The Effect of Chronic Alprazolam Intake on Memory, Attention and Psychomotor Performance in Healthy Human Volunteers of Bangladesh

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Overall, the authors aim to test the effect of long-term administration of clinical dose of alprazolam on memory, attention and psychomotor performance. They divided 26 healthy volunteers into two groups: one group taking alprazolam 0.5 mg (Group A) and the other taking placebo (Group B) daily for two weeks. They selected Delayed Matching to Sample (DMS) and Paired Associates Learning (PAL) tests for visual memory; Rapid visual information processing (RVP) for attention and Choice Reaction Time (CRT) for psychomotor performance from Cambridge Neuropsychological Test Automated Battery (CANTAB) software before and after treatment in either groups. They found statistically significant impairment of visual memory in three parameters of DMS and one parameter of PAL in group A. Total correct matching was affected by alprazolam intake in 0 second delay, 4 seconds delay, and in all delay situations. The PAL mean trial to success was also affected in group A. The attentive performance, although decreased initially was improved significantly in RVP total hits after two weeks of alprazolam treatment in RVP test. The authors concluded that tolerance against memory impairment does not develop within two weeks of alprazolam administration although the effect on attention and psychomotor performance seemed to recover partially.

Comment: I commend the authors for choosing this topic as benzodiazepines are often misused and abused by patients with mood disorders and remitted substance users. They also impair both cognitive abilities and global functioning and their use should therefore be better monitored or minimized. I therefore think that this paper deserves to be published but a stronger rationale and additional background information need to be provided. Further, the conclusions need to be restructured to include a more critical explanation of the findings by referring to chemical/physiological changes induced by benzodiazepine use, what future research needs to achieve in this field, clinical relevance of the findings and identification of limitations and weaknesses of the study.

-Abstract: I would highly recommend that the authors mention means/SDs for the age of the participants for each group. p-values are usually not mentioned in the abstract.

-I would provide additional background information on the effects of Alprazolam (or benzodiazepine in general) on the brain in terms of sedation, cognitive function and mood

-since benzodiazepines are often administrated in case of panic disorder, generalized anxiety disorder (GAD) or social anxiety disorder (SAD) and alongside mood-stabilizing drugs in MDD/BDD I would briefly mention this too.

-I would also recommend that the authors provide additional information on the pharmacokinetic and pharmacodynamics profile of alprazolam.

-I would provide 1-2 references at the end of their introduction when they mention CANTAB, selection of the study period and drug dosage. Overall the authors should provide a more thorough explanation of what previous studies did in terms of duration and dosage. 1 sentence at the end of the introduction is not sufficient.

-In the methods section I would highly recommend to mention Table 1 and provide means and SDs for age in each group. Why only men? Inclusion/exclusion criteria should also be mentioned, specifically in terms of medical health status, lifetime of psychiatric disorders, family history of psychiatric disorders, medication etc.

-Cognitive assessment: could the authors mention IQ values, education level or estimated intellectual abilities (e.g. based on the local NART, WRAT etc.), and employment status

-Statistical analyses: could the authors please mention how they corrected for multiple comparisons. (per test and/or experiment-wise approach?). also did the authors assess potential mood symptoms such as depression/hypomania (e.g. MADRS, HAMD, YMRS) in these participants?

-Given their findings did the authors think about calculating an RT to accuracy ratio to see if individuals on alprazolam compensated for reduced alertness by taking additional time to complete the task? Have other studies in individuals using opiates, alcohol etc. shown similar findings? addressing these points will make your conclusions more effective and compelling.

-their findings make me think of what is usually observed in individuals with past history of substance use. This may not be surprising since both substances act on GABA receptors but it is not that clear. Although abstinence is associated with recovery of most cognitive function, authors have observed that even after a few years individuals still show problems with non-verbal abstract reasoning diminished mental flexibility and diminished visual-spatial abilities. Given that all these functions are related to attention I wonder if the authors could comment further in terms of brain regions that may be more susceptible to the potential upregulation of NMDA receptors leading to excessive glutamate activity and excitotoxicity (due to benzodiazepine) which may result in neurodegeneration. Have there been studies showing how quickly brain-related changes may occur? Please comment on this in your discussion.

-one of the primary problems with benzodiazepines is tolerance and dependence. Could the authors comment on potential long-terms effects of benzodiazepine use on cognition? Also since mood state is closely linked to cognitive abilities how would the authors expect to see in populations with anxiety or mood disorders? Findings in this field of psychiatry could also be mentioned in the discussion.