PRINCIPAL/OVERALL INVESTIGATOR
Virginie-Anne Chouinard, MD
Phone: (617)855-3034
Email: vchouinard@partners.org

Schizophrenia and Bipolar Disorder Program
McLean Hospital
115 Mill St, 108
Belmont, MA 02478

PROTOCOL TITLE
Effects of intranasal insulin on neuroimaging markers and cognition in patients with psychotic disorders.

ClinicalTrials.gov ID
NCT03943537

BACKGROUND SUMMARY

Psychotic disorders are common and severe psychiatric disorders. Despite advances in understanding the pathophysiology of these disorders, more effective and tolerable treatments are still needed. Several lines of evidence have shown metabolic abnormalities in psychotic disorders in the brain and periphery. There is a disproportionately high rate of T2DM in patients with psychotic disorders, which is two to three-fold that found in the general population[1, 2]. Recent evidence shows that glucose metabolism abnormalities are present at psychotic illness onset and in drug-naïve patients with psychotic disorders[3-6]. We recently found that both first episode psychosis patients and unaffected, untreated, siblings, who share genetic determinants, have impaired insulin signaling compared to controls[7]. The brain is an insulin sensitive organ and insulin receptors and insulin-activated pathways are prominent in the brain [8-10]. Given insulin's effects on metabolism, impaired insulin signaling may play a key role in the emergence of neuronal dysfunction in psychosis. Metabolic functions are essential for maintaining fundamental processes in the brain, including synaptic neurotransmission, intracellular signaling and maintenance of ion gradients. Targeting these processes may thus be promising for treatment of psychotic disorders. We will examine whether intranasal insulin can modulate neurometabolic markers and improve cognition in patients with psychotic disorders. The study will use magnetic resonance spectroscopy (MRS) technology to measure changes in neurochemical markers, before and after the administration of intranasal insulin. We will also measure changes in cognition with the administration of intranasal insulin.

SUBJECT SELECTION

ELIGIBILITY:
Patients:
Eligible patient participants will be women and men ages 18-40 with Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses of schizophrenia, schizoaffective disorder or bipolar disorder with psychotic features. Eligible participants must be stable with respect to their psychiatric and medical conditions, documented by no hospitalizations in the prior 4 weeks. We will not alter the dosing of any previously prescribed medication.

Controls:
Healthy controls will be women and men ages 18-40 with no history of DSM psychiatric diagnoses, nor history of the same in first-degree relatives.

We will exclude participants who:

1. Have unstable/active disease or potential contraindications, such as liver disease (AST>2*ULN; ALT> 2*ULN; A1c>6.5%), kidney disease (creatinine≥1.4 mg/dL or GFR<60 mL/min/1.73m^2), uncontrolled hypertension (BP > 140 / 90), cardiac arrhythmia (QTc>500ms on ECG), significant or unstable medical illness.
2. Have a known diagnosis of diabetes or by fasting plasma glucose concentration at 126 mg per deciliter, according to the criteria of the American Diabetes Association[11].
3. Are currently prescribed any antidiabetic agents, including oral antidiabetic medications and insulin, intranasal medications, steroids, weight loss agents.
4. Are pregnant or breast-feeding, and/or have not been using an effective form of contraception for at least 3 months or abstinent for 1 month prior to enrollment.
5. Have a history of significant head injury.
6. Have a contraindication to MR scan (claustrophobia, cardiac pacemakers, metal clips and stents on blood vessels, artificial heart valves, artificial arms, hands, legs, etc., brain

stimulator devices, implanted drug pumps, ear implants, eye implants or known metal fragments in eyes, exposure to shrapnel or metal filings, other metallic surgical hardware in vital areas, certain tattoos with metallic ink, certain transdermal patches, metal-containing IUDs).
7. Have any medical condition that would prevent blood draws.
8. Have a history of electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) within the last 3 months.
9. Have a current diagnosis or history of a substance use disorder in the last month.
10. Have a BMI >35 or body weight >350 lbs or a BMI <18

RECRUITMENT: We will recruit patients with schizophrenia, schizoaffective disorder or bipolar disorder with psychotic features from the Psychotic Disorders Division at McLean (outpatient programs, including OnTrack program for first episode psychosis, Schizophrenia and Bipolar Disorder Outpatient Clinic, Program of Assertive Community Treatment (PACT), and the Waverley Place community program, as well as both inpatient programs (AB2 and NB2), and the McLean Appleton residential program). Patients will also be recruited through RALLY and Mass General Brigham RPDR.
In addition, we will recruit age- and sex-matched controls using online RALLY advertisements and flyers. We will additionally post flyers in the greater Boston area on community boards, college campuses, and agreeable storefronts and businesses.
The research team will approach potential participants to describe the study, go through the screening document, obtain consent, and schedule the initial visit. All participants will provide written informed consent.

STUDY PROCEDURES

This study will be a single center, single dose study of the acute effects of intranasal insulin on neurochemical markers and cognitive function in patients with schizophrenia, schizoaffective and bipolar disorders, compared to healthy controls. 40 units of insulin (Novolin-R) will be administered using a ViaNase device (Kurve Technologies, Inc.), as directed by study staff. Assessments for neuroimaging markers and cognitive symptoms will be performed prior to administration of the intranasal insulin and immediately following administration. The Eligibility Screening procedures may be scheduled over one or two visits. Study procedures for each visit are outlined below.

Study Procedures
Eligibility Screening Visit(s)

• Medical Screening
  ○ Fasting Blood Samples
  ○ Vital Signs
  ○ Medical History and Interview with MD
  ○ ECG (for participants with a history of cardiac issues)
  ○ Urine Toxicology and Pregnancy Test (for female participants)
• Clinical Interview
• Diagnostic MRI

Intervention Visit: Neuroimaging, cognitive assessments and administration of intranasal insulin

Baseline assessments:	• Participants will be instructed to fast for 8 hours prior to the study visit. • Blood draw for glucose and insulin levels • Vital signs, finger stick for glucose, review of systems • Columbia Suicide Rating Scale • Urine Toxicology and Pregnancy Test (for female participants) • Cognitive Assessment • 31P MRS Scan
Intranasal Administration of 40units of Novolin-R	• Finger glucose stick • Collect Vital Signs • Intranasal insulin administration • Assess Medication Tolerance
Final assessments	• 31P MRS Scan • Scanner Debriefing Interview • Cognitive Assessment • Finger Glucose Stick • Assess Medication Tolerance • Blood draw for glucose and insulin levels • Vital Signs • Meal provided from the McLean Cafeteria

Participants will undergo a urine toxicology screening and pregnancy test (for female subjects) prior to all imaging procedures.

Screening Fasting Blood Samples: Comprehensive Metabolic Panel (CMP), Complete Blood Count with Differential (CBC diff), Lipid panel, Hemoglobin A1c, serum Insulin, plasma Glucose, Prolactin, Magnesium, TSH, free T4 and total T3, C-Reactive Protein.

Vital Signs: Assessment of blood pressure, heart rate, temperature, height, weight, waist and hip circumference.

Clinical Interview:
A standard structured clinical evaluation (SCID), lasting approximately 2 hours, will be conducted in order to verify participants' psychiatric diagnoses and to assess for severity of psychiatric symptoms.

MRI Scan Protocols:
All scans will take place at the Brain Imaging Center at McLean Hospital using either a Siemens 3T Prisma or Prisma-Fit whole-body clinical MR scanner or full-body Varian/UnityInova 4 Tesla scanner. All MRS processing will be carried out blinded to diagnosis and disease episode. All MRS/MRI recordings will be obtained using parameters that are within FDA safety guidelines for exposure to static magnetic fields, radio-frequency energy deposition, magnetic field switching rates and acoustic noise levels.

Cognitive Measures: Brief Assessment of Cognition in Schizophrenia and Stroop Task

Cognitive function will be assessed using the Stroop task and 3 items from the Brief Assessment of Cognition in Schizophrenia (BACS) battery[12]. Our Cognitive Assessments will include the following:

- Stroop task
- BACS Symbol coding (WMs-III Spatial Span, Letter-Number Span)
- BACS Digit Sequencing (Brief Visuospatial Memory Test-Revised)
- BACS Verbal Fluency (Mayer-Salovey-Caruso Emotional Intelligence Test)

Study Medication:
The study physician will prescribe a one-time dose of 40 units of insulin (Novolin-R), which will be administered using a ViaNase device (Kurve Technologies, Inc.).

Statistical analysis plan

Chi-square and t-tests will be used as appropriate to compare baseline demographic, clinical, metabolic, cognitive and MRS variables between groups. Within-group comparisons between the pre- and post-insulin administration measures of MRS and cognitive function in either patients or healthy controls will be conducted using paired t-tests. Hypothesis tests will be two-sided at a significance level of 0.05.

X. REFERENCE

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