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

Ishøy PL, Fagerlund B, Broberg BV, Bak N, Knop FK, Glenthøj BY, Ebdrup BH. No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia.

Objective: Schizophrenia is associated with profound cognitive and psychosocial impairments. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are used for diabetes and obesity treatment, and animal studies have indicated cognitive-enhancing effects. In this investigator-initiated, double-blind, randomized, placebo-controlled trial, we tested non-metabolic effects of exenatide once-weekly (Bydureon™) in obese, antipsychotic-treated patients with schizohrenia spectrum disorder.
Method: Before and after 3 months of exenatide (N = 20) or placebo (N = 20) treatment, patients were assessed with the following: Brief Assessment of Cognition in Schizophrenia (BACS), Rey–Osterreith complex figure test (REY), Short-Form Health Survey (SF-36), Personal and Social Performance Scale (PSP) and the Positive and Negative Syndrome Scale (PANSS). We used BACS composite score as the main outcome measure.
Results: Repeated measures analysis of variance on BACS composite score showed significant effect of 'Time' ($P < 0.001$), no effect of 'Group' ($P = 0.64$) and no 'Time*Group' interaction ($P = 0.77$). For REY, SF-36, PSP and PANSS, only significant 'Time' effects were found.
Conclusion: The non-significant results of this first clinical trial exploring non-metabolic effects of a long-acting GLP-1RA in patients with schizophrenia could reflect a general problem of translating cognitive-enhancing effects of GLP-1RAs from animals to humans or be explained by factors specifically related to schizophrenia spectrum patients with obesity such as antipsychotic treatment.

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Key words: schizophrenia; cognitive impairment; neurocognition; randomized controlled trial; quality of life

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Significant Outcomes

- Three-month treatment with the glucagon-like peptide-1 receptor agonist, exenatide 2 mg once-weekly (Bydureon™), did not improve cognition or psychosocial function in schizophrenia spectrum patients.
- The non-significant results could reflect a general problem of translating cognitive-enhancing effects of GLP-1RAs from animals to humans or be explained by factors specifically related to schizophrenia spectrum patients with obesity such as antipsychotic treatment.

Limitations

- A trial duration of 3 months may be insufficient to induce cognitive-enhancing effects.
- Cognitive-enhancing effects of higher exenatide doses and effects of other glucagon-like peptide-1 receptor agonists have not been investigated.
- The trial may lack statistical power to detect subtle cognitive-enhancing effects.

Introduction

Schizophrenia was termed *dementia praecox* (1) in late 1800s owing to the marked cognitive impairments often accompanying the characteristic clinical symptoms. Today, cognitive deficits are still considered core features of schizophrenia, and the deficits are strong indicators of course of illness and functional outcome (2,3). Antipsychotic treatment constitutes the core of medical care in schizophrenia (4). It is well established that adherence to antipsychotic treatment decreases the risk of re-hospitalization as well as suicidal behaviour and that antipsychotics are associated with higher remission rates compared to intermittent antipsychotic use and placebo (5). Furthermore, continuous antipsychotic treatment improves the global level of functioning and quality of life (6,7). While antipsychotics primarily relieve the positive symptoms, the negative symptoms and cognitive deficits remain largely unaffected (4). Somatically, antipsychotic treatment is often complicated by the development of obesity and diabetes (8,9), and these factors have independently been linked to increased risk of accelerated brain aging, cognitive impairments and dementia (10,11). Thus, effective treatment regimens for both cognitive deficits and metabolic disturbances in patients with schizophrenia are needed.

Glucagon-like peptide-1 (GLP-1) is a peptide hormone, mainly synthesized in the intestinal mucosa and secreted into circulation following food consumption (12). GLP-1 exerts important gluco-regulatory effects via glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion and promotes satiety sensations (12,13). Accordingly, GLP-1 receptor agonists (GLP-1RAs) have been developed for the treatment of type 2 diabetes and shown to improve glycemic control, promote weight loss and reduce blood pressure and blood lipids (13). The GLP-1 receptor is widely expressed in the human brain (12,14), and high density of GLP-1 receptors is present in regions crucial for maintaining cognitive functioning such as memory formation, learning and emotional processing (15,16). Animal studies have indicated beneficial effects of GLP-1RA treatment on cerebral metabolism, neuro-inflammation and neuro-regeneration (17–20). Based on these observations, GLP-1RAs have been proposed as a potential therapy for patients with neurodegenerative disorders (21,22).

In an animal model of amyloid-independent dementia (i.e. non-Alzheimer's disease), short- and long-term memory improved after 9 months of GLP-1RA (exenatide twice-daily) treatment (23). Another animal study reported that exenatide twice-daily upregulated neurotrophic factor gene expression and improved cognitive performance in diabetic mice (24). Besides the central pro-cognitive effects of GLP-1RAs, weight loss in itself may also be associated with subtle cognitive improvements in obese individuals (25). Based on these potential favorable central effects, we and others have suggested GLP-1RAs as a potential promising treatment avenue in psychiatric populations (26–28). Specifically, we proposed GLP-1RAs as a potential cognitive-enhancing treatment for patients with schizophrenia (27).

We conducted the first clinical trial to investigate the potential effects of GLP-1RA treatment in schizophrenia, the TAO trial (Treatment of Antipsychotic-associated Obesity with a GLP-1 receptor agonist) (29). TAO is an investigator-initiated, double-blinded, randomized, placebo-controlled, 3-month (12–16 weeks) intervention trial in non-diabetic, antipsychotic-treated, patients with obesity and schizophrenia spectrum disorder. Patients were randomized to treatment with exenatide 2 mg once-weekly (Bydureon™) or placebo for 3 months. Data on the protocolized primary endpoint, weight loss and secondary metabolic parameters have been published elsewhere, and no body weight-lowering effect of exenatide once-weekly compared to placebo was observed (30).

Aims of the study

In this study, we investigated non-metabolic effects of 3-month treatment with exenatide 2 mg once-weekly (Bydureon™). Global cognitive performance on the Brief Assessment of Cognition in Schizophrenia (BACS) was applied as the main outcome measure. Additional outcome measures comprised specific neurocognitive domains, subjective quality of life, psychosocial functioning and schizophrenia symptom severity.

Material and methods

Study population

A detailed description of the study design has been published previously (29). Between March 2013 and June 2015, we included antipsychotic-treated, clinically stable (current and unchanged antipsychotic treatment for a minimum of 3 months) schizophrenia spectrum patients (ICD-10 diagnoses F20.x and F25.x) between 18 and 65 years of age with obesity (body mass index (BMI) $\geq$30 kg/m^2). Patients were recruited from psychiatric clinics in the Capital Region of Denmark. P.L.I. assessed all referrals

according to inclusion and exclusion criteria. Exclusion criteria included diabetes and other severe somatic diseases, ongoing substance dependency, pregnancy and coercive measures (the complete list is provided in the TAO study protocol (29)). Data were collected on four scheduled trial visits: 'baseline' (week 0), '1 week' (7 ± 2 days), '4 weeks' (4–6 weeks) and 'end of trial' (12–16 weeks). A CONSORT (31) flow diagram of the study is provided in Fig. 1.

Trial medication

The trial medication was the GLP-1RA exenatide 2 mg once-weekly (Bydureon™, AstraZeneca AB, Södertälje, Sweden). The once-weekly administration profile of Bydureon™ was selected as a means to optimize trial adherence in our psychiatric patient sample. Patients received once-weekly subcutaneous administration with either exenatide 2 mg (fixed dose) or placebo by unblinded trial personnel otherwise not involved in the study. Placebo injections were solvent from the Bydureon™ kit (without exenatide). The first two treatments were injected at the psychiatric research facility to monitor tolerability. Subsequent injections were administered in the home of the patient. After termination of the trial, plasma exenatide measurements were performed to verify that therapeutic plasma exenatide levels had been achieved in exenatide-treated patients (30).

Neurocognitive measures

Baseline neurocognitive assessments were conducted before the initiation of treatment and included the BACS (32) and the Rey-Osterreith complex figure test (REY) (33). Patients were re-tested at the 'end of trial' visit. All tests were performed by trained personnel.

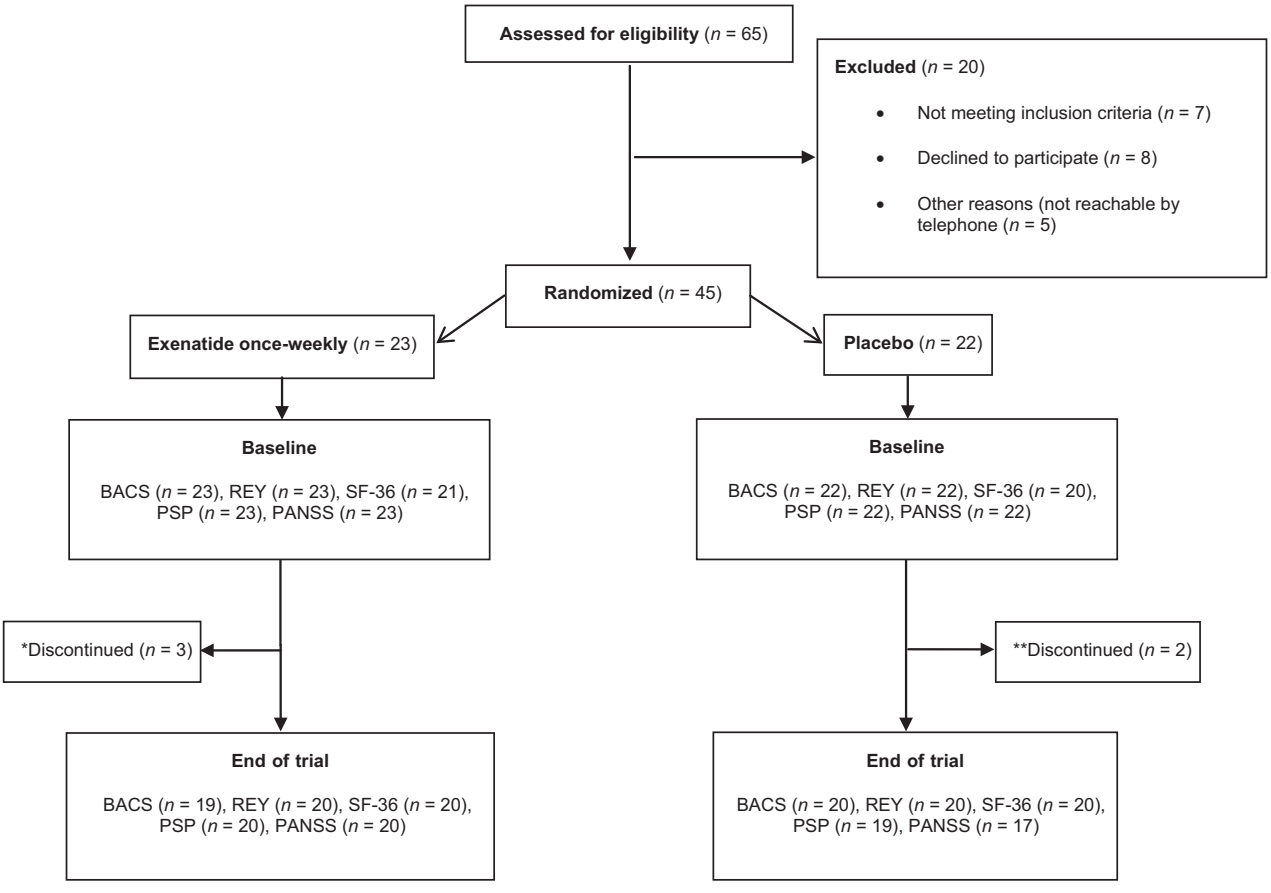

Fig. 1. Shows the CONSORT diagram (31) of the TAO trial. Of the 65 patients referred to the study, 45 initiated the 3-month treatment. Five patients dropped out from trial, resulting in a completion of $n = 40$ ($n = 20$ exenatide only-weekly, $n = 20$ placebo). At each time point, the number of complete assessments is shown ($n = x$). BACS: Brief Assessment of Cognition in Schizophrenia (32); REY: Rey-Osterreith complex figure test (33); SF-36: the Short-Form 36 survey of the International Quality of Life Assessment (39); PSP: the Personal and Social Performance Scale (40); PANSS: Positive and Negative Syndrome Scale (41). *In the exenatide group, two patients dropped out because of intolerable gastrointestinal side-effects and one due to dissatisfaction with unchanged body weight after 9 weeks of treatment. **In the placebo group, one patient dropped out due to severe nausea and dizziness, and one due to worsening of psychotic symptoms.

Brief assessment of cognition in schizophrenia

The BACS test battery has been developed to enable detection of treatment-related cognition changes (32). BACS consists of six tests covering five cognitive domains: verbal memory and learning, working memory, motor function, verbal fluency and executive function. The BACS instrument has been validated both in patients with schizophrenia and in healthy controls, and the BACS composite score (considered our main outcome measure) shows a high test–retest reliability (34).

We used the Danish version (version A) of BACS. The cognitive deficits observed in first-episode and chronic schizophrenia patients generally range from 0.6 to 1.2 standard deviations below healthy controls (35,36). To calculate our primary cognitive measure, the six subtest measures: 'List learning', 'Digit sequencing', 'Token motor test', 'Verbal fluency (total), 'Symbol coding' and 'Tower of London' were first standardized using the mean baseline performance and the baseline standard deviation. The BACS composite score was then calculated for each participant as their mean of Z-scores (baseline or end of trial respectively) (32). Secondary neurocognitive outcome measures comprise the specific subtests from BACS (37) and REY (33).

List learning (verbal memory). The patient was presented with 15 words and asked to recall as many as possible in five consecutive trials. An identical word list was used at baseline and end of trial. Measure: The total number of words recalled across trials (range: 0–75).

Digit sequencing (working memory). The patient was presented with clusters of random digits of increasing length. The patient had to sequence the digits in order, from the lowest to highest. Measure: The number of correct responses (range: 0–28).

Token motor test (processing speed). One-hundred plastic tokens were placed on a table in front of the patient. The patient was asked to pick up and place two tokens simultaneously into a container as quickly as possible. Measure: The number of tokens correctly placed into the container (60 s) (range: 0–100).

Verbal fluency (total) (semantic fluency and phonetic fluency). Consisted of two subtests. First, the patient was asked to name as many words as possible within a given category (items from a supermarket). Second, the patient was asked to generate as many different words as possible beginning with a given letter. The patient underwent this subtest twice, provided with the letters 'F' and 'S' respectively. Measure: The number of correct words generated per test (60 s).

Symbol coding. The patient was presented with a response key matching symbols to the digits 1–9 which were displayed on a chart. The patient was asked to fill in as many correct digits as possible below the symbols. Measure: The number of correctly matched digits (90 s) (range: 0–110).

Tower of London (version A) (reasoning and problem-solving). The patient was presented simultaneously with two pictures of coloured balls arranged on three pegs. The patients were asked to estimate the least number of moves needed for the balls in one picture to match the array of balls displayed on the other picture. There were up to 22 trials of increasing levels of difficulty. Measure: The number of correct trials (range: 0–22).

REY. We used the REY (33) to assess visual perceptual organization and memory. During assessment, each element of the figure was scored for both accuracy of formation and spatial location (scores ranging from 0 to 36), with a higher score indicating greater accuracy. We report data on the three subscores: 'Immediate Recall', 'Delayed Recall' and 'Recognition'.

Psychosocial measures

Short-form 36. The validated Danish version 1.1 (38) of the short form of health survey IQOLA SF-36 (39) (SF-36) to monitor the patients' subjective quality of life. SF-36 is a patient-reported quality of life measure consisting of 36 health-related questions, which are subsequently scored in eight scales (Table 3) (39). Patients were instructed to fill in the survey 1 day prior to the scheduled trial visit (baseline and end of trial).

The personal and social performance scale. The Personal and Social Performance Scale (40) (PSP) was used to assess social and occupational functioning. PSP was administered by principal investigator (PLI) at 'baseline', '4 weeks' and 'end of trial', and a total PSP score was calculated. PSP provides an operational measure of the patient's psychosocial level of functioning.

The positive and negative syndrome scale. The Positive and Negative Syndrome Scale (41) (PANSS)

was used to assess severity of schizophrenia symptoms. PANSS interviews were performed by trained personnel at 'baseline', '4 weeks' and 'end-of-trial'.

Ethics and approvals

All patients received oral and written information about the trial prior to enrolment, and written informed consent was required (29). The study was conducted according to the Declaration of Helsinki II, the CONSORT 2010 Statement (31) and Good Clinical Practice (GCP). The GCP Unit at Copenhagen University Hospital monitored the trial according to ICH-GCP guidelines (42). The trial was approved by 'The National Committee on Health Research Ethics' (project no.: 36378), 'The Danish Health and Medicines Authority' (EudraCT no.: 2012-005404-17) and 'The Danish Data Protection Agency' (project no.: RHP-2012-027). ClinicalTrials.gov Identifier: NCT01794429 (29).

Statistical analysis

Data analysis on the neurocognitive outcomes, that is BACS and REY, was performed according to the 'per-protocol' principle. Demographic variables and clinical characteristics are reported in frequency (percentage) for categorical data and mean values with standard deviations and range for normally distributed, continuous variables. Group comparisons for demographic data were performed using independent *t*-tests for continuous variables and chi-squared tests for nominal and ordinal variables. Outcome measures were tested using repeated measures analysis of variance (rmANOVA). The 'within-subject factor' between time points was denoted 'Time', and the 'between-subject factor', that is exenatide vs. placebo, was denoted 'Group'. The 'Time*Group' interaction indicates a difference in the response between the two groups, that is a treatment effect. Correlations between variables were evaluated using Pearson's *r*. IBM SPSS version 22 (IBM Corporation, Armonk, New York, USA) was used for statistical analyses. Level of significance was set to $P < 0.05$, two-sided.

Results

Demographics and clinical data

A total of 65 patients were referred to the TAO trial, of which 87.7% (57 of 65) were out-patients. Twenty referrals met exclusion criteria (Fig. 1) as previously reported (30). Forty-five patients were included in the trial and initiated treatment with either exenatide once-weekly ($n = 23$) or placebo ($n = 22$). Three patients in the exenatide group and two patients in the placebo group dropped out, corresponding to an attrition rate of 11%**.** Twenty patients in each group completed the 3-month intervention as planned in the TAO protocol (29). Completing patients had received a similar number of trial medication injections: mean ± standard deviation (SD), 14.2 ± 1.0 SD in the exenatide group vs. 14.2 ± 1.2 SD in the placebo group ($P = 0.89$). Baseline characteristics and demographics did not differ between the two groups (*P* values ≥ 0.35), with the exception of tobacco use; there were seven smokers in the exenatide group compared to one in the placebo group ($P = 0.02$) (Table 1). At baseline, the groups did not differ with regard to cognition (composite score) ($P = 0.43$) or psychopathology: PANSS positive ($P = 0.92$), PANSS negative ($P = 0.95$), PANSS general ($P = 0.69$) and PANSS total ($P = 0.79$).

Patients were treated with a variety of antipsychotics (both antipsychotic monotherapy and antipsychotic polypharmacy), including typical (first-generation) antipsychotics (perphenazine, zuclopenthixol and chlorprothixene) and atypical (second-generation) antipsychotics (clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride and sertindole), but the distribution of first- vs. second-generation antipsychotics, and mono- vs. polypharmacy, did not differ between the groups (*P* values ≥ 0.30). Likewise, we found no baseline group differences (*P* values ≥ 0.08) regarding use of medication with potential influence on cognition and wakefulness (anticholinergics, benzodiazepines, Z-drugs, mood stabilizers, antidepressants, melatonin, antihistamines and levothyroxine) (Table 1).

Neurocognitive outcome measures

Repeated measures analysis of variance (rmANOVA) on BACS composite score showed a significant effect of 'Time' ($P < 0.001$), no effect of 'Group' ($P = 0.64$) and no 'Time*Group' interaction, that is no 'treatment' effect ($P = 0.77$) (Table 2). As clozapine and olanzapine exert relatively strong anticholinergic effects, we performed a *post hoc* analysis excluding all patients receiving either clozapine or olanzapine, comprising 5 of 23 in the exenatide group and 10 of 22 in the placebo group. Repeated measures ANOVA on the remaining patients did not significantly change our results on

Table 1. Demographical data for patients enrolled in the TAO trial ($n = 45$)

	Exenatide ($n = 23$)	Placebo ($n = 22$)	P value (χ^2)
Age in years mean ± SD [range]	37.1 ± 10.6 [19–65]	34.5 ± 10.1 [19–56]	0.40
Gender (n = male)/(n = female)	11/12	10/12	0.53
Ethnicity (%)			
Caucasian	47.5	45.0	
Mongolian	2.5	5.0	0.60
Education in years mean ± SD [range]	12.6 ± 2.9 [8–18]	12.1 ± 2.6 [7–20]	0.51
Smoking yes/no (%)	7/16 (30.4)	1/21 (4.5)	0.02*
Lifetime substance dependency yes/no (%)	7/16 (30.4)	5/17 (22.7)	0.36
Diagnosis yes/no (%)			
Schizophrenia, F20.x	21/2 (91.3)	20/2 (90.9)	0.54
Schizoaffective, F25.x	2/21 (8.7)	2/20 (9.1)	
Duration of illness (years) mean ± SD [range]	14.0 ± 9.4 [0.73–30]	11.1 ± 8.2 [0.5–27]	0.28
BMI (kg/m^2) mean ± SD [range]	39.2 ± 3.8 [31–48]	38.4 ± 6.1 [30–55]	0.59
Antipsychotic monotherapy (typical) yes/no (%)	1/22 (4.3)	1/21 (4.5)	0.97
Antipsychotic monotherapy (atypical) yes/no (%)	15/8 (65.2)	11/11 (50)	0.30
Antipsychotic polypharmacy yes/no (%)	7/16 (30.4)	10/12 (45.5)	0.30
Antipsychotic with anticholinergic effects (clozapine or olanzapine) yes/no (%)	5/18 (21.7)	10/13 (45.5)	0.09
Anticholinergics yes/no (%)			
Daily intake	0/23 (0)	1/21 (4.5)	0.58
Pro re nata	2/21 (8.7)	2/20 (9.1)	
Benzodiazepines yes/no (%)			
Daily intake	2/21 (8.7)	2/20 (9.1)	0.86
Pro re nata	2/21 (8.7)	1/21 (4.5)	
Z-drugs[1] yes/no (%)			
Daily intake	0/23 (0)	0/22 (0)	0.16
Pro re nata	2/21 (8.7)	0/22 (0)	
Mood Stabilizers yes/no (%)	3/20 (8.7)	3/19 (13.6)	0.95
Antidepressants yes/no (%)	10/13 (43.5)	11/11 (50)	0.66
Melatonin yes/no (%)	3/20 (13)	0/0 (0)	0.08
Antihistamines yes/no (%)			
Daily intake	0/0 (0)	0/0 (0)	0.08
Pro re nata	3/20 (13)	0/0 (0)	
Levothyroxine yes/no (%)	2/21 (8.7)	1/21 (4.5)	0.58

Group differences were tested by independent two-sample t-test and chi-squared tests, and significant group differences are indicated by asterisks (*). BMI, body mass index. Typical antipsychotic medication included monotherapy with either perphenazine or zuclopenthixol. Atypical antipsychotic medication included monotherapy with the following: clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride or sertindole. Polypharmacy included combination of at least two typical and/or atypical antipsychotics. Anticholinergics included orphenadrine, biperiden and hyoscyamine. Benzodiazepines included the following: oxazepam, lorazepam, clonazepam and diazepam. Z-drugs[1] (non-benzodiazepines used for treatment of insomnia) included zopiclone and zolpidem. Mood stabilizers included the following: lithium, lamotrigine and valproate. Antidepressants included the following: citalopram, escitalopram, sertraline, fluoxetine, pregabalin, venlafaxine, duloxetine, amitriptyline and nortriptyline. Antihistamines included cetirizine and promethazine.

BACS composite score. Change in body weight or BMI (in the total sample regardless of treatment group ($N = 40$)) was not correlated with changes in BACS composite score ($r = 0.11$, $P = 0.48$) and ($r = 0.1$, $P = 0.56$) respectively. Using baseline BMI as a covariate in rmANOVA did not significantly alter the results.

For the BACS subtests 'List learning' and 'Tower of London', we found significant effects of 'Time' (P values ≤ 0.009), but no effects of 'Group' (P values ≥ 0.21), nor any 'Time*Group' interactions (P values ≥ 0.68). In the four remaining BACS tests: 'Digit sequencing', 'Token motor test', 'Verbal fluency' (total) and 'Symbol coding', we found no effects of 'Time' (P values ≥ 0.06), 'Group' (P values ≥ 0.21) or 'Time*Group' interactions (P values ≥ 0.50).

Results on REY items 'Immediate Recall', 'Delayed Recall' and 'Recognition' showed significant effect of 'Time' (P values ≤ 0.001), no effect of 'Group' (P values ≥ 0.35) and no 'Time*Group' interactions (P values ≥ 0.63) (Table 2).

Psychosocial outcome measures

In SF-36, the parameter 'functioning limitations due to emotional problems' showed an effect of 'Time' ($P = 0.01$) and no effect of 'Group' ($P = 0.43$), but a significant 'Time*Group' interaction ($P = 0.02$) with the exenatide-treated patients scoring higher than placebo-treated patients at the end of trial (Table 3). We also found an effect of 'Time' on the SF-36 scales, 'energy/fatigue' ($P = 0.02$) and 'social functioning' ($P = 0.04$), but

Table 2. Cognitive performance before and after 3 months of exenatide once-weekly treatment

	Exenatide	Placebo	Time *P* value	Group *P* value	Time*Group *P* value
BACS composite score					
Baseline	0.05 ± 0.73 [−1.54 to 1.26]	−0.05 ± 0.78 [−1.41 to 1.08]	<0.001*	0.64	0.77
End of trial	0.29 ± 0.76 [−1.25 to 1.56]	0.16 ± 0.72 [−1.24 to 1.41]			
BACS – List learning					
Baseline	38.6 ± 11.15 [21–55]	38.3 ± 11.4 [17–53]	<0.001*	0.84	0.74
End of trial	44.5 ± 12.3 [20–63]	43.4 ± 10.0 [25–58]			
BACS – Digit sequencing					
Baseline	15.7 ± 5.4 [8–25]	15.5 ± 4.7 [7–25]	0.76	0.74	0.50
End of trial	16.1 ± 5.2 [9–24]	15.3 ± 4.9 [7–23]			
BACS – Token motor test					
Baseline	56.7 ± 13.6 [30–88]	51.0 ± 16.5 [22–80]	0.06	0.21	0.99
End of trial	60.6 ± 14.0 [40–90]	54.8 ± 18.0 [6–84]			
BACS – Verbal fluency (total)†					
Baseline	39.2 ± 13.9 [18–62]	40.7 ± 14.7 [25–77]	0.10	0.86	0.64
End of trial	42.2 ± 17.2 [17–80]	42.4 ± 13.6 [27–69]			
BACS – Symbol coding					
Baseline	43.6 ± 14.1 [18–71]	40.9 ± 11.7 [21–67]	0.24	0.64	0.54
End of trial	44.2 ± 13.5 [18–65]	43.0 ± 14.0 [18–67]			
BACS – Tower of London					
Baseline	16.2 ± 4.5 [4–21]	16.0 ± 3.4 [11–22] (*n* = 19)	0.009*	0.82	0.91
End of trial	17.4 ± 3.5 [11–22]	17.1 ± 3.4 [10–22] (*n* = 19)			
REY – Immediate Recall					
Baseline	16.1 ± 9.9 [4–32] (*n* = 18)	18.8 ± 7.5 [8–30] (*n* = 18)	0.001*	0.43	0.64
End of trial	19.4 ± 11.3 [0–34] (*n* = 18)	21.1 ± 7.4 [4–33] (*n* = 18)			
REY – Delayed Recall					
Baseline	15.8 ± 9.6 [1–32]	18.3 ± 7.5 [5.5–31] (*n* = 19)	<0.001*	0.41	0.65
End of trial	20.0 ± 10.2 [2–33]	21 ± 7.6 [3–33] (*n* = 19)			
REY – Recognition					
Baseline	18.2 ± 2.8 [12–21]	18.8 ± 2.8 [10–23]	<0.001*	0.35	0.79
End of trial	19.8 ± 2.5 [15–24]	20.5 ± 1.6 [18–23]			

Cognition was measured with Brief Assessment of Cognition in Schizophrenia (BACS) (32) and Rey-Osterreith complex figure test (REY) (33). Values are mean BACS and REY scores ± standard deviation and [range]. '*n*' is provided, when the number of complete data sets was <20. Data were analysed using repeated measures analysis of variance, and significant differences are indicated by asterisks (*). Columns represent effects of 'Time', 'Group' and 'Time*Group' interaction, that is the treatment effect. †Comprise the mean BACS scores of 'Category fluency' and 'Phonetic fluency' (letters S and F).

no effect of 'Group' (P values > 0.06) and no 'Time*Group' interactions (P values > 0.65).

PSP did not show effect of 'Time' ($P = 0.53$) or 'Group' ($P = 0.77$) or 'Time*Group' interaction ($P = 0.37$).

In PANSS, we found a significant effect of 'Time' on 'PANSS total' ($P = 0.002$), no effect of 'Group' ($P = 0.42$) or 'Time*Group' interaction ($P = 0.86$) (Table 4). In *post hoc* analyses, we found an effect of 'Time' on 'PANSS positive symptoms' ($P = 0.03$) and 'PANSS general symptoms' ($P = 0.008$), without effect of 'Group' ($P > 0.30$), or 'Time*Group' interaction ($P > 0.71$). For 'PANSS negative symptoms', we found no effect of 'Time' ($P = 0.09$), 'Group' ($P = 0.57$) or 'Time*Group' interaction ($P = 0.99$).

Post hoc correction for smoking status did not alter the significance level any of the results above. Thirteen of 20 patients treated with exenatide once-weekly developed antiexenatide antibodies, compared to none in the placebo group ($P = 0.004$) (30). *Post hoc* analyses excluding these 13 patients did not alter the significance level on any of the results above.

Discussion

This is the first randomized, placebo-controlled trial investigating non-metabolic effects of GLP-1RA treatment in schizophrenia patients with obesity. Despite growing evidence for cognitive-enhancing effects of GLP-1RA treatment in various neurodegenerative disorders, we did not find indications of cognitive-enhancing effects after 3 months of exenatide treatment in patients with schizophrenia spectrum disorder. Currently, it is not fully elucidated how subcutaneously administered GLP-1RAs engage the central nervous system in humans. Specifically, it is unclear to what degree peripherally administered GLP-1RA may exert its actions directly in the human brain. Preclinical studies in mice (43) and in primates (44) have shown that peripherally administered liraglutide can be detected in brain areas involved in

Table 3. Subjective quality of life and level of functioning before and after 3 months of exenatide once-weekly treatment.

	Exenatide	Placebo	Time *P* value	Group *P* value	Time*Group *P* value
Physical functioning (SF-36)					
Baseline	70 ± 20.5 (*n* = 20)	61.6 ± 24.7 (*n* = 19)	0.08	0.37	0.52
End of trial	74 ± 22.1 (*n* = 20)	70 ± 28.0 (*n* = 19)			
Functioning limitations due to physical problems (SF-36)					
Baseline	44.7 ± 46.8 (*n* = 19)	55.3 ± 41.3 (*n* = 19)	0.14	0.95	0.19
End of trial	65.8 ± 38.4 (*n* = 19)	56.6 ± 40.7 (*n* = 19)			
Functioning limitations due to emotional problems (SF-36)					
Baseline	52.6 ± 47.6 (*n* = 19)	56.1 ± 43.1 (*n* = 19)	0.01*	0.43	0.02*
End of trial	80.7 ± 25.6 (*n* = 19)	57.9 ± 42.8 (*n* = 19)			
Energy/fatigue (SF-36)					
Baseline	50.0 ± 22.4 (*n* = 18)	36.7 ± 24.0 (*n* = 18)	0.02*	0.06	1
End of trial	57.8 ± 21.4 (*n* = 18)	44.4 ± 23.6 (*n* = 18)			
Emotional wellbeing (SF-36)					
Baseline	67.3 ± 23.2 (*n* = 17)	59.8 ± 23.7 (*n* = 18)	0.08	0.20	0.50
End of trial	74.1 ± 18.7 (*n* = 17)	62.9 ± 24.0 (*n* = 18)			
Social functioning (SF-36)					
Baseline	65.1 ± 33.2 (*n* = 19)	64.5 ± 35.4 (*n* = 19)	0.04*	0.73	0.65
End of trial	78.3 ± 27.0 (*n* = 19)	73.0 ± 25.4 (*n* = 19)			
Pain (SF-36)					
Baseline	85.9 ± 19.2 (*n* = 19)	66.6 ± 31.9 (*n* = 17)	0.18	0.02*	0.56
End of trial	88.7 ± 15.3 (*n* = 19)	73.7 ± 24.6 (*n* = 17)			
General health (SF-36)					
Baseline	54.4 ± 25.5 (*n* = 18)	47.5 ± 17.9 (*n* = 18)	0.09	0.27	0.83
End of trial	60.8 ± 22.8 (*n* = 18)	52.5 ± 23.0 (*n* = 18)			
PSP					
Baseline	46.9 ± 15.3	49.1 ± 14.2 (*n* = 19)	0.53	0.77	0.37
End of trial	48.4 ± 14.2	48.5 ± 12.8 (*n* = 19)			

SF-36: the short form of health survey IQOLA SF-36 (39). PSP: the Personal and Social Performance Scale (40). Values are mean, standard deviation (SD) and [range] (in square brackets). '*n*' is provided, when the number of complete data sets was <20. *P*-values were analysed using repeated measures analysis of variance, and significant differences are indicated by asterisks (*). Columns represent effects of 'Time', 'Group' and 'Time*Group' interaction, that is the treatment effect.

regulation of appetite, satiety and feeding behaviour, as well as in areas involved with memory and learning. Additionally, a study exploring blood-to-brain penetration of exendin-4 (exenatide is a synthetic version of exendin-4) in mice found that exendin-4 crossed the blood-brain barrier (45). Christensen et al. reported that small concentrations of liraglutide were measurable in the cerebrospinal fluid in humans after subcutaneous liraglutide exposure (46). Collectively, these data from studies in both animals and humans support that, by various mechanisms, small peptides such as liraglutide and exenatide are able to access and exert their actions directly in the human brain.

Of note, most indications of GLP-1RA-associated cognitive improvements in neurodegenerative disorders have emerged from animal studies. A recent randomized, placebo-controlled, double-blind clinical trial of patients with Alzheimer's disease ($n = 38$) detected no pro-cognitive effects after 6 months of GLP-1RA treatment (liraglutide) (47). Another recent small 4-week open-label clinical study of patients with mood disorder ($n = 19$) indicated a pro-cognitive effect of liraglutide (48), but the lack of a placebo group and the short study duration hinder possibilities to control for learning effects after cognitive re-testing (49). Based on this, we cannot infer whether our data reflect a general problem of translating GLP-1RA effects from animals to humans (50) or whether our negative results are explained by factors specifically related to our antipsychotic-treated schizophrenia patients with obesity.

We found effects of 'Time' on several cognitive outcome measures, and as noted above, we interpret these as expected re-test effects, a well-known phenomenon in neurocognitive testing (32,49). Although weight loss itself has been shown to improve cognition in non-psychiatric overweight and obese persons (25,51), our exploratory analyses did not reveal significant correlations between change in weight (or BMI) and change in BACS composite score. It remains unknown whether a more pronounced and clinically relevant weight loss would have improved cognition in our trial.

We did not find an overall significant effect of exenatide compared to placebo on the subjective quality of life or psychosocial level of functioning (Table 3). Still, exenatide-treated patients reported significant improvement on the SF-36 category 'functioning limitations due to emotional problems'. As this was the only significant treatment

Table 4. Severity of schizophrenia symptoms for before and after 3 months of exenatide once-weekly treatment

	Exenatide ($n = 20$)	Placebo ($n = 20$)	Time *P* value	Group *P* value	Time*Group *P* value
PANSS, positive					
Baseline	16 ± 4.6 [10–26]	16.7 ± 5.9 [7–27]	0.03*	0.30	0.71
End of trial	14.2 ± 4.0 [7–25]	15.3 ± 4.9 [8–29]†			
PANSS, negative					
Baseline	16.6 ± 4.5 [9–26]	16.7 ± 4.8 [8–27]	0.09	0.57	0.99
End of trial	15.7 ± 5.1 [8–25]	16.2 ± 5.1 [10–24]†			
PANSS, general					
Baseline	31.2 ± 8.5 [19–47]	32.5 ± 8.7 [16–52]	0.008*	0.55	0.70
End of trial	29.3 ± 8.2 [18–50]	30.9 ± 7.8 [17–44]†			
PANSS, total					
Baseline	63.7 ± 15.2 [42–94]	65.9 ± 16.5 [38–94]	0.002*	0.42	0.86
End of trial	59.2 ± 15.9 [39–95]	62.4 ± 12.7 [37–83]†			

PANSS: the Positive and Negative Syndrome Scale (41). Values are mean, standard deviation (SD) and [range]. The two groups did not differ in PANSS scores at baseline (*t*-tests showed *P* values > 0.69). P values testing effect of trial were analysed using repeated measures analysis of variance on significant differences indicated by asterisks (*). Columns represent effects of 'Time', 'Group' and 'Time*Group' interaction, that is the treatment effect. †Data available for seventeen subjects.

effect observed in this study, and because it emerged from exploratory analyses not corrected for multiple testing, it may represent a chance finding. However, we cannot rule out that this self-reported improved emotional regulation is similar to the effect of improved wellbeing (independently of metabolic changes), which has previously been observed in diabetic patients treated with exenatide (52). As no other parameters of SF-36 or PSP significantly improved after exenatide treatment, the potential clinical impact of the self-reported relieve of emotional problems in our psychiatric population may be limited.

Both in the exenatide and in the placebo group, we observed significant improvements in psychosocial level of functioning and psychopathology after 3 months (Tables 3 and 4). More specifically, the improvement in PANSS total score was driven by reductions in positive and general symptoms, whereas the negative symptoms remained unchanged. Contrary to the observed effects of 'Time' on cognition, level of functioning and severity of psychopathology are not known to be subjected to re-test effects. Rather, we assume that effect of 'Time' and effects on level of functioning and psychopathology reflects an unspecific placebo effect or 'trial effect'. A theoretical dissection of the effective components of the TAO trial could point to regular, scheduled social interaction with professional, trial personnel as well as trial adherence as specific factors, which may have contributed to improvements in level of functioning and enhanced the effect of stable antipsychotic treatment. Notably, this trial effect did not involve improvement in the patients' negative symptoms (Table 4). It is, however, well described that negative symptoms are particularly resistant to both pharmacologi -cal and non-pharmacological interventions (53). Currently, one ongoing study is investigating the effects of 24-week exenatide once-weekly treatment on negative symptoms and cognition in schizophrenia (ClinicalTrials.gov Identifier: NCT02417142).

Strengths of our trial were the double-blinded, placebo-controlled design with a low attrition rate of 11% in both groups. The weekly injections by trial personal at patients' home ensured 100% medication compliance, and our previously reported plasma exenatide measurements showed therapeutic levels of exenatide comparable to studies in patients with diabetes (30).

We used a fixed dose of exenatide once-weekly 2 mg for 3 months. Due to our off-label use of exenatide, both regulatory and ethical considerations restricted us from using higher doses. We cannot exclude that a higher dose and/or longer treatment duration would have produced different results. However, inspection of our cognitive effects (Table 3) does not suggest general numerical improvements favouring exenatide. The power calculation in the TAO trial was based on the primary endpoint, which was weight loss (29,30), and cognitive measures were key secondary outcomes. Although each group comprised four more patients than the 16 patients we needed to detect weight loss, this study may still be underpowered to detect subtle cognitive effects of exenatide. We recognize that lack of power is a common challenge in trials exploring cognitive-enhancing effects (54). However, we would argue that considering the price of GLP-1RAs and the subcutaneous route of administration, a cognitive-enhancing effect should be detectable in our cohort to be clinically relevant. Overall, our results do not support the use of exenatide once-weekly as cognitive-enhancing treatment in schizophrenia.

This first clinical trial exploring non-metabolic effects of exenatide once-weekly in schizophrenia spectrum patients neither found cognitive-enhancing effects nor improvements in psychosocial function over 3 months. Improvements in psychopathology and quality of life irrespective of treatment group could suggest that regular, scheduled social interaction enhances effect of antipsychotic medication and relieves suffering in chronic schizophrenia spectrum patients. Our non-significant results could reflect a general problem of translating cognitive-enhancing effects of GLP-1RAs from animals to humans or be explained by factors specifically related to schizophrenia spectrum patients with obesity such as antipsychotic treatment.

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The TAO study is investigator-initiated and not sponsored by pharmaceutical industry.

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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Letter to the editor

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

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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Letter to the editor

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

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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