Editorial

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Ketamine Addiction

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Editorial

Ketamine was developed in 1962 as an anaesthetic agent [1] for use in pediatrics, oncology, and veterinary practice [2]. Ketamine primarily and non-competitively antagonizes NMDA (N-methyl-D-aspartate) receptors, thereby interfering with the excitatory amino acid transmission, which underlines its analgesic and dissociative effects [2]. Ketamine also has weak effects on opioid, muscarinic and monoamine receptors [1], enhances the neurotransmission of noradrenaline, serotonin and dopamine in a dose-dependent fashion, which, together with its effects on glutaminergic system, accounts for its psychotomimetic and sympathomimetic effects [2] and addiction potential [3].

During the past decade, ketamine has been proven efficacious in treatment-resistant depression [4]. Due to its unique neurochemical profile, ketamine, and its analogue phencyclidine, has also been tried as a new treatments for psychosis [5] and addiction [6,7]. In contrast to increasing research efforts to understand ketamine's potential as a therapeutic agent, only a few studies focused on understanding ketamine addiction.

Ketamine misuse started in the United States in the 1970s, soon after its development and wider availability [2]. Ketamine is still a commonly abused drug around the world [8], particularly in East Asia [9]. Ketamine is the second and third most commonly abused drug in Hong Kong [10] and in mainland China and Taiwan [9], respectively. Ketamine is predominantly consumed by young people [10,11], gay clubbers [12,13] and poly-substance users [8].

Heavy ketamine users suffer from both physical and mental problems. Serious lower urinary tracts symptoms (increased urinary frequency, urgency, incontinence, hematuria, and dysuria) [14-16], gastritis and liver and kidney dysfunction [16,17] are also common in this population. Psychiatric disorders are often comorbid by ketamine include depression, which is remarkably prevalent among chronic ketamine users [18,19], psychosis [18] and cognitive impairment [20-22]. Although there are no typical withdrawal symptoms, craving, anxiety and dysphoria are the main reasons for continuous ketamine use despite of its adverse consequences [23,24].

How ketamine affects human brain is not yet clear. A few neuroimaging studies revealed structural and/or functional abnormalities in the frontal regions in chronic users. For example, compared to controls ketamine users had less bilateral prefrontal grey matter [25], lower white matter integrity and more axon damage in the prefrontal regions [26,27], altered regional synchrony of metabolism in the precentral frontal gyrus and anterior cingulate cortex (ACC) [28] and altered resting state functional connectivity (RSFC) between thalamic nucleus and several cortical regions including the prefrontal area [29]. However, it is still not clear if chronic ketamine intake is the cause or consequence of these brain alterations due to the cross-sectional design of these studies [28].

Further, white matter microstructural abnormalities were found predominantly in left prefrontal region in ketamine chronic users when [27], restricted to the right hemisphere white matter regions when compared with poly-drug users [26]. While a significant correlation between the subgenual ACC-dorsal medial prefrontal cortex connectivity and depression score was found in female ketamine users but not in female controls, it is hard to draw a conclusion whether it was ketamine use or depression that accounted for the discrepancy between ketamine users and controls [30].

To date, there has been no established treatment for ketamine addiction. Abstinence seems to be the essential step for treating physical symptoms induced by ketamine [31] and probably depressive symptoms as well as cognitive impairments [20]. Lamotrigine, a glutamate release inhibitor showed promising effect in reducing ketamine craving in a case report [32].

Taken together, ketamine addiction remains a major challenge in mental health. The mechanism of ketamine addiction is still unclear. For example, although ketamine increases dopamine release in the brain reward system, this effect is weaker compared to stimulants such as amphetamine, but the role of dopamine in the pathomechanism of ketamine addiction has not yet been investigated [33]. While craving [24] and depression

[20] are most common problems in chronic users, the link between them and ketamine addiction is largely unknown. On the other hand, studying ketamine addiction might also help to elucidate many pending questions about other psychiatric disorders [34]. Intensive investigations about ketamine addiction are certainly warranted.

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