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Response

Reply to: Does acamprosate really produce its anti-relapse effects via calcium? No support from the PREDICT study in human alcoholics

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We have recently published surprising findings on the mode of action of acamprosate (Campral—calcium-bis (*N*-acetylhomotaurinate), which is clinically used for relapse prevention in alcohol-dependent patients. In this publication we concluded that *N*-acetylhomotaurinate is a biologically inactive molecule and that the effects of systemic applied acamprosate may be attributed to calcium (Spanagel *et al*, 2014). For this conclusion, we invested several years of work and provided convergent evidence from three different animal models and two different laboratories, with all animal experiments done in a blinded manner. In the same publication we also included an explorative human study where we provided additional evidence that calcium is the active component of acamprosate.

Mann *et al* (2015) now challenge the human data provided by us and show in their PREDICT sample that plasma calcium levels are not correlated with treatment outcome. Here we argue that the PREDICT sample cannot be used to prove or disprove our conclusions. First, the PREDICT study failed to show any treatment effect of acamprosate in comparison to placebo treatment (Mann et al, 2013). The logic is as follows: if calcium is the active moiety of acamprosate, and acamprosate does not produce a positive treatment effect in a randomized controlled trial, how then should calcium be associated with treatment outcome? Second, the now presented re-evaluation of the PREDICT data based on 76 acamprosate- and 25 placebo-treated patients with available plasma calcium levels was underpowered to detect any treatment effect (Rösner *et al*, 2010).

Mann and colleagues bring up also two other points of criticism: they state 'While Spanagel *et al* (2014) used systemic application *others* have shown that the effects of intracerebral microinjection of sodium acamprosate are site-specific (only effective in the bed nucleus of the stria terminalis) and dose dependent… These data provide evidence that sodium acamprosate is an active molecule affecting ethanol self-administration.' *Others* relate to a single experiment published as an abstract 12 years ago, in comparison to > 100 original investigations in rats that used systemic injections. However, the critical point here is that we never claimed that *N*-acetylhomotaurinate given intracerebrally is devoid of effect. But as long as we do not inject acamprosate into the bed nucleus of the stria terminalis of alcohol-dependent patients, all of our statements about the inefficiency of systemic *N*-acetylhomotaurinate application are still correct.

Mann *et al* also raised doubts as to whether our animal models can produce meaningful results. However, they should take into account that the efficacy of acamprosate on excessive alcohol consumption was discovered first in animal models and then translated to the human situation (Boismare *et al*, 1984).

In conclusion, we provide convincing evidence that *N*-acetylhomotaurinate is a biologically *inactive* molecule and that the effects of systemically given acamprosate can be attributed to calcium. The results provided by Mann *et al* (2015) do not contradict our conclusion. What is in fact needed to prove or disprove our findings is an adequately powered prospective clinical investigation studying the effects of calcium salts in terms of relapse prevention.

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