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 nalmeftine. Nalmefene is an opiate receptor modulator licensed in EU and other countries outside NA 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).

Design:
First study day confirmed the participant tolerated the ‘alcohol clamp’ target breath alcohol level (BrAC) of 0.8% within 20 minutes maintained for 30 minutes. On the 2nd and 3rd study days a week apart, either 18 mg nalmefene or a matched placebo was given in a randomised order. After ~4 hours, the MR scanning session began (Siemens Tim Trio 3T) (see Figure 1) together with the initiation of alcohol infusion and its maintenance at 80 mg/dL BrAC during scan sessions (see figure 3). Pulses arterial spin labelling (pASL) pre and during alcohol infusion (BrAC: 0.8%) was undertaken to evaluate the impact of alcohol on blood flow. During the alcohol infusion, participants completed our fMRI protocol to assess reward, impulsivity and stress responsiveness in addiction using the MID, go-nogo and an evocative tasks (ICCAM; 2.3). We report here only the primary outcome measures: pASL and MID (contrast: “reward anticipation > neutral anticipation”). 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) were conducted.

Outcome measures and statistical analysis
Statistical maps for each subject and treatment were derived from the raw images and task response data following fMRI imaging, such that the signal change due to contrasts of interest could be determined. For each imaging session, the 2 runs of each task were combined for each subject by taking the mean of their whole brain statistical results. The processed data included 1 contrast with placebo and 1 contrast with nalmeftine for each subject and task.

The change in BOLD signal within each bilateral region of interest (ROI) for each contrast task, drug condition and order. After ~4 hours, the MR scanning session began (Siemens Tim Trio 3T) (see Figure 1) together with the initiation of alcohol infusion and its maintenance at 80 mg/dL BrAC during scan sessions (see figure 3). Pulses arterial spin labelling (pASL) pre and during alcohol infusion (BrAC: 0.8%) was undertaken to evaluate the impact of alcohol on blood flow. During the alcohol infusion, participants completed our fMRI protocol to assess reward, impulsivity and stress responsiveness in addiction using the MID, go-nogo and an evocative tasks (ICCAM; 2.3). We report here only the primary outcome measures: pASL and MID (contrast: “reward anticipation > neutral anticipation”). 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) were conducted.

Baseline physical, psychiatric, and neurological examination using SADIQ (mean 20, SD 7.4)and DrInC (Total DrInC Score: 73, SD 20.1) confirmed the subjects’ eligibility to participate in the study. 9 subjects were current nicotine users. Complete data were available for 18 men (44 ± 11 yrs; exclusions: 1 did not tolerate MR; 2 excess motion, 1 poor task performance). The alcohol infusion resulted in an increase in blood perfusion (eg thalamus: ~15 ml/100g/min) however no difference in perfusion was observed between nalmeftine and placebo on alcohol.

A significant decrease in the contrast “reward anticipation > neutral anticipation” on nalmeftine compared with placebo in the striatal ROI: t = 2.78, p = 0.013, d.f. = 17. Analysis confirmed that this was due to a decrease in BOLD response during reward, not an increase during neutral anticipation.

Further, whole brain analyses observed three clusters (Z > 2.3, p < 0.05 corrected for multiple comparisons), encompassing the dorsal striatum bilaterally and parts of brain stem. Response time was slower (~6%, t = 2.61, p = 0.018, d.f. = 17) and less money won (~11%, t = 2.16, p = 0.045, d.f. = 17) on nalmeftine, compared with placebo. Motion did not differ between sessions.

In the presence of alcohol, nalmeftine 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 nalmeftine is indicated.