

# **Change in cognitive function and biomarkers of neurotoxicity following abstinence of ketamine: A prospective longitudinal study**

## *Executive summary*

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The objectives of the study were to 1) ascertain the pattern of change in cognitive function following abstinence from ketamine; 2) examine the pattern of change in the blood levels of neurotoxicity biomarkers following abstinence from ketamine; and 3) evaluate the correlations between the changes in cognitive function and levels of biomarkers.

Four hundred participants were recruited at baseline from June 2012 to December 2017 in Hong Kong. The participants were divided into three groups: primary ketamine users, poly ketamine users and healthy controls. Psychiatric assessments included self-rated questionnaires and face-to-face interviews. All participants completed a detailed cognitive battery that assessed working memory, verbal and visual memory and executive functions. Blood samples were also taken for biomarker analysis. After 12 weeks, all ketamine users were re-assessed with the same tests. The final sample consisted of 95 healthy controls and 165 ketamine users (82 primary ketamine users and 83 poly ketamine users).

The primary ketamine users often co-abused other drugs, such as cocaine and cannabis. The primary and poly ketamine users reported more severe depressive symptom than healthy controls at both baseline and follow up. More psychiatric diagnoses were found in both primary and poly ketamine users than in healthy controls at baseline.

Following 12 weeks of abstinence, ketamine users' cognitive functioning improved, especially their verbal and visual memory, with performances comparable to those of the normal controls. At follow up, all ketamine users scored higher on the WMS III Logical Memory (immediate recall, delayed recall, recognition and percent retention), ROCF (copy, immediate recall, delayed recall, recognition), WCST (total attempts,

categories completed, perseverative errors) and Stroop Test (total reaction time). The most prominent improvements were on the WMS III Logical Memory (delayed recall), ROCF (immediate and delayed recall) and WCST (perseverative errors), with 25.4%, 24.6%, 21.6% and 24.8% changes in scores, respectively.

Primary ketamine users scored higher at follow up on the WAIS III Digit Span (forward), WMS III Logical Memory (immediate recall, delayed recall, recognition and percent retention), ROCF (copy, immediate recall, delayed recall and recognition), WCST (total attempts, categories completed and perseverative errors) and Stroop Test (total reaction time). The most prominent improvements were on the WMS III Logical Memory (immediate and delayed recall), ROCF (immediate and delayed recall) and WCST (perseverative errors), with 26.4%, 39.3%, 27.2%, 22.7% and 21.8% changes in scores, respectively.

Poly ketamine users scored higher at follow up on the WAIS III Digit Span total, WMS III Logical Memory (delayed recall, recognition, percent retention and possibly immediate recall), ROCF (immediate recall, delayed recall and possibly recognition), WCST (total attempts, categories completed and perseverative errors), Stroop Test (total reaction time) and GO/NOGO Test (commission errors). The most prominent improvements were on the ROCF (immediate and delayed recall), WCST (perseverative errors) and GO/NOGO Test (commission errors) with 22.0%, 20.5%, 27.9% and 25.4% changes in scores, respectively.

There were no significant differences in ketamine users' serum BDNF and NGF levels between baseline and follow up, and the difference in GDNF levels was of borderline significance ( $p = 0.06$ ). Serum BDNF, NGF and GDNF levels did not differ significantly between ketamine users and healthy controls at either baseline or follow up.

In the group of all ketamine users at baseline, a significant partial correlation was found between serum BDNF levels and number of categories completed on the WCST ( $r = -0.167$ ,  $p = 0.039$ ). At follow up, significant partial correlations were found between serum BDNF levels and WCST total attempts ( $r = 0.173$ ,  $p = 0.032$ ) and categories completed ( $r = -0.226$ ,  $p = 0.005$ ). A significant partial correlation was also found between serum NGF level and reaction time on the GO/NOGO Test ( $r = -0.349$ ,  $p = 0.010$ ).

In the primary ketamine users at follow up, significant partial correlations were found between serum BDNF levels and WCST total attempts ( $r = 0.247$ ,  $p = 0.033$ ) and categories completed ( $r = -0.324$ ,  $p = 0.005$ ). In the poly ketamine users, a significant partial correlation was found between serum BDNF levels and the Digit Span (backward) test ( $r = -0.241$ ,  $p = 0.039$ ).