**Obesity and Schizophrenia: Results of a Feasibility Study with Semaglutide to Assist Weight Loss**

**Running title**: **GLP-1 Therapy for Obesity in Schizophrenia**

Adrian H. Heald1,2, Gavin Reynolds3, Isabel Nash4, Onagh Boyle4, Chris Daly4, Damien Longson1,4, Donal O’Shea5, Joseph Ingram4, Richard Holt6, Joseph Firth4, Mike Stedman7, Akheel Syed1,2, Marc de Hert8

1University of Manchester, Manchester, UK; 2Salford Royal Hospital, Salford, UK; 3University of Sheffield, Sheffield, UK; 4Greater Manchester Mental Health, Manchester, UK; 5St Vincents Hospital, Dublin. Eire; 6University of Southampton, Southampton, UK, 7Res Consortium, Andover, UK; 8Psychiatry, Leuven Brain Institute, Leuven, Belgium

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Corresponding author:

Professor Adrian Heald

University of Manchester

adrian.heald@nca.nhs.uk

Telephone: + 44 7470 532162

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**Abstract**

Introduction

Weight gain has come to define the life experience of many individuals with schizophrenia and other severe enduring mental illnesses (SMI). In this clinical intervention study, we aimed to determine whether weekly treatment with the glucagon-like peptide-1 (GLP-1) agonist, semaglutide, as part of usual care, is feasible and acceptable to individuals in a psychiatric inpatient setting.

Methods

15 inpatients (11 men / 4 women) in a secure care environment, diagnosed with schizophrenia or schizoaffective disorder and with body mass index (BMI) of a least 30 kg/m2 were commenced on weekly subcutaneous semaglutide as per standard of care. BMI and glycated haemoglobin (HbA1c) were measured at baseline and monthly follow-up to 6 months, and quality of life (QOL) was surveyed at baseline and 6 months. Analysis was based on intention-to-treat.

Results

Mean age of patients was 37 years (range 23–63). Time since diagnosis varied from 2 to 25 years. Mean initial BMI was 48.7 kg/m2 for women and 37.2 kg/m2 for men. Duration of semaglutide treatment ranged from 2–6 months. The EuroQol 5-Dimensional Questionnaire, 5-Level Version Visual Analogue Scale (EQ5D5L QOL VAS) showed a mean improvement of +7.5 (from 60 to 67.5) points. Improvement in QOL was overall significantly greater in those who remained on semaglutide (+9.5) than those who discontinued.

Six patients discontinued semaglutide before the study end, including two who were discharged and no longer able to receive the intervention, and four who withdrew due to medical concerns or patient choice.

Individual percentage weight change varied from +1% to -12% (median 5%), and weight reduction was seen in all except two patients. All but one patient demonstrated a reduction in HbA1c levels.

Mean HbA1c fell significantly from 41 (range 34–47) mmol/mol to 35.3 (31–45) mmol/mol (5.9% to 5.4%). Importantly, all patients with baseline HbA1c in the non-diabetic hyperglycaemia range (42-47 mmol/mol) (6.0% to 6.5%) demonstrated a reduction of HbA1c to below 42 mmol/mol (6.0%) by 3 months into semaglutide treatment.

Prior to initiation of semaglutide, mean blood pressure was 127 (range 117–145) mmHg systolic and 82 (62–99) mmHg diastolic. At last assessment, average blood pressure was reduced to 121 (107–136) mmHg systolic and 79 (65–96) mmHg diastolic.

Conclusion

In this feasibility study, weekly semaglutide treatment was associated with improvement in self-rated overall QOL and reductions in BMI, HbA1c and blood pressure at up to 6 months follow-up. Even in patients who discontinued

 treatment before 6 months, initial benefits of weight reduction and improved QOL were still demonstrated.

Further evaluation, including health economic assessment and longer-term follow up, may support the expanded use of GLP-1 agonists in improving the cardiometabolic profile and longitudinal health outcomes in individuals with SMI.

**Why we carried out the study**

Weight gain has come to define the life experience of many individuals with schizophrenia and other severe enduring mental illnesses (SMI).

In this clinical intervention study, we aimed to determine whether weekly treatment with the glucagon-like peptide-1 (GLP-1) agonist, semaglutide, as part of usual care, is feasible and acceptable to individuals in a psychiatric inpatient setting.

**What was learnt from the study**

In this open real-world evaluation of the feasibility of prescribing and administering semaglutide as part of standard care in a secure inpatient setting, we saw an improvement in self-rated overall quality of life, a reduction in BMI and clinically significant reduction in HbA1c (even in those who discontinued semaglutide),

Four out of 15 patients permanently discontinued semaglutide because of adverse effects / patient choice, with one other patient after a short break, restarting with close monitoring of liver enzymes. 2 patients were not able to continue because of no funding to continue the semaglutide on discharge.

Further work, including health economic assessment and full evaluation of experienced side effects, may inform the opportunity of GLP-1 agonist therapy being offered more widely in this group of very vulnerable patients.

We hope that our findings will support the use of semaglutide and potentially similar agents to help people with severe enduring mental illness who are overweight to achieve a healthier health profile.

**Introduction**

Weight gain with all its adverse health consequences has come to define the life experience of many people with schizophrenia and other severe enduring mental illnesses (SMI). Weight gain associated with treatment of serious mental illness (SMI) is a determinant of future diabetes, dysmetabolic profile and increased cardiometabolic risk in people treated with antipsychotic agents (1,2). Early weight gain predicts greater magnitude of longer-term weight gain, with the attendant long-term consequences including premature cardiovascular events and death (3).

Considerable variability in weight gain and metabolic effects exists between individuals in both the intermediate and longer term (4). Young and antipsychotic-naïve individuals as well as women are at particularly high risk of weight gain in the short to intermediate term (5,6,7). Genetic factors likely play a significant part in the degree to which weight gain occurs with antipsychotic treatment (8). It is well established that antipsychotic related weight gain is a common reason for non-initiation, discontinuation, and dissatisfaction with psychotropic agents, which may result in adverse health outcomes and increased cost of illness (9,10).

Glucagon-like peptide-1 (GLP-1) receptor agonists and other incretin based therapies or intensive weight reduction programmes have been shown to lower body weight, improve cardiovascular outcomes and lower blood glucose levels (11).

A host of randomized control trials have demonstrated the weight-loss efficacy of GLP-1 receptor agonists in both diabetes and non-diabetes cohorts, In the STEP 1 trial of adults, without diabetes, after 68-weeks 86.4% of the GLP-1 agonist (Wevoyy) group lost at least 5% on baseline weight, compared with 31.5% for placebo. Semaglutide led to 69.1% (vs 12.0%) losing ≥10% weight (69.1 vs 12.0%) with ≥20% reduction of baseline weight achieved in 32.0% (vs 1.7%) of participants (12). The SURMOUNT-1 trial found that in people / individuals with overweight but without diabetes, 72 weeks of the combined GLP-1/GIP agonist, tirzepatide, at doses of 5, 10, or 15 mg led to 15.0%, 19.5%, and 20.9% weight loss, respectively, compared with 3.1% in people taking placebo (13). For the co-primary endpoint of the proportion of people attaining at least a 5% reduction in their baseline bodyweight, the corresponding values were 85%, 89%, and 91% versus 35%.

It therefore seems likely that GLP-1 receptor agonists and other incretin therapies could be of substantial value in addressing the challenge of obesity in people with SMI, given the well-established evidence for their ability to reduce weight in individuals with overweight (12,13)

In this pragmatic intervention, we aimed to determine whether weekly semaglutide treatment is feasible and acceptable to individuals in a psychiatric inpatient setting and can enable weight reduction in people with a history of psychosis who are facing major challenges in relation to their weight management. No-one in the study had a diagnosis of type 2 diabetes, hence the novelty of this study.

**Methods**

15 people (11 men and 4 women) with a diagnosis of schizophrenia or schizoaffective disorder according to ICD-10 (14) with a body mass index (BMI) of at least 30 kg/m2 were commenced on the GLP-1 agonist semaglutide (Wegovy), administered as a weekly subcutaneous injection as per the British National Formulary (BNF) in increasing dose increments and if tolerated up to a maximum dose of 2.4mg / week (in monthly increments).

All participants were inpatients on a medium secure psychiatric unit in North-West England and were detained under the Mental Health Act (1987) (15) and had been treated with high doses of antipsychotic medication. No-one had a diagnosis of type 2 diabetes.

This was a clinical intervention as part of usual care, according to NICE guidance (16) for prescribing of semaglutide according to its licence for treatment of obesity, in collaboration with the local specialist weight management clinic. This was not a clinical trial, rather examination of the practicality of offering this medication to patients in an inpatient setting.

This was a service improvement project. The UK Health Research Authority decision tool did not consider this study to be research and therefore NHS Research Ethics Committee review was not required. All patients who received semaglutide gave verbal consent to receiving this medication as part of their usual care. Their consent was recorded in the electronic patient hospital record.

Body mass index (BMI) and glycated haemoglobin (HbA1c) were assessed at baseline and follow-up. All individuals receiving semaglutide underwent a dietetic assessment with advice given regarding healthy eating and avoidance of calorie excess.

In relation to a patient reported outcome measure (PROM), we assessed quality of life using EuroQol 5-Dimensional Questionnaire, 5-Level Version Visual Analogue Scale (EQ5D5L) (17) Licence Agreement number 155361. This was completed at baseline and follow-up. The licence to use this is held by the Northern Care Alliance.

Statistics

Data Collation, Cross-sectional and Longitudinal Analysis was carried out in EXCEL. Data are shown as mean and range.

**Results**

The group who were treated with semaglutide comprised 11 men and 4 women. All had a diagnosis of schizophrenia or schizoaffective disorder The mean age of patients was 37 years (range 23-63) (Table 1). Time since diagnosis varied from 2 to 25 years 12 were of white ethnicity and 3 were of Asian British or Black British ethnicity. The minimum duration of treatment with semaglutide was 2 months.

Mean BMI at baseline was 38.7 (range 32.7-52.9) kg/m2.

Four individuals elected to come off the semaglutide. Reasons for discontinuation included unhappiness with the treatment and nausea (likely compounded by gallstones).

The mean duration on the intervention was 20 weeks (range 8-27 weeks). The patients stayed on semaglutide for average of 23 weeks. In 1 patient (in addition to the four above) the semaglutide was stopped because of concerns about elevation of the liver enzyme alanine transaminase (ALT) - they then did restart semaglutide with close blood monitoring of liver enzyme levels. Two other patients had to discontinue semaglutide because this medication could no longer be continued on their discharge, as there was no funding for outpatient treatment with semaglutide, once they left hospital.

The EuroQol 5-Dimensional Questionnaire, 5-Level Version Visual Analogue Scale (EQ5D5L VAS) (17) showed mean improvement of 9.7 (range 0 to 30.1 (Figure 1). Improvement in QOL was overall greater in people who stayed on semaglutide vs those who discontinued but in fact QOL was actually overall already better at baseline for those who discontinued semaglutide by their own choice (excluding those who had to stop because they left hospital.

**Table 1.** Summary Patient Characteristics (data are shown as means)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age (years) | Duration of Illness (years) | Duration weeks | BMI start  | BMI Latest | HbA1c start | HbA1c latest |
| Men | 35.6 | 8.0 | 18 | 37.2 | 35.4 | 43 | 38 |
| Women | 40.5 | 18.4 | 19 | 48.7 | 47.1 | 41 | 34 |

Outcomes

The degree of weight change over the period of intervention with semaglutide varied from +1% to -12% (Figure 2), median 5%. Some degree of weight loss occurred in all but one patient. including the 2 people who were discharged and no longer able to receive semaglutide and for 4 patients who elected to come off semaglutide.

For all but one patient HbA1c fell at 3 months (Figure 3). Importantly all those with a baseline HbA1c in the range 42-47 mmol/mol (6.0% to 6.5%) compatible with non-diabetic hyperglycaemia saw a reduction of HbA1C below 42mmol/mol (6.0%) at 3 months into the intervention. Mean HbA1c fell from 41.3 (range 34-47) mmol/mol. to 35.3 (31-45) mmol/mol (5.9% to 5.4%).

Prior to the imitation of semaglutide, mean systolic blood pressure was 127 (range 117-145) mmHg and diastolic blood pressure 82 (62-99) mmHg. At the last assessment the average systolic blood pressure had fallen to 121 (107-136) mmHg and diastolic blood pressure to 79 (65-96) mmHg.

**Discussion**

In this open real world evaluation of the feasibility of prescribing and administering semaglutide in a secure inpatient setting, we saw a reduction in BMI, clinically significant reduction in HbA1c and improvement in self-rated overall quality of life in people with major mental and physical health challenges at up to 6 month follow-up.

Four out of 15 patients discontinued the semaglutide as they did not wish to continue the treatment either because of nausea or perceived lack of efficacy. The fact that 2 patients were not able to continue semglutide because of no funding to continue the semaglutide on discharge is a concern. At present, availability of incretin therapies for weight reduction in the absence of a diagnosis of type 2 diabetes in England and in many other publicly funded health care systems is very limited, even for those people at high cardiometabolic risk.

Reduction in weight was associated with improvement in QOL VAS was significant ((p<0.009) (mean change +9.7) for those who remained on semaglutide. For those who requested to discontinue semaglutide of their own choice QOL VAS did not improve. However those discontinuing semaglutide did have a higher baseline QOL VAS than those who stayed on semaglutide. All patients, even those who discontinued semaglutide expressed a positive view on being on this medication in relation both to their expectations and the experience of receiving semaglutide.

All those with an HBA1c in the non-diabetic hyperglycaemia range reduced their HbA1c below the range of non-diabetic hyperglycaemia (below 42-47mmolmol) (6.0%-6.5%). One person who had to discontinue semaglutide because of elevation or serum ALT restarted the semaglutide with close monitoring of liver enzymes.

Thus offering and using semaglutide is feasible in in-patients in a medium secure unit setting. Semaglutide is effective at lowering body weight and improving metabolic profile in relation to HbA1c, with an associated improvement in quality of life for those who remained on semaglutide as seen here. This is important in the context of acceptability of this approach to people with SMI.

It is well established that antipsychotic related weight gain is a common reason for non-initiation, discontinuation, and dissatisfaction with psychotropic agents (18). The benefit of lifestyle change and behavioural modification to mitigate antipsychotic weight gain in people with SMI is established (19). One can speculate that weight reduction and attendant improvement in quality of life may lead to better antipsychotic concordance and so better psychiatric outcomes.

In addition, obesity is associated with reduced health-related quality of life and psychosocial function (20). Evidence from mortality studies also indicates that cardiovascular disease, for which obesity is a modifiable risk factor, is the most common cause of premature and excess mortality among patients with mood and psychotic disorders (21,22,23). Thus any intervention that is tolerated by people with SMI that enables weight reduction, particularly if this is 5% or more, is likely to have benefit in relation to longer term health outcomes including premature mortality (24). Furthermore any reduction of HbA1c has the potential to improve the cardiovascular risk calculus for any individual (25).

The reduction seen in both systolic and diastolic blood pressure was not anticipated and provides further evidence for the value of GLP-1 treatment in improving the cardiovascular risk profile in people with SMI (26).

It is also relevant to point out that the group of people who received the semaglutide at the severe end of the spectrum of SMI as they were all at the time of the intervention formally detained under the Mental Health Act (27) in a medium secure unit setting. Thus leave to the community was limited and subject to the approval of the psychiatrist in charge of their care (deemed Section 17 leave in England and Wales) and at weekends the opportunities for leave off the ward were limited for logistical reasons on Saturdays, Sundays and national holidays.

There are other potential benefits of incretin treatment in people with schizophrenia and schizoaffective disorder. In addition to the body of evidence in the area of weight reduction, GLP-1 agonists have also been reported to improve cognitive processing in humans. However the results tend to show an improvement in some domains (for example hippocampal connections, cerebral glucose metabolism, hippocampal activation on functional magnetic resonance imaging) without demonstrating a strong correlation to cognitive scores (28).

In animal models, GLP-1 agonist administration has been shown to reduce addiction driven behaviours (29). Most of the work on GLP-1 in the alcohol field has been done with the drug exenatide and, more recently, with liraglutide and dulaglutide, but literature is scarce on the potential impact of semaglutide, on alcohol-related outcomes, Nevertheless a recent study reported that analogue semaglutide decreased alcohol intake across different drinking models in different species with related modulation of central GABA neurotransmission (30).

Limitations

This is a short term feasibility intervention with relatively low numbers. We accept this as a limitation. Not all patients remained on semaglutide. However all but one did lose weight.

We accept that that it was far from ideal that when patients left hospital, they were no longer able to access semaglutide. However there was no funding available to continue the prescription at the time of the study, because of delays in conformation of clinical pathways in the UK.

**Conclusion**

At up to 6-month follow-up following initiation of semaglutide, we have seen a reduction in BMI, reduction in HbA1c and improvement in self-rated overall quality of life in people with schizophrenia and schizoaffective disorder with major mental and physical health challenges.

While there are costs attached to the prescription of incretin therapy in people with SMI, further evaluation, including health economic assessment may support them being offered more widely with a view to improving cardio metabolic profile and longer time health outcomes in people with SMI, many of whom are at high or very high cardiometabolic risk.

We hope that our findings will support the use of semaglutide and potentially similar agents to help people with severe enduring mental illness who are overweight to achieve a healthier health profile.

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Author Contributions: Adrian Heald and Gavin Reynolds conceived the study. Adrian Heald arranged funding of the semaglutide intervention in consultation with Onagh Doyle and Chris Daly. Joseph Firth provided essential input in relation to the implementation of the intervention and its evaluation as did Damien Longson. Isabel Nash and Onagh Doyle enabled the intervention to take place with ongoing regular input and guidance from Chris Daly. Isabel Nash supervised follow-up of all patients involved. Data analysis was undertaken by Mike Stedman. Marc de Hert, Joseph Ingram, Richard Holt and Donal O’Shea provided context in relation to the relevance of the intervention and the implications of the findings while providing clinical context. Akheel Syed provided guidance concerning obesity management. All authors reviewed the manuscript during its development, approved the final version and agree to be accountable for all aspects of the work.

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Data availability; The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

Adrian H Heald, Gavin Reynolds, Isabel Nash, Onagh Boyle, Chris Daly, Damien Longson, Donal O’Shea, Joseph Ingram, Richard Holt, Joseph Firth, Mike Stedman, Akheel Syed, Marc de Hert have no conflict of interest.

Ethics: This intervention formed part of usual care based on clinical need. Therefore ethical approval was not sought. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. This was a service improvement project. The UK Health Research Authority decision tool did not consider this study to be research and therefore NHS Research Ethics Committee review was not required. All patients who received semaglutide gave verbal consent to receiving this medication as part of their usual care. Their consent was recorded in the electronic patient hospital record.

Guarantor Statement: AH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Participants: We thank the participants in the study

**Figure Legends:**

## Figure 1: Change in EuroQol 5-Dimensional Questionnaire, 5-Level Version (EQ5D5L) Visual Analogue Scale (VAS) score after initiation of semaglutide

## Figure 2: Change in Body Mass Index (BMI) after initiation of semaglutide

## Figure 3: Change in glycated haemoglobin HbA1c (mmol/mol and %) after initiation of semaglutide. HbA1c was checked every 2-3 months

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