrenia in terms of both weakened excitation of inhibitory γ-aminobutyricacidergic interneurons that synchronize cortical networks and disinhibition of principal cells. Individuals with prenatal NMDA receptor aberrations might experience the onset of schizophrenia towards the completion of synaptic pruning in adolescence, when network connectivity drops below a critical value. In that review, they conclude that a ketamine challenge is useful for studying the positive, negative, and cognitive symptoms, dopaminergic and GABAergic dysfunction, age of onset, functional disconnectivity, and abnormal cortical oscillations observed in acute schizophrenia. Since the prevalence of ketamine abuse is increasing, it supposed that incidence of ketamine-induced psychosis would be observed more frequently. However, we have currently no available information about ketamine-induced psychosis. It might be under-reported for several reasons. One is the patient wouldn't visit the hospital while using ketamine with associated complications due to the illegality; the other is that ketamine could only be detected in urine for 2-4 days after using. In some countries, for example in Taiwan, the diagnosis is not covered by national health insurance. Conversely, ketamine is recently found to have rapid antidepressant effects. There are emerging studies which confirm the promising effects of ketamine in the treatment of depression. The ketamine studies stimulated a new generation of basic antidepressant research that identified new neural signaling mechanisms in antidepressant response and provided a conceptual framework linking a group of novel antidepressant mechanisms (Krystal et al., 2013). There are also reviews of ketamine and antidepressant effect recently. The widely replicated observation that a single subanesthetic dose of the N-methyl-D-aspartate glutamate receptor antagonist ketamine produced meaningful clinical improvement within hours, suggested that rapid-acting antidepressants might be possible. It's reasonable to some to hypothesize that the prevalent ketamine use among adolescents might be due to self-medicated depression. However, there is limited evidence of the association between ketamine use and depression. As previously mentioned, studies of ketamine abusers showed to have more depressed mood. Depression and substance abuse might be a reciprocal causation to each other. It points out that the evaluation of depression is quite important in treating and preventing ketamine abuse.

Although ketamine was originally believed to have a low potential for dependence, 78.9% of Hong Kong ketamine abusers, developed into dependence after regular use for 1 year (Chen R, 2004). In addition, upon cessation of ketamine use, 53.5% of these abusers reported withdrawal symptoms including fatigue, excessive yawning, and aggressive or hostile behavior, feeling angry, irritable, or depressed (Li et al., 2011). In clinical experience, besides physical withdrawal symptoms, patients reported a strong psychological craving after discontinuing ketamine use.

Considering the increase of ketamine abusers, especially among adolescents and early adults, a more detailed assessment about the psychiatric co-morbidity and complications of ketamine are needed. Ketamine abuse patients with evidence of psychosis should be treated carefully to prevent psychotic symptom-related consequences. Besides, all patients with ketamine abuse should be comprehensively evaluated for depressive symptoms. It is certain that patients with depressive disorders with adequate antidepressant treatment could stop the vicious cycle of patients' self-medication by ketamine for depression.

Management of ketamine use disorder

To make a more individual and effective

treatment program for ketamine abuse/dependence, it is important to manage both the physical and psychiatric symptoms. Managing patients with substance abuse is always challenging, especially among adolescents. Adolescents usually have lower self-awareness, under-estimating the consequence of risky behaviors and less self-control abilities. It needs a comprehensive bio-psycho-social evaluation and management with a multidisciplinary approach. A continuum of care that includes a customized treatment regimen- addressing all aspects of an individual's life, including medical and mental health services and follow-up options (e.g. community- or family-based recovery support systems) can be crucial to a person's success in achieving and maintaining a drug-free life style.

Currently there is not a specific medication for treating ketamine abuse. From a pharmacological perspective, ketamine is a NMDA receptor antagonist and has been shown to increase glutaminergic neurotransmitters. Glutamate is an excitatory neurotransmitter and is considered to cause the psychomimic effect of ketamine. Therefore, pharmacological agents that decrease glutamate release may be useful to reduce the ketamine-induced effect. There are researches showing that lamotrigine might decrease the acute effect of ketamine. Lamotrigine is an anticonvulsant that stabilizes neuronal membranes and attenuates cortical glutamate release via inhibition of sodium channels (APAIC, 2009; Marshall, 1999). Studies showed that lamotrigine significantly decreased ketamine-induced perceptual abnormalities, positive and negative and cognitive symptoms under ketamine infusion (Anand et al., 2000). Lamotrigine pre-treatment prevented many of the BOLD signal changes (Deakin et al., 2008). But there is still a lack of studies regarding the lamotrigine effect on chronic ketamine abusers. It is still uncertain if it could have the same effect on chronic ketamine abusers. It is also questionable that lamotrigine could reduce the craving of ketamine or prevent ketamine use behaviors. Further research is needed to explore the possible pharmacological treatment for ketamine abuse.

Discussion

Seeing the need, some facilities are available for managing ketamine use disorders, including outpatient service, inpatient acute care, and therapeutic communities for prolonged care. For example, there are mainly two kinds of therapeutic communities in Taiwan now: one is religious-based, the other is government supported and hospital-based. Therapeutic communities proposed of comprehensive treatment programs without standard medications. It provides a relative isolated environment and makes patients learn how to live life without drug use. There are many kinds of individual and group therapy programs inside the therapeutic communities. Patients could improve their stress coping skills, interpersonal interaction and relapse risk reduction through group life there. In the past, those members who lived in therapeutic communities were mainly adult patients with heroin dependence. However, in the past one to two years, ketamine abuse adolescents became the main members in the therapeutic communities. It's more complicated to manage the group therapy with adolescents of drug abuse. Multidisciplinary management is needed, but, there appears to be a shortage of professional staff in this field. Although there are some facilities, further work is needed to assess the effectiveness of these treatment programs.

Future scope

Although we have a rising problem of ketamine abuse, especially among adolescents and young adults, we still lack a comprehensive understanding of it. From the risk factors of abuse, the short term and long term effect of ketamine use and the appropriate and practical program of management, further study and exploration are needed.

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