## Title

Response to Letter to the Editors regarding 'A Meta-Regression of Trial Features Predicting the Effects of Alcohol Use Disorder Pharmacotherapies on Drinking Outcomes in Randomized Clinical Trials: A Secondary Data Analysis'



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**Response to Letter to the Editors regarding "A Meta-Regression of Trial Features Predicting the Effects of Alcohol Use Disorder Pharmacotherapies on Drinking Outcomes in Randomized Clinical Trials: A Secondary Data Analysis"**

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Short Summary (50 words)

The Letter to the Editors regarding our article was reviewed. The take home message is that substantively, the authors of the letter are referencing a paper that asks a different research question in a different set of studies. When we ask different questions, we are not surprised when we reach different answers.

Dear Editors,

We received and read the letter to the Editors from Drs. Guiraud and van den Brink regarding our article entitled “A Meta-Regression of Trial Features Predicting the Effects of Alcohol Use Disorder Pharmacotherapies on Drinking Outcomes in Randomized Clinical Trials: A Secondary Data Analysis”.

We believe that the comments provided by the authors are derived from differing findings in their recently published paper “Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration”. We would like to highlight that the two manuscripts took different approaches to answer different questions. Our manuscript used a meta-regression approach with two arms (pharmacotherapy treatment vs. control) to answer the question of what trial features predict the efficacy of pharmacotherapies on drinking outcomes across a range of 19 pharmacotherapies. Guiraud and colleagues used a network meta-regression approach focused solely on one pharmacotherapy, sodium oxybate, as a treatment for alcohol use disorder. It is therefore unsurprising that different methodological approaches to solve different questions resulted in different answers.

Regarding our choice of predictors, pre-trial abstinence and pre-trial diagnosis of AUD, we assert that these are critical design features that were previously unexplored in the area of clinical trial design for AUD. Previous work had focused on outcome measures (Falk et al., 2010; Falk et al., 2014), multi-site versus single-site trials (Feinn and Kranzler, 2005), missing data approaches (Hallgren et al., 2016; Witkiewitz et al., 2014), and participant treatment-seeking status (Ray et al., 2017; Rohn et al., 2017). Therefore, we selected pre-trial abstinence, with a duration of least 1 week and pre-trial AUD diagnosis. We used the duration of 1 week as

it was the end range of common pre-trial abstinence duration requirements (3-7 days; reviewed in (Rösner et al., 2010a; Rösner et al., 2010b)). We selected pre-trial AUD diagnosis as it had not previously been investigated and remained an open question for the field. Furthermore, the ability to analyze predictors of trial outcomes hinges on those variables being consistently reported in the original studies. As stated in the original manuscript, pre-trial abstinence and pre-trial diagnosis of AUD were consistently reported in clinical trials, lending themselves to reliable analyses of their predictive value.

Secondly, the authors question of choice to aggregate the 19 interventions together. We assert that this was the underlying goal of the manuscript; in other words, we wanted to investigate what trial features were predictive of outcome in AUD pharmacotherapy trials, and thus aggregated all pharmacotherapies. We also performed a sensitivity analysis with an *a priori* goal of investigating only FDA-approved treatments, which led to the aggregation of acamprosate and naltrexone trials. These trials had a range of efficacy yet the pharmacotherapies are FDA-approved and thus warranted investigation in this unique "subgroup".

Thirdly, we would like to offer a clear rebuttal the notion that our methods were suboptimal simply because they do not align with the methods implemented by authors of the commentary. This was a technically sound report including 118 studies, testing 19 different medications, and representing 21,032 treated participants. A considerable collaborative effort by quantitative psychologists (Du and Bujarski) and clinical scientists (Grodin, Donato, Green, and Ray).

The last point is in regard to yet another manuscript by our group (Ray et al. 2021). We consider it excessive and unnecessary to have to address another published manuscript in this

reply. Instead, we would like to underscore the take home message of this Reply. Specifically, the authors of the letter are referencing a paper that asks a different research question in a different set of studies. When we ask different questions, we are not surprised when we reach different answers.

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