

Novel experimental clinical design exploring brain processes in patients with alcohol dependence under the influence of alcohol.

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The Methodological Question Being Addressed:

To investigate BOLD changes in brain regions of interest to the reward system in subjects with alcohol dependence when under the influence of alcohol with or without preceding nalmefene administration.

Introduction:

The aim of the fMRI study was to investigate changes in BOLD in brain regions of interest to alcohol relapse and/or high risk consumption prevention (reward, impulsive and stress) in individuals with alcohol dependence when under the influence of alcohol, using the intravenous ‘alcohol clamp’ technique, with and without preceding administration of nalmefene. Nalmefene is an opiate receptor modulator licensed for the reduction of alcohol intake in subjects with alcohol dependence and a high drinking risk level (>60 g/day for men and >40 g/day for women).

Methods:

22 non-treatment seeking alcohol dependent men (mean age: 46±11years) were recruited to this cross-over, double-blind study through advertisements. Before randomisation it was confirmed that the participant would tolerate the ‘alcohol clamp’ with alcohol infused to achieve the target alcohol level (BrAC) of 0.8‰. On the 1st and 2nd study days a week apart, either 18 mg nalmefene or matched placebo was given in a randomised order in the morning. After ~4 hours, the MR scanning session began (Siemens Tim Trio 3T). Pulsed arterial spin labelling (pASL) pre and during alcohol infusion evaluated the impact of alcohol on blood flow. During the alcohol infusion, participants completed an fMRI protocol to assess reward, impulsivity and stress responsivity in addiction using the MID, go-nogo, and an evocative task (ICCAM; [1, 2]). A whole brain and an a priori striatal region of interest (ROI; 5 mm radius spheres centred at ±14,+12,-4 encompassing parts of nucleus accumbens, putamen, caudate, and globus pallidus) analysis were conducted.

Results:

In the presence of alcohol, nalmefene pretreatment resulted in reduced BOLD response in the striatum during anticipation of reward in non-treatment seeking alcohol dependent individuals. This is consistent with the underlying mechanism of opiate antagonists involving modulation of the dopaminergic mesolimbic pathway. This study has several methodological strengths, such as its within-subject design and maintaining constant alcohol levels with an alcohol infusion. Also Heavy-drinking, alcohol-dependent participants and protocol reflected the clinical circumstances for which nalmefene is indicated.

Conclusions:

This experimental design can be used at an early stage of drug development in addiction since it offers an opportunity to assess functional target engagement and pharmacodynamics properties of an investigational drug [3].

Words: 395(limit 500)

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Disclosures:

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