Clinical Protocol

METFORMIN IN THE TREATMENT OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN SCHIZOPHRENIA

Version 3.1
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1. **SPECIFIC AIMS**

Life expectancy for individuals with schizophrenia is up to 25 years shorter than for the general population. Weight gain and metabolic abnormalities that are associated with morbidity and mortality are common in schizophrenia and have been linked with several antipsychotic medications. However, the most appropriate strategies to ameliorate the risks of weight gain and metabolic abnormalities have not been established. One innovative approach, adjunctive treatment with metformin, has shown promising results in randomized studies of patients early in the course of psychotic illnesses, but this approach has not been systematically tested on a large scale among individuals with chronic schizophrenia or schizoaffective disorder.

This study will enroll 140 individuals with schizophrenia or schizoaffective disorder who have a BMI $\geq 27$ and are treated with one or a combination of two antipsychotic medications. Participants will be randomized to augmentation treatment with metformin or placebo. All participants will receive a manualized behavioral intervention aimed at reducing their risk of cardiovascular disease.

**Specific Aims:**

1. To compare the efficacy of metformin (1000-2000 mg per day) on body weight in patients with schizophrenia or schizoaffective disorder who have a BMI $\geq 27$. It is hypothesized that adjunctive metformin therapy will be associated with greater weight loss from baseline to study endpoint when compared to placebo.

2. To assess the effect of metformin on waist-hip ratio, fasting lipid levels (total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin, HgA1c.

2. **BACKGROUND AND SIGNIFICANCE**

Obesity and associated metabolic disorders represent a substantial and increasing source of morbidity and mortality in patients with schizophrenia. Patients with schizophrenia have a 50% increased risk of death from medical causes (Harris et al, 1998) with the greatest proportion of excess mortality stemming from cardiovascular deaths (Osby et al, 2000). Remarkably, the CATIE Schizophrenia Trial found that, at study baseline, 40.9% of males and 51.6% of females met NCEP criteria for metabolic syndrome (McEvoy et al., 2005). The metabolic syndrome represents a constellation of clinical features (abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance) that is particularly associated with increased cardiovascular risk (National Cholesterol Education Program [NCEP], *Circulation* 2002).

While a number of factors contribute to weight gain and poor health status in patients with schizophrenia, it has been well documented that many of the second generation antipsychotic medications are associated with weight gain. Clozapine and olanzapine have the greatest propensity to produce weight gain, followed by risperidone and quetiapine, while aripiprazole and ziprasidone appear to be least prone to cause weight gain (Newcomer, *CNS Drugs* 2005).
Illustrative, though, of the potential for all antipsychotics to be associated with weight gain is the just published European First Episode Schizophrenia Trial (EUFEST). In this study, patients with first-episode schizophrenia were randomized to 12 months of haloperidol, amisulpride, quetiapine, olanzapine, or ziprasidone. Olanzapine-treated patients had the highest mean weight gain (13.9 kg), followed by quetiapine (10.5 kg), amisulpride (9.7 kg), haloperidol (7.3 kg), and ziprasidone (4.8 kg) (Kahn et al, 2008). These data indicate that even for treatments that are generally considered relatively “weight neutral” such as haloperidol and ziprasidone, considerable weight gain does occur, at least early in the course of treatment.

Other than switching from one antipsychotic medication to another, there are few options available to patients that have experienced antipsychotic-induced weight gain. Unfortunately, such a switch also places an otherwise stable patient at potential risk of clinical decompensation. Metformin is an oral antihyperglycemic agent that is indicated for type 2 (non-insulin dependent) diabetes mellitus. It acts primarily by inhibiting hepatic gluconeogenesis and to a lesser extent by increasing insulin sensitivity. Metformin does not by itself produce hypoglycemia. A number of studies have found that metformin treatment is associated with weight loss in the management of type 2 diabetes mellitus (reviewed by Hermansen and Mortensen, 2007). However, few studies have examined the effect of metformin augmentation in the setting of obesity associated with antipsychotic treatment. The effect of metformin therapy on atypical antipsychotic-induced weight gain in children and adolescents was examined in a double-blind study, demonstrating stabilization of weight gain and improved insulin sensitivity with metformin (Klein et al. 2006). Open-label metformin augmentation was also studied in a similar population, demonstrating moderate weight loss (Morrison et al. 2002). Metformin has been studied in 80 adults with schizophrenia or bipolar disorder receiving olanzapine (Baptista et al 2007). Subjects were randomized to either 12 weeks of metformin or placebo while continuing on olanzapine. In the metformin arm, patients experienced modest weight loss. Recently, a study conducted in China with 128 first-episode schizophrenia patients that had gained at least 10% of body weight since starting atypical antipsychotics (clozapine, olanzapine, risperidone, sulpiride) were randomized to 12 weeks of metformin 750 mg/d with or without lifestyle intervention, lifestyle with placebo and placebo without lifestyle (Wu et al, 2008). The greatest weight loss was achieved in the combined metformin/lifestyle group, followed by metformin-alone and lifestyle/placebo. The placebo-alone group continued to gain weight.

In summary, studies to date indicate that metformin is associated with weight loss in type 2 diabetes mellitus and in pre-diabetic individuals, and that patients with first-episode patients that have experienced early weight gain with atypical antipsychotics can lose weight with metformin and lifestyle intervention. What remains uncertain is the more generalized question of whether metformin is a useful adjunctive treatment for patients with chronic schizophrenia who are obese and are taking atypical antipsychotics. The current study is designed to address this question.
3. RESEARCH DESIGN AND METHODS

3.1. OVERVIEW
This study is a double-blind, multi-site, randomized placebo-controlled trial that will enroll 140 patients with schizophrenia or schizoaffective disorder who have a body-mass index (BMI) ≥27. After baseline assessments have been completed, these patients will be randomly assigned to receive metformin or placebo. Patients will be followed for up to 16 weeks. All patients will receive a behavioral therapy intervention focused on diet and exercise.

This study will compare the effects of the two study conditions on body weight in patients as well as to assess the effect of metformin on waist-hip ratio, fasting lipid levels (i.e., total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin and HgA1c.

3.2. SUBJECTS
A sample of 140 men and women, 18-65 years of age, who currently meet or have met in the past DSM-IV-TR diagnostic criteria for schizophrenia or schizoaffective disorder and who meet the following inclusion and exclusion criteria, will be enrolled across 16 sites.

3.2.1. Inclusion Criteria
1. Outpatients with a diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV-TR criteria (see Appendix 2 and Appendix 3) and confirmed by the Structured Clinical Interview for DSM-IV (SCID).
2. Duration of illness must be greater than one year, as defined by having initiated antipsychotic treatment at least 1 year prior to study enrollment.
3. Patients must be 18-65 years of age.
4. Patients must demonstrate adequate decisional capacity to make a choice about participating in this research study and must provide informed consent to participate.
5. BMI ≥27
6. Currently treated with one or a combination of two antipsychotic medications (typical or atypical antipsychotics) AND on that drug regimen for at least two months prior to study entry (with stable dosages for at least 1 month).
7. If the patient is taking antidepressants, mood stabilizers, and/or anxiolytics, the dose must be stable for at least 1 month prior to study entry.
8. Women who can become pregnant must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimized. Acceptable methods include oral, injectable or implanted contraceptives, intrauterine devices or barrier methods such as condoms, diaphragm and spermicides. Women who can become pregnant must have a negative serum pregnancy test at the Screening Visit.

3.2.2. Exclusion Criteria
1. Inpatient status
2. Clinical Global Impression Severity (CGI-S) score >6
3. Current treatment with more than 2 antipsychotics
4. Fasting glucose > 125
5. Diagnosis of diabetes mellitus or treatment with insulin or oral hypoglycemics
6. Previous or current treatment with metformin
7. Diagnosis of congestive heart failure
8. Renal impairment (serum creatinine > 1.5 in males; > 1.4 in females) or creatinine estimated glomerular filtration rate (GFR) outside of normal limits.
9. Hepatic disease (AST, ALT or GGT > 1.5 times upper limit of normal (ULN), total bilirubin > 1.2 times ULN)
10. Metabolic acidosis (serum CO2 < lower limit of normal)
11. Known hypersensitivity to metformin
12. Women who are pregnant or breastfeeding
13. Recent (in the past 30 days) or scheduled radiological studies involving iodinated contrast material
14. Alcohol abuse/dependence as determined by SCID within the past month
15. Other serious and unstable medical condition in the judgment of the investigator
16. DSM-IV-TR diagnosis of mental retardation, delirium or dementia
17. Any medication used for weight loss must have been discontinued four weeks prior to study entry.
18. Concurrent treatment with the following drugs that are known to increase metformin blood levels should be discussed with the Project Medical Officer: furosemide, nifedipine, and cationic drugs including cimetidine, amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, and vancomycin.

3.2.3. Diagnostic Criteria
Diagnosis will be determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-P) (Spitzer, Williams et al. 1992). The SCID will be used to confirm diagnostic inclusion criteria and assess for co-morbid psychiatric diagnoses.

3.3. ASSESSMENT OF DATA
Patient outcomes will be evaluated twice a month during study visits as outlined in the Schedule of Events (Appendix 1). Clinical care will be provided during weekly visits during the first two weeks of the study and more frequently as indicated.

Outcome measures will be obtained from a variety of sources, including direct measurement of patient weight and waist circumference, laboratory tests, patient self-report, clinician ratings and ratings by trained study personnel. All investigator-rated scales will be performed by qualified raters.
3.3.1. Specific Aims

1. To assess the mean difference in body weight between patients assigned to metformin compared to patients assigned to placebo at the last observation. Only patients who have at least one post-baseline measurement of weight will be evaluable for this aim.

2. To assess the effect of metformin on waist-hip ratio, fasting lipid levels (i.e., total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin and HgA1c.

3.3.2. Other Outcomes

- Frequency and Severity of Adverse Events/Side Effects
- Clinical Global Impressions-Severity Scale (CGI-S)

3.4. RANDOMIZATION METHOD

Study treatments will be randomly assigned using a central computerized system. Randomization will be stratified by site.

3.5. PHARMACOLOGIC TREATMENTS

The following medications are used in this trial:

- Metformin supplied in dosages of 500 mg
- Placebo

3.5.1. Dosing of Study Medications

Starting dose for metformin will be 500 mg bid and this will be titrated up weekly by 500 mg up to a final dose of 1000 mg bid, as tolerated.

3.5.2. Treatment Group Assignment

After a 3-14 day observation period (i.e. screening visit through baseline visit), patients who continue to meet entry criteria at the baseline visit will be randomized to one of the two treatment groups according to a computerized system.

Treatment assignments will be governed by a fixed randomization schedule designed to allocate patients between metformin and placebo in a 1:1 ratio. Within each site, approximately equal numbers of patients will be assigned to each treatment group. Randomization will be stratified by site across each of the 16 sites.

3.5.3. Concomitant and Adjunctive Medications

Concomitant medications (e.g., antidepressants, mood stabilizers, anxiolytics) are allowed if at stable dose for at least 1 month prior to study entry. The addition of these medications during the study must be discussed with the Project Medical Officer. The use of these medications and the indication must be documented using the Other Medications Record (OMR) form.
3.5.4. **Prohibited and Restricted Therapies During the Study**

Treatment with insulin or any oral antihyperglycemic or hypoglycemic agent is not permitted. Certain drugs have been found to increase metformin plasma or blood levels in healthy volunteers (furosemide, nifedipine, cimetidine) or present a theoretical risk of such an increase (cationic drugs). Cimetidine is a cationic drug that can raise metformin peak plasma levels by 60% in healthy controls, probably due to competition for shared renal tubular transport systems for elimination. Cimetidine and other cationic drugs (including amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) are permitted only with the permission of the Project Medical Officer. Furosemide and nifedipine can also increase peak plasma levels of metformin by 20% and are also permitted only with the permission of the Project Medical Officer.

3.5.4.1. **Precautions**

The patient’s best medical interests should guide the Investigator in the management of conditions that are preexisting or that develop during the study (i.e., intercurrent illnesses or AEs). The use of all medications, for any indications, must be documented on the Other Medications Record (OMR). Medications that were given for any preexisting illness will be recorded on the Other Medications Record (OMR) at the Baseline Visit. Any changes to medications that are given for any preexisting conditions must be documented.

Patients should not undergo any elective medical procedure without prior consultation with the Investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalization or anesthesia should be deferred until after the study whenever clinically appropriate.

3.5.5. **Discontinuation from Study Treatment**

Study treatment MUST be immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject’s decision to withdraw for any reason) or if patient loses the ability to provide continued informed consent in the study
- Any clinical adverse event, clinical rating, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy
- Termination of the study
- Patient no longer meets inclusion or exclusion criteria, with exception of BMI criterion

3.5.6. **Drug Supply and Administration**

Study medication will be overencapsulated so that study assignment will not be known to patient or clinicians.

3.5.6.1. **Storage and Inventory Management**

All study drugs will be stored in a secure, limited access area at controlled room temperature.
3.5.6.2. Accountability
The investigator, his/her designee or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all trial supplies using the Drug Accountability Form and Drug Inventory Log. These forms must be available for inspection at any time. Trial drug prescription, dispensing and compliance will be captured on the case report forms and will be source validated by study monitors.

3.6. BEHAVIORAL TREATMENTS
A behavioral treatment aimed at modifying cardiovascular risk factors, including weight, activity level, blood sugar, blood pressure, and lipids will be provided to all study participants (see Appendix 7. This intervention will be provided by a trained clinician in individualized sessions at all study visits after the Baseline Visit. After the first two sessions, interim telephone calls will be made between study visits to each participant to reinforce elements of the program and to answer questions. The intervention will use the principles of “Behavioral Group-Based Treatment for Weight Reduction in Schizophrenia and Other Severe Mental Illnesses” developed by Rohan Ganguli, MD, and colleagues at the University of Pittsburgh. Nine individual sessions will each last approximately 30 minutes. A rating of adherence to the behavioral treatment program will be made using the Behavioral Treatment Adherence Record at each session. The topics of each session are as follows:

Week 1: Self-monitoring: Awareness of Body Weight and What One Eats
Week 2: Burning up Calories by Exercise
Week 3: Phone reinforcement
Week 4: Controlling Urges to Overeat and Snack
Week 5: Phone reinforcement
Week 6: Burning up calories by Using Energy
Week 7: Phone reinforcement
Week 8: Decreasing Food Cues to Overeat and Snack
Week 9: Phone reinforcement
Week 10: Developing good eating habits
Week 11: Phone reinforcement
Week 12: Self-control of overeating
Week 13: Phone reinforcement
Week 14: Changing snack habits
Week 15: Phone reinforcement
Week 16: Increasing success

3.7. STUDY VISITS
Patients will attend visits every two weeks at which structured assessments will be conducted according to the study Schedule of Events in Appendix 1. During the first two weeks of study treatment, all patients will be assessed clinically at Weekly Visits 1 and 2.
3.8. PROCEDURES BY VISIT
The required procedures and assessments for patient evaluation are outlined in the Schedule of Events in Appendix 1.

All investigator rated scales must be performed by qualified clinicians. Every effort should be made to complete the required procedures and evaluations at the designated visits.

3.8.1. Fasting Laboratory Visits
Patients must be fasting (i.e., at least 8 hours without caloric intake) for the Screening Visit and Visits 7 and 11 or discontinuation visit. Fasting laboratory tests are required for patients to be randomized to study treatment. Study sites should call participants the day before study visits to remind them of the appointment and the need to fast. Fasting is not required for laboratory tests for Visits 5 and 9.

3.8.2. Screening Visit (Visit 1)
The purpose of the screening visit is to:
- Ensure that appropriate patients are entered into the trial;
- Determine that the patient meets eligibility criteria;
- Complete medical diagnosis screen
- Measure vital signs, height and weight, and waist and hip circumference
- Other Medications Record
- Measure metabolic parameters including fasting laboratories (i.e., lipid profile, glucose, Hemoglobin A1C, insulin and lipids)
- Blood draw for laboratory assessment
- Collect specified demographic and medical data
- Assess each patient’s reliability and ability to participate in the ratings and the likelihood that the patient will follow the prescribed treatment regimen and protocol requirements;

Screening evaluations consist of:
- Informed consent: study explanation, questions answered, consent form signed
- Psychiatric diagnostic evaluation using SCID modules A-E;
- Verification that all inclusion/exclusion criteria are met (see Section 3.2.1 and 3.2.2), including confirmation of medication eligibility
- General clinical evaluation; physical exam and medical history (to include all events/conditions within the last 2 years and all events /conditions of clinical significance or relevance to the study)
- Clinical Global Impressions-Severity (CGI-S)
3.8.3. **Baseline Visit (Visit 2)**
The patient will complete baseline evaluations at the baseline visit prior to randomization and prior to beginning study therapy. The visit is to be scheduled 3-14 days following the screening visit.

The following assessments must be completed:
- Vital signs, weight (patient's weight at this visit will constitute baseline weight), and waist circumference
- Other Medications Record
- Clinical Global Impressions-Severity (CGI-S)
- Clinician Alcohol Use Scale and Drug Use Scale (AUS/DUS)
- Alcohol Use Questionnaire
- Study Medication Dispensing
- Adverse Events Form

The patient will be eligible for the study at the completion of the baseline visit evaluation and if:
- An adequate screening evaluation is completed (including a fasting laboratory evaluation);
- The patient is a woman who can become pregnant, she has a negative pregnancy test at the Screening Visit and, if sexually active, agrees to continue with adequate contraceptive precautions;
- All criteria outlined in inclusion/exclusion criteria in Sections 3.2.1 and 3.2.2 continue to be met.

After all eligibility requirements have been verified and documented, the patient can be randomized into the study. The investigator will randomize the patient at the baseline visit following the randomization method described in section 3.4. All safety and efficacy baseline evaluations must be completed at this visit before study medication is administered.

3.8.4. **Visit 3 and 4 (Weeks 1 and 2)**
These visits will occur weekly after the Baseline Visit. The purpose of these visits is for medication management (i.e., assess symptoms, side effects, adherence, adjust dose as indicated) vital sign collection (including weight, and waist circumference), assess daily alcohol intake, and to provide the behavioral therapy intervention. The Other Medications Record and Medication Adherence Forms will be completed at these Weekly Visits.

3.8.5. **Visit 5 (Week 4)**
This visit will include completing:
- Vital Signs, weight, and waist circumference
- Study Medication Dispensing
- CGI-S
• Substance Use Scale
• Alcohol Use Questionnaire
• Other Medications Record
• Study Medication Adherence Form
• Adverse Events Form
• Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.6. Visit 6 (Week 6)
This visit will include completing:
• Vital Signs, weight, and waist circumference
• Alcohol Use Questionnaire
• Other Medications Record
• Study Medication Adherence and Dispensing Form
• Adverse Events Form
• Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.7. Visit 7 (Week 8)
This visit will include completing:
• Vital Signs, weight, and waist circumference
• Study Medication Dispensing
• CGI-S
• Substance Use Scale
• Alcohol Use Questionnaire
• Other Medications Record
• Study Medication Adherence Form
• Adverse Events Form
• Behavioral Treatments and Behavioral Treatment Adherence Forms
• Fasting laboratories (i.e., lipid profile, fasting glucose, Hemoglobin A1C, fasting insulin)

3.8.8. Visit 8 (Week 10)
This visit will include completing:
• Vital Signs, weight, and waist circumference
• Alcohol Use Questionnaire
• Other Medications Record
• Study Medication Adherence and Dispensing Forms
• Adverse Events Form
• Behavioral Treatments and Behavioral Treatment Adherence Forms
3.8.9. Visit 9 (Week 12)
This visit will include completing:
- Vital Signs, weight, and waist circumference
- Study Medication Dispensing
- CGI-S
- Substance Use Scale
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.10. Visit 10 (Week 14)
This visit will include completing:
- Vital Signs, weight, and waist circumference
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.11. Visit 11 or Discontinuation Visit (if patient is discontinuing the assigned treatment condition early)
This visit will include completing:
- Vital Signs, weight, waist and hip circumference
- CGI-S
- Substance Use Scale
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms
- Global Behavioral Treatment Adherence Form
- Fasting laboratories (lipid profile, fasting glucose, Hemoglobin A1C, fasting insulin)
- Reason for Assigned Treatment Discontinuation
3.8.12. Unscheduled Visits
Unscheduled visits may occur at any time during the study and may occur for many reasons. These visits require completion of the appropriate Unscheduled Visit form only if the visit occurs for one of the following reasons:

- Assessment of possible change in psychiatric symptoms
- Assessment of possible change in drug tolerability, adverse event
- Assessment of possible change in medical status
- Assessment of need for medication changes or adjustment

Forms available for these visits will include: CGI-S, Side Effect/Adverse Event Form, Vitals signs, Alcohol Use Questionnaire, Laboratory tests and/or Other Medication Record.

3.9. DETAILS OF PROCEDURES

3.9.1. Study Materials
Sites will be provided with Gulick II tape measures for waist and hip measurements, a stadiometer for measuring height, specimen collection kits and instructions for clinical laboratory specimen collection, study documents (source documents, behavioral treatment manual, drug logs, etc) and study medication. In addition, sites will be provided with pedometers, digital scales, and behavioral treatment handbooks for enrolled participants.

3.9.2. Structured Clinical Interview for DSM-IV (SCID)
The Structured Clinical Interview for DSM-IV (SCID) will be used to confirm the diagnosis of schizophrenia or schizoaffective disorder and the presence or absence of alcohol abuse or dependence. Detailed instructions for administration of this interview will be provided. A qualified clinician should administer the SCID.

The SCID is a semi-structured interview designed to evaluate DSM-IV Axis I diagnoses (Spitzer, Williams et al. 1992). It enables trained clinical raters to reliably determine Axis I diagnoses in diverse patient populations (Skre, Onstad et al. 1991; Segal, Hersen et al. 1994; Ventura, Liberman et al. 1998). Because the SCID is completed by a trained clinician who may rely on medical records, staff reports, and information from caretakers, an accurate diagnostic picture may be obtained even when the patient is limited in ability to provide accurate self-report, as may be true for patients who are severely disorganized or cognitively impaired.

The SCID will be administered at screening.

3.9.3. Physical Examination
Patients will undergo a routine physical exam during screening.
3.9.3.1. Vital Signs
Arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured while the patient is seated at the scheduled visits designated in the Schedule of Events in Appendix 1. Vital signs measurements scheduled at the same visit as blood samples are to be completed before blood is drawn.

3.9.3.2. Height
Height will be measured at the screening visit. Patients will be measured without shoes.

3.9.3.3. Body Weight
Body weight will be recorded at screening, baseline and every visit through the 16-week treatment phase. The following guidelines will aid in the standardization of these measurements:

- The same scale should be used to weigh a given patient at every visit.
- Scales should be calibrated: scales should be at zero just prior to each patient’s weigh-in session.
- A patient should void prior to being weighed and be minimally clothed (i.e., no shoes or heavy over garments).
- Weight should be recorded before a patient’s meal and at approximately the same time at each visit.

3.9.3.4. Body Mass Index (BMI)
Body mass index (BMI) will be determined with the patient’s height and weight at the screening visit. BMI must be calculated using the following formula: A person’s (Weight in pounds divided by their height in inches squared) x 703. This should then be confirmed using the BMI chart provided in Appendix 4. The BMI for each patient will be calculated by the Data Management System to verify accuracy.

3.9.3.5. Waist and Hip Circumference
Waist circumference will be recorded at screening, baseline, and all study visits. Hip circumference will be recorded at screening and Visit 11 (or discontinuation visit). The following guidelines will aid in the standardization of these measurements:

- Sites will be provided with Gulick II tape measures that ensure consistent tension is used when making waist measurements.
- The patient should be minimally clothed (i.e., no shoes or heavy overgarments; lightweight clothing).
- Waist circumference should be recorded before a patient’s meal and at approximately the same time at each visit.
- The patient’s waist circumference will be measured midway between the inferior margin of the last rib and the crest of the ilium. (See Appendix 7 for full description).
• The patient's hip circumference will be measured at the widest part of the hip. (See Appendix 7 for full description).

3.9.4. Clinical Global Impressions Scale (CGI)
The Clinical Global Impressions (CGI) Severity Scale will be used for repeated evaluations of global psychopathology. The CGI scale is widely used in schizophrenia research. The CGI-S is a single Likert scale rating severity of psychopathology on a scale of 1 (normal, not ill) to 7 (very severely ill). The CGI will be completed at screening, baseline, Week 4, Week 8, Week 12 and Week 16.

3.9.5. Substance Use Scale
The Alcohol Use Scale (AUS) and Drug Use Scale (DUS) are 5-point scales based on DSM-III-R criteria for severity of disorder: 1 = abstinence, 2 = use without impairment, 3 = abuse, 4 = dependence, and 5 = severe dependence.

3.9.6. Adverse Event/Side Effects Form
The Adverse Events/Side Affects Form records the results of a systematic inquiry of a set of pre-specified side effects that are common with the study medication. The rater also inquires about any additional side effects or adverse events that may have occurred. Each side effect or adverse event is recorded and rated for severity. Ratings are completed by a clinician.

3.9.7. Concomitant/Adjunctive Medications
Concomitant and Adjunctive Medications will be documented using the Other Medications Record (OMR) form at Baseline and all study visits. The addition of or change in dose of lipid-lowering medication will be captured on the Lipid lowering Agent Form (LLA) at Baseline and all study visits.

3.9.8. Study Medication Adherence
Participants will be asked about his/her medication adherence at each appointment. Study personnel will count and record the number of pills in the patient’s study medication bottles and provide immediate feedback, reinforcing the behaviors of patients who appear to be taking medications as prescribed and problem-solving with those who appear not to be. Clinicians will review with patients the use of pill-minder boxes, as needed.

3.9.9. Behavioral Treatment Adherence
Participation in the Behavioral Treatment Intervention must be documented at each visit using the Behavioral Treatment Adherence Record—BY VISIT form. At the final study visit (Week 16 or Study Discontinuation), overall adherence to the Behavioral Treatment will be rated using the Behavioral Treatment Adherence Record—GLOBAL form.
3.9.10. Laboratory Test Assessments
A central laboratory will be used for all laboratory testing required during the study. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled, follow-up laboratory tests, if needed). Blood will be drawn from each patient at the screening visit, and at the scheduled visits designated in the study Schedule of Events in Appendix 1. The following fasting tests will be performed:

- Hematology: hemoglobin, HBA1C, hematocrit, RBC, WBC, differential white blood cell count, and absolute platelet count
- Serum chemistries: sodium, potassium, chloride, calcium, AST, ALT, GGT, LDH, alkaline phosphatase, CPK, total protein, total bilirubin, creatinine, creatinine estimated GFR, BUN, uric acid, CO2, lactate, total cholesterol, LDL-C, HDL-C, and triglycerides, TSH
- Fasting blood glucose and insulin levels
- Urine screen for drugs of abuse
- Serum pregnancy test for women who can become pregnant must also be performed at the Screening Visit and at 8 weeks

Any value outside the normal range will be highlighted for the attention of a physician Investigator at the site. The Investigator will indicate whether or not a highlighted value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. With the exception of fasting glucose, GRM, total bilirubin and creatinine, if the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening or baseline visits, the patient will NOT be randomized into the study without the permission of the Project Medical Officer. (Guidelines for identifying potentially clinically significant laboratory values will be provided).

3.9.11. Alcohol Use Questionnaire (AUQ)
This scale quantifies the daily intake of alcoholic beverages since the previous visit and the highest number of drinks in a single 24 hour period since the last assessment. Given the increased risk for alcohol-potentiated lactic acidosis, the goal is for the clinician to know how much alcohol each subject is drinking so as to help identify any individuals who begin to meet criteria for alcohol abuse or dependence after study randomization.

4. DISCUSSION OF STUDY DESIGN AND APPROACH
There is a very high comorbid prevalence of obesity and related metabolic disorders with schizophrenia. Given the fact that these comorbidities stem at least in part from clearly established side-effects of antipsychotic medications, it is notable that there are no pharmacological approaches that have been established as safe and effective ways to achieve weight reduction in patients with obesity and schizophrenia. Current FDA-approved agents for obesity management include phentermine, sibutramine (Meridia™), methamphetamine (Desoxyn™) and orlistat (Xenical™). For different reasons, none of these medications have
emerged as useful adjuncts to manage obesity in the setting of schizophrenia. Phentermine and methamphetamine both have significant abuse potential and the potential to exacerbate psychosis. Sibutramine has been associated with serotonin syndrome and needs be used with caution with SSRIs, lithium and certain other psychotropic medications. Orlistat is associated with a number of unpleasant gastrointestinal side-effects and is unlikely to be acceptable to many patients with schizophrenia who are already challenged to remain compliant with their side-effect prone psychiatric medications.

In light of this background, evidence suggesting that patients with type 2 diabetes mellitus often lose weight during metformin treatment and metformin’s relatively benign side-effect profile provides a rationale to study metformin for weight loss in schizophrenia. Several small studies of metformin in children and adolescents with atypical antipsychotic-associated weight gain and in adults with olanzapine-associated weight gain provided early indications that metformin may either attenuate weight gain or produce weight loss. More recently, a larger study in China was conducted in 128 patients in their first episode of schizophrenia that had gained at least 10% of their baseline body weight since starting an atypical antipsychotic (Wu et al. 2008). This study found that metformin alone or in combination with a lifestyle intervention program led to significant weight loss and only the placebo group with no behavioral intervention continued to gain weight.

To extend on the findings in the Chinese study, it would be of considerable value to know whether adjunctive metformin in conjunction with exercise and dietary modification can be used to treat obesity in patients with chronic schizophrenia and in patients that are on any antipsychotic regimen (not just the atypical antipsychotics most associated with weight gain). Patients with schizophrenia generally end up taking the antipsychotic medication that is consistent with the best symptom response and best level of functioning. Weight loss in the setting of psychotic decompensation is rarely if ever desirable. Thus, it is imperative that anti-obesity agents are developed that can address obesity in the setting of any concurrent antipsychotic medication.

The results from this study are intended to be generalizable and therefore the inclusion/exclusion criteria are not restrictive with the exception of several specific safety issues. Patients must be overweight as defined by a BMI > 27. The study will allow any patient with schizophrenia or schizoaffective disorder who is not in the first-episode of illness. Concurrent affective illness, substance abuse (except alcohol abuse or dependence) and other axis I disorders are allowed. Patients can be on one or two antipsychotics, typical or atypical. Stable concurrent treatment with other classes of psychotropic medications is allowed. Enrollment will be limited to clinically stable outpatients. The most serious risk associated with metformin is lactic acidosis, a very rare but often fatal condition. The incidence is about 3 cases in 100,000 patient-years, with about 50% mortality when it occurs however, in more than 20,000 patient-years exposure to metformin in clinical trials, there are no known reports of fatalities. Lactic
acidosis usually occurs in diabetic patients with renal insufficiency and in the setting of multiple serious medical and surgical conditions including congestive heart failure. Patients with evidence of renal insufficiency, significant hepatic disease, alcohol abuse, or serious and unstable medical conditions will be excluded. Lactic acid levels and liver function tests will be measured at screening and every four weeks during the study.

Finally, the specific outcome measures were chosen primarily to assess the effects of metformin on weight and secondarily on waist-hip ratio, fasting lipid levels (i.e., total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin, and HgA1c. Improvement on these measures – especially weight – will inform on the utility of adjunctive metformin as a weight loss agent in overweight patients with schizophrenia. Furthermore, these basic assessments are straightforward, can easily be implemented across a number of different sites, and are relatively inexpensive.

5. STUDY MONITORING AND OVERSIGHT

5.1. SITE MONITORING
Representatives of the University of North Carolina at Chapel Hill will visit all study site locations periodically to assess the data quality and study integrity. Monitors will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator and verify that the facilities remain acceptable.

5.2. RECORD RETENTION
The site investigator must retain investigational product disposition records, copies of CRFs or eCRFs and source documents for a minimum of four years after the trial is complete or for the maximum period required by Institutional policies, whichever is longer.

6. SAFETY AND ADVERSE EVENTS
It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator of each site is responsible for ensuring compliance with all procedures.

6.1. ADVERSE EVENTS
The definitions of adverse events (AE’s), serious adverse events (SAE’s) and other significant adverse events (OAE’s) are given below. An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable
medical condition occurring at any time, including run-in or wash-out periods even if no study treatment has been administered.

6.1.1. Serious Adverse Events
The trial period is defined from the time that the informed consent document is signed until 30 days after administration of the last dose of the trial drug. All serious AEs occurring during the trial period (including death due to any cause) or within 30 days after administration of the last dose of the trial drug must be communicated within 1 day of the investigator becoming aware of the event to designated personnel, using the telephone or fax numbers provided in the Study Reference Manual. Any fatal or life threatening AEs must be reported immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment must be provided for all serious AEs. Critical follow-up information on serious AE’s must be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information. Other essential, but not critical, information may be reported within the following 5 days. Although it is important to report all serious AEs within 1 day, extra measures must be taken to ensure that any serious, unexpected, possibly drug-related AE be communicated immediately.

A serious AE is defined as one that satisfies any of the following criteria:

- Results in death.
- Is immediately life-threatening, including potentially life threatening suicidal behavior or suicidal behavior that results in hospitalization.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix 5 and 6.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s). For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendices 5 and 6.

6.1.2. Death
All deaths occurring within the trial period or within 30 days after the last dose of trial drug is given must be reported within 1 day of the investigator becoming aware of the event.

If an autopsy has been performed, results of the autopsy must be obtained and forwarded along with any available toxicology reports.
6.1.3. Pregnancy
Pregnancy is an exclusion criterion and women who can become pregnant should use adequate methods of birth control as outlined in the inclusion criteria.

Should a pregnancy occur it must be reported in accordance with the procedures described below. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. The Adverse Events/Side Affects form will be used for this purpose.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. All other outcomes of pregnancy must be reported on the Adverse Events/Side Affects form.

6.1.4. Reporting of Serious Adverse Events
The process flow for reporting serious adverse events along with associated documents and contact information will be presented in the Study Reference Manual to accompany this protocol, as well as the Instructions for Completing the Serious Adverse Event Report. The investigator must provide the minimal information: i.e. subject’s initials and date of birth, study ID number, medication, period of intake, and nature of the adverse event and investigator's causality assessment. The sites will also have the opportunity to make initial contact with the Project Safety Officer for clarifying the event seriousness criteria.

A report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. If a non-serious case becomes serious, this and other relevant information should also be reported.

After initial notification, The University of North Carolina at Chapel Hill (UNC-CH) will inform the Project Safety Officer of the event and he/she will perform a medical review of the Serious Adverse Event Report. UNC-CH will be responsible for collecting source documents and confirming the seriousness, relationship to study product and expectedness. Narratives and all supporting documentation will be written and gathered by the PMO and sent to the National Institute of Mental Health at the same time.

UNC-CH will forward any follow-up information to the DSMB.

It is the investigator's responsibility to report the AE’s which are classified as serious and related to the use of the study drug to the Institutional Review Board (IRB) which has approved the protocol unless otherwise required and documented by the IRB.
All SAEs must be reported, whether or not considered causally related to the study drug. All SAEs will be recorded in the data management system. The investigator is responsible for informing the IRB of the SAE as per local requirements.

6.2. DATA SAFETY MONITORING BOARD
The safety of the study will be monitored by the Data and Safety Monitoring Board (DSMB) convened by the Schizophrenia Trials Network. The STN DSMB will independently review the protocol and consent document, adverse events and outcome data at least twice a year for studies conducted by the STN. The DSMB will evaluate issues of participant safety, the adequacy and integrity of accumulating data and studies’ ability to test the study’s hypotheses. The DSMB will also identify if any study procedures should be altered or stopped in the event of an indication of clinical benefit or harm to participants attributable to the study interventions.

7. STATISTICAL ANALYSES

7.1. ANALYSIS POPULATIONS
Patients who are screened but not randomized will not be included in any efficacy or safety analyses of study data. However, the number of patients screened and reasons for any screen failures will be reported. SAEs occurring during the screening period will also be reported.

7.1.1. Safety Population
The Safety Population will consist of all subjects randomized to treatment who received at least one dose of study medication. This population will form the basis for all safety analyses and selected secondary efficacy analyses.

7.1.2. Efficacy Evaluable Population
The Efficacy Evaluable Population will include all subjects in the Safety Population who completed at least one post-baseline weight measurement. This population will form the basis for the primary efficacy analyses and most secondary efficacy analyses.

7.1.3. Per-Protocol Population
The Per-Protocol Population will consist of 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. This population will form the basis for selected secondary analyses.

7.2. STATISTICAL CONSIDERATIONS
The statistical analysis planned has three aspects: (1) Descriptive, (2) Inferential and (3) Exploratory.

(1) Descriptive: We will explore the data and calculate descriptive statistics and will use graphics, including box plots by treatment group, stem-and-leaf plots, normal probability plots,
histograms and bar charts, and other graphics. These will be useful in exploring anomalies or potential errors in our data, understanding distributional aspects of our data and understanding the results of our statistical analyses.

(2) Inferential: For Specific Aim 1, the outcome is endpoint body weight. In addition to descriptive statistics and graphics, we will use a mixed model analysis 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 an blocking factor. We will plan on using an AR(1) covariance structure among the repeated measures but will compare it to both an unstructured covariance structure and to compound symmetry in order to examine the utility of that choice. The primary outcome will be a contrast examining the difference between treatment least squares means at the 16 week point.

(3) Exploratory: For Specific Aim 1, the outcome is endpoint body weight. In addition to the analyses above, we will perform additional sensitivity analyses to examine the effect of metformin on fasting glucose, LDL cholesterol. In addition, we will consider the effect of metformin among participants entering the study on atypical antipsychotics with higher risk of weight gain (i.e. clozapine, olanzapine, quetiapine, risperidone, paliperidone) versus first generation antipsychotics with lower risk (i.e., aripiprazole, ziprasidone, fluphenazine, haloperidol, perphenazine, thiothixine). If imbalance in type of concomitant antipsychotic use is observed between groups, we will repeat the primary analysis adjusting for this potential confounding factor. If either distributional or equal variance assumptions appear to be grossly violated, we will use a two-sample randomization test on the baseline to endpoint weight changes.

We will follow the above plan for other key secondary weight and metabolic-related variables. These analyses are all exploratory. Adverse events will be tabulated by treatment arm.

7.2.1. Power and Sample Size Calculations:

For the primary aim, treatment effect on weight, we approximated power and sample size calculations using simple models using power calculations for a two-group t-test, because we do not know important information such as the correlation between baseline and endpoint weights, the number and pattern of dropouts, the site effect, etc. The literature (Klein et al, 2006; Baptista et al 2007; Wu et al. 2008; Pavo et al. 2003) indicated standard deviations of change scores for weight in kg of approximately 0.4 to 6.25 kg (the 0.4 was probably an SE although Pavo et al called it an SD). In our power and sample size calculations, we did our calculations using estimates of 2, 4, 5, and 6 for the SD. We felt that a 2 kg change was a clinically important change, and hence, a difference between treatment groups of 2 kg (or more) in change from baseline represented a clinically important effect. We did calculations using a two-tailed test with a significance level of 0.05. We believed the 4 kg SD was probably the most likely SD, and the sample size we found was 128 subjects. We chose to use slightly more than that to allow for a possible underestimate of the standard deviation.
7.2.2. Specific Aim #1
This aim will use weight measures to calculate means and standard deviations, along with their 95% confidence intervals, at each time point, along with correlations among time points.

7.2.3. Specific Aim #2
The response variable is the effect of metformin on waist-hip ratio, fasting lipid levels (i.e., total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin, and HgA1c. These variables are all numeric, and the analyses will be identical to those performed for weight.

7.2.4. Missing Data
Data may become missing in several ways. Data may be sporadically missing because a subject failed to attend a scheduled visit and there are usually relatively few of these instances. The missing at random values are easily handled in longitudinal models. Data may become missing when subjects drop out, and there is a danger that such missing data are informative, especially problematic when the proportion of the missing data is large (more than 20%). We will use sensitivity analyses to determine whether the missingness of the data is informative or noninformative, and the effect of such missing data on the results.

8. HUMAN SUBJECTS RESEARCH

8.1. PROTECTION OF HUMAN SUBJECTS
This study will be conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol and any amendments.

The rights, safety and well-being of the patients are the most important considerations and should prevail over interests of scientists and society.

Personnel involved in conducting this study will be qualified by education, training and experience to perform their respective tasks.

8.2. RISKS AND BENEFITS

8.2.1. Risks
Metformin, which received FDA approval in 1995 as an oral agent to treat diabetes mellitus Type II, has been one of the most prescribed medications for this indication world-wide. Its side-effect profile is well established and it is generally safe, with several common, less serious side-effects and a few rare but very serious side-effects.
The most common side effects associated with metformin therapy include diarrhea, nausea, vomiting, abdominal discomfort as well as headache, weakness, muscle pain. Gastrointestinal symptoms are usually time limited.

A rare but very serious side-effect is lactic acidosis. The incidence is about 3 cases in 100,000 patient-years, with about 50% mortality when it occurs. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), low blood pH, increased anion gap, and increased lactate to pyruvate ratio. When metformin is implicated, elevated metformin levels (>5 micrograms/mL) are usually found. Symptoms of lactic acidosis are generally non-specific and include weakness, somnolence, myalgia, dyspnea, dizziness, syncope, hypotension, bradycardia, hypothermia. Lactic acidosis primarily occurs in diabetic patients with renal insufficiency and in the setting of multiple serious medical and surgical conditions. Lactic acidosis also occurs in patients with congestive heart failure. The risk of lactic acidosis increases with age and degree of renal dysfunction and the risk may therefore be reduced by regular monitoring of renal function.

Metformin should not be administered to patients with impaired renal function, defined by serum creatinine levels >1.5 in males and >1.4 in females. During ongoing treatment, hematologic parameters and renal function should be measured at least annually. Metformin should not be administered to patients with hypoxemia, dehydration or sepsis. Metformin should also be avoided in patients with impaired hepatic function because of reduced lactate clearance. Alcohol potentiates the effects of metformin on lactate metabolism and therefore patients with alcohol abuse or dependence should not receive metformin. Iodinated intravascular contrast material can lower renal clearance acutely and metformin should be discontinued temporarily in anticipation of such procedures. If patients are suspected of having lactic acidosis, it represents a medical emergency and must be treated in a hospital setting.

While metformin is not a hypoglycemic agent under usual circumstances, hypoglycemia can occur in settings of deficient caloric intake, strenuous exercise without adequate compensatory caloric intake, concomitant use of hypoglycemic agents or alcohol.

Metformin can cause reduced serum levels of vitamin B12 in <10% of patients by an unclear mechanism. This has only rarely been associated with anemia and it has been rapidly reversible with vitamin B12 supplementation or metformin discontinuation.

Drug-drug interactions are possible with metformin. In particular, oral hypoglycemic agents can potentiate a hypoglycemic state. However, patients in this study cannot have diabetes mellitus or be receiving treatment with a glucose-lower agent. Furosemide can increase blood metformin levels as can nifedipine. Cimetidine has been shown to increase metformin blood levels substantially and other cationic drugs are theoretically liable to increase levels, such as amiloride, digoxin, morphine, procainamide, quinidine, ranitidine, triamterene, trimethoprim, and vancomycin.
Metformin is rated in the Pregnancy Category B for teratogenic effects. Metformin has not been found teratogenic in rats and rabbits up to 600 mg/kg/day. Well-controlled safety data in humans is not available. Females in this study must not be pregnant and must agree to use medically acceptable contraception or abstinence during the study. If they become pregnant during the study they will be discontinued.

In addition, blood draws will be done at specified visits. There may be temporary discomfort when blood samples are taken and there is a small risk of bruising, infection or inflammation at the needle stick site. Some people may feel faint or dizzy after giving only a small amount of blood. We will use routine blood draw procedures (e.g. sterile technique) to minimize risk of the blood draw.

8.2.1.1. Moderation of Risk
All of the medications to be used in this study have been evaluated and approved by the FDA for clinical use. The risks and benefits of the specific study medications, of specific study procedures, and of the study as a whole will be explained to participants. After a thorough history, subjects will undergo careful physical, psychiatric, and laboratory examinations to assure the clinical appropriateness and safety of their participation. Close clinical monitoring will ensure the appropriateness and safety of their continued participation including monthly laboratory tests assessing renal and hepatic function. Given the increased risk of lactic acidosis in the setting of alcohol abuse and metformin, daily alcohol intake will be recorded for the purpose of helping to identify any subject who begins to meet criteria for alcohol abuse or dependence following study randomization. Adjunctive medications are allowed to relieve specific clinical symptoms or manage study medication adverse events.

8.2.2. Potential Benefits to Participants
Study medication (metformin) will be provided free of charge. All screening tests, laboratory tests, and assessments outlined in this protocol will be provided free of charge. The Behavioral Treatments that will be provided to all participants free of charge is expected to benefit subjects by enhancing their knowledge and providing strategies for dietary modification, exercise, and weight loss. In addition, participants could potentially receive 16 weeks of metformin therapy that, together with the Behavioral Intervention, may be effective in reducing obesity associated with antipsychotic treatment. For any subjects that experience weight loss during the study, it is uncertain whether they can maintain their weight loss after the end of the study. However, the behavioral modification program that all subjects received during the study may be associated with more enduring beneficial effects for those subjects that continue to implement these in their daily life routine.

8.2.3. Risk/benefit ratio
The risks associated with participation in this study include benign but relatively frequent gastrointestinal-related side-effects (e.g. diarrhea, nausea/vomiting, and flatulence) that occur
early in the course of metformin treatment and usually disappear with continued treatment. A rare but very serious side-effect is lactic acidosis which occurs in about 3 in 100,000 patient years with about 50% mortality rate. While lactic acidosis is very serious, it primarily occurs in diabetic patients with renal insufficiency, in the setting of multiple serious surgical and medical conditions, including congestive heart failure, and in alcohol abuse. The risk of lactic acidosis increases with age and degree of renal dysfunction. Given these known risk factors of lactic acidosis, the risk of developing lactic acidosis in the current study is limited further by excluding any patients that have one or more of these risk factors or laboratory evidence of reduced renal function.

Participants could potentially benefit by receiving a medication treatment that, in combination with behavioral modification, is effective in reducing their weight, and could result in reduced morbidity and risk of other medical conditions. The benefits which subjects will receive from closely monitored treatment, in addition to the societal benefits of important treatment data concerning a disorder with substantial morbidity and mortality, outweigh the risks to participating subjects.

8.2.4. Subject Payments
Participants will receive a payment ($20 for each visit, plus an additional $5 for visits when medication bottles are brought in is recommended) for each scheduled study visit attended to help compensate for effort and for transportation costs.

8.2.5. Costs to Patients
Costs for inpatient care will be billed to each research participant’s usual payer. Case management, where available, will also be billed in the usual manner. No participant or third party payer will be charged for visits, study medications, or assessments related only to this research project.

8.3. INSTITUTIONAL REVIEW BOARD (IRB) CONSIDERATIONS
Before study initiation, site investigators will be required to have written and dated approval from an IRB for the protocol, consent form, subject recruitment materials/process and any other written information to be provided to subjects. Site investigator should also provide the IRB with a copy of the product labeling for all investigational products used.

Site investigators should provide the IRB with reports, updates and other information (e.g., safety updates, amendments, administrative letters, DSMB letters) according to regulatory requirements or Institution procedures.

8.4. INFORMED CONSENT
Informed consent will be sought using a process of repeated instruction regarding the risks, benefits, and nature of the study. Prospective participants will be given an opportunity to ask questions and have them answered to their satisfaction. The informed consent document
explains, in simple terms, study procedures, risks, and benefits. The document makes clear that consent is freely given, that participants are aware of the risks and benefits of the study, and that participants are free to withdraw at any time.

8.5. PARTICIPANT CONFIDENTIALITY

Research staff will be required to adopt confidentiality procedures consistent with the study protocol described herein. All study related documents, medical records and other identifying information should be kept in locked cabinets. All study related documents (case report forms, source documents, lab requisition forms, test tubes etc.) should be coded using a study number and not the patient's name. Research participant's name or other identifying information should never be kept with their case report forms or source documents. The list linking study participants to their study numbers should be kept in a separate locked cabinet. All computerized records and schedules must be password protected, coded with a subject ID number, so that there will be no personal identifying information included on these records.

Data will only be published or presented in aggregate form.

8.5.1. Certificate of Confidentiality

A Certificate of Confidentiality will be obtained for this study. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

9. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index expressed in kilograms per meter squared (kg/m²)</td>
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<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness</td>
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<tr>
<td>CV</td>
<td>Cardiovascular (disease)</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision</td>
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Rating Scales

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>CGI-S</td>
<td>Clinical Global Impressions-Severity</td>
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<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short Form Health Survey</td>
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<td>SURFs</td>
<td>Service Utilization and Resources Form – Short Form</td>
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10. LITERATURE CITED


Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of


### Appendix 1. Schedule of Events

<table>
<thead>
<tr>
<th>Assessments</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
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Appendix 2. DSM-IV-TR Criteria for Schizophrenia

A. **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g., frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms, i.e., affective flattening, alogia, or avolition

**Note:** Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other.

B. **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. **Duration:** Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and Mood Disorder exclusion:** Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. **Relationship to a Pervasive Developmental Disorder:** If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

**Classification of longitudinal course** (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

- **Episodic With Interepisode Residual Symptoms** (episodes are defined by the reemergence of prominent psychotic symptoms); *also specify if: With Prominent Negative Symptoms*
- **Episodic With No Interepisode Residual Symptoms**
- **Continuous** (prominent psychotic symptoms are present throughout the period of observation); *also specify if: With Prominent Negative Symptoms*
- **Single Episode In Partial Remission; also specify if: With Prominent Negative Symptoms**
- **Single Episode In Full Remission**
- **Other or Unspecified Pattern**
Appendix 3. DSM-IV-TR Criteria for Schizoaffective Disorder

A. An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia.

Note: The Major Depressive Episode must include Criterion A1: depressed mood.

B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.

C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type:

Bipolar Type: if the disturbance includes a Manic or a Mixed Episode (or a Manic or a Mixed Episode and Major Depressive Episodes)

Depressive Type: if the disturbance only includes Major Depressive Episodes
### Appendix 4. BMI Calculation Chart

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Appendix 5. Definition of an SAE

Results in death

Any death resulting from an AE occurring during the trial period or within 30 days after the last dose of the trial drug is given. However, should a death be reported to an investigator at any time following the completion or discontinuation/withdrawal of a subject from the trial, including any protocol required post-treatment follow-up, the investigator has an obligation to report the serious AE if the investigator feels it is related to study drug.

Life threatening

The subject must have been at an immediate risk of dying from the AE as it occurred or it was suspected that use or continued use of the product would result in the subject’s death. This does not include events that might have caused death if they had occurred in a more serious form (e.g., drug-induced hepatitis that resolves without hepatic failure).

Hospitalization

Any AE resulting in hospital admission and usually an overnight stay. The term “prolongs hospitalization” means delayed planned or anticipated discharge date (again usually by at least 1 overnight stay). Hospital admissions and/or surgical operations planned before or during a trial are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected way during the trial. Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). For the purpose of this trial, hospitalizations for social reasons, respite care, elective treatment or surgery, or lack of efficacy will not be regarded as serious AEs.

Results in persistent or significant disability or incapacity

Any AE resulting in impairment of, damage to, or disruption in the subject’s body function, structure, or both; physical activities; or quality of life.

Important medical event/medical intervention

Medical and scientific judgment should be exercised in deciding whether an event is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity, but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of a serious event. These should usually be considered serious. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

Discontinuation of the trial treatment or of routine administration of prescription medications, or changes in their dosages should not be considered medical intervention.
Appendix 6. A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this
Appendix 7. Instructions for Measuring Waist and Hip Circumference, Adapted from the World Health Organization

**Abdominal circumference (adapted from references 2 and 9)**

The subject stands comfortably with his or her weight evenly distributed on both feet, and the feet about one foot apart. The measurement is taken midway between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane. Each landmark should be palpated and marked, and the midpoint determined with a tape measure and marked. The observer sits by the side of the subject and fits the tape snugly but not so tightly as to compress underlying soft tissues. The circumference is measured to the nearest 0.5-inch at the end of normal expiration.

**Hip (buttocks) circumference (adapted from reference 2)**

Wearing only nonrestrictive briefs or underwear, or a light smock over underwear, the subject stands erect with arms at the sides and feet together. The measurer sits at the side of the subject so that the level of maximum extension of the buttocks can be seen, and places the tape measure around the buttocks in a horizontal plane. An assistant may be needed to help position the tape on the opposite side of the subject’s body. The tape is snug against the skin but does not compress the soft tissues. The measurement is recorded to the nearest 0.5-inch.

Appendix 8.

Individual Behavioral Treatment for Antipsychotic-Induced Weight Gain in Schizophrenia

Adapted from

A BEHAVIORAL GROUP-BASED TREATMENT FOR WEIGHT REDUCTION IN SCHIZOPHRENIA AND OTHER SEVERE MENTAL ILLNESSES

Rohan Ganguli, M.D.
Jaspreet Singh Brar, M.B.B.S., MPH
University of Pittsburgh School of Medicine
Schedule of Events

Week 1  Self-monitoring: Awareness of Body Weight and What One Eats  
Week 2  Burning Calories by Exercise  
Week 3  Phone reinforcement  
Week 4  Controlling Urges to Overeat and Snack  
Week 5  Phone reinforcement  
Week 6  Burning Calories by Using Energy  
Week 7  Phone reinforcement  
Week 8  Decreasing Food Cues to Overeat and Snack  
Week 9  Phone reinforcement  
Week 10  Developing good eating habits  
Week 11  Phone reinforcement  
Week 12  Self-control of overeating  
Week 13  Phone reinforcement  
Week 14  Changing snack habits  
Week 15  Phone reinforcement

Introduction
This is a behavioral intervention designed to help people with schizophrenia and schizoaffective disorder lose weight and lower their risk for heart disease. There are a total of 8 in-person sessions and 7 phone sessions. In-person sessions should be part of the study visit and should take about a half-hour (approximately 10 minutes weigh-in/homework check, 10 minutes instruction, 10 minutes review). Phone sessions should take 10-15 minutes.

At each session, the clinician starts by checking the participant’s homework and weight. If the participant is achieving their goals, give plenty of positive reinforcement. If the participant is not meeting their goals, see if you can think of creative ways to find success or see if you can revise the goal to make it more achievable for the participant. Next, the clinician “teaches” the lesson for the day. The lessons are written as scripts, but the wording can be revised so it feels comfortable for the clinician. Finally, during the review phase, the participant should be able to demonstrate understanding of the lesson as well as the homework that should be done in the coming weeks.

At each session, participants receive a diary in which they record their homework and their progress. Participants receive a new diary for each session and hand in the diary from the previous session.
Week 1

Self Monitoring: Awareness of Body Weight and What One Eats

Begin by orienting participant to program and setting weight loss goals (Appendix A).

**Lesson:**
Food is like fuel that is required for play, work, and exercise. There is a close relationship between what you eat, how much energy you use, and how much you weigh. If you take in more food than you can use for work, play, or exercise, you gain weight. If you take in less food than you use for work, play, or exercise, you lose weight. If you eat just enough food for your work, play, or exercise, then your weight will stay the same.

Many overweight people don’t realize how much food they actually eat each day. Also, they may not realize that the food they eat might be high in calories (“fatty” foods). One way to help people recognize how much they eat is to have them keep a record of everything they eat throughout the day. This can help people lose weight by helping them realize how much they eat, and by serving as a reminder to eat less.

We’d like for you to record what you eat each day and also to record your weight every day. Again, this serves two purposes: 1) it will point out the relationship between how much you eat and how it affects your weight, and 2) it will be a reminder to you that you are dieting and should eat less.

In order to record what you eat and your weight, we have a diary for you to use. We’ve also included some descriptions of which foods belong to which food groups and what an average serving size looks like (Appendix B). It is important to weigh yourself on the same scale, at the same time of day, and with the same amount of clothes on. It is also important to complete the Record of Daily Food Eaten before all meals and snacks. Do you have any questions about how to use the diary?

Before we end today’s session, let’s look at some common problems that people have when trying to lose weight and what some solutions might be:

**Problem Eating Patterns & Solutions**

1. Skipping breakfast or having a light breakfast
   *Solution: Must eat all meals, but less quantity*

2. Not eating vegetables or fruit
   *Solution: You need a balanced diet. You should eat vegetables at lunch and supper and fruit at all meals*

3. Snacking heavily, especially when meals have been skipped
   *Solution: Snack foods are generally high in calories. You should eat three meals a day, evenly spaced*

4. Drinking two to three cans of soda a day
   *Solution: Cut down to one can a day and switch to diet soda. Drink more water instead of soda*

5. Snacking / heavy eating on weekends
**Solution:** One tends to eat more because there is more free time on weekends. You should engage in more physical activities and reduce sitting activities (e.g., watching TV).

6. Excessive eating of candy, cake, ice cream, and potato chips, etc

**Solution:** Decrease the amount of each by half (e.g., cut down from two candy bars per day to one).

7. Excessive cereal / bread eating

**Solution:** You may tend to fill yourself up on these. Cut down to half. Serve half-pieces of toast, rolls, or buns. Buy cereal with fewer calories.

It is also very important to remember that not all people lose weight the same way. Some lose weight steadily and others lose weight in spurts. Also, there are times when your weight might stay the same for days or sometimes for a week. Don’t get discouraged if you’re not losing weight quickly. If you eat less food than you need for energy to work, play, and exercise, you will lose weight!

**Homework**

Remember, your homework for next week is to:

1. Write down what you eat before all meals and snacks.

2. Weigh yourself at the same time every day and record your weight as well as how far you’ve walked.

3. Read the instruction sheet in your diary at least once a day (you should read it more often if you want).
Lesson:
People today tend to burn fewer calories than they did years ago. Some of the reasons for this are that we have modern appliances (eg, dishwashers and vacuum cleaners) to ease our work in the home; we have jobs in which machinery does most of the work automatically; we often use cars or buses instead of walking or riding a bike; and we spend a lot of time sitting and watching TV. As a result of these modern conveniences, we are less active and we burn fewer calories. This situation usually leads to weight gain. One way for people to change this situation is to increase their activity levels. We can increase our activity levels by 1) doing daily exercise and 2) using energy.

Many people believe that exercising increases one’s appetite. This is not true. So you don’t have to worry that exercising will make you hungry and make you want to eat more. People often ask how much they need to exercise in order to lose weight. The answer depends on what kind of exercise you do. We have a chart that shows how many calories you burn doing different kinds of exercise (Appendix C). In order to be effective, exercise must be done regularly over a long period of time. We’d like you to schedule two 10-minute exercise periods each day to start. One exercise period should be before breakfast and the second should be before your evening meal.

Each week, you should try to increase your total exercise time by 5 minutes. This week, you’ll do two 10-minute exercises each day, for a total of 20 minutes. Next week, you can do one 10-minute period and one 15-minute period, for a total of 25 minutes. If it’s more convenient, you can do all of your exercise at one time during the day. It’s a great idea to plan to exercise with a friend – that way you’ll both be more likely to do it.

Homework
Remember, your homework for next week is to:

1. Write down what you eat before all meals and snacks.
2. Record weight and pedometer daily
3. Choose 3 different exercises and do them twice each day!

Week 3

Phone reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.
Week 4

Controlling Urges to Overeat and Snack

Lesson:
Many overweight individuals have frequent urges to overeat. Unfortunately, they often give-in to these urges, which results in more calories being consumed and more weight being gained. These eating urges may come at any time throughout the day. The urges to eat tend to be stronger at certain times or places. For example, eating urges may appear in mid-morning when breakfast has been missed or when one is shopping at the mall and passes by an ice cream or candy store.

You can stop, or at least delay, an urge to overeat or snack if you use positive self-talk. For example, you might be walking by a donut shop and you want to go in and buy a donut. Before going in the store, you could think to yourself, “I know I can walk right by that store without buying a donut, and then maybe I’ll fit into those pants I want to wear.” When you do manage to resist these urges, you should compliment yourself. For example, you could tell yourself “I’m a great dieter.” By praising yourself, you’ll probably feel much better about resisting that urge. If you do this every time you have an urge to overeat or snack, these urges should decrease over time.

These are some common places where people get an urge to overeat or snack:

- At an all you can eat buffet
- At a picnic with lots of food left on the table
- At the end of a meal at home with dessert still on the table
- At a party with a variety of favorite foods available
- At the mall walking by a candy shop
- Walking by an ice-cream shop
- Walking by a vending machine
- Walking by McDonald’s, Wendy’s, Dairy Queen, etc

Can you think of what you could tell yourself in order to resist these urges?

Homework
Remember, your homework for next week is to:

1. Record weight and pedometer daily
2. Choose 3 different exercises and do them twice each day.
3. Resist the urge to overeat and make a note of when you do!
Week 5

Phone reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.

Week 6

Burning Calories by Using Energy

Lesson:
Another way to burn up food calories is to use energy while carrying out normal, everyday activities. Using energy means doing an activity the long and hard way rather than the short and easy way. For example, walking up a flight of stairs rather than taking the elevator uses energy by burning up food calories. Some ways to use energy are:
- Walk instead of getting a ride to the store
- Stand in lines; do not sit; do not lean against the wall while standing
- Get off the bus at the stop before your stop
- Walk the longest way to the clinic
- Walk fast up hills

Can you think of other ways to use energy?

Homework
Remember, your homework for next time is to:
1. Record weight and pedometer daily.
2. Increase your exercise to 15 minutes twice per day.
3. Choose three ways to use energy and do them each day!

Week 7

Phone Reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.
Week 8

Decreasing Food Cues to Overeat and Snack

Lesson:
Many times, overweight people eat or snack even when they aren’t hungry. The reason for this unnecessary eating is that a large number and variety of food cues are present in most individuals’ living environments. The sight and smell of food or eating places are common cues to eat.

These food cues can encourage us to eat even when we’re not hungry. Some examples of this are: 1) the sight of a candy shop at the mall, even though you’ve just had lunch; 2) the smell of fresh donuts when you’re driving to work; and 3) a cookie jar in the kitchen. Food cues are present everywhere, but some people respond stronger to some cues than others (eg, candy is a strong cue for some people, while potato chips are a strong cue for others).

We want to practice three methods for decreasing the influence of food cues. The first method requires you to restrict your eating to one setting in the home and/or work. Through consistent practice of this technique, the food cues in other areas will be weakened. So if you only eat meals and snacks in the kitchen, you won’t have as much of an urge to snack while you’re watching TV in the living room. Where do you want to eat all your meals and snacks?

The second method requires you to restrict how much food you have on your plate. Most people eat all the food on their plate even though they are full. The food on your plate is a cue to eat. One way to solve this problem is to have one serving of each food at a meal. This way, the food cues will be less than if you took two or three servings of food. Also, by limiting the size of food helpings, fewer calories are consumed, which will lead to weight loss. It is important to understand that one helping does not mean an excessive helping. The helping should be of a moderate size.

The third method requires that you make eating the only activity during meal time. You should not eat while looking at magazines, walking down the street, watching TV, or listening to music in the bedroom. The purpose for making eating a single activity are that: (1) eating will become a more pleasurable event by itself; and (2) if one frequently eats while also doing other activities, these activities soon become strong cues for eating. As a result, eating will become a more distinct and, it is hoped, pleasurable experience by itself. At the same time the other activities mentioned will lose their food eating cue strength.

Homework
Remember, your homework for next week is to:

1. Record your daily weight and pedometer
2. Record your activities
3. Eat only in designated areas and choose smaller portion sizes.
Week 9

Phone Reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.

Week 10

Developing Good Eating Habits

Lesson:
Many overweight individuals eat meals very quickly and rarely pause while eating. These people often finish their meals in 5-10 minutes and still feel hungry. The reason for this is that it takes 15-20 minutes before foods are processed sufficiently in the body to reduce feelings of hunger. If a person eats very fast, his/her stomach still feels hungry and the person will continue to eat food until his/her stomach feels full. This is a bad habit that contributes to weight gain. You can change this habit by chewing all food completely and swallowing the food before taking another bite. This technique forces you to lengthen the time in which it takes to eat a meal so that your stomach has a chance to feel full.

Another way to change this habit is to put your utensils down after taking a bite of food. Don’t pick your utensils up to get another bite of food until the food in your mouth has been chewed and swallowed.

Homework
Remember, your homework for next time is to:
1. Record your daily weight and pedometer
2. Record your activities
3. Chew food completely before your next bite

Week 11

Phone reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.
Week 12

Self-Control of Overeating

Lesson:
In many families, individuals are encouraged from an early age to eat everything on their plate. Thus, the food on your plate becomes a cue to eat even though you may be full. This pattern can result in eating more food than you need. One way to stop or break this practice is to leave some food on one’s plate at the end of each meal or snack. You can either share this food with a friend, or save it for another time.

You can start by leaving small amounts of food, like a small bite of toast or a few kernels of corn. You can also start by leaving the foods that are least preferable to you. As you become more successful at leaving food on your plate, you can start to leave larger amounts, and you can leave your favorite foods. Remember, leaving food applies for both meals and snacks.

Homework
Remember, your homework for next time is to:
4. Record your weight and pedometer daily
5. Add more exercise everyday
6. Leave food on your plate

Week 13

Phone reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.
Week 14

Changing Snack Habits

Lesson:
Many times, snacking occurs because of the presence of food cues around us rather than because of hunger. Snacking habits must be changed because the excessive food calories lead to weight gain.

Cutting back on snacking is difficult to do. A good way to start is to delay your snack for a brief period of time. At first, you should try to delay your snack by 5-10 minutes and then the delay should be gradually increased to 30 or 40 minutes. If you use this, snacking habits can be changed because the food cue that gave you an urge to eat will probably not be present any longer.

Another way to cut down on snacking is to engage in a favorite activity instead of snacking. When you have an urge to snack, you can say to yourself, “No, instead of snacking I’ll go for a walk or call a friend”. By engaging in a favorite activity instead of snacking, you won’t feel like you’re missing out on a pleasurable activity. What are three activities you can do instead of snacking?

A third way to cut down on snacking is to substitute low-calorie foods as much as possible when you snack. A list of low-calorie foods is:

Liquid
- 10 ounces of water
- 10 ounces of diet beverage
- 10 ounces of iced tea with artificial sweetener
- A cup of caffeine free coffee without sugar

Solid
- Popcorn without butter, low-salt crackers, saltines, pretzels, rice cakes, etc
- Fresh Fruits : apple, grapefruit, oranges, strawberries, blueberries, cantaloupe, etc
- Vegetables : celery sticks, carrots

We hope that all of these techniques worked for you, but chances are that some strategies worked better than others. The best way to increase the success you’ve had is to continue doing what works.

Remember that the only way to lose weight is to decrease the food you eat and increase the calories you burn. How you decrease your intake and increase your output is up to you. Let’s take some time to review your goals and see how you did. Did you lose the weight you wanted to lose? If not, did you follow the lessons and complete your homework? If so, which strategies did you find most helpful? Do you think you’ll continue to use these strategies? Your homework for this session is simply to continue what works. If any of the worksheets might be helpful in continuing your success, we can make some copies for you.
Homework
Remember, your homework for next time is:
1. Record your weight and pedometer daily
2. Add more exercise everyday
3. Delay snacking
Week 15

Phone Reinforcement

Talk with patient by phone to assess progress. Trouble-shoot if there are problems, otherwise encourage continued success.

Weight Loss Goals

~ Weekly:

► Week 1 through Week 4 = _______ lbs.
► Week 5 through Week 12 = _______ lbs.
► Week 13 through Week 20 = _______ lbs.
► Week 21 through Week 28 = _______ lbs.

Average weight loss is 0.5-1 pound per week

~ Target:

► Current weight = _______ lbs.
► Total weight loss = _______ lbs.
► Target weight = _______ lbs.
### Week 1 Homework

#### Daily Weight and Pedometer Record

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**Reminders:**
- Record at same time of day, same scale, same clothes.
- Reset pedometer after each reading.

#### Daily Food Eaten Record

**Awareness of What One Eats**

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<thead>
<tr>
<th>Date</th>
<th>Meal</th>
<th>Meat, Fish, Eggs</th>
<th>Bread, Cereal, Pasta, Rice, Potatoes/Fries</th>
<th>Vegetables</th>
<th>Fruit</th>
<th>Cake, Cookies, Candy, Ice Cream</th>
<th>Chips (1 bag = 1 oz.)</th>
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Mark an "X" for each serving of food eaten. Must be completed **BEFORE** meals and snacks. Must **ALSO** be completed **AFTER** meals and snacks.
**Week 2 Homework**

### Daily Weight and Pedometer Record

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**Reminders:**
- Record at same time of day, same scale, same clothes.
- Reset pedometer after each reading.

### Daily Food Eaten Record

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Mark an "X" for each serving of food eaten. Must be completed **BEFORE** meals and snacks. Must **ALSO** be completed **AFTER** meals and snacks.
## Exercise Habit Record

**Burning Calories Through Exercise**

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Mark an "X" for each time you complete your exercise.
**Week 4 Homework**

**Daily Weight and Pedometer Record**

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Weight

Pedometer

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

**Exercise Habit Record**

**Burning Calories Through Exercise**

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<td>10 min exercise pm</td>
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</table>

Mark an “X” for each time you complete your exercise

<table>
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<th>Date</th>
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<tbody>
<tr>
<td>10 min. exercise am</td>
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**Eating Habit Record**

**Resisting Urges through Self-talk**

<table>
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<tbody>
<tr>
<td>Resisted Urge to Overeat</td>
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</table>

Mark an “X” for each time you resist the urge to overeat or snack using positive self-talk
# Week 6 Homework

## Daily Weight and Pedometer Record

<table>
<thead>
<tr>
<th>Date</th>
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<td>Weight</td>
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<td>Pedometer</td>
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</tbody>
</table>

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

## Exercise Habit Record

### Burning Calories Through Exercise

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
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<td>15 min. exercise am</td>
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<td>15 min exercise pm</td>
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<tbody>
<tr>
<td>15 min. exercise am</td>
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<td>15 min exercise pm</td>
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</tbody>
</table>

Mark an “X” for each time you complete your exercise.
### Activity Habit Record

#### Choosing to Use More Energy

<table>
<thead>
<tr>
<th>Date</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Get off bus early</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take stairs instead of elevator</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walk instead of driving</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walk fast up hills</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Walk the long way</td>
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<tr>
<td>Stand instead of sitting</td>
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</tbody>
</table>

Mark an “X” for each time you use this strategy.

### Week 8 Homework

#### Daily Weight and Pedometer Record

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<thead>
<tr>
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<tr>
<td>Pedometer</td>
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</tbody>
</table>

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

#### Exercise Habit Record

#### Burning Calories Through Exercise

<table>
<thead>
<tr>
<th>Date</th>
<th><strong>/</strong>/__</th>
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</tr>
</thead>
<tbody>
<tr>
<td>20 min. exercise am</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>20 min exercise pm</td>
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</tbody>
</table>

Mark an “X” for each time you complete your exercise.
### Activity Habit Record

**Choosing to Use More Energy**

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Stand instead of sitting</td>
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</table>

Mark an “X” for each time you use this strategy.

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### Week 10 Homework

#### Daily Weight and Pedometer Record

<table>
<thead>
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</thead>
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<tr>
<td>Weight</td>
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<tr>
<td>Pedometer</td>
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</tr>
</tbody>
</table>

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

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#### Exercise Habit Record

**Burning Calories Through Exercise**

<table>
<thead>
<tr>
<th>Date</th>
<th><strong>/</strong>/__</th>
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</thead>
<tbody>
<tr>
<td>25 min. exercise am</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>25 min exercise pm</td>
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</thead>
<tbody>
<tr>
<td>25 min. exercise am</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>25 min exercise pm</td>
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</tbody>
</table>

Mark an “X” for each time you complete your exercise.
### Eating Habit Record

**Decreasing Food Cues to Overeat and Snack**

<table>
<thead>
<tr>
<th>Date</th>
<th>1/1</th>
<th>1/2</th>
<th>1/3</th>
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<th>1/5</th>
<th>1/6</th>
<th>1/7</th>
<th>1/8</th>
<th>1/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resist Urge through self-talk</td>
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<tr>
<td>Limit eating to 1 or 2 locations</td>
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<tr>
<td>Limit to 1 serving</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>No other activities at meal time</td>
<td></td>
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</table>

Mark an “X” for each time you use this strategy.

### Week 12 Homework

### Daily Weight and Pedometer Record

<table>
<thead>
<tr>
<th>Date</th>
<th>1/1</th>
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<th>1/3</th>
<th>1/4</th>
<th>1/5</th>
<th>1/6</th>
<th>1/7</th>
<th>1/8</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
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<tr>
<td>Pedometer</td>
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</tr>
</tbody>
</table>

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

### Exercise Habit Record

**Burning Calories Through Exercise**

<table>
<thead>
<tr>
<th>Date</th>
<th>1/1</th>
<th>1/2</th>
<th>1/3</th>
<th>1/4</th>
<th>1/5</th>
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<th>1/7</th>
<th>1/8</th>
<th>1/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min. exercise am</td>
<td></td>
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<td>30 min exercise pm</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Date</th>
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<th>1/5</th>
<th>1/6</th>
<th>1/7</th>
<th>1/8</th>
<th>1/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min. exercise am</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min exercise pm</td>
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<td></td>
</tr>
</tbody>
</table>

Mark an “X” for each time you complete your exercise.
# Eating Habit Record
Decreasing Food Cues to Overeat and Snack

| Date  | _/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___|
|-------|------|--------|--------|--------|--------|--------|--------|
| Resist Urge through self-talk |       |         |         |         |         |         |         |
| Limit eating to 1 or 2 locations |       |         |         |         |         |         |         |
| Limit to 1 serving |       |         |         |         |         |         |         |
| No other activities at meal time |       |         |         |         |         |         |         |

Mark an “X” for each time you use this strategy

---

## Week 14 Homework

### Daily Weight and Pedometer Record

| Date  | _/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___|
|-------|------|--------|--------|--------|--------|--------|--------|
| Weight |       |         |         |         |         |         |         |
| Pedometer |   |         |         |         |         |         |         |

Record at same time of day, same scale, same clothes.
Reset pedometer after each reading.

---

### Exercise Habit Record
Burning Calories Through Exercise

| Date  | _/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___| ___/___|
|-------|------|--------|--------|--------|--------|--------|--------|
| 30 min. exercise am |       |         |         |         |         |         |         |
| 30 min exercise pm |       |         |         |         |         |         |         |

Mark an “X” for each time you complete your exercise
Eating Habit Record
Decreasing Food Cues to Overeat and Snack

<table>
<thead>
<tr>
<th>Date</th>
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<th><em>/</em>__</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resist Urge through self-talk</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit eating to 1 or 2 locations</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit to 1 serving</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No other activities at meal time</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chew food completely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Put utensils down before next bite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leave food on plate</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Mark an “X” for each time you use this strategy
Appendix B

Food Groups and Serving Sizes

Serving Size: Visualize the Right Portion Size

Healthy eating includes making healthful food choices and understanding serving sizes. It can be difficult to visualize a half-cup or three ounces, let alone "one serving." Here are some everyday comparisons to help you figure out your serving sizes:

- A teaspoon of margarine is the size of the tip of your thumb to the first joint
- Three ounces of meat is the size of a deck of cards
- One cup of pasta is the size of a tennis ball
- One half of a medium bagel is the size of a hockey puck
- An ounce and a half of cheese is the size of three dominoes
- Two tablespoons of peanut butter are the size of a ping pong ball
- One-half cup of vegetables is the size of a light bulb.

Once you get a good sense of serving sizes, you can compare them to the amount you eat and make any necessary modifications.


<table>
<thead>
<tr>
<th>Food Groups</th>
<th>One Serving Size Equals...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breads, Cereals, Rice, Pasta, and other Grains Group</td>
<td>1 slice bread or 1/2 bagel the size of a hockey puck.</td>
</tr>
<tr>
<td></td>
<td>1/2 cup cooked rice equals a cupcake wrapper.</td>
</tr>
<tr>
<td></td>
<td>1/2 cup pasta equals an ice cream scoop.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit and Vegetable Groups</td>
<td>One fruit and vegetable serving is equal to one piece the size of a tennis ball or 1/2 cup the size of a light bulb.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat, Chicken, Fish, Dry Beans and Peas, Eggs, and Nuts Group</td>
<td>3 ounces lean meat, chicken, or fish measures up to a deck of cards or a check book.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy Group</td>
<td>1 ounce cheese equals about 4 dice.</td>
</tr>
<tr>
<td></td>
<td>Use sparingly. For a teaspoon of fat, look to the tip of your thumb.</td>
</tr>
</tbody>
</table>

This tip sheet is adapted from American Dietetic Association, Eat Right Minute Nutrition Tip of the Day located at www.eatright.org

Food Groups:

**Group 1 - MEAT, POULTRY, FISH, DRY BEANS, EGGS & NUTS GROUP**

This group provides:

*Meat, Poultry and Fish supply: Protein, B-Vitamins, Iron and Zinc
*Dry beans, eggs and nuts are similar to meat. They provide protein and most vitamins and minerals

**Selection Tips:**

*Choose lean meat, chicken without skin, fish, dry beans and peas. These are lowest in fat
*Prepare meats in low-fat ways:
  *Trim all the fat you can see
  *Broil, roast or boil these foods instead of frying them
*Go easy on egg yolks, they are high in cholesterol. Use only 1 egg yolk per person in egg dishes. Make larger portions by adding extra egg whites.
*Nuts and seeds are high in fat, so eat them in moderation

**Group 2 - BREAD, CEREAL, RICE & PASTA GROUP**

This group provides:

*Carbohydrates (i.e. starches): An important source of energy
*Vitamins and Minerals
*Fiber (i.e. whole wheat bread and whole grain cereal)

**Selection Tips:**

*Try to eat foods without fat or sugar (i.e., bread, English muffins, rice, or pasta)
*Baked goods made from flour are part of this food group, but are high in fat and sugar (cookies, cakes, pastries)
*Go easy on fats and sugars that you add yourself (i.e., butter, margarine, sour cream, syrup)

**Group 3 - VEGETABLE GROUP**

This group provides:

*Vitamins and Minerals: Vegetables are rich in vitamins A and C and minerals such as iron and magnesium
*Fiber
*Are naturally low in fat

**Selection Tips:**
*Eat a variety of vegetables to provide different nutrients.
*Legumes also provide protein. They can be used in place of meat
*Go easy on the fats you add. Spreads and toppings, such as mayonnaise and salad dressing count as fat

**Group 4 - FRUIT GROUP**

This group provides:

*Important vitamins like A and C, and minerals like potassium
*Low in fat and sodium
*A good natural source of carbohydrates for quick energy
*Assist in appetite control
*Fiber

**Selection Tips:**

*Choose fresh fruits, fruit juices and frozen, canned, or dried fruit. Pass up fruit canned or frozen in heavy syrups and sweetened fruit juices
*Eat whole fruits often they are higher in fiber than fruit juices
*Have citrus fruits, melons, and berries regularly. They are rich in vitamin C
*Count only 100% fruit juice as fruit. Punches, Kool-Aid and most fruit drinks contain only a little juice and lots of added sugars. Grape and orange sodas don’t count as fruit juice

**Group 5 - MILK, YOGURT & CHEESE GROUP**

This group provides:

*Protein, vitamins, minerals and calcium
*2 servings are right for most people

**Selection Tips:**

*Choose skim milk and nonfat yogurt. They are lowest in fat
*1 to 2 ounces of cheese or 8 ounces of yogurt count as a serving, they supply the same amount of calcium as 1 cup of milk
*Cottage cheese is lower in calcium than most cheeses. 1 cup counts as only ½ serving of milk
*Go easy on high fat cheese and ice cream. They can add a lot of fat to your diet
*Choose “part skim” or low-fat cheese when available and lower fat milk desserts, like frozen yogurt

**Group 6 - FATS AND OILS (USE SPARINGLY)**

This group can cause problems:

*Increase risk of heart disease
*Supplies calories but little or no vitamins and minerals

**Selection Tips:**
*Use unsaturated vegetable oils and margarine that list a liquid vegetable oil as the first ingredient on the label
*When eating out, you cannot control actual food preparation, but you can control your food selection. Choose foods with ingredients and preparation methods that have low fat and cholesterol
*Avoid or eat small amounts of fried or deep fried foods (i.e. have a baked potato instead of French fries).

**Group 7 - SUGAR**

Don’t use too much sugar:
*A low sugar diet helps keep weight down
*A sugar rich diet contributes to tooth decay

What is sugar:
White sugar, brown sugar, honey, molasses

Some foods sugar is added to:
Cookies, Jam, Jelly, Donuts, Canned fruit in syrup, Chocolate bar, Low-fat yogurt, Sherbet, Soda, etc.
Appendix C

Exercise Information

<table>
<thead>
<tr>
<th>TYPE OF EXERCISE</th>
<th>CALORIES BURNED PER HOUR</th>
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<tbody>
<tr>
<td>Sleeping</td>
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<tr>
<td>Eating</td>
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<tr>
<td>Sewing</td>
<td>85</td>
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<tr>
<td>Knitting</td>
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<tr>
<td>Sitting</td>
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<td>Standing</td>
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<tr>
<td>Driving</td>
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<td>Office work</td>
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<tr>
<td>Housework</td>
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<tr>
<td>Golf, without trolley</td>
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<tr>
<td>Gardening, planting</td>
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<tr>
<td>Dancing, ballroom</td>
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<tr>
<td>Walking, 3mph</td>
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<tr>
<td>Table Tennis</td>
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<tr>
<td>Gardening, hoeing</td>
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<tr>
<td>Tennis</td>
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<tr>
<td>Water aerobics</td>
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<tr>
<td>Skating, rollerblading</td>
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<tr>
<td>Dancing, aerobic</td>
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<tr>
<td>Aerobics</td>
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<td>Bicycling, moderate</td>
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<tr>
<td>Jogging, 5mph</td>
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<tr>
<td>Gardening, digging</td>
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<td>Swimming, active</td>
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<tr>
<td>Cross country ski machine</td>
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<tr>
<td>Hiking</td>
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<tr>
<td>Step Aerobics</td>
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<td>Rowing</td>
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<td>Squash</td>
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<tr>
<td>Skipping rope</td>
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<tr>
<td>Running</td>
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