

Response to ‘Nalmefene in alcohol-dependent patients with a high drinking risk: A limited efficacy in reducing alcohol consumption’

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Palpacuer and colleagues pointed out that Nalmefene for reducing alcohol consumption in alcohol-dependent patients was authorized in Europe based only on subgroup analyses of ESENSE 1, 2 and SENSE studies.¹ We agree with this concern and are glad that we were able to demonstrate the efficacy of Nalmefene in reducing alcohol consumption in alcohol-dependent patients with a high or very high drinking risk level (DRL) *via* a prospective randomized controlled trial. As such, this is the first study to validate the efficacy of Nalmefene without the use of a post-hoc analysis.

On the other hand, we can understand some of the concerns that Palpacuer and colleagues raised in their letter.

First, we fully understand the issue of attrition bias² and had mentioned this as a limitation in our paper.³ We also performed two kinds of imputation analyses and it was shown that heavy drinking day (HDD) and total alcohol consumption (TAC), the main analyses, were robust with sensitivity analysis complementing missing data.³

The other point raised was the study period of 12 and 24 weeks. It should be noted that 12 or 24 weeks have generally been adopted as the evaluation period for alcohol dependence treatments in clinical trials^{4–6}; however, we agree that 6 months is too short to evaluate efficacy for harm reduction.

In terms of the point on harm reduction, we value outcome measures including mortality or quality of life, and consider accident, injuries, and somatic alcohol-related complications as crucial endpoints, which should be included in “harm reduction” with reducing alcohol intake.⁷

Quality of Life was evaluated in our study, and a significant difference was found between placebo and Nalmefene groups at 12 weeks for the Alcohol Quality of Life Scale (AQOLs) evaluation.³ However, as Palpacuer and colleagues pointed out, no significant differences were found between placebo and Nalmefene groups at 24 weeks for AQOLs, SF-36 and EQ-5D evaluations.³ As neither the number of patients nor the study plan had been designed for QOL evaluation in this study, another clinical study to evaluate crucial endpoints with appropriately designed population and study period is warranted.

Palpacuer and colleagues also mentioned that the clinical significance of a statistically significant difference on a surrogate outcome should be critically appraised. As discussed earlier, the goal for harm reduction should include many aspects, although we consider HDD and TAC as reliable endpoints to evaluate treatments for short-term reduction in alcohol consumption. HDD counts the number of days with heavy drinking and TAC records how much alcohol is consumed by patients. These markers are surrogate for harm reduction, however, both of them directly measure alcohol consumption. Both HDD and TAC are recommended as primary endpoints of treatment for reducing alcohol consumption by the European Medicines Agency (EMA) guideline because “HDD are associated with specific risks such as acute cardiovascular outcomes or accidents”.⁸ It has also been reported that high volumes of drinking per occasion predicted negative social consequences independently of overall drinking volume.⁹ In addition, it was suggested that “Any reduction in WHO risk drinking level during treatment was associated with significantly fewer alcohol-related consequences and improved mental health at the end of treatment and for up to 1 year post-treatment.”¹⁰ These results suggest that HDD is a reliable marker that affects

events of relatively short period. However, as we agree that both measures evaluate short-term efficacy, long-term or real-world based studies need to include other markers to evaluate clinical significance of the treatment as discussed earlier.

We recognize the importance of long-term psychosocial interventions by trained professionals, but in addition to them, it should be beneficial for patients to have multiple treatment choices, especially when they can use some interventions in combination.

Disclosure statement

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Exploring the links between specific depression symptoms and brain structure: A network study

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Various patterns of structural brain abnormalities have been associated with depression, yet sensitive, specific and clinically predictive brain correlates have proven to be difficult to characterize.¹ The currently best available empirical evidence on neuroanatomical differences between patients with major depression (MDD) and healthy controls are two meta-analyses of approximately 10 000 individuals.^{2,3} These reports show widespread alterations in cortical regions and in hippocampal volume, but no associations between depression severity and brain structure. Inconsistencies in the neuroimaging literature may be explained by the fact that depression is highly heterogeneous, featuring over 50 symptoms,⁴ where

symptom constellations may reflect different phenomena with distinct underlying biological causes.¹

Understanding the neural substrates of specific symptoms may provide important information about mechanisms underlying depression vulnerability. A growing body of research under the umbrella term ‘network approach’ has recently received considerable attention⁵; the approach understands and aims to model mental disorders as systems of causally interacting symptoms. So far, network studies have been based on symptoms and environmental factors, ignoring relevant neurobiological factors.⁶ Here, we address this knowledge gap by modeling a joint network of depression-related brain structures and individual depression symptoms, using 21 symptoms and five regional brain measures. The sample is a mixed group of individuals that previously have been treated for one or more major depressive episodes (MDE) and never depressed individuals, with the goal to model a continuum of depression severity.

Depression symptoms were measured using the Beck Depression Inventory (BDI-II). MRI images were obtained from a 3T Philips scanner. Whole-brain volumetric segmentation and cortical surface reconstruction of MRI images was performed with FreeSurfer 5.3 (<https://surfer.nmr.mgh.harvard.edu/>). Five regional brain measures were selected based on the MDD case-control differences showing the largest bilateral effects in the studies from the ENIGMA MDD working group^{2,3}: hippocampal volume and cortical thickness in four regions - medial orbitofrontal cortex (mOFC), fusiform gyrus, insula and cingulate (weighted average of rostral anterior cingulate, caudal anterior cingulate and posterior cingulate). Brain structure measures were averaged across the left and right hemisphere for each participant, and z-residuals of hippocampal volume (controlling for sex and estimated intracranial volume) were calculated for further analyses. A Gaussian graphical model of the 26 variables were

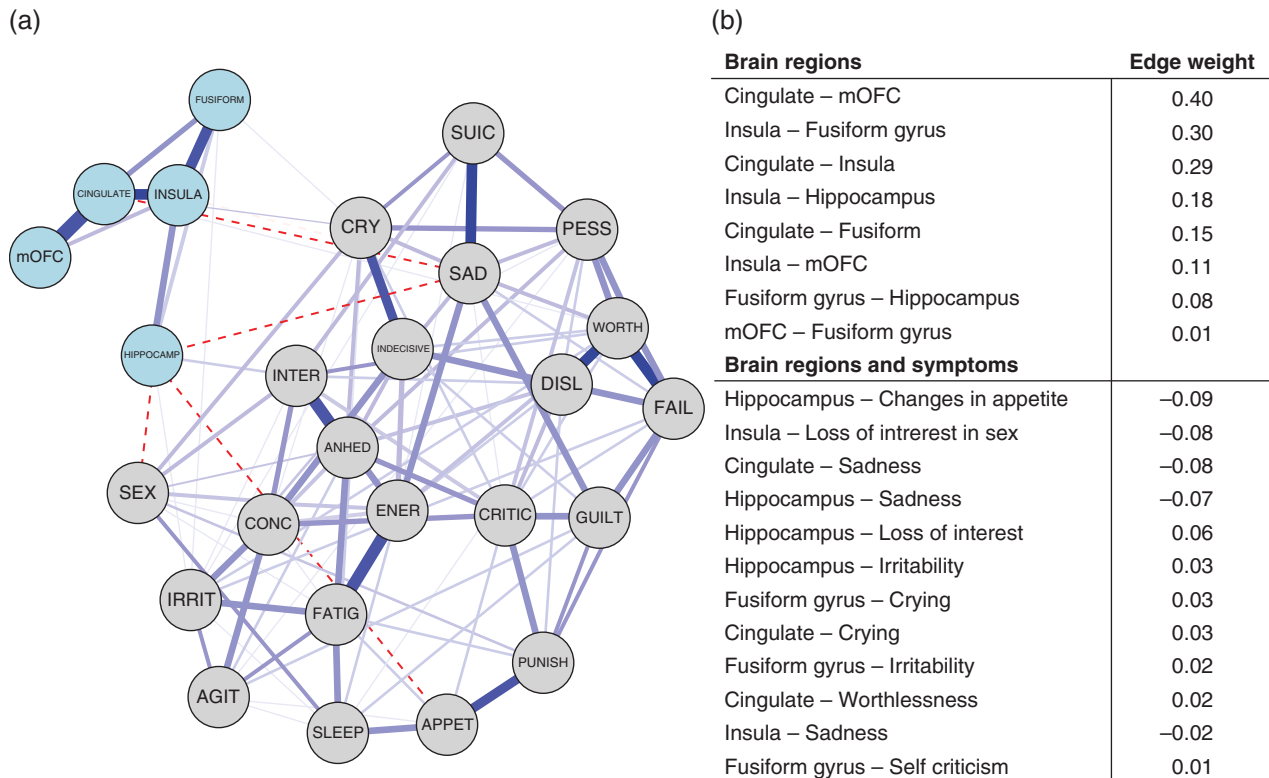


Fig. 1 (a) Depression symptom network including five brain areas. Blue lines represent positive associations, red lines negative associations, and the thickness and brightness of an edge indicate the association strength. AGIT, agitation; ANHED, loss of pleasure; APPET, changes in appetite; CINGULATE, rostral-, medial-, and anterior cingulate cortex; CONC, concentration difficulty; CRITIC, self-criticism; CRY, crying; DISL, self-dislike; ENER, loss of energy; FAIL, past failure; FATIG, tiredness or fatigue; FUSIFORM, fusiform gyrus; GUILT, guilty feelings; HIPPOCAMP, hippocampus; INDECISIVE, indecisiveness; INSULA, insula; INTER, loss of interest; IRRIT, irritability; mOFC, medial orbitofrontal cortex; PESS, pessimism; PUNISH, punishment feelings; SAD, sadness; SEX, loss of interest in sex; SLEEP, changes in sleep pattern; SUIC, suicidal thoughts or wishes; WORTH, worthlessness. (b) Sparse partial correlations between brain structure measures, and between brain structure measures and depressive symptoms in the network model.