INTRODUCTION TO THE METS STUDY

Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia

BIOS 669

Goal of METS

Evaluate the efficacy of metformin in reducing weight gain and other metabolic abnormalities associated with the use of antipsychotic medications in patients with schizophrenia.

What is metformin?

- An oral anti-diabetic drug that is the first-line drug of choice for treatment of type 2 diabetes – the most widely prescribed anti-diabetic drug in the world.
- Works by suppressing glucose production by the liver.
- Sold under the name Glucophage.
- Causes few adverse effects, with the most common being possible gastrointestinal upset (cramps, diarrhea, increased flatulence, etc.).

Specific comparisons between metformin and placebo patients

- Mean differences in
  - Body weight
  - Waist-hip ratio
  - Fasting lipid levels
  - Fasting glucose, insulin, and HgA1c (glycated hemoglobin)
- Also, comparison of
  - Medication adherence
  - Frequency of treatment discontinuation
  - Adverse effects

METS Study Design

- Double-blind, multi-site, randomized placebo-controlled trial (double-blind: neither participant nor investigator knew treatment assignment)
- Participants have schizophrenia or schizoaffective disorder with BMI>=27
- 70 patients randomized to receive metformin, 70 placebo (148 patients were actually randomized)
- Follow-up period of 16 weeks
- 17 field centers
- Besides medication, all patients received behavioral therapy intervention focused on diet and exercise

Inclusion Criteria

- Diagnosed with schizophrenia or schizoaffective disorder
- BMI >= 27 kg/m^2
- 18-65 years old
- On one or two antipsychotic medications with no change in drug regimen for at least 2 months
- Must not be pregnant and must be on contraceptives if still able to become pregnant

Reasons for exclusion (partial list)

- Currently an inpatient, on more than two antipsychotic medications, or having a CGI-S score>=6 (so very psychotic)
- Diabetic, treated with insulin, or fasting glucose>125
- Previous use of metformin or known sensitivity
- Recent alcohol abuse or dependence
- Recently taking weight loss medication
- Has dementia
- Pregnant or breastfeeding

Reasons for discontinuation from the study

- Withdrawal of informed consent
- Pregnancy
- Patient no longer meets inclusion or exclusion criteria, with the exception of the BMI criterion
- Any clinical adverse event, clinical rating, laboratory abnormality, or illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject.

What happens during the 16 weeks of follow-up?

- Weekly behavioral treatment aimed at modifying CVD risk factors – in person or by phone
- Study visits to receive medication and be evaluated at week 1, week 2, and then every two weeks

Schedule of Events

Assessments	V1 SCR	V2 BASE	V3 WK1	V4 WK2	V5 WK4	V6 WK6	V7 WK8	V8 WK10	V9 WK12	V10 WK14	V11/DC WK16
Demographics	X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
SCID/Psychiatric History	X										
Med History & Physical Exam	X										
Inclusion/Exclusion Criteria	X										
Study Medication Dispensing and/or Adherence		X	X	X	X	X	X	X	X	X	X
Clinical Global Impressions - S	X	X			X		X		X		X
Substance Use Scale		X			X		X		X		X
Alcohol Use Questionnaire		X	X	X	X	X	X	X	X	X	X
Other Medications Record		X	X	X	X	X	X	X	X	X	X
Lipid Lowering Agent Form		X	X	X	X	X	X	X	X	X	X
Randomization Form		X									
Adverse Events/Side Effects		X	X	X	X	X	X	X	X	X	X
Behavioral Tx Counseling and Adherence Record			X	X	X	X	X	X	X	X	X
Global Behavioral Tx Adherence											X
Reason for Assigned Trt. Discont.											X
Unscheduled Visit Form											
Serious Adverse Events											
LABS											
Biospecimen Shipping Form	X				X		X		X		X
Pregnancy Screen (serum)	X										
Chemistry, CBC	X										X
TSH	X										
Lactate	X				X		X		X		X
LFT	X				X		X		X		X
Urine Drug Screen	X										
Fasting Plasma Glucose	X						X				X
Fasting Insulin	X						X				X
Fasting Lipid Profile	X						X				X
HgbA1C	X						X				X

Analysis Populations

- Safety Population
- Efficacy Evaluable Population
- Per-Protocol Population

Safety Population

- All subjects randomized to treatment who received at least one dose of study medication.
- Will be used for all safety analyses and selected secondary efficacy analyses.

Efficacy Evaluable Population

- All subjects in the safety population who completed at least one post-baseline weight measurement.
- Will be used for the primary efficacy analyses and most secondary efficacy analyses.

Per-Protocol Population

- All patients completing the 16-week assessment of weight measures and in reasonable compliance with the study protocol. This includes compliance with study medication and excludes use of a disallowed medication.

- Will be used for selected secondary analyses.

Primary Inferential Analysis

- For the primary aim of the study, the outcome is endpoint body weight.

- The analysis will involve a mixed model predicting change from baseline to post-baseline body weight as the response variable, with treatment group as the primary predictor, baseline body weight as the covariate, and site as a blocking factor.

- The primary outcome will be a contrast examining the difference between treatment least squared means at the 16-week point.

Power and Sample Size Calculations

- Power calculations were done for a two-group t-test.
- Investigators felt that a 2 kg change in body weight was clinically important.
- The most likely standard deviation was considered to be 4 kg (based on a literature review and expert opinion).
- The resulting necessary sample size to detect this difference with this SD was 128.
- To allow for a possible underestimate of the SD, a slightly larger sample size of 140 was planned.
- The actual sample size ended up being 148.

Payments to participants

Participants were paid $20 per visit, or $25 if they brought in medication bottles to help with adherence evaluation. This was not considered pay, but rather to help with travel expenses and compensate for effort.

Important Forms

- Demographics (DEM, screening only) – age, gender, race, marital status, education, etc.
- Medical history (MHX, screening only) – mostly yes/no information on 31 health issues
- Vital signs (VSF, every visit) – weight, waist and hip circumferences, blood pressure
- Alcohol use (AUQ, every visit)
- Other medications (OMR, every visit)
- Lipid-lowering agents (LLA, every visit)
- Adverse events and side effects (AES, every visit)

Important Forms (continued)

- Study medication dispensing and adherence (SMF, every visit)
- Behavioral treatment adherence (BTA, every visit)
- Clinical Global Impressions-S (CGI, every other visit)
- Substance use scale (DUS, every other visit)
- Reason for assigned treatment discontinuation (RTD, at the visit of discontinuation)

Other forms

- SCID/Psychiatric history (SCD) – screening only (evaluate eligibility)
- Inclusion/exclusion criteria (IEC) – screening only, DMS fills in automatically
- Randomization (RDM) – baseline only; important but not for our purposes (we only have randomized patients)
- Global behavioral treatment adherence (GBT) – final visit only (Visit=11 or discontinuation)
- Unscheduled visit form (UVF) – as necessary
- Serious adverse events (SAE) – as necessary; would be important, but there were only 15 possible SAEs in this study
- Bio-specimen shipping form (BSF) – visits where lab specimens were collected, for tracking them

Key Concept: Adherence

- Basically, adherence for any pill-based medication is

  100 x (pills taken / pills expected to be taking)

- Pills expected to be taking is generally straightforward to compute, but pills taken is difficult to know exactly.

- In METS, the adherence calculation is complicated further by varying time periods between pill dispensing.

- Adherence is a variable contained in the EE (Efficacy Evaluable) data set, so we might re-visit it in more detail later.

Key Concept: Weight Liability

- Recall that all study participants had to be taking one or two antipsychotic medications in order to be eligible
- Antipsychotic medications tend to cause weight gain, with some known to cause more weight gain than others
- Based on the medications they were taking at baseline, each participant was classified as in the “Low only”, “High only”, or “Both” weight liability category
- This variable was to be used as a covariate in some secondary analyses and possibly adjusted for in the primary analysis (if there was imbalance between treatment groups).

CSCC Role: Data Coordinating Center

- Form design and data management system (DMS) implementation
- Training of clinic personnel and on-going QC activities
- Periodic reporting on study status to sites, the study steering committee, and an independent monitoring board (involved conversion of the study database to SAS data sets for reporting purposes)
- Study wrap-up: coordinating clinic closure, data freeze and creation of limited access data sets for submission to NIH, helping with final results paper

METS Data Sets for BIOS 669

- One data set per form
- Variable names match form question numbers
- Cleaned data – a version of the limited access data sets made for NIH
- Simulated but realistic date variable values
- Sort order of each data set: BID VISIT FSEQNO
- DR data set – treatment status (TRT), race (RACE1), clinic (PSITE)

Metformin vs. Placebo

The TRT variable in the DR data set identifies whether the participant was in the treatment group (taking Metformin) or not (taking a placebo).

A = Metformin

B = Placebo

Meaning of Visit Values

1 – Screening visit (determine eligibility for study)

2 – Baseline visit

3 – First follow-up visit

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11 – Last possible follow-up visit