

## Letter to Editor

### L-cysteine and the Treatment of Alcohol Hangover: A Commentary on Eriksson *et al.* (2020)

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#### To the Editor:

Recently, Eriksson *et al.* (2020) assessed the effects of L-cysteine on alcohol hangover. Using randomized, double-blind, placebo-controlled methodology, Eriksson *et al.* (2020) examined the effects of two dosages of L-cysteine (600 mg and 1200 mg) on alcohol hangover symptom severity. As discussed by the authors, correlational analysis revealed positive effects of L-cysteine administration on the prevention or alleviation of hangover symptoms. Following the 1200 mg dosage, improvements were reported for self-rated hangover, nausea and headache severity, while the 600 mg dosage alleviated stress and anxiety. While the study is important, there are several important issues and major limitations that were not in this publication.

Firstly, the use of correlational analysis does not directly assess the effectiveness of L-cysteine in treating or preventing alcohol hangover symptoms. While correlational analyses assess the linear relationship between L-cysteine and hangover symptoms, assessment of treatment efficacy requires statistical comparisons of hangover (symptom) severity between treatment and placebo. These essential comparisons were performed by the authors, although they are only reported in small print in the figure legends and not discussed elsewhere in the paper.

Secondly, no power analysis was presented. Instead, the authors justify their sample size with claim that ‘... it is known that L-cysteine binds to acetaldehyde and consequently diminishes alcohol-related hangover symptoms: nausea, headache, stress and anxiety.’ This claim was also used to justify the incorrect use of one-tailed hypotheses testing and is somewhat at odds with the statement that ‘... our study is the first to prove the prevention and the alleviation of alcohol-related hangover symptoms: nausea, headache, stress and anxiety with L-cysteine ...’.

In general, it is unknown whether a new treatment will improve hangover severity. In theory, the treatment may also be ineffective, or aggravate hangover severity. The two-tailed hypothesis test appropriately reasserts the possibility that the investigator’s beliefs about the efficacy of an intervention might be wrong. Therefore, by convention,

statistical analysis comparing hangover severity after treatment and placebo should be two-sided in randomized clinical trials. Eriksson *et al.*, however, supported by their belief that the effects of L-cysteine could only be in a positive direction, used one-tailed tests to analyze their data.

As reported by the authors, paired samples t-test analysis of seven male participants revealed a significant reduction in stress ( $P = 0.039$ ) following the 600 mg dosage. There were no other significant effects of the 600 mg dosage. According to related-samples Wilcoxon sign rank tests, the 1200 mg dosage resulted in significant improvements in nausea ( $P = 0.013$ ) headache ( $P = 0.010$ ) and hangover severity ( $P = 0.043$ ), while improvements in anxiety approached statistical significance ( $P = 0.052$ ).

However, using two-sided tests, the 600 mg dosage no longer significantly improves stress ( $P = 0.078$ ) and the 1200 mg dose no longer significantly improves hangover severity ( $P = 0.086$ ). The significant effects of the 1200 mg dosage on nausea ( $P = 0.026$ ) and headache ( $P = 0.020$ ) remain. After applying a Bonferroni’s correction for multiple comparisons of individual symptoms with  $P < 0.010$  as cut off for statistical significance (five comparisons; i.e. treatment vs placebo for hangover, nausea, stress, headache, and anxiety), no significant differences concerning L-cysteine and hangover symptom severity remain.

Contrary to the title and authors conclusions, L-cysteine had no significant effect on alcohol hangover severity. These results are consistent with the findings of a recent study (Scholey *et al.*, 2020) which failed to find any significant differences between L-cysteine (650 mg) and placebo on hangover severity. Taken together, there is currently no evidence to suggest that, at the dosages investigated, L-cysteine reduces hangover severity.

There are, however, conceptual reasons to believe that L-cysteine may contribute to the reduction or prevention of hangover symptoms. L-cysteine has antioxidant properties, and as such may counteract oxidative stress. The current thinking regarding the pathology of the alcohol hangover suggests that oxidative stress and the related inflammatory response to alcohol consumption are primary causes

of alcohol hangover (Van de Loo *et al.* 2020). This hypothesis is supported by evidence demonstrating that biomarkers of oxidative stress (e.g. elevations of malondialdehyde and 8-isoprostrane), as well as elevated inflammatory cytokines significantly correlate with hangover severity (Van de Loo *et al.* 2020). It is notable that, in addition to L-cysteine, the active treatment (but not placebo) contained B vitamin complex (which has known anti-inflammatory properties) and Vitamin C (an antioxidant) at levels at or exceeding recommended daily intakes. Therefore, even if a convincing treatment effect existed, it could not definitively be attributed to L-cysteine.

As such, future research should continue to evaluate whether L-cysteine is effective in reducing or preventing alcohol hangover. Such studies should use placebo-controlled, randomized, counterbalanced and within subject designs to directly compare alcohol hangover

severity following placebo and L-cysteine, using two-tailed statistical tests.

## REFERENCES

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