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Debate Section

Letters to the editor

Comment on 'No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia'

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To the editor,

We read with interest the article by Ishoy et al. entitled 'No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia' (1). In this analysis, the authors concluded that exenatide did not improve scores on the Brief Assessment of Cognition in Schizophrenia (BACS), Rey-Osterrieth complex figure test (REY), Short-Form Health Survey (SF-36), Personal and Social Performance Scale (PSP), and the Positive and Negative Syndrome Scale (PANSS). As presented in their Discussion section, these conclusions are in contrast to some previous studies.

Although impressive, we believe that some methodological issues should preclude the authors from reaching the conclusions they present, namely:

(i) 'Statistical power': The original sample size calculation (2) was estimated based on a primary outcome of weight loss rather than on any of the secondary endpoints. Also, the power analysis was based on a comparison between both interventions and was therefore not powered for a comparison of change over time between the two arms. The latter will usually require a greater number of subjects. In conclusion, the study is not adequately powered to reach the conclusions provided in the manuscript.

(ii) 'Measurement of change over time': The authors used repeated measures analysis of variance to compare both groups. When this method was demonstrated to be unreliable, an analysis of covariance was used to control for baseline variables (3).

In the face of these limitations, we believe that the results by Ishoy et al. should be deemed exploratory or post hoc, rather than issuing from a trial specifically designed to test the hypotheses presented by the authors.

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'No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia': authors' response

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We thank Sperandeo et al. for their interest in our recent paper (1) from the TAO trial (ClinicalTrials.gov identifier: NCT01794429). Sperandeo et al. raise the concern that limited statistical power and suboptimal statistical methods disqualify the conclusion that exenatide once-weekly did not show evidence of cognitive improvement in obese, antipsychotic-treated schizophrenia patients.

First, we thoroughly discussed the limited statistical power in the Discussion, and this concern was highlighted in the Limitation section: '*The trial may lack statistical power to detect subtle cognitive-enhancing effects*'. We acknowledge that a larger sample size may have detected an academically

interesting pro-cognitive effect of exenatide. However, as we noted, a visual inspection of the data in Table 2 did not even indicate subtle numerical cognitive changes favouring exenatide. The choice of statistical method was decided *a priori* and was identical that used in our study on the primary outcome (i.e. weight loss) (2). Therefore, *post hoc* application of any statistical method, which could provide significant *P*-values from the data provided in Table 2 would be profoundly problematic. Finally, we argued that given the price and the subcutaneous route of administration of exenatide, the intervention should at least have induced a small signal of a cognitive-enhancing effect to be clinically worthwhile – even in this limited sample.

Second, the TAO trial never aimed to provide the ultimate evidence for the pro-cognitive potential of exenatide. The published TAO protocol (3) stated that 'Secondary endpoints will explore the effects of exenatide on various parameters including psychopathological, cognitive, behavioural…'. Accordingly, our conclusion: 'The non-significant results of this first clinical trial exploring non-metabolic effects of a long-acting GLP-1RA in patients with schizophrenia…' clearly states the exploratory nature of this study (1).

Interestingly, this debate originates from publication of a study showing negative results. As such, this debate scholastically illustrates an important and well-known paradox in biomedicine: That proving the absence of an effect (i.e. failure to reject the null hypothesis) often requires further endeavours to be accepted by the scientific community than do positive results (4). We commend the Editorial Board of Acta Psychiatrica Scandinavica for taking on the important task of also publishing negative results.

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Declaration of interest

Drs. Ishøy, Fagerlund, Broberg and Bak report no competing interests. Prof. Knop has received lecture fees is part of Advisory Boards of and/or has consulted for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Zealand Pharma. Prof. Glenthøj is the leader of a Lundbeck Foundation Center of Excellence for CINS, which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen and other foundations. All grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them. Dr. Ebdrup has received lecture fees and/or is part of Advisory Boards of Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia and Takeda Pharmaceutical Company.

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Comment on Vitamin D serum levels are cross-sectionally but not prospectively associated with late-life depression

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To the Editor,

Vitamin D deficiency is widely prevalent in the general population and is even more prevalent among those with major depressive disorder. This finding has generated considerable interest in whether vitamin D deficiency may have a causative role in depression and whether vitamin D replenishment may have a therapeutic role in major depressive disorder (1, 2).