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Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study

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ABSTRACT

Background: There is a paucity of treatments that are capable of reliably and robustly improving cognitive function in adults with mood disorders. Glucagon-like peptide-1 is synthesized centrally and its receptors are abundantly expressed in neural circuits subserving cognitive function. We aimed to determine the effects of liraglutide, a GLP-1 receptor (GLP-1 R) agonist, on objective measures of cognition in adults with a depressive or bipolar disorder.

Methods: In this 4-week, pilot, open-label, domain-based study (e.g. cognition), we recruited 19 individuals with major depressive disorder (MDD) or bipolar disorder (BD) and an impairment in executive function, defined as a below-average performance in the Trail Making Test-B (TMTB). Liraglutide 1.8 mg/day was added as an adjunct to existing pharmacotherapy.

Results: Participants had significant increases from baseline to week 4 in the TMTB standard score (age and education corrected) (Cohen's d=0.64, p=0.009) and in a composite *Z*-score comprising multiple cognitive tests (i.e. Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, Stroop test) (Cohen's d=0.77, $p < 0.001$). Neither changes in mood rating scales nor metabolic parameters were associated with changes in cognitive performance (all $p > 0.05$); however baseline insulin resistance (IR) and body mass index (BMI) moderated the changes in the composite *Z*-score (p=0.021 and p=0.046, respectively), indicating larger responses in individuals with higher IR and BMI at baseline. There was a significant increase in lipase ($p < 0.001$), but individual values were above the upper limit of normality.

Limitations: Small sample size, open-label design, lack of a placebo group.

Conclusions: Liraglutide was safe and well tolerated by a sample of non-diabetic individuals with mood disorders and had beneficial effects on objective measures of cognitive function. Larger studies with controlled trial designs are necessary to confirm and expand the results described herein.

1. Introduction

Mood disorders (i.e. major depressive disorder [MDD] and bipolar disorder [BD]) are highly prevalent conditions (Kessler et al., 2005; Vos et al., 2012), which often pursue a chronic, unremitting course, underscoring a major impact on morbidity. Cognition is considered a

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core domain of psychopathology in both MDD and BD (Bourne et al., 2013; Snyder, 2013). It is reported that approximately 25–50% of individuals with mood disorders exhibit a persistent and clinically relevant deficit in one or more domains of cognitive function (Gualtieri and Morgan, 2008; Martino et al., 2008). It is also reported that deficits in cognitive function are a quality of life detractor and a principle mediator of psychosocial impairment (Depp et al., 2012; McIntyre et al., 2013a), and disproportionately account for overall illness-associated costs (Kessler et al., 2008; Kleine-Budde et al., 2014). Notwithstanding the established efficacy of currently available treatments for mood symptoms, there are relatively few interventions that have replicated evidence of efficacy demonstrating pro-cognitive effects in mood disorders. For example, most antidepressants have not been shown to improve measures of cognitive control and executive function (Rosenblat et al., 2016), with the main exception being vortioxetine, which was reported to improve performance in objective measures of cognition (McIntyre et al., 2016; McIntyre et al., 2014). In addition, many treatments may endanger and/or amplify pre-existing cognitive impairment (Dias et al., 2012; McIntyre et al., 2013a). The proximate effect that cognitive dysfunction has on patient-reported outcomes (e.g. quality of life, psychosocial function) indicates that effective, safe, and well-tolerated treatments capable of offering improvement in this dimension would be expected to offer significant beneficial effects in health outcomes (McIntyre et al., 2015).

Convergent evidence also indicates that adults with primary metabolic disorders also exhibit significant deficits across multiple domains of cognitive function (Geijselaers et al., 2014; Yogi-Morren et al., 2014). For example, results from studies conducted in healthy individuals and clinical populations indicate that impaired glucose metabolism (Geijselaers et al., 2014; Yogi-Morren et al., 2014), visceral adiposity (Bove et al., 2013), and dyslipidemia (Karlamangla et al., 2014; Yogi-Morren et al., 2014) are independently associated with deficits in executive function. The convergent phenomenology of cognitive dysfunction in adults with a mood disorder and/or a metabolic disorder suggests overlapping subserving neurobiological processes. A derivative of this conclusion is that currently available agents that target metabolic systems may also be capable of mitigating deficits in cognitive functions transdiagnostically.

Glucagon-like peptide 1 (GLP-1) is an endogenous incretin hormone, that is synthesized in enteroendocrine L-cells in the ileum and colon and in discrete regions of the central nervous system (CNS) (e.g. nucleus tractus solitarius). Activation of GLP-1 receptor (GLP-1R) signaling promotes facilitation of glucose utilization through increased insulin secretion and suppression of glucagon (Cabou et al., 2008; Drucker, 2003; During et al., 2003; McClean et al., 2010). GLP-1R receptors are expressed in diverse CNS structures and regions relevant to general cognitive processes, as well as both positive and negative valence systems (e.g. prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala) (Alvarez et al., 2005; Farr et al., 2016). Multiple studies have demonstrated that GLP-1R agonists (e.g., liraglutide, exenatide) cross the blood-brain barrier (BBB) and exert biological effects (Kastin et al., 2002; Rinaman, 1999; Yamamoto et al., 2002). Recent preclinical studies have demonstrated the neurotrophic effects of GLP-1 and GLP-1RA on substrates subserving learning and cognition (McClean et al., 2011; Porter et al., 2010). Additional evidence indicates that GLP-1 modulates neuroplastic processes, as evidenced by effects on long-term potentiation (Gault and Holscher, 2008; Gengler et al., 2012; Wang et al., 2010). Accordingly, given the good safety profile to date, the mechanistic plausibility of direct central GLP-1R effect(s), and availability of GLP-1RA, these agents are promising candidates for repurposing, and may be viable therapeutic options for brain disorders.

Herein, we aimed to assess whether a GLP-1R agonist (i.e. liraglutide) improves measures of cognitive function in a mood disorders population. Secondarily, we aimed to explore the relationship between changes in cognitive function and changes in mood and metabolic parameters, including the updated homeostasis model assessment of insulin resistance (HOMA2-IR) a validated, well-established index of insulin resistance (Wallace et al., 2004). We also aimed to evaluate if cognitive improvement was directly mediated by liraglutide, rather than indirectly mediated via depressive symptom or metabolic parameters improvement. In this pilot study, we recruited individuals with MDD or BD and a measurable impairment in executive function, defined as a below-average (i.e. ⩾1 standard deviation [SD] below norm) performance in the Trail Making Test-B (TMTB). The primary efficacy endpoint was performance in the TMTB, as this is one of the most widely used neuropsychological tests of executive function and is a simple user-friendly measure of cognitive flexibility (an aspect of executive function), with demonstrated sensitivity to be used in a repeated measures design (Mahableshwarkar et al., 2015; McIntyre et al., 2014; Snitz et al., 2013; Wolinsky et al., 2013). Secondary outcomes included the Digit Symbol Substitution Test (DSST), the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test-A (TMTA), the Stroop test, and a composite cognition score comprising all of the aforementioned tests.

2. Methods

2.1. Study population

This is a 4-week pilot, open-label trial with adjunctive liraglutide in adults with mood disorders (n=19) and a measurable impairment in executive function. Participants were recruited from the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network (UHN), Toronto, an outpatient, tertiary clinic, whose principal objective of referral is diagnostic clarification and treatment recommendations. The study was conducted in accordance with the principles of Good Clinical Practice (1996) and the Declaration of Helsinki (WMA, 2008). Local research ethics committees approved the trial design, and all eligible patients provided written informed consent before participating.

For inclusion, participants had to be between the ages of 18 and 55, meet DSM-5 criteria for BD or MDD; and have a below-average (i.e. 1 SD below norm) performance in the TMTB. We further required that there had been no changes in medication for at least 4 weeks prior to enrollment, and this dose was kept constant during the trial. Exclusion criteria included: (1) use of anti-diabetic medications; (2) diagnosis of possible or probable dementia; (3) history of a neurological disorder or evidence of neurologic or other physical illness that could produce cognitive deterioration; (4) actively suicidal or evaluated as being a suicide risk (operationalized as a score of ≥3 on Hamilton Depression Rating Scale (HAM-D) suicide item and/or by clinical assessment); (5) a severe mood episode, defined as a 17-item HAM-D total score of >23 or a Young Mania Rating Scale (YMRS) total score of >20; (6) a substance use disorder within 3 months before screening or a positive baseline toxicology screen; (7) presence of an absolute or relative contraindication to liraglutide (e.g. hypersensitivity to liraglutide, hepatic impairment, renal impairment with CKD stage 3 and above); (8) history of pancreatitis or pancreatic cancer; (9) presence of a clinically unstable general medical illness; and (10) pregnant or breastfeeding women.

2.2. Study procedures

One-hundred and one individuals were screened; of those, 47 (46.5%) had a 1SD below-average performance in the TMTB. A total of nineteen patients were enrolled; of the remaining 28 with a SD below-average performance in the TMTB, 14 patients were lost to follow-up, 10 declined participation and 4 were ineligible. After determining that inclusion criterion were met, participants had a routine physical exam, with vital signs, anthropometric measurements and fasting laboratory measures, which included serum pregnancy

screen for female participants and a urine toxicology screen. After a screening period of 4–14 days, study participants received, in addition to 'standard of care' treatment, adjunctive liraglutide administration. Liraglutide was initiated at 0.6 mg/day, increased to 1.2 mg/day for the second week, and then titrated to 1.8 mg/day for the final two weeks. Liraglutide was adjunctively administered to a conventional antidepressant, antipsychotic, and/or mood stabilizing agent at guideline-concordant therapeutic plasma levels. Patients were seen weekly. Main outcomes, including neuropsychological testing, as well as rating scales and anthropometric measures, were acquired at baseline and endpoint.

2.3. Outcome measures

The primary outcome was performance on the TMTB (executive function). Secondary outcomes included the DSST (executive function, speed of processing, attention), RAVLT (learning, memory), TMTA (speed of processing), Stroop test (congruent and incongruent: executive function). In addition, the Perceived Deficits Questionnaire (PDQ), a patient-reported cognitive measure, was also completed at baseline and week 4. The cognitive test battery was administered by a trained investigator supervised by a clinical psychologist and took approximately one hour. As the TMT-A/B and the Stroop Test are psychomotor tasks determining reaction time, higher values indicate poorer test performance. The HDRS, YMRS, Snaith-Hamilton Pleasure Scale (SHAPS), Global Assessment of Functioning (GAF) and Clinical Global Impression – Severity of Illness (CGI-S) were completed at baseline and endpoint.

Anthropometric data and whole blood samples were obtained from all participants at baseline and endpoint. All samples were collected after a 12 h fasting. Metabolic parameters were measured immediately in a single laboratory with the same assay. Body mass index (BMI) was measured using the formula BMI = weight (Kg) / height (meters)^2. Insulin resistance was calculated from fasting plasma glucose and fasting insulin using the HOMA2 calculator (http://www.dtu.ox.ac.uk) (Levy et al., 1998).

2.4. Statistical analyses

The primary efficacy analysis was the change from baseline to week 4 in TMTB performance. A composite *Z*-score, defined as the equally weighted sum of the *Z*-scores in the TMTB, TMTA, DSST, RAVLT and STROOP, was calculated to indicate performance across a broad range of cognitive domains, including executive function, attention, processing speed, and learning and memory. The DSST score was assigned a weight of 0.25, and the two subtest scores of the RAVLT (acquisition [learning] and delayed recall [memory]), the TMT (A/B) and the Stroop (congruent and incongruent) were each assigned a weight of 0.125. The composite *Z*-score is used for the first time in this study and is based on the vortioxetine studies of patients with MDD (McIntyre et al., 2014). Comparisons between baseline and endpoint were performed using paired samples *t*-tests (SPSS Inc., Chicago, IL, USA) and Cohen's *d* effect sizes were calculated. A repeated-measures general linear model (GLM) was administered to test for co-variations and main effects. Interactions between changes in cognitive function and possible moderating variables (e.g. changes in mood scales, metabolic parameters) were assessed by adding the product term to the test models. Associations between changes in cognitive function and anthropometric measurements were assessed with Pearson correlations and linear regressions. The significance level was set at a p-value < 0.05.

3. Results

3.1. Sample characteristics

Nineteen participants were enrolled, and 17 completed the 4-week trial. Mean age at baseline was 38.21 (SD 7.81, range 22–54), and 11 participants were female (57.9%). Thirteen patients were diagnosed with MDD (68.4%) and 6 with BD (31.6%). No participant was in a severe mood episode, the mean HAM-D score at baseline was 12.63 (range 5–18) and the mean YMRS at baseline was 3.84 (range 0–11). Mean TMTB standard score (i.e. age and education corrected) at entry was 45.41 (SD 11.71). There were no differences between MDD and BD participants in baseline socio-demographic characteristics, as well as in cognitive and mood rating scales (all $p > 0.05$).

3.2. Safety, tolerability and withdrawals from the study

There were no serious adverse events for any participant during the study. Nausea was the most commonly reported side effect (36.8%); 2 participants (10.6%) reported severe nausea and voluntarily discontinued the liraglutide. Other treatment-emergent adverse events included dizziness (10.6%) and indigestion/feeling full (10.6%). There were no significant changes between baseline and endpoint in hepatic, renal and thyroid parameters (all *p*-values > 0.05). There were no changes in amylase values (mean =56.41, SD 21.82 vs. 58.35, SD 19.34, $p=0.206$), whereas lipase values increased (mean =24.70, SD 13.22 vs. 35.29, SD 14.45, $p < 0.001$). Nonetheless, no individual baseline or endpoint values were above the upper limit of normality (range 18–64).

3.3. Main Outcomes

In the pre-defined primary outcome, there was a significant increase from baseline to week 4 in the TMTB standard score (Table 1). There were also significant improvements in the DSST, RAVLT acquisition, Stroop congruent and incongruent, patient-rated PDQ and composite *Z*-score (Fig. 1). In addition, we observed significant changes in the HAM-D (mean =12.18, SD 4.82 vs. 8.41, SD 6.12, Cohen's *d* 0.68, $p=0.022$), SHAPS (mean =38.35, SD 6.41 vs. 42.88, SD 7.73, Cohen's d 0.64, p=0.010), GAF (mean =58.53, SD 6.40 vs. 74.71, SD 8.17, Cohen's d 2.20, $p < 0.001$) and CGI-S (mean =3.71, SD 0.68 vs. 2.53, SD 0.62, Cohen's d 1.81, $p < 0.001$)..

There was no difference in response between MDD and BD participants in mean TMTB scores ($p=0.452$) or in the composite *Z*-score ($p=0.958$). Finally, changes in the HAM-D did not moderate the changes between baseline and endpoint TMTB performance (p=0.150) or in the composite *Z*-score ($p=0.288$); similarly there was no moderating effect of changes in the SHAPS ($p=0.686$ and p=0.493, respectively).

Table 1
Differences between baseline and endpoint in cognitive measures.

	Baseline		Endpoint			
	Mean	SD	Mean	SD	% Change	*p*-value
TMTB (T-score)	46.41	11.71	53.18	9.36	14.59	0.009
TMTB (time)	65.80	27.81	50.39	14.15	−23.42	0.021
TMTA (time)	28.58	8.23	25.74	5.50	−9.94	0.172
DSST (number of symbols)	53.47	10.93	60.00	13.36	12.21	< 0.001
RAVLT acquisition (number of words)	7.18	3.67	8.53	2.91	18.80	0.021
RAVLT delayed recall (number of words)	7.35	3.92	8.41	3.31	14.42	0.185
STROOP – Congruent (time)	39.94	13.11	30.29	7.30	−24.16	0.001
STROOP – Incongruent (time)	58.00	13.07	51.94	10.25	−10.45	0.005
Composite z-score (all tests)	−0.26	0.74	0.26	0.60	20.51	< 0.001
PDQ (total score)	44.17	14.30	24.94	14.15	−43.54	< 0.001

SD: standard deviation; TMT, trail making test; DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; PDQ, Perceived Deficits Questionnaire

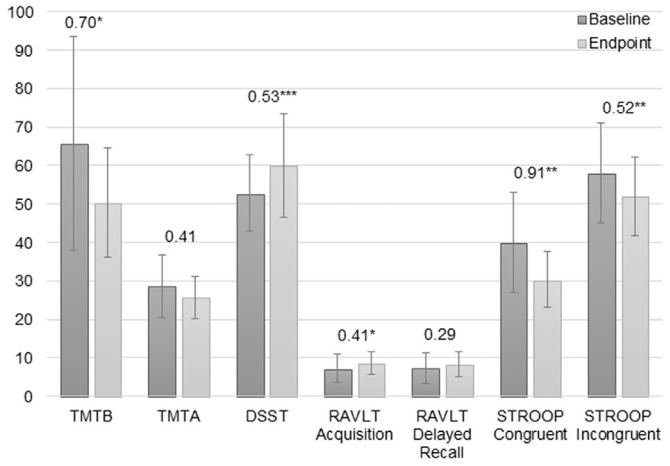

Fig. 1. Standardized effect size (Cohen's d) for the neuropsychological tests. DSST: Digit Symbol Substitution Test; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

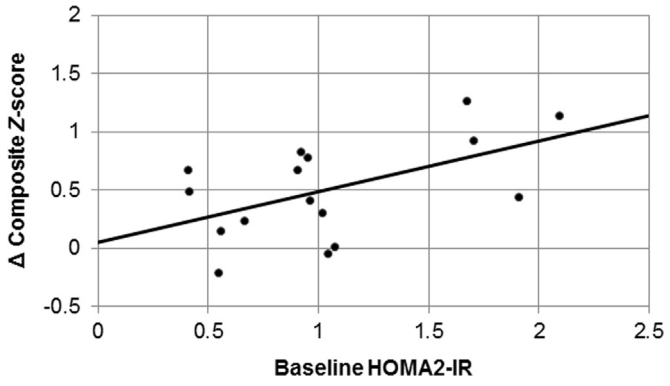

Fig. 2. Correlation between percentage change in the composite *Z*-score and baseline HOMA2-IR. HOMA2-IR: homeostasis model assessment - insulin resistance.

Changes in BMI or HOMA2-IR between baseline and endpoint did not moderate the changes in the TMTB (p=0.075 and 0.872, respectively) or in the composite z-score (p=0.309 and p=0.969, respectively). Interestingly, there was a significant moderating effect of baseline HOMA2-IR on changes in the composite z-score ($F_{1,15}$ =6.762, p=0.021), but not on the TMTB ($F_{1,15}$=1.409, p=0.255). Similarly, baseline BMI moderated changes in the composite z-score ($F_{1,15}$=4.771, p=0.046), but not in the TMTB ($F_{1,15}$=1.271, p=0.279). After adjustment for age and gender, there were positive associations between percent- change between baseline and endpoint in the composite z-score and baseline HOMA2-IR (β=0.409, 95% CI 0.090; 0.727, p=0.012) (Fig. 2) and baseline BMI (β=0.032, 95% CI 0.004; 0.061, p=0.025)..

4. Discussion

The primary result of this pilot clinical trial is that 4-week administration of adjunctive liraglutide was associated with significant improvement in objectively measured cognitive performance. The changes from baseline to endpoint were significant for multiple domains of cognitive function, including executive function, memory and a composite cognition score based on tests covering several domains of relevance for patients with MDD and BD. Effects sizes were relatively large (0.29 – 0.91) and were above the clinically meaningful threshold of 0.2 (Cohen, 1988). Although subjective cognitive function and objective neuropsychological assessments in patients with mood disorders are not strongly correlated (Naismith et al., 2007; Svendsen et al., 2012), we also documented that liraglutide administration concurrently improved subjective measures of cognitive function, as assessed by the PDQ. The magnitude of these effects, however, should be contextualized, as the open-label design and lack of placebo did not allow for the control of possible placebo and training effects.

These findings herein are largely consistent with the extensive preclinical literature on the cognitive effects of liraglutide and other GLP-1R agonists (McIntyre et al., 2013b). This is the second report on the effects of GLP-1 R agonists on cognition in human subjects. A recent 6-month, placebo-controlled randomized trial in individuals with Alzheimer's disease (AD) did not detect an effect of liraglutide on measures of cognitive function (Gejl et al., 2016). Instead, it was reported that liraglutide administration prevented the decline of cerebral glucose metabolism, which has been consistently associated with AD's pathological progression and, consequently, cognitive impairment (Engler et al., 2006; Mosconi, 2005). In addition to having a different patient population (i.e. individuals with manifested AD) and study design, Gejl et. al (2016) also studied a markedly older population (mean age 65.15) than the study herein (mean age 38.21). Of note is also a lower BMI at baseline (24.6 vs. 31.45), which, in this present study, was a moderator of response to liraglutide. These differences may at least partially explain the discrepant results between these studies.

Preliminary evidence suggests that the effects of GLP-1R signaling on cognition may be mediated by its neurotrophic and neuroprotective effects, which, in turn, are thought to be at least partially mediated through the facilitation of glucose and insulin signaling, as well as by the suppression of oxidative stress and inflammation. Vildagliptin, a drug that inhibits the inactivation of GLP-1 by the enzyme dipeptidyl peptidase-4 inhibitor (DPP-4), was shown to prevent neuronal insulin resistance by improving neuronal insulin receptor phosphorylation, and improve brain mitochondrial function in rats fed a high-fat diet (Pipatpiboon et al., 2013). A study of GLP-1 treated cell cultures demonstrated that GLP-1 treatment protected neurons from apoptosis induced by methylglyoxal (MG), a product of chronic hyperglycemia, which is considered a marker of oxidative imbalance (Iwai et al., 2009). Furthermore, studies have reported that liraglutide and exenatide administration reduced inflammatory activation in murine models of AD and cerebral ischemia (Darsalia et al., 2012; McClean and Holscher, 2014; Teramoto et al., 2011).

GLP-1R agonists have been associated with increased activation of neural circuits. Animal studies reported that peripheral GLP-1 administration induced a significant increase in the neuronal activity of the hypothalamic ventromedial and paraventricular nuclei, as well as of the parabrachial nucleus (Katsurada et al., 2014; Parkinson et al., 2009; Richard et al., 2014). In humans, an increase in hypothalamic connectivity was shown 2 h after a single intravenous dose of exenatide in obese male volunteers (Schlogl et al., 2013). A separate study demonstrated increased brain responses in reward-related brain regions (insula and amygdala) following administration of exenatide, with the effects being largely blocked by prior GLP-1R blockade (van Bloemendaal et al., 2014).

We observed that baseline BMI and IR moderated the response to liraglutide in our study, insofar as individuals with higher BMI and HOMA-IR were more likely to experience cognitive improvement. Evidence from preclinical studies indicates that GLP-1R agonists may improve brain insulin sensitivity and glucose metabolism. Reduced levels of brain insulin resistance, characterized by a decrease in insulin receptor substrate phosphorylation following administration of GLP-1R agonists, were reported (Bomfim et al., 2012; Long-Smith et al., 2013). One recent study documented that peripheral exposure to liraglutide resulted in increased insulin sensitivity in the hippocampus of patients with mild cognitive impairment (Talbot and Wang, 2014). The administration of GLP1-R agonists (i.e. liraglutide, exenatide) was reported to raise the cerebral metabolic rate in various brain regions (Daniele et al., 2015; Gejl et al., 2012; Gejl et al., 2016).

There is no direct evidence of abnormal central insulin signaling in

mood disorders, but there is consistent evidence that peripheral insulin resistance is associated with central insulin dysregulation (Heni et al., 2012; Kullmann et al., 2015a 2015b). Accumulating evidence indicates that metabolic comorbidities (e.g. obesity, type 2 diabetes mellitus [T2DM] and dyslipidemia), are highly prevalent in the mood disorders population (Crump et al., 2013; Gomes et al., 2013; McIntyre et al., 2010; Perugi et al., 2015; Vancampfort et al., 2013). Evidence also indicates that these metabolic comorbidities adversely affect MDD and BD outcomes; for instance, obesity, insulin resistance (IR) and T2DM are associated with an unfavorable course of BD, characterized by an overrepresentation of atypical features, a predominance of chronic / persistent trajectories, higher risk of suicide, treatment resistance and functional disability (Calkin et al., 2015; Goldstein et al., 2013; Handley et al., 2015; Mansur et al., 2016a; Ruzickova et al., 2003; Shapiro et al., 2016). Interestingly, it has been recently reported that elevated triglycerides, which are frequently correlated with IR (Mansur et al., 2016a; Ram et al., 2014), were also associated with poorer executive function among adolescents with BD (Naiberg et al., 2016). Conversely, evidence indicates that executive dysfunction is associated with suicide ideation and behavior (Bredemeier and Miller, 2015; Keilp et al., 2013; Malloy-Diniz et al., 2009), underscoring the relevance of adequately addressing cognitive deficits in the mood disorders population, particularly in the presence of a comorbid metabolic condition.

It has also been reported that obesity and T2DM are associated with neurostructural and neurochemical alterations in individuals with mood disorders (Hajek et al., 2015; Hajek et al., 2014), as well as with differences in peripheral markers, such as antioxidant enzymes and the brain-derived neurotrophic factors (Mansur et al., 2016b; Mansur et al., 2016c). Hence, it is possible to hypothesize that subpopulations of individuals with mood disorders that have manifested or underlying metabolic dysfunction and, putatively, would have, in its pathophysiology, a more prominent engagement of metabolic pathways, would be more responsive to an intervention that targets glucose and insulin metabolism (Mansur et al., 2015). Nonetheless, this is a hypothesis that needs to confirmed or refuted by larger and more refined studies. Specifically, larger, randomized controlled trials could use stratification strategies, using *a priori* defined subgroups based on phenotypes (e.g. obesity, T2DM), laboratorial parameters (e.g. HOMA-IR) or combinatorial approaches, as *post-hoc* subgrouping analyses have been successfully used by previous studies (Raison et al., 2013; Shelton et al., 2015). Mechanistic approaches, exploring not only potential predictors of response, but also upstream and downstream effector system (e.g. mammalian target of rapamycin [mTOR] signaling), should as well be incorporated.

Limitations of this pilot study include the small sample size, the open-label design, the lack of a placebo group or comparison with active glycemic-lowering agent, and its relative short duration (i.e. 4 weeks). The low statistical power of this study also limits the interpretation of the described moderational effects, as well as the separation between possible direct and indirect effects of liraglutide. Finally, we did not correct for multiple comparisons.

In conclusion, results from this pilot, open-label study indicate that GLP-1R agonists may be safe and well tolerated for non-diabetic individuals with mood disorders and may have beneficial effects on objective measure of cognitive function, which are possibly independent from its effects on mood and might be moderated by metabolic status. Our findings provide justification for exploration of GLP1R agonists on mood disorders, to characterize their efficacy, tolerability, and safety, as well as to examine possible stratification strategies, in larger samples, with controlled trial designs. We also believe that taking a dimensional/domain-based approach to therapeutic discovery and development represents an opportunity, insofar as we notionally view GLP-1 target engagement as offering beneficial effects in some psychopathological domains (e.g. cognitive systems) rather than others (e.g. circadian rhythms).

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