Study Protocol

The Effect of Adjunctive Exenatide Treatment on Psychopathology, Cognition and Metabolism in Patients with Schizophrenia

PI: Xiaoduo Fan, MD, MPH

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INSTRUCTIONS:

1) Title

Exenatide weekly injection as an adjunctive treatment in patients with schizophrenia

2) IRB Review History*

N/A

3) Objectives*

This is a 24-week, randomized, double-blind, placebo-controlled trial of exenatide weekly injection (2mg per dose) as an adjunctive therapy in 70 schizophrenia subjects to examine exenatide's effects on negative symptoms and cognition.

Primary aim: Examine the efficacy of exenatide weekly injection in improving negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) total score.

Secondary aims: Examine the efficacy of exenatide in improving cognition as measured by the MATRICS Consensus Cognitive Battery (MCCB) composite score.

Tertiary/exploratory aims:

1. Examine exenatide's effect on schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) total score.
2. Examine the efficacy of exenatide in improving social function as measured by the Instrumental Activities of Daily Living Scale (IADL) and the Heinrichs Carpenter Quality of Life Scale (QLS).
3. Examine exenatide's effect on neuro-protection as measured by the change in hippocampal volume.
4. Examine exenatide's effects on inflammatory markers including serum levels of high sensitivity CRP, IL-6, and TNF-α.
5. Examine the potential moderator role of baseline serum levels of CRP, IL-6, TNF-α, and baseline hippocampal volume for exenatide's effects on negative and cognitive symptoms.
6. Examine the potential mediator role of changes from baseline in serum levels of CRP, IL-6, TNF-α, and hippocampal volume for exenatide's effects on negative and cognitive symptoms.
7. Examine the efficacy of exenatide in reducing body weight and improving glucose metabolism as measured by fasting plasma glucose and HbA1c.
8. Examine the safety and tolerability of exenatide as measured by changes in the side effects questionnaire (SEQ, SEQabbrev), EKG and vital signs

4) Background*

Negative symptoms and cognitive deficits in schizophrenia: Schizophrenia can be a devastating illness for patients, often producing life-long disability. Two major factors contributing to

functional disability in schizophrenia are negative symptoms and cognitive impairment, which are the biggest obstacle to achieving an independent and productive lifestyle, with these deficits being refractory to current drug treatments.

(1-3).

Inflammation and negative symptoms: Evidence of immune dysfunction and inflammation has been described in patients with schizophrenia (4-7). A series of recent studies from our group have demonstrated abnormal patterns of immune activation, including elevated serum levels of IL-1β, IL-6, TNF-α, interferon-γ, increased nuclear factor-κB (NF-κB) activation and its mRNA expression in peripheral blood mononuclear cells (PBMC) in first episode schizophrenia patients (8, 9). The findings from our group and others also support an altered immune function characterized by shifting from a Type 1 (cellular) to a Type 2 (humoral) immune response (10, 11). Several studies have suggested that the dysregulation of inflammatory and immunological processes is likely related to the manifestation of symptoms and treatment response of schizophrenia (12, 13). We reported that specific markers for inflammation, including elevated blood levels of C-reactive protein (CRP) and white blood cell count (WBC), are associated with negative symptoms of schizophrenia (14, 15).

Inflammation and cognition: Considerable evidence links inflammation to cognitive impairment in non-schizophrenia populations (16). Higher plasma levels of CRP and interleukin-6 (IL-6) have been associated with poorer cognitive performance at baseline and with a greater risk of cognitive decline over a 2-year follow-up period in well-functioning elders (17). In the community-based Framingham study cohort, higher levels of IL-1 and TNF-α both were markers of future risk of Alzheimer disease in older individuals (18). Further, it has been suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) offers some protection against the development of Alzheimer's disease (19). Inflammation is also associated with cognitive impairment in schizophrenia. In a sample of 413 patients with schizophrenia, Dickerson et al. measured the levels of CRP, reported that those with CRP $\geq$ 5 mg/mL had significantly lower cognitive scores than those with CRP < 5 mg/mL (20). We recently found that schizophrenia patients with a TNF-α –308G/G genotype (N=83) had better executive function than those with G/A or A/A genotypes (N=31).

Hippocampal volume loss in schizophrenia: Studies have found evidence for a progressive loss of cortical tissue volume in the early phase of schizophrenia. First episode patients have shown cortical volume reductions of 1% or more per year; these changes are thought to be most active during the first few years of the illness, with some leveling off of this degenerative process as the disease becomes chronic. Progressive volume loss seems most pronounced in the frontal and temporal gray matter areas (21). Reduced hippocampal volume has been consistently reported in both first episode psychosis and chronic schizophrenia (22-24). Postmortem studies in schizophrenia patients have also demonstrated subtle anomalies in limbic structures, most consistently in the hippocampus (25).

Hippocampal volume loss – in relation to cognitive deficits, negative symptoms and functional impairment in schizophrenia: The hippocampus is a highly plastic brain region; new neurons are continuously produced in the dentate gyrus of the hippocampus throughout life. The amount of neurogenesis correlates closely with the hippocampal function of learning and memory (26, 27). Hippocampal pathology has been proposed to underlie clinical, cognitive and functional impairments in schizophrenia (28). Progressive cortical loss is associated with more negative symptoms, cognitive decline and a more severe course of illness (21). A significant inverse correlation between left hippocampal volume and negative symptoms of schizophrenia has been reported previously (29). Studies also demonstrated a significant correlation between reduced hippocampal volume and cognitive deficits in patients with schizophrenia (30). Further, a recent study reported that bilateral hippocampal increase occurs in a minority of patients following their first psychotic episode and is associated with good outcome across clinical, cognitive and functional domains (31).

Inflammation and hippocampal volume loss in schizophrenia: Overwhelming evidence from animal studies indicates that activation of microglia and the subsequent release of pro-inflammatory cytokines including IL-1β, TNF-α and IL-6 have negative effect on hippocampal neurogenesis. Activated microglia and inflammatory cytokines may reduce cell proliferation, survival and function of new neurons in hippocampus (32). The initial work demonstrating that classically activated microglia impair hippocampal neurogenesis was reported by Monje et al. (33) and Ekdahl et al. (34) following lipopolysaccharide (LPS) administration in rats. Earlier post-mortem studies have shown the presence of microglial activation in the brains of patients with schizophrenia (35, 36). More recent studies using positron emission tomography (PET) in live patients with schizophrenia further demonstrated microglia activation especially in temporal-limbic gray matter (37, 38). Microglia, a major source of various inflammatory cytokines and free radicals such as superoxide and nitric oxide in the brain, play a crucial role in apoptosis and the neurodegenerative process (39). Negative symptoms and cognitive deficits in schizophrenia may in part be related to inflammation-induced reduction in adult hippocampal neurogenesis and volume loss.

Anti-inflammatory treatment and hippocampal neurogenesis: Administration of the microglia inhibitor, minocycline, blocked the LPS-induced decrease in new neuron survival in the hippocampus (34). In another study, inflammatory blockade with indomethacin, a common nonsteroid anti-inflammatory drug, restores hippocampal neurogenesis after LPS-induced inflammation in rats (33). Anti-inflammatory treatment may preserve hippocampal neurogenesis, therefore slow down or even reverse the hippocampal volume loss process in schizophrenia.

Anti-inflammatory treatment in schizophrenia: Muller et al. conducted a 6-week trial of celecoxib augmentation to amisulpride treatment in patients with first episode of schizophrenia, and found a significant therapeutic effect of celecoxib as measured by the PANSS total score and the negative symptom subscale score (40, 41). Another commonly used anti-inflammatory agent, aspirin, was also studied in the schizophrenia population. It was reported that aspirin as an adjuvant therapy to antipsychotic treatment reduced schizophrenia symptoms as measured by

the PANSS total score (42). A recent study also found minocycline, a second-generation tetracycline that exerts anti-inflammatory and antimicrobial effects, was associated with improvement in negative symptoms and executive function in early phase schizophrenia (43, 44). Despite the promise of potential benefit of celecoxib, aspirin and minocycline in schizophrenia treatment, there are both important scientific and safety issues to be addressed: Scientifically, it is unclear which brain target is engaged in anti-inflammatory treatment, and by which mechanism these anti-inflammatory drugs affect the target. On the safety aspect, the adverse side effects related to these drugs limit their potential clinical therapeutic utility in the schizophrenia population. Celecoxib and other COX-2 inhibitors have been associated with an elevated risk of cardiovascular disease (45), which is a serious comorbid medical condition in patients with schizophrenia. The cardio-protective non-selective COX inhibitor aspirin is arguably preferable. However, it is well established that aspirin, especially used in a relatively high dosage, is associated with a significant risk for GI bleeding. Tetracyclines are known to have side effects of pigmentation changes, pediatric tooth discoloration and photosensitivity reactions (46).

GLP-1 and its analogues: Glucagon-like peptide-1 (GLP-1) is an endogenous 30-amino acid peptide hormone, which is secreted from the intestinal L-cells in response to ingested carbohydrate and fat. It stimulates insulin secretion in a glucose-dependent manner and inhibits glucagon secretion from the pancreas. Exendin-4 is a peptide agonist of GLP-1 receptor (GLP-1R) that promotes insulin secretion. Two longer-lasting GLP-1 analogues (exenatide - a synthetic exendin-4, and liraglutide) are two FDA-approved medications for diabetes treatment. In addition to glycemic control, treatment with GLP-1 analogues is also associated with moderate weight loss, and improvement in cardiovascular risk factors (47). Given the overall favorable safety profile and weight effect, a low risk of hypoglycemia, and clinically meaningful improvements in HbA1c in various patient populations, the guidelines of the American Association of Clinical Endocrinologists (AACE) and the recently updated guidelines from the American Diabetes Association (ADA) assign exenatide and liraglutide a central role in the treatment of diabetes (48).

Exenatide, a synthetic exendin-4, is available in two formulations: twice daily and once weekly. Exenatide twice daily is the first glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes. Exenatide once weekly is the first glucose-lowering agent that is administered once per week. This long-acting formulation contains the same active ingredient as exenatide twice daily, except that the exenatide is encapsulated in dissolvable microspheres.

GLP-1 and inflammation: Recent evidence has shown that GLP-1 and analogues have anti-inflammatory activity. It has been shown that both activated microglia and activated astrocytes bind GLP-1 and that GLP-1 can prevent lipopolysaccharide (LPS)-induced increase in interleukin-1β (IL-1β) in these cells (49). Other studies reported that exendin-4 can reduce monocyte adhesion to aortic endothelium in a model of atherosclerosis and prevent LPS-induced cytokine and chemokine mRNA synthesis in both human and mouse monocytes (50, 51).

Recent clinical studies also have demonstrated that exenatide exerts a potent anti-inflammatory effect (52-54). In a double-blinded, 16-week study with 23 patients with diabetes and inadequate glucose control, subjects were randomly assigned to receive exenatide (5μg twice daily for 4 weeks followed by 10μg twice daily for 12 weeks) or placebo; exenatide treatment significantly reduced oxidative stress and high sensitivity CRP (55). In a more recent study, 24 patients with diabetes were randomized to be on exenatide 10μg twice daily or placebo for 12 weeks; the results showed that exenatide significantly decreased reactive oxygen species generation, NF-κB binding, the mRNA expression of TNF and IL-1β in PBMC, and serum levels of IL-6 (56). In another study, patients with diabetes were treated with exenatide 2mg once weekly or 10μg twice daily for 30 weeks; in addition to improving glycemic control and lipids, both the once weekly and twice daily exenatide regimens significantly reduced serum levels of high sensitivity CRP (57).

GLP-1 and neuro-protection: GLP-1Rs are found in cerebral cortex, hippocampus, hypothalamus, and thalamus. The distribution of GLP-1 receptors (GLP-1Rs) in the brain suggests they may play an important role in the regulation of neuronal activity. In pre-clinical studies, GLP-1 and analogues protect motor activity, modulate long-term potentiation and synaptic plasticity, enhance neurogenesis, reduce apoptosis, protect neurons from oxidative stress, and reduce plaque formation in the brain in mouse models of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, stroke and other neurodegenerative diseases (58-60).

GLP-1 and longer-lasting analogues cross the blood-brain barrier (BBB) by simple diffusion, a property that is of great importance in order to be effective in the brain (61). In contrast, several neuro-protective growth factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) do not cross the BBB, therefore have no effect in the brain if injected peripherally.

GLP-1 and hippocampus: Li et al. found that intraperitoneal treatment of exendin-4 in mice for 4 weeks increases cell proliferation and neuroblast differentiation in the adult mouse hippocampal dentate gyrus (62). Another study in mice demonstrated that intrahippocampal LPS injection induces cognitive decline via activation of NF-κB related inflammatory response; intraperitoneal treatment of exendin-4 reduces the inflammation and protects against cognitive impairment (63). A more recent study in mice reported that subcutaneous exendin-4 treatment presents traumatic brain injury induced changes in hippocampus gene expression and memory deficits (64). These studies demonstrated that peripheral administration of exendin-4 can inhibit inflammation and preserve neurogenesis in the hippocampus.

GLP-1 and cognition: In animal studies, treatment with GLP-1 analogues has been demonstrated to improve measures of cognitive function (65). For example, Mice injected daily for 8 weeks with GLP-1 exhibited significant improvement in recognition index on an object recognition test, indicating enhanced learning and memory (66). GLP-1R -/- knockout mice

demonstrate impaired spatial learning and memory as shown by their performance in the Morris water maze task, longer time to completion, and poorer recall of landmarks. They also performed poorly on an object recognition task, demonstrating inability to differentiate between familiar and novel objects (67).

Summary of GLP-1: Activation of the GLP-1R has shown neurotrophic, neuroprotective, and functional and behavioral benefit under numerous physiological and pathophysiological paradigms in pre-clinical studies. As GLP-1R stimulation has proven to be beneficial and well tolerated in diabetes treatment, it is reasonable to hypothesize that GLP-1 analogues including exenatide would likely be beneficial in human neurological or neuropsychiatric diseases. Several clinical trials are currently underway, testing GLP-1 analogues in mild cognitive impairment, Alzheimer disease and Parkinson disease (www.clinicaltrials.gov). Based on the extensive evidence of its anti-inflammatory and neuro-protection effects, GLP-1 might be a potential novel treatment target for negative symptoms, cognitive deficits and metabolic problems in patients with schizophrenia. GLP-1 analogues show great promise as a novel treatment for schizophrenia.

5) Inclusion and Exclusion Criteria*

Inclusion Criteria:

1) age 18-65 years;
2) diagnosis of schizophrenia or schizoaffective disorder;
3) stable dose of the current antipsychotic drug for at least one month;
4) well established compliance with outpatient treatment per treating clinician's judgment;
5) able to complete the cognitive assessment battery (must be English speaking);
6) Female subjects will be eligible to participate in the study if they are of non-childbearing potential or of child-bearing potential and willing to practice appropriate birth control methods during the study.

Exclusion Criteria:

1) inability to provide informed consent, or for individuals with a legal guardian, inability to provide assent or a lack of informed consent from the legal guardian
2) current substance abuse
3) Subjects who are not on a stable dose of an antipsychotic medication for at least a month prior to enrollment
4) psychiatrically unstable per treating clinician's judgment
5) Uncontrolled medical condition including uncontrolled hypertension, diabetes, seizure disorder, severe cardiovascular, cerebrovascular, pulmonary, thyroid diseases, and gastroparesis.
6) history of ketoacidosis
7) currently taking insulin
8) currently taking meglitinides (repaglinide and nateglinide)

9) currently on immunosuppressant medication regularly including oral steroids; topical and inhalant steroids are allowed
10) currently on sulfonylurea drugs (e.g. glyburide)
11) Current, active chronic infection (including tuberculosis, HIV and hepatitis), malignancy, organ transplantation, blood dyscrasia, central nervous system demyelinating disorder, and any other known autoimmune or inflammatory condition
12) pregnant or breastfeeding.
13) prisoners
14) Exclusionary labs: eGFR < 35 ml/min

Hematology (CBC)	
Leukocytes	<2 or >17.5 x 10^3/mm^3
Platelets	<75 or >700 x 10^3/mm^3
Comprehensive Metabolic Panel	
Sodium	<1.1 times the lower limit (≤121.5) or >1.1 times upper limit (≥159.5) of the reference range
Potassium	<1.1 times the lower limit (≤3.15) or >1.1 times upper limit (≥5.83) of the reference range
Glucose	>2 times the upper limit (>198) of the reference range
Blood Urea Nitrogen (BUN)	>1.3 times upper limit (>29.9) of the reference range
Creatinine	>1.3 times upper limit (>1.69) of the reference range
Total bilirubin	>2 times the upper limit (>2.4) of the reference range
Aspartate amino transferase (AST)	>3 times upper limit (>120) of the reference range
Alanine amino transferase (ALT)	>3 times upper limit (>120) of the reference range
Alkaline phosphatase (ALP)	>3 times upper limit (>345) of the reference range
Hemoglobin A1C	Patients with a value ≥ 9.0%

All exclusionary labs will be reviewed prior to administration of the study drug.

We will continue our recruitment efforts to assure a meaningful representation of women and minority populations.

Ages of subjects will range from 18-65 years. In recent years, there has been an increased use of antipsychotic agents in the younger population. The literature about antipsychotic treatment related to metabolic disturbances in children and adolescents is accumulating. The proposed studies included in this application will focus on the adult schizophrenia population. Only individuals in the range of 18-65 years of age will be included.

6) Study-Wide Number of Subjects*

This is a single site study. We expect to enroll 110 subjects in this study with the goal of randomizing 70 subjects.

7) **Study-Wide Recruitment Methods***

This is a single-site study being conducted solely at UMass Medical School. For information on how potential subjects will be recruited, see section 24 ("Recruitment Methods").

8) **Study Timelines***

The duration of an individual subject's participation in the study will be 24 weeks. It is anticipated that 110 subjects will be enrolled, and 70 subjects will be randomized. This study received an extension to continue until our goal of 70 randomized patients is met. The investigators plan on completing primary analysis of the data within six months of the study's completion.

9) **Study Endpoints***

Primary Study Endpoint:

Improvement in negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) total score.

Secondary Study Endpoint:

Improvement in cognition as measured by the MATRICS Consensus Cognitive Battery (MCCB) composite score.

Safety Endpoints:
An EKG will be conducted at the beginning and end of the study to assess safety. Vital Signs including blood pressure will be collected at every visit. Data on adverse events will be collected at every visit using the side effects questionnaires (SEQ and SEQabbrev) to assess safety and tolerability.

10) **Procedures Involved***

This is a 24-week, randomized, double-blind, placebo-controlled trial of exenatide weekly injection (2mg per dose) as an adjunctive therapy in 70 schizophrenia subjects to examine exenatide's effects on negative symptoms, cognition and potential moderators or mediators of exenantide's effects on negative and cognitive symptoms.

Informed consent will be obtained prior to the screening visit (see Section 30 "Consent Process").

Screening visit: Fasting blood samples for glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity CRP, eGFR and TNF-α will be obtained at the screening visit. Subjects will not receive study medication until all baseline labs have been completed, reviewed, and determined to fall within range**.** Potential subjects will undergo a diagnostic evaluation. Psychiatric diagnosis will be determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). A medical evaluation, including weight, height, vital signs (heart rate, sitting, and standing blood pressures), a physical examination, and review of systems will be performed. The screening process includes a comprehensive review of medical history & evaluations, which is then reviewed by the PI before continuing with randomization. The study doctor discusses the patient's medical history with the patient, completes a review of systems, a physical exam, assesses the patient's overall health status, and reviews all available medical records, previous laboratory assessments and other relevant medical information in addition to the patient's self-report. Based on all of the information gathered, the PI then assesses the patient's eligibility for the study utilizing their clinical judgment. A urine pregnancy test will be performed on women of childbearing potential. Weekly reminders will be provided to the subject to use condoms or other appropriate birth control. The subjects will be given an appointment card for their next visit which will also provide a reminder for the use of appropriate birth control. In addition, a urine drug screening, and a 12-lead EKG will be performed. The screening visit will take about 2 hours. While the study team plans to complete all assessments in one study visit, it is likely that due to symptoms of psychosis, including avolition, apathy and cognitive disturbances subject may have inconsistent behavior and variable tolerance to screening procedures and assessment batteries. In such cases the subject may be called for an additional visit to complete the remaining procedures or they will be completed in the following visit. Following the screening visit, the subjects' primary care provider and/or psychiatrist will be notified of their participation in the study in order to adequately screen subjects, ensure that only eligible subjects are enrolled, and minimize subject risk. Ongoing subjects will be re-consented and informed of this notification during that time.

Baseline visit: The baseline visit will take about 5 hours to complete. Eligible subjects will come to the clinic for the baseline visit. Subjects will complete the clinical symptoms assessment, the extrapyramidal symptoms (EPS) assessment, and vital signs. On a separate day, subjects will come to the UMass Imaging Center at the university campus, or UMass Memorial MRI & Imaging Center at Shields MRI Imaging Suite to complete the brain MRI scans. Then the subjects will receive the study medication (either exenatide weekly injection (2mg per dose) or placebo injection). The UMass research pharmacy is responsible for randomization and preparation of study medication. The randomization is based on a double-blinded 1:1 ratio using permuted block randomization with randomly varying block size.

Follow-up visits (week 1-23): These visits will take about one hour to complete. Subjects will come to the clinic weekly to receive the study medication injection (exenatide or placebo); possible side effects will be assessed weekly. At week 6, 12, 18 visits, vital signs, the clinical symptoms assessment and the EPS assessment will be repeated; fasting blood samples for glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity

CRP, eGFR and TNF-α will be obtained. In the event that research staff are unable to obtain a subject's blood sample at an indicated visit, subject's blood will be drawn in a week's time by a professional phlebotomist at UMass. In the event that a subject misses a visit where a routine blood draw is required, the subject will be scheduled to complete the routine blood draw prior to receiving the next dose of study medication. Once the lab results have been reviewed and signed off by the PI, the subject will be scheduled for their next study visit and will resume receiving the study medication.

Week 24 visit: This visit will take about 5 hours. The week 24 visit consists of vital signs, and side effects assessment. A 12-lead EKG will also be obtained during this visit. The clinical symptoms assessment and the EPS assessment will be repeated. Fasting blood samples for glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity CRP, eGFR and TNF-α will be obtained. In the event that research staff are unable to obtain a subject's blood sample at an indicated visit, subject's blood will be drawn in a week's time by a professional phlebotomist at UMass. On a separate day, subjects will come to the UMass Imaging Center at the university campus, or UMass Memorial MRI & Imaging Center at Shields MRI Imaging Suite to repeat the brain MRI scans.

Clinical symptoms assessment: The clinical symptoms assessment includes: The Scale for Assessment of Negative Symptoms (SANS), the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression Scale (CGI), the Calgary Depression Scale for Schizophrenia (CDSS), the Heinrichs Carpenter Quality of Life Scale (QLS), the Instrumental Activities of Daily Living Scale (IADL), and the MATRICS Consensus Cognitive Battery (MCCB).

Side effects/safety/EPS assessment: Possible side effects related to exenatide treatment will be monitored during each visit. Vital signs (blood pressure, pulse, temperature) and EPS will be evaluated at baseline, week 6, week 12, week 18 and week 24 using the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS).

Bioassay: Routine blood tests (glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity CRP, eGFR) will be performed at the UMass Core Lab. Plasma levels of IL-6 and TNF-α will be measured using enzyme-linked immunosorbent assay (ELISA) (R & D Systems) by Quest Diagnostics.

Structural MRI data acquisition, processing and analysis methods: To measure hippocampal volume at baseline and week 24, a structural MRI imagining examination will be performed at the UMass Advanced MRI facility on a Philips Achieva 3T system, or UMass Memorial MRI & Imaging Center at Shields MRI Imaging Suite on a GE 3T scanner. Segmentation of brain structures from T1-weighted 3D structural MRI data and estimation of structure volumes will be performed using the Freesurfer toolkit, which is freely available to the research community (http://surfer.nmr.mgh.harvard.edu/). This suite of methods uses a probabilistic brain atlas for

representation of spatial priors for brain labels (71). The current subcortical, cortical and white matter parcellation segmentation methods are fully automated. Each subject will result in a complete set of segmentations for volume and cortical surface. Each of these regions generates a volume; whole brain, cerebreum and white matter volumes are also available for normalization with respect to overall brain size.

MRI Procedure: Anatomic acquisitions will include: (1) a T2/PD double echo fast spin echo sequence, (2) a multi-flip angle 3D spoiled gradient echo (MPRAGE type) compatible with the UMASS/CANDI protocol, (3) an proton PRESS and single voxel MEscher-Garwood Point-REsolved Spectroscopy Sequence (MEGA-PRESS) (TE:68msec, TR:2000msec) MRS scans from the ACC, (4) a diffusion scan sequence that uses a standard single shot, spin echo, echo planar acquisition with diffusion weighting gradient pulses comprised of 32 diffusion-encoding directions with an additional baselineT2 weighted image and (5) Echo Planar MRI (EPI) / Functional MRI (fMRI) scan will measure brain fluctuations while at rest. Total scan time will be approximately 60 minutes. Post-processing will be performed with standard software (LCModel, Freesurfer, and FSL) to quantify the MRS metabolites, and regional gray and white matter structural properties in the brain.

A trained neuroradiologist associated with the MRI imaging center at University of Massachusetts Medical School will read the diagnostic MRI scans. In the event that there is a suspicious reading on the MRI the PI will be informed of this. The PI will share with the subject the findings and will facilitate in helping them determine what follow up care is needed and appropriate.

It is possible that a subject may not complete the MRI scan in the study either because the subject is not interested in this component or because it may not be appropriate (for example, claustrophobia or implanted metal in the subject's body). Only those subjects who qualify will complete the MRI scan throughout the study.

11) **Data and Specimen Banking***

Extra blood samples will be collected for future research related to schizophrenia. We will store samples for future genetic testing. These samples will be labeled with a unique study ID code. Only members of the research team will be able to derive an individual's identity from their study ID code. The key to the code is stored on secure server and can only be accessed through password-protected computer.

Extra blood samples will be drawn at Biotech One, Suite 100 or at Community Health link and stored in a -80^{o}F freezer, which is located in a locked room at Biotech One.

While there are no definitive plans yet for use of these samples, the Principal Investigator plans to store these blood samples indefinitely after the study's completion. A log system will be put in place to ensure that only authorized research personnel have access to the samples. The PI will be held responsible for the safety and security of these samples. A separate IRB approval will be requested to utilize these stored samples in the future.

12) **Data Management***

All data management will be conducted in the research offices of the Biotech One building. Standard data forms for the clinical rating scales will be used for this project. Individual notebooks will be maintained for each subject that will include signed consent, letter to halfway house, subject information sheets, raw data from clinical rating scales, laboratory measurements and a study timetable or flow sheet for that subject. A study database will be created using the REDCap system. The data will be stored on a secure server in the UMass HIPAA-compliant data center with daily backup. The database will be designed by the PI and maintained by the PI and the research staff. Data entry will be performed by research coordinators and will be reviewed by the research manager and the PI for accuracy. Access to the database will be restricted by password. All data will be stored safely for 5 years.

There are no published data yet about exenatide's effects on clinical symptoms and cognition in the schizophrenia population. This study is intended as an initial test of efficacy. Repeated measures of clinical symptoms and cognitive performance will be analyzed in separate linear mixed models with fixed effects of visit, treatment group, baseline score, and visit x treatment and visit x baseline score interactions and random participant-specific intercepts and slopes. Potential confounding variables will be included as covariates. The effect of exenatide on 24-week change from baseline will be determined by the estimated regression coefficient of the visit x group interaction term. The sample of 60 evaluable subjects will have 80% power to detect an effect size of 0.74 based on a two-tailed t-test at alpha = 0.05.

13) **Provisions to Monitor the Data to Ensure the Safety of Subjects***

The PI and all key personnel involved in this study have completed the Collaborative IRB Training Initiative (CITI), a mandatory tutorial on the responsible conduct of human subject research. The tutorial and institutional policies and procedures governing the conduct of human subjects research are available on the UMass Medical School intranet website and may be accessed by the Investigator and key study personnel if questions arise.

The PI will immediately report to the IRB any unanticipated problems or adverse events that occur during the conduct of the study, after study completion, or after subject withdrawal in accordance with adverse event and unanticipated problems reporting guidelines.

Safety monitoring will have two components. The first will focus on change in psychiatric symptoms. Safety monitoring will also assess the incidence and severity of side effects and the frequency and reason for any medication changes and study medication discontinuation. The PI will discuss likely side effects of exenatide and potential risks of study procedures as part of the informed consent procedure.

Investigators and research personnel who are trained and experienced at conducting assessments in persons with schizophrenia, will assess for deteriorating mental status and/or suicidal ideation. Participants will meet with a study psychiatrist at each visit and have routine monitoring of psychiatric symptoms. The PI will be notified immediately if subject expresses suicidal ideation. The PI is a board certified psychiatrist and has the necessary training and experience to address such events.

The PI can be contacted by phone at all times and the UMass Memorial Emergency Service is available for psychiatric and medical assessment of research subjects. Female patients will be screened for pregnancy during enrollment by a urine pregnancy test.

Any adverse effect reported to study personnel will be reviewed with the PI who will determine whether they are mild, moderate or serious. Potentially serious adverse events will be reviewed by an external monitoring team to determine the likelihood (unlikely/possible/probable) that it is related to the study medication and whether it is safe for the subject to remain in the study.

Continuous data and safety monitoring will be conducted by the PI. The monitoring will include all adverse events (AEs and SAEs) both expected and unexpected, enrollment, dropout rates and protocol deviations in addition to the results of special studies and laboratory tests that are conducted to ensure patient safety, subject interview and conduct, review of subject symptom or performance status, review of clinical test results, review of subject physical examination, review of all vital signs, diagnostic tests, and evaluations. The investigator will report adverse events to the IRB in accordance with IRB guidelines.

The PI will create a Data Safety Monitoring Board (DSMB) to independently oversee this clinical trial. The DSMB for this study will be composed of at least three people and will include a psychiatrist, an endocrinologist and a biostatistician who will be independent of the study group. The group will follow the NIH policy for data and safety monitoring and guidelines as published on http://www.nimh.nih.gov/research-funding/grants/nimh-policy-on-data-and-safety-monitoring-in-extramural-investigator-initiated-clinical-trials.shtml. Study data regarding subject enrollment, characteristics, symptoms, adverse events and serious adverse events will be submitted to the DSMB for review and analysis annually. The DSMB will review study data, the safety of study participants and conduct of the study. It will advise the PI on continuation of the study and provide reports to the IRB regarding recruitment of appropriate subjects and presence of adverse effects.
An explicit stopping rule will be followed for a potentially serious psychiatric decompensation in order to further enhance patient safety: active subjects will be terminated from the study if they experience an increase in PANSS total score greater than or equal to 20 compared to their baseline score at any point during the study.

Subjects will be terminated from the study if their eGFR falls below 30 ml/min at any point during the study.

14) **Withdrawal of Subjects***

Subjects will be withdrawn from the study if they are determined to meet ineligibility criteria after enrollment. If subjects have laboratory results that meet the exclusionary criteria range during the study, the subject will have his/her labs repeated before being withdrawn from the study.

The study medication will be stopped if a subject has a serious adverse event, but will not necessarily be stopped for exacerbation of psychiatric symptoms or any other adverse event. If the PI or co-investigator considers continuation of the study medication to be safe after a worsening of psychiatric symptoms, and the subject wishes to continue, the subject's treating psychiatrist will be contacted and will make the final decision whether the subject will be allowed to continue taking study medication.

Female subjects may be terminated from the study if they become pregnant at any time while participating in the study. Subjects who fail the urine screening for illegal drugs during the screening visit will be deemed a screen fail and terminated from the study. We will not document the results from the urine drug screen in the patient study records. We will maintain a separate log of the reasons for screen fail. This log will have the counts of screen fails for various exclusion factors including current substance abuse. This log will have no subject information and will have no link to subject id.

Subjects may also withdraw their consent from the study at any time for any reason, including: physical or emotional discomfort associated with taking the study medication, physical or emotional discomfort associated with performing study procedures, or inability to come in for required study visits.

If at any time the study sponsor or research personnel at UMass decide to terminate the study, subjects' consent will be withdrawn involuntarily.

For subjects terminated or withdrawn from the study, they will be asked to have an "exit" visit. Vital signs, ECG, side effect assessment and routine blood tests (CBC, basic metabolic profile) will be performed during the visit.

15) **Risks to Subjects***

Potential Side effects of Exenatide:

1) Risk of Thyroid C-cell tumors.

   In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥ 2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether exenatide will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies.

2) Acute Pancreatitis.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.

3) Hypoglycemia

   The endocrine responses of exenatide treatment are glucose dependent. Exenatide by itself usually does not cause hypoglycemia. Hypoglycemia may occur if it is prescribed with other anti-diabetic medications such as sulfonylurea. Therefore, patients who are currently on sulfonylurea are excluded from the study.

4) Kidney Problems

   There have been postmarketing reports of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

5) Allergic Reaction

   There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with exenatide.

6) Common Side effects

   The most common side effects of exenatide include nausea, diarrhea, headache, vomiting, constipation, itching at the injection site, small bump at the injection site and indigestion.

Common	Less Common	Rare
Nausea, vomiting, diarrhea, injection site nodule, constipation, headache	dyspepsia	Pain in the stomach area (abdomen)
	Low blood sugar (shakiness, confusion, feeling jittery, weakness, drowsiness and dizziness, hunger,	Shortness of breath, swelling of eyes, face, tongue, lips, throat,

	irritability and fast heartbeat)	arms, hands, feet, ankles or lower legs. Lump or swelling in the neck, hoarseness, trouble breathing or swallowing,

Risk of EKG testing: There are also small risks in using EKG equipment, such as skin irritation. However, all research members involved in EKG testing have experience in operating the machinery.

Risk of Blood draws: The risks of having blood drawn include slight pain when the needle is inserted. Subjects may develop a harmless black and blue mark, and their arm may be sore. Occasionally, some people feel dizzy or lightheaded when blood is drawn. They may become sweaty, feel cold or tingly, and may faint or throw up. Risks that are possible but unlikely include infection, nerve damage, and puncturing an artery instead of a vein. Standard high quality clinical practice will be used to draw blood in order to avoid discomfort and infection.

Risk of MRI scans: Risks of MRI are rare and limited mainly to the risks associated with the interactions between metal objects and the very strong magnetic field of the magnet. One such potentially lethal interaction is the superheating of metal fragments in a patient's body that result in high temperature internal burns. Injury and death can also occur from metal objects being pulled at high speed into the center of the magnet field. There is the extremely low theoretical risk of oxygen depletion from the release of helium gas in the event that the magnet had to be emergently quenched (this being an occurrence that is on its own extremely rare).

Claustrophobia while inside the magnet for the MRI assessments can potentially precipitate a panic attack in some subjects. Subjects with known claustrophobia will be excluded from this study.

Some subjects report dizziness, mild nausea, headaches, a metallic taste, double vision, or seeing flashing lights while in the MRI scanner. These symptoms, if present, disappear shortly after leaving the MRI scanner.

In rare cases, a very slight, uncomfortable tingling of the back can occur in the MRI scanner. The scan can be modified to prevent this if the subject notifies the technologist of this feeling.

There is also a remote possibility that subjects' confidentiality may be compromised. However, members of the research team will do everything in their power to maintain their confidentiality. The PI is responsible for oversight of the proposed studies.

Risks of Genetic Testing: Since genetic information is unique to every subject there is a small chance that it can be traced back to the individual. However the risk of this happening is very small, but may grow in the future. The federal law called the Genetic Information Nondiscrimination Act (GINA), in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate based on an individual's genetic information. However, it does not protect against discrimination by companies that sell life insurance, disability insurance, or long-term care

insurance. If the subject does not share information about the blood samples in this study, he or she will reduce this risk.

16) Potential Benefits to Subjects*

There may be no direct benefits to taking part in this study. However, exenatide may have a beneficial role in improving the psychopathology profile and cognition in patients with schizophrenia.

The results of this study may also lead to an increased understanding of how exenatide might affect psychiatric symptoms, cognition and metabolic profile in individuals suffering from schizophrenia.

17) Vulnerable Populations*

Adults suffering from schizophrenia comprise the subject population for this study. Due to the nature of the disease, some subjects may exhibit some level of cognitive impairment. Thus, individuals interested in participating in the study must be evaluated for capacity to provide informed consent by a research coordinator. Subjects must score 100% on a true-false questionnaire consisting of important questions relating to the study procedure in order to participate.

Pregnant women, children, and neonates are excluded from participating in the study.

18) Multi-Site Research*

This is not a multi-site study.

19) Community-Based Participatory Research*

N/A

20) Sharing of Results with Subjects*

During the informed consent process, members of the research team will ask for subjects' permission to have their blood test and electrocardiogram (ECG) results sent to their primary care provider or treating psychiatrist for safety purposes. Results from the urine drug test will not be included. Clinically significant lab tests, EKG readings, and MRI findings will be relayed to the subject's primary care provider to ensure their safety. We will also ask for subject's permission to share clinically significant MRI findings with his primary care provider. If the subject's PCP or treating psychiatrist contacts the PI regarding his/her lab or EKG results then the subject's PCP or treating psychiatrist will consult with the PI and if they both agree then the subject may continue in the study. The letter to share EKG, labs findings with the subject's PCP or treating psychiatrist is used only to communicate results after the subject is enrolled in the study. It is not used as a recruitment tool.

Subjects will be informed if their results from a treatment efficacy assessment or diagnostic blood test warrant termination from the study. If a subject becomes pregnant

at any point during the study or fails the drug screening urine test, their health care providers will not be notified. Results from these tests will, however, remain part of the subject's study record indefinitely.

21) **Setting**

Potential subjects will be recruited from UMass health care facilities and the local community. Research procedures will be conducted at the Clinical Research Unit in Biotech One, Suite 100, Community Healthlink, and the Clinical Research Center located in the Ambulatory Care Center at 55 Lake Avenue North, Worcester, MA.

MRI scans will take place at the MRI imaging suite at the University of Massachusetts Medical School's main campus.

We were informed on 8/23/2017 that the MRI machine at the UMass site would be inoperative until early November due to scheduled maintenance. The MRI scans serve as study assessments, and are not related to patient safety. As we have ongoing subjects that require scans during this time, we established temporary services with UMass Memorial's MRI & Imaging Center at Shields MRI Imaging Suite on 214 Shrewsbury Street, Worcester MA 01604 to complete scans for subjects while the original MRI machine undergoes maintenance.

22) **Resources Available**

All research personnel have completed CITI training and are aware of Good Clinical Practices (GCP). The PI is a senior psychiatrist who specializes in schizophrenia treatment and research. Both the Principal Investigator and Co-Investigator each have more than 10 years of experience working with individuals suffering from schizophrenia and substance abuse.

The study coordinator (i.e. research assistant) will be involved in activities such as reviewing study procedures with each subject, obtaining informed consent, data-entry, and blood sample collection. The study coordinator will also be responsible for administering questionnaires and conducting assessments. The study coordinator is certified in phlebotomy, and has completed sufficient training in order to obtain informed consent, conduct study assessments, enter data, etc.

The PI will be held responsible for oversight of the study procedure. The PI and Co-Investigator will also be responsible for identifying AEs and SAEs and for terminating a subject if their physical and/or mental health is compromised as a result of the study treatment.

Research nurses who are qualified registered nurses (RN) may be involved in study activities such as administering Exenatide injections and completing questionnaires and other study assessments.

The PI will discuss individual roles with each member of the research team once the study commences.

The PI can be contacted by phone and the UMass Memorial Emergency Service is available for psychiatric and medical assessment of research subjects.

23) Prior Approvals

We have received IBC approval for all of our studies on 10/30/2015. The IBC approval letter has been uploaded.

24) Recruitment Methods

Potential subjects will be recruited from Community Health Link (CHL, 72 Jacques Avenue) and the Ambulatory Psychiatry Clinic (located at 26 Queen Street & UMass Hahnemann Campus). Members of the study team will be stationed at these sites to help facilitate recruitment. All research staff will have access to electronic medical records of patients at these outpatient departments. CHL is the largest, multi-service, private, non-profit mental health organization in central Massachusetts with 5,000 outpatients over 18 years of age. CHL cares for many with severe and persistent mental illness. Approximately 1,000 individuals are diagnosed with schizophrenia or schizoaffective disorder, and 700 with bipolar disorder. Dr. Fan is Director of the schizophrenia specialty clinic and the early psychosis clinic at CHL. Currently CHL has about 200 active schizophrenia patients. *T*he Ambulatory Psychiatric Clinic serves patients aged 18 and up. The clinic handles more than 40,000 visits per year. Patients come from a wide range of socioeconomic backgrounds.

Due to the patient population at this site, the research team will have access to many eligible patients. Both the PI and Co-Investigator also have extensive connections with several clinicians working at CHL, which will streamline recruitment efforts. Frequent communication with other clinicians at CHL will provide the basis for recruitment for this study.

Subjects will also be recruited from two inpatient psychiatric clinics at University campus, 8 East and PTRC, as well as Emergency Mental Health services. All research personnel (study coordinator(s), Co-Investigator, and PI) will have access to the electronic medical records of patients residing in these units. This is necessary in order to have immediate access to patients' medical records once they are admitted to these clinics and to expedite the recruitment process. Subjects will also be recruited (using electronic medical records) from the Outpatient Psychiatry Clinic located at 26 Queen Street. In the event that the research team identifies a potential candidate for the study, the research team will contact the patient's clinician regarding the individual's study eligibility. If the clinician believes his or her patient would be a good candidate for the study, the clinician will provide information (via study fliers, brochures, etc.) on how to contact the research team, or if the subject provides a verbal permission to be contacted to his/her clinician the research team will reach out to the patient. Members of the research team will not contact prospective subjects directly. Utilizing this method of recruitment will allow the researchers to access more potential subjects.

In situations where an individual's attending physician or psychiatrist is the referral source, the attending doctor will initiate the study discussion with the eligible individual. If the individual expresses interest and agrees to be contacted by a member of the study team, the study coordinator or one of the investigators will follow-up with the potential subject.

In addition, a permission to contact form will be administered to potential subjects in both inpatient and outpatient care settings by treating clinicians or research staff. This form allows patients to provide their name, contact information, and permission to be contacted by a member of our research team to discuss the study further.

Due to difficulties in recruiting patients in this population, we propose sending out a letter to eligible study participants. A research staff member will screen for eligible study patients in advance. The letter will be generic; simply notifying the patient that he/she may receive a telephone call after 7 days of receipt of that letter from a member of the UMass Psychotic Disorders Program. We believe this will give sufficient time for patients to have received our letter. The letter will also provide the PI contact information in case any patient wishes to decline participation or discuss the study prior to talking with a research staff member. We will make note of any patient declining to participate at this stage so that all staff are aware not to recruit these patients. The letter will be signed by Dr. Xiaoduo Fan who is the PI for the study and also the Director of the Schizophrenia Clinic within Community Healthlink. Additionally the Community Healthlink logo has been appropriately placed at the top of the letter head to provide familiarity to patients who will be receiving this letter.

Advertisements will be utilized in the form of fliers and brochures, as well as a description on the Psychotic Disorders Program website, to increase access to potential participants. IRB-approved text will also be submitted to selected local newspapers and magazines in order to broaden our recruitment efforts in the local community. In addition, we will be utilizing the internet and various forms of social media to advertise the study. Ads containing IRB-approved language will be posted on various websites such as Craigslist, Facebook, Twitter, etc. Each ad will also contain information on other studies being conducted by the Principal Investigator (again, only language that has been approved by the IRB will be included in these advertisements). A multi-study tear away flier will be used including IRB-approved text about this study, as well as other IRB-approved text detailing other IRB approved studies. The shell of the multi-study flier as well as the text specific to this study has been submitted for approval. A program business card will also be used including contact information that potential participants can call and see if they may be eligible for one of our studies. The business card will not include study specific language. Also, we will be using the Conquering Diseases Volunteer Database Docket #H-12562 as a recruitment tool. All aforementioned modes of advertisement have been approved by the IRB, and any advertisements in the future will consist only of IRB-approved language. We will also have a secure lock box available in the Community Healthlink (CHL) Outpatient waiting area with permission to contact forms for those who are interested to leave their contact information to be reached in the future. The key to the lock box will remain with the research staff at all times. The following instructions will be posted on the box for potential subjects to read: “If you are interested in being contacted to learn more about our studies, please provide your contact information on one of the forms below and put the form in the secure lock box at CHL so that we may contact you to tell you more about the studies and see if you are eligible.”

If an individual appears eligible and expresses interest in participating, the study coordinator will initiate the screening process. The screening process is described in Section 10 “Procedures Involved”.

The study will be advertised via IRB-approved fliers and brochures which will be placed at strategic locations at CHL and across the UMass Medical School campus. The study will also be advertised via fliers and brochures at local homeless shelters, various group

homes, bus stops, and grocery stores in the Central Massachusetts area. We will also advertise at various private practice clinics, local hospitals, mental healthcare facilities, peer support centers, and club houses in the Worcester area. We will also distribute IRB-approved fliers and brochures to selected locations in the broader Central Massachusetts area, including towns surrounding the Greater Boston area.

To improve our recruitment efforts, we would like to host Lunch and Learns with the clinicians and staff at CHL, UMass Medical School, and various private practice clinics in the Worcester and Greater Boston area. During the Lunch and Learn, we will provide information to the attendees regarding the purpose and general procedures of this research study, and how potential subjects can be referred for this study. Referrals will be handled as stated earlier in Section 24. We will only use IRB approved material and text for these Lunch and Learn sessions.

We will also be using a "Service Provider" letter to improve recruitment. This letter will be sent from the PI to psychiatric patient care workers in the Worcester and Greater Boston area. The letter will contain information about our research program, a list our ongoing research studies, and the study team's contact information. If the recipient has a potential subject they would like to refer for this study, they will inform the study team using the contact information in the letter. The study team will confirm with the recipient that the potential subject has expressed interest in this research study, and the study team will follow-up with the potential subject.

Subjects will be compensated for their participation after each study visit. Subjects will be paid $15 for screening visit, $20 for the baseline visit, $10 each for week 1 to 11, week 13 to 17, and week 19 to 23; $25 each for week 6, 12, 18 and 24 visit. Subjects will receive retention material in the form of a pen with our study team information upon randomization in the study. An image of the pen has been uploaded to the eIRB site. Subjects will also receive retention material in the form of a water bottle upon completion of their week 12 visit. Subject will have two MRI scans and will be compensated $30 per MRI scan for a total of $60 Thus, if a subject completes the study, they will be paid a total of $395 over the course of 24 weeks.

In an effort to improve recruitment and completion rates of our subjects, we would like to offer taxi vouchers or additional travel compensation of $10 for select patients, on a case by case basis, for certain study visits.

25) Local Number of Subjects

A total of 110 subjects are expected to be enrolled, with the goal of randomizing 70 of those subjects.

26) Confidentiality

Data will be obtained in study binders in a locked room located at Biotech One, Suite 100. Participant data will be coded to protect privacy. Each participant will be assigned a unique identification number. The list of participant names and identification numbers will be kept separate from the database. Only members of the research team will be able to derive an individual's identity from their study ID code. The key to the code is stored on secure server and can only be accessed through password-protected computer. All hard copies of research records will be kept in separate locked files. Access to the computerized data system is carefully protected by a secured password entry system.

Access to participants' data will be restricted to project investigators on a need to know basis. Data entry will be performed by the study coordinator and will be reviewed by the research manager and the PI for accuracy. Access to the database will be restricted by password.

The secure lock box that will be used for recruitment purposes will only be accessed by the research staff assigned to this study. The research staff will be responsible for securely collecting the contents of the lock box on a weekly basis and transporting them to a secure location where the confidential information will be safely stored at Biotech One, Suite 100. The keys to the lock box will remain with the study coordinator at all times in a secure location.

Stored blood samples for future research use will be drawn at Biotech One, Suite 100, and stored in a -80F, which is located in a locked room at Biotech One. A log system will be put in place to ensure that only authorized research personnel have access to the samples. The PI will be held responsible for the safety and security of these samples.

27) Provisions to Protect the Privacy Interests of Subjects (HIPAA)

Identifiable health information from a subject's medical record will be collected by members of the research team. This information will only be used for purposes related to the study and will not be used to identify the subject in any way by non-members of the research team.

Results from study assessments, study questionnaires, blood tests, and psychiatric evaluations will only be made available to the research team. The research team will send a subject's lab, electrocardiogram (ECG) and clinically significant MRI results to their primary care providers or their treating psychiatrist.

Subjects who do not receive treatment through the UMass Memorial Healthcare system will be asked to sign a protected health information release form. This form will serve two purposes. First, the release form will allow the research staff to gather information on a given subject's medical record from their primary care doctor or psychiatrist (residing outside of the UMass Memorial Healthcare system) in order to determine study eligibility. Second, the form will also enable research staff to send laboratory and EKG results to the subject's primary care doctor or treating psychiatrist.

Subjects are free to contact the research team regarding study related questions at any point while they are a participant in the study. Subjects are encouraged to confide in the research team if they are at all concerned or unsure about specific aspects of the study. Each subject must also score 100% on a brief true-false questionnaire designed to ensure that the subject understands the study procedure and is aware of their rights as a study participant. Subjects may contact the PI by phone if they have questions regarding the study.

28) Compensation for Research-Related Injury

If the subject is injured as a direct result of his or her participation in the study, there will be no compensation provided by the research team. No funds have been set aside. In the unlikely event of injury, subjects or their insurance will be responsible for coverage.

29) Economic Burden to Subjects

Exenatide will be provided for study subjects at no cost. All medical tests, blood tests, and study assessments will also be conducted at no additional cost for each subject. Subjects will otherwise continue to pay for their routine medical care in the usual way.

30) Consent Process

A potential subject who expresses interest in the study will be met by the study coordinator at Biotech One, Suite 100 or Community Healthlink and verify that the patient is interested in participating, understands that participation is voluntary, and understands that declining participation will not affect his or her treatment at the facility.

The PI, Co-Investigator, and study coordinator(s) will clearly explain the study procedure, risks and benefits of participating (including potential risks involving the study medications), and other aspects of the study that are of interest to each subject. Specifically, the study coordinator will review logistical aspects of the study (study timeline, study visit procedures, etc.), while the PI or Co-Investigator will provide information on the study medications. Individuals who express interest will be evaluated by the study coordinator for capacity to provide informed consent. We have developed a questionnaire consisting of approximately 10 true-false questions about important aspects of the study procedures, potential risks, the subject's right to end participation at any time or to speak to a patient advocate, etc. Subjects must score a 100% to participate in the study. Subjects who are judged to be competent will then be asked to sign the study consent form. In addition, prior to starting the study medication, the PI or Co-Investigator will meet with each subject to review the risks of taking the study medication, as well as which medications should be avoided while taking exenatide. In addition, potential participants will also be asked if they would like us to notify their primary care physician or their psychiatrist of their participation in the study.

Many of our potential subjects live in supported living/group home facilities that are staffed with individuals who offer day to day support for these subjects. These staff members are also involved in patient care. As such, we would like to notify a potential subject's supported living/group home staff of the subject's participation in this study. The study team will ask all potential subjects if they live in a supported living/group home facility, and if so, the study team will ask permission to notify the staff at the subject's supported living/group home facility.

We want to enroll a diverse patient population with different levels of cognitive function and varied levels of schizophrenia symptom severity. If the subject lacks the capacity to provide informed consent, then the subject's authorized legal guardian will be present for the consent process. Potential participants and guardians are encouraged to read the consent form and ask questions. After providing a detailed overview of the study, the study coordinator will present the questionnaire consisting of approximately 10 true-false questions about important aspects of the study procedures, potential risks, the subject's right to end participation at any time or to speak to a patient advocate, etc. to the subject and the subject's authorized legal guardian. Participants are further encouraged to solicit input from significant others and/or care providers, if appropriate. To minimize coercion, the consent form has language that clearly spells out that participation in the study is voluntary and refusal to participate will not affect a person's health/mental health care. Subjects and their authorized legal guardians will be required to sign both the informed consent form and the true-false questionnaire form if they agree to participate. We will explain the study in a language understandable to the subject and obtain his or her

assent. Subject will be particularly closely monitored. Subject will be withdrawn if they appear unduly distressed.

The consent process will take place at Community Health Link or at Biotech One, Suite 100. Research personnel will follow HRP-090.

All currently enrolled subjects will be informed of the most recent modification and at their next study visit they will be "re-consented" to the recent changes to the consent form.

31) Process to Document Consent in Writing

Subjects will review the informed consent document with a study coordinator or the PI. Subjects will give their consent by signing the informed consent document. Each subject will receive a paper copy of the signed consent form.

Standard Operating Procedures HRP-090 (Informed Consent Process for Research) and HRP-091 (Written Documentation of Consent) will be followed.

32) Drugs or Devices

Subjects will be given weekly injections of exenatide (2mg per dose) or placebo for 24 weeks as an adjunctive therapy. The medication will be administered by the PI or the co-investigator, or a medically qualified designate such as a registered nurse. The UMass research pharmacy is responsible for randomization and preparation of study medication.

The use of exenatide in this study does not constitute an IND. It is exempt under Section 5 of the Drug Worksheet (HRP-306):

- The drug is lawfully marketed in the United States
- The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug
- The research is not intended to support a significant change in the advertising for the product
- The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks or decreases the acceptability of the risks associated with the use of the drug product
- The research is conducted in compliance with the marketing limitations described in 21 CFR 312.7).

Please see attached email from the FDA. In addition, the endocrine responses of exenatide treatment are glucose-dependent, which explains the low risk of hypoglycemia with exenatide in both diabetic or non-diabetic patient populations (Kendall et al., 2005, Aviles-Olmos et al., 2013), as well as healthy volunteers (Khoo et al., 2010). Therefore the PI feels that it will not affect their acceptability.

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