12 Month Follow Up of Metabolic Measures Following a Randomised Controlled Trial of Treatment of Clozapine Associated Obesity and Diabetes with Exenatide (CODEX)

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Background

Clozapine is associated with obesity and type 2 diabetes (T2DM). Glucagon-like peptide-1 (GLP-1) receptor agonists such as exenatide can counter clozapine-associated GLP-1 dysregulation in animals, and may be beneficial in people on clozapine. Our randomized, controlled (RCT), open-label, pilot trial of once-weekly extended-release subcutaneous exenatide or treatment as usual (TAU) for 24 weeks (n=28), found 6 of 14 people on exenatide achieved >5% weight loss vs 1 of 14 receiving usual care (P = .029). Compared with TAU, participants on exenatide had greater mean weight loss (−5.29 vs −1.12 kg; P = .015) and body mass index (BMI) reduction (−1.78 vs −0.39 kg/m²; P = .019), and reduced fasting glucose (−0.34 vs 0.39 mmol/L; P = .036) and glycated haemoglobin (HbA1c) levels (−0.21% vs 0.03%; P = .004).

Methods

We followed up CODEX trial participants at 12 months following the end of the trial. We collected information on weight, BMI, waist circumference, blood pressure, fasting glucose, HbA1c, and use of metformin. The primary outcome of interest was change in weight. Change in these parameters from trial baseline to 12 months post endpoint and trial endpoint to 12 months post endpoint was compared between those formerly in the exenatide and TAU arms

Results

There were no significant differences between baseline and 12-months post endpoint for any of the variables. Data from endpoint to 12-month follow up point showed significantly greater increases among the former exenatide group compared to the former TAU group for weight, BMI, and proportion with >5% weight gain. When results for were stratified by whether participants were on metformin six months after the end of the trial (5 former TAU and 7 former exenatide were on metformin), the former exenatide group had a greater proportion with >5% weight gain between endpoint and 12 months post endpoint irrespective of whether or not they were on metformin.

Figure 1. Study Flow Chart

Figure 2: GLP-1 agents regulate satiety behaviour via efferent outflow from the central nervous system (CNS) by both direct activation GLP-1Rs in brain centres involved in feeding (via blood-brain barrier leaks) and indirectly via vagal afferents originating in the intestine. Through the effects of GLP-1R activation in the brain (particularly hypothalamic and brainstem nuclei), GLP-1 and its analogues reduce food intake thereby causing weight loss. Glycaemic control by GLP-1 occurs through the combined contribution of all CNS dependent and independent pathways. Dashed arrows represent indirect effects of GLP-1 not mediated by direct interaction with GLP-1 receptors. Figure adapted from “Heppner KM, Perez-Tilve D. GLP-1 based therapeutics: simultaneously combating T2DM and obesity. Frontiers in neuroscience. 2015;9:92”.

Table 1 Change in Variables	Mean Diff	Std. Error	P value
Baseline to 12 Months Post			
Weight	4.11	2.59	0.125
BMI	1.40	0.89	0.13
Systolic Blood Pressure	0.70	3.49	0.843
Diastolic Blood Pressure	-4.02	3.21	0.224
Waist Circumference	0.89	3.10	0.779
Fasting Plasma Glucose	0.39	0.63	0.544
HbA1c	0.68	0.25	0.022
Triglycerides	0.02	0.46	0.970
HDL Cholesterol	0.03	0.08	0.711
LDL Cholesterol	-0.02	0.39	0.968
Total Cholesterol	-0.11	0.39	0.778
Endpoint to 12 Months Post			
Weight	8.28	2.03	<.0.001
BMI	2.83	0.67	<0.001
Systolic Blood Pressure	2.59	3.39	0.453
Diastolic Blood Pressure	2.38	3.88	0.545
Waist Circumference	3.04	2.81	0.296
Fasting Plasma Glucose	1.24	0.68	0.084
HbA1c	0.81	0.24	0.009
Triglycerides	0.04	0.46	0.924
HDL Cholesterol	-0.07	0.10	0.495
LDL Cholesterol	0.35	0.27	0.217
Total Cholesterol	-0.02	0.35	0.961

Table 2 >5% weight gain	<5% weight gain	>5% weight gain	P value
All participants			
Former TAU (n=14)	14 (100%)	0 (0%)	<0.001
Former Exenatide (n=13)	5 (38.5%)	8 (61.5%)	
On Metformin			
Former TAU (n=5)	5 (100%)	0 (0%)	0.038
Former Exenatide (n=7)	2 (40%)	3 (60%)	
Not on Metformin			
Former TAU (n=8)	8 (100%)	0 (0%)	
Former Exenatide (n=5)	3 (42.9%)	4 (57.1%)	

Conclusions

Although there were no significant differences in weight and BMI between baseline and 12-month post endpoint, there were significant increases in weight and BMI in the 12 months post endpoint for the former exenatide group. This was irrespective of metformin use. This is in keeping with other GLP-1RA studies. This information suggests the need for continued use of exenatide among people on clozapine who have achieved weight loss.