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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