MEtformin and **L**orcaserin for Weigh**T** Loss in People with Schizophrenia

(MELT)

Clinical Protocol

Version 7.0

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1. SPECIFIC AIMS

Metformin has emerged as a safe and modestly effective intervention for antipsychotic-associated weight gain, with several meta-analyses demonstrating mean weight loss of 3 kg in studies ranging from 12 to 24 weeks. Among FDA-approved weight loss agents, there have been few pharmacological options for people with schizophrenia because of the risk for psychotic exacerbation associated with sympathomimetic drugs which characterize a number of these agents. Lorcaserin is a 5-HT2C agonist that has recently been approved for weight loss and represents a potentially important option for people with schizophrenia since it does not have sympathomimetic properties. The current study will examine the effectiveness of two novel weight loss approaches in schizophrenia – lorcaserin monotherapy and lorcaserin/metformin combination treatment – compared to placebo.

This study will enroll 110 overweight people with schizophrenia or schizoaffective disorder who have a BMI≥ 27 and are treated with one or a combination of two antipsychotic medications. Participants will be randomized to receive 52 weeks of lorcaserin/metformin combination treatment, lorcaserin monotherapy or placebo. All participants will receive a manualized behavioral intervention aimed at increasing physical activity and improving their diets.

Specific Aims:

1. Aim #1: Determine the efficacy of lorcaserin/metformin combination treatment and lorcaserin monotherapy on body weight in overweight people with schizophrenia.
    a. Primary hypothesis:

       Lorcaserin/metformin combination treatment will demonstrate greater weight loss compared to placebo.
    b. Secondary hypothesis:

       Lorcaserin monotherapy will demonstrate greater weight loss than placebo.

2. Aim #2: Determine the efficacy of lorcaserin/metformin and lorcaserin monotherapy compared to placebo for improving lipid and glucose metabolism.
    a. Lorcaserin monotherapy and lorcaserin/metformin combination treatment will demonstrate greater improvement in markers of lipid and glucose metabolism compared to placebo.

3. Aim #3:
    a. Determine the safety and tolerability of lorcaserin monotherapy and lorcaserin/metformin combination treatment using adverse event monitoring.

b. Determine the effect of lorcaserin/metformin and lorcaserin monotherapy on the appetite regulating hormones. Peripheral leptin, total and acylated ghrelin, PYY3-36 and GLP-1 levels will be measured.

c. Determine the effect of lorcaserin monotherapy and lorcaserin/metformin combination treatment on body composition, and energy intake and expenditure.

- Dual X-ray absorptiometry will be performed at baseline and end of study in a subset of subject to assess the effects of study interventions on fat storage.
- Appetite rating scales and 24-hour food recall assessments will be administered to examine the effect of lorcaserin monotherapy and lorcaserin/metformin combination treatment on appetite regulation and energy intake compared to placebo.
- Accelerometry will be performed to examine the effects of each treatment on energy expenditure.

2. BACKGROUND AND SIGNIFICANCE

Lifespans in patients with schizophrenia are reduced by approximately 20% (Hennekens et al., 2005; Tiihonen et al, 2009). Cardiovascular disease (CVD) represents the major natural cause of this excess mortality; it is estimated that the relative risk of CVD is about twice that of the general population and that patients with schizophrenia are twice as likely to die from CVD (Brown et al., 2000; Daumit et al., 2008; Henderson et al., 2005). Obesity is an important modifiable risk factor for CVD that is highly prevalent in people with schizophrenia. A recent meta-analysis of 77 studies (N=25,692) found 49.4% of people with schizophrenia met criteria for obesity (Mitchell et al., 2013). Furthermore, conditions for which obesity is an important risk factor including diabetes mellitus and hypertension are both 2-2.5 times as common in persons with schizophrenia compared to the general population (Dixon et al., 2000, De Hert et al. 2011).

Many factors contribute to weight gain in patients with schizophrenia, among which antipsychotic medications are primary contributors. Weight gain from antipsychotics is often rapid and most noticeable in people with new onset psychosis, but weight gain commonly continues chronically as patients continue treatment. For example, in people with chronic schizophrenia, the 18 month Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found $\geq$7% of baseline weight gain for following antipsychotics: olanzapine 30%, quetiapine 16%, risperidone 14%, perphenazine 12%, and ziprasidone 7% (Lieberman et al., 2005).

Behavioral Weight Loss Interventions:

Given the high prevalence of obesity in people with schizophrenia in the U.S., research on interventions for weight loss in this population is relatively sparse. In a 14-week study of 72 overweight patients with schizophrenia or schizoaffective disorder, subjects were randomized to 20 sessions of group-based behavioral treatment or usual medical care (Brar et al., 2005). Mean weight loss in the behavioral intervention group was 2.0 kg while the usual care group lost

1.0 kg. While baseline to end-of-study weight loss was significant for each group, the between-group difference was not significant and the absolute weight loss achieved in each group was modest. In a recent 18-month study, 291 overweight people (BMI≥25) with serious mental illness (~60% with schizophrenia/schizoaffective disorder) receiving care in outpatient psychiatric rehabilitation programs were randomized to individualized weight-management and exercise sessions versus standard care. The active treatment group achieved a significant between-group 3.2 kg weight loss over 18 months, demonstrating a potentially meaningful but still modest effect on weight. 37.8% of active treatment participants lost ≥5% of their baseline weight as compared to 22.7% of those in the control group (Daumit et al., 2013). Taken together, these data suggest that while behavioral interventions alone can achieve modest weight loss, the outcomes are generally not sufficient to achieve the needed weight loss in this population.

Antipsychotic Switching for Weight Loss:

Switching from an antipsychotic with a higher liability for causing weight gain to one with a lower liability for causing weight gain is another strategy that has been studied in overweight people with schizophrenia. In a 6-month study, 215 overweight people (BMI≥27) with schizophrenia were randomized to either stay on their current antipsychotic (olanzapine, risperidone or quetiapine) or to switch to aripiprazole (Stroup et al., 2011). The differential weight change between switchers and stayers was -2.9 kg in favor of switching to aripiprazole. Although switching was generally safe and not associated with an excess number of psychotic relapses, changing antipsychotics must be undertaken with considerable care and close clinical monitoring. Furthermore, there are patients for whom a switch may be associated with an unacceptable risk of psychotic exacerbation, such as those stabilized on clozapine or other antipsychotics from which they have previously decompensated following an antipsychotic switch. For such patients, and for others who do not wish to change antipsychotics or who have already switched antipsychotics without achieving acceptable weight change, adjunctive treatment would be preferable.

Adjunctive Pharmacological Interventions for Weight Loss

Overview: Pharmacological options for weight loss for people with schizophrenia are limited. Among FDA-approved weight loss agents, phentermine, diethylpropion and the recently approved combination treatment phentermine/topiramate (Qsymia™) have sympathomimetic properties that raise the risk of psychotic exacerbation in people with schizophrenia due to the association of such drugs with psychotic symptoms. Their use in schizophrenia has not been systematically studied and, given the risk of worsening psychosis, must be used with considerable caution. Orlistat, a peripherally acting pancreatic lipase inhibitor with a high incidence of gastrointestinal side effects, has generally been associated with limited efficacy for weight loss and a 16-week study of orlistat in overweight people with schizophrenia did not lead to significant weight loss compared to placebo (Joffe et al., 2008). Lorcaserin (Belviq™), another recently FDA-approved weight loss agent, is a 5-HT2C agonist, suggesting a more favorable

risk/benefit ratio for patients with psychotic disorders compared to sympathomimetics, but to date it has not been studied in people with schizophrenia.

Several agents without an FDA-approved indication for weight-loss have been studied for weight loss in schizophrenia. Several recent meta-analyses found that metformin and topiramate are associated with significant weight loss in overweight people with chronic psychotic disorders. Topiramate has significant side effects, especially cognitive impairment, that often makes it unsuitable for people with psychotic disorders. Metformin, however, is generally well-tolerated and has been associated with ~3 kg weight reduction across 10 studies (757 total subjects). This is also consistent with metformin-associated weight loss that our group demonstrated in a 16-week study of overweight and obese outpatients with chronic schizophrenia (Jarskog et al., 2013).

Thus, among adjunctive pharmacological interventions for weight loss that have been studied in overweight people with schizophrenia, metformin represents the agent with the most solid evidence-base, while lorcaserin has a novel mechanism but has not been studied in this population. Taken individually, metformin and lorcaserin both demonstrate relatively modest effects on weight, around 3 kg. However, treatment using drugs with different mechanisms of action can lead to significantly greater weight loss in combination than either agent alone. This has been demonstrated with, for example, the combination of topiramate and phentermine, which provides a rationale for testing other drug combinations with better safety profiles in people with schizophrenia.

Lorcaserin:

Lorcaserin (Belviq™), a 5-HT2C agonist for weight loss, was FDA approved in 2012. Lorcaserin binds 5-HT2C receptors expressed in hypothalamic pro-opiomelanocortin (POMC) neurons which in turn leads to melanotropin-α release and exerts appetite-suppressing effects via stimulation of melanocortin receptor 4 (MC4R). It remains unknown how lorcaserin affects key appetite-regulating hormones such as leptin, ghrelin, GLP-1 or PYY. Three large placebo-controlled studies have demonstrated weight-loss efficacy for lorcaserin. In the 2-year BLOOM trial, 3182 overweight/obese adults (BMI: 27-45) were randomly assigned to lorcaserin 10 mg BID or placebo (Smith et al., 2010). At 52 weeks, 47.5% of patients taking lorcaserin had lost $\geq$5% of their baseline body weight compared to 20.3% of patients taking placebo. Associated mean weight change for lorcaserin was -5.8 kg compared to -2.2 kg for placebo. The differential advantage for lorcaserin over placebo was 3.6 kg. Similar results were documented in the BLOSSOM (Fidler et al., 2011) and BLOOM-DM (O'Neil et al., 2012) studies.

Metformin:

Metformin is a well-tolerated biguanide antihyperglycemic approved for type II diabetes mellitus. Metformin normalizes blood glucose levels by blocking hepatic gluconeogenesis and increasing peripheral insulin sensitivity. Since metformin does not increase insulin production, hypoglycemia is a rare side effect and it can typically be taken safely by people without diabetes (Kirpichnikov et al., 2002). Metformin is known to cause modest weight loss in persons with pre-

diabetes and with type II diabetes (DeFronzo and Goodman, 1995; Knowler et al., 2002). Mechanisms contributing to metformin-induced weight loss are thought to include hypothalamic appetite suppression as well as slowing of gastric emptying related to stimulation of glucagon-like peptide-1 (GLP-1) secretion (Kirpichnikov et al., 2002; Mannucci et al., 2001).

Meta-analyses of studies of metformin to produce weight loss or prevent antipsychotic-induced weight gain in non-diabetic patients with schizophrenia have demonstrated mean weight loss of ~3 kg with metformin across available studies, ranging from 12-24 weeks duration (Correll et al., 2013; Mizuno et al., 2014). The study by Jarskog et al. (2013) demonstrated a generalizable effect of metformin on weight loss in overweight and obese non-diabetic psychiatrically stable adult outpatients with chronic schizophrenia or schizoaffective disorder.

Overweight patients with schizophrenia have been consistently found to have increased circulating leptin levels (Jin et al, 2008). Increased circulating levels of orexigenic ghrelin hormone in long-term antipsychotic treatment studies have also been found in patients who gained weight while taking antipsychotics with a high weight gain liability (Jin et al, 2008). Notably, no appetite-regulating hormones have been measured in prior studies of metformin for weight loss in schizophrenia. The current proposal will measure leptin, ghrelin (total and acylated), GLP-1 and PYY at baseline, 6 months and 12 months to gain insight into how key appetite regulatory hormones may contribute to weight loss by examining their relationships to body weight, fat distribution, and measures of appetite, energy intake and energy expenditure.

3. RESEARCH DESIGN AND METHODS

3.1. OVERVIEW

This study will be conducted over a 4-year period at four clinical sites – UNC-Chapel Hill, Columbia University, Carolina Behavioral Care, and Augusta University. This is a double-blind, randomized study of 52 weeks of LOR/MET combination treatment and lorcaserin monotherapy compared to placebo in overweight people with schizophrenia. **See Table 2 for timeline, Figure 2 for study design.**

Study startup activities include obtaining IRB approval, preparation of study medications (NYSPI/Columbia University Investigational Drug Services), and establishing the electronic database (REDCap). Subject enrollment will begin ~3 months after the start of the grant. Enrollment will continue for ~30 months (end of 3Q, YR 3) so that the last study subject enrolled will finish at end of 3Q, YR4. Data analysis will begin during 3Q, YR4 and will be completed during 4Q, YR4. Manuscript preparation will occur 4Q, YR4.

Table 2. Overview and Timeline.

Study Activity	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
Study startup																

Recruitment/enrollment																
Subject participation																
Data analysis																
Manuscript preparation																

3.2. SUBJECTS

Approximately 110 subjects will be recruited at four clinical sites (UNC Chapel Hill, Columbia University, Carolina Behavioral Care, and Augusta University) over a 30-month period, with the goal of randomizing 90 subjects. At UNC Hospitals in Chapel Hill, NC, ~650 outpatients with chronic psychotic disorders (80% of whom have schizophrenia or schizoaffective disorder) receive care in the Schizophrenia Treatment and Evaluation Program (STEP). A newly established UNC-STEP clinic in Raleigh, NC has an additional 500 schizophrenia patients. Dr. Jarskog runs a half-day clinic at both locations. He is also Research Director of the North Carolina Psychiatric Research Center, which is integrated into the STEP clinic infrastructure and thereby has full access to these patient populations. Dr. Stroup will recruit subjects through the Lieber Schizophrenia Research Clinic at the New York State Psychiatric Institute (NYSPI). In addition he has access to ~1,100 patients with schizophrenia spectrum disorders in the Washington Heights Community Service Clinics, which serve the catchment area in New York City surrounding Columbia/NYSPI. Both of these sites successfully recruited for the METS study, which had similar inclusion/exclusion criteria.

3.2.1. Inclusion Criteria

1. Outpatients with a diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV-TR criteria (see Appendix 3 and Appendix 4) and confirmed by the Structured Clinical Interview for DSM-IV (SCID).
2. Duration of psychotic 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 written informed consent to participate.
5. BMI $\geq$ 27 kg/m^2
6. Currently treated with one or a combination of two FDA-approved antipsychotic medications (typical or atypical antipsychotics) AND on that drug regimen for at least 2 months prior to study entry (with stable dosages for at least 1 month).
7. Concomitant medications are allowed if agents and doses are unchanged for at least 1 month prior to study entry and if these medications are not among those excluded in the Exclusion Criteria.
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 $\geq$6
3. Current treatment with more than 2 antipsychotics
4. HbA1c$\geq$6.5%
5. Diagnosis of diabetes mellitus or current treatment with insulin or oral hypoglycemics
6. Current or prior treatment with metformin within the past 3 months
7. Current or prior treatment with lorcaserin within the past 3 months
8. Current or prior treatment with a 5-HT2B agonist (e.g. cabergoline) within the past 45 days due to potential risk for heart valve defects
9. Current treatment with two or more antidepressants
10. Current treatment with a single antidepressant prescribed in excess of the maximum approved dose
11. Current treatment with monoamine oxidase inhibitor (MAOI) class of antidepressants (isocarboxazid, phenelzine, selegiline, tranylcypromine)
12. Concurrent treatment with any of the following pro-serotonergic drugs: meperidine, buspirone, dextromethorphan, triptans, tramadol, ritonavir, tryptophan, ginseng, St. John's wort
13. Diagnosis of congestive heart failure
14. Uncorrected thyroid disorder
15. Renal impairment as evidenced by estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2
16. Hepatic disease (ALT, AST, or GGT > 2 times upper limit of normal (ULN), total bilirubin > 1.2 times ULN)
17. Metabolic acidosis (serum CO2 <20 mEq/L)
18. Known hypersensitivity to metformin or lorcaserin
19. Women who are pregnant or breastfeeding
20. Recent (in the past 30 days) or scheduled radiological studies involving iodinated contrast material
21. Alcohol abuse/dependence as determined by SCID within the past month
22. Other serious and unstable medical condition in the judgment of the investigator
23. DSM-IV diagnosis of mental retardation or dementia
24. Any medication (prescription or non-prescription) used for weight loss must have been discontinued 3 months prior to study entry.

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 at least monthly during study visits as outlined in the Schedule of Events (Appendix 1 and Appendix 2). 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, 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. In a 52-week, double-blind, randomized trial, determine the effect of LOR/MET combination treatment compared to placebo on weight change in overweight people with schizophrenia. The efficacy of LOR monotherapy compared to placebo for weight loss will be assessed as secondary outcomes.
2. Determine the effect of LOR/MET and LOR compared to placebo on measures of lipid and glucose metabolism in overweight people with schizophrenia. Measures of lipid (total cholesterol, HDL, LDL, triglycerides) and glucose (fasting plasma glucose, HbA1c, insulin) metabolism will be analyzed using a mixed longitudinal model over 52 weeks.
3. Determine the effect of LOR/MET and LOR on appetite regulating hormones, body composition, and energy intake and expenditure. Measures of appetite regulating hormone levels, energy intake and energy expenditure, as well as change in fat mass, lean mass and fat percentage will be analyzed using a mixed longitudinal model over 52 weeks.

3.3.2. Other Outcomes

- Placebo-controlled weight change in LOR monotherapy across 52 weeks,
- Number of subjects that achieve $\geq$5% weight loss compared to baseline for each treatment

- Adverse events will be assessed using a structured adverse event checklist that will list expected side effects associated with lorcaserin and metformin. Results will be tabulated. Serious adverse events will be collected.
- All subjects will have the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression – Severity (CGI-S) scale and Columbia Suicide Severity Rating Scale (C-SSRS) performed at each visit to evaluate for any evidence of psychiatric decompensation.

3.4. RANDOMIZATION METHOD

Study treatments will be randomly assigned using a system set up by our biostatistician, Dr. Anastasia Ivanova. Prior to the start of the trial, Dr. Ivanova will generate a randomization plan. 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
Lorcaserin supplied in dosages of 10 mg
Placebo

3.5.1. Dosing of Study Medications

Subjects will be randomized to 3 groups, see Figure 1.

- Lorcaserin and Metformin-
    - Max dose of 10mg BID of Lorcaserin and max dose of 1,000mg BID of Metformin
- Lorcaserin-
    - Max dose of 10mg BID
- Placebo

Subjects will be randomized to receive lorcaserin 10mg qAM in the MET/LOR and LOR arms or PBO^{L} qAM. If tolerated, the dose will be titrated up to 10 mg BID at week 1 for 4 weeks. Subjects who tolerate the initial 4 weeks of treatment, in the LOR/MET arm will begin MET 500mg BID at week 4, while the LOR arm and placebo arm will begin PBO^{M}. At week 6, the LOR/MET arm will have the MET dose increased to 1,000 mg qAM and 500 mg qHS, with corresponding increases in the PBO^{M} in the other two arms. At week 8 (Visit 6), in the LOR/MET arm, MET is increased to 1,000 mg (2 capsules) BID, with corresponding increases in PBO^{M} in the other two arms. If this is well tolerated, then subjects continue LOR/MET, LOR/PBO^{M}, or PBO^{L}/PBO^{M} to the end of the study at week 52 (EOS/Visit 17).

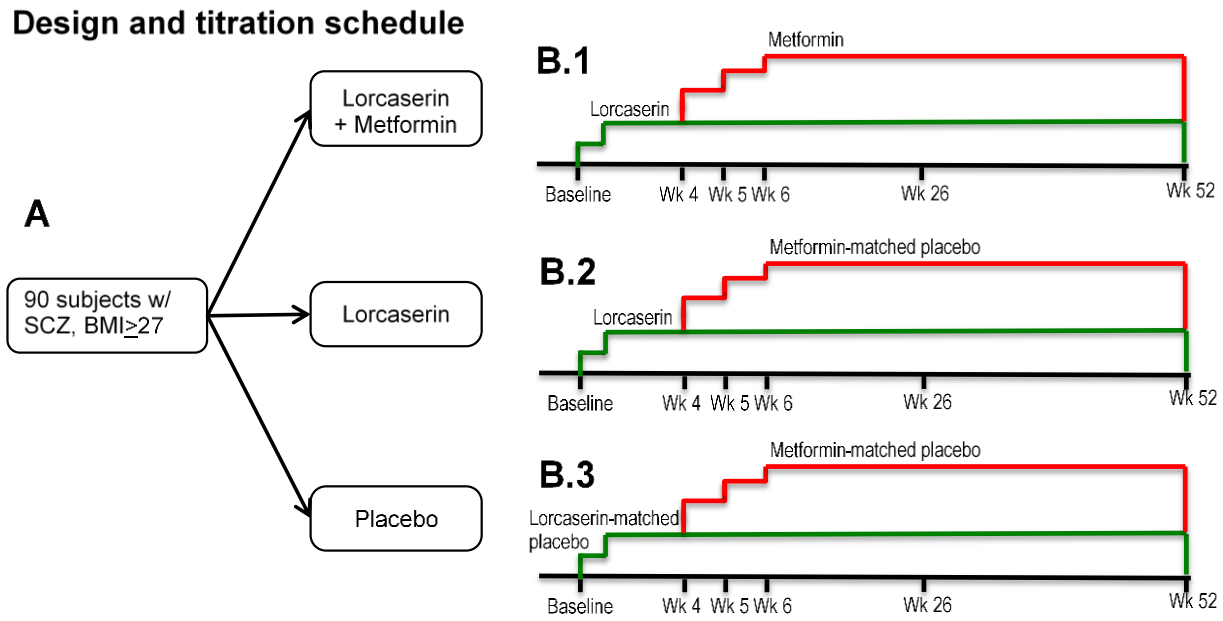

Figure 1. 52 week randomized, controlled study of lorcaserin/metformin combination treatment, lorcaserin monotherapy or placebo for weight loss in overweight people with schizophrenia. **A.** Subjects are randomized into 3 groups. **B.** Timeline and dose titration for lorcaserin/metformin combination (B.1), lorcaserin monotherapy with placebo to match metformin (B.2), and full placebo arm (B.3) with matching placebos for lorcaserin and metformin, respectively. Subjects continue all study drug until Week 52. SCZ=schizophrenia; BMI=body mass index.

3.5.2. Treatment Group Assignment

After a screening period that is not to exceed 28 days (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 three treatment groups according to a computerized system.

Treatment assignments will be governed by a fixed randomization schedule designed to allocate patients between lorcaserin/metformin, lorcaserin, and placebo in a 1:1:1 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 2 sites.

3.5.3. Concomitant and Adjunctive Medications

Concomitant medications are allowed if at stable dose for at least 1 month prior to study entry and if they are not on the prohibited list of therapies. The addition of any medications during the study must be discussed with the PI. 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

Pro-serotonergic drugs pose an increased risk of serotonin syndrome when taken together with lorcaserin. Prohibited pro-serotonergic drugs include meperidine, buspirone, dextromethorphan, triptans, tramadol, ritonavir, cabergoline, tryptophan, ginseng, St. John's wort. 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 Co-I (Dr. Kirkman) together with the PI (Jarskog). Furosemide and nifedipine can also increase peak plasma levels of metformin by 20% and require permission of Drs. Kirkman and Jarskog.

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

Study treatment must be reevaluated for the following reason:

- Brief Psychiatric Rating Scale total score increase by $\geq$ 20% compared to baseline will trigger a clinical evaluation to include the site's PI. This may include the subject's regular mental health provider, as needed.

Pre-specified Discontinuation Criteria:

1) Subject has gained >7 kg compared to baseline weight (V0) at any visit
2) Subject is unwilling to continue taking study drug for any reason
3) Clinical Global Impression-Severity scale (CGI-S) score $\geq$6 or worsening of CGI-S score by $\geq$2 points compared to baseline
4) Evidence for new onset suicidal ideation, plan or evidence of self-harm based on Columbia Suicide Severity Rating Scale (C-SSRS)

5) eGFR <45 mL/min/1.73 m^2
6) ALT, AST, GGT >2.5xULN (upper limit of normal), total bilirubin >1.3xULN
7) Serum CO2 <19 mEq/L
8) Meets criteria for alcohol abuse or dependence

3.5.6. Drug Supply and Administration

Study medication will be over encapsulated so that study assignment will not be known to subjects 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 an investigational drug pharmacist must maintain an adequate record of the receipt and distribution of all trial supplies. 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 9. 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 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 14: Phone reinforcement
Week 16: Changing snack habits

Week 18: Phone reinforcement
Week 20: Revisit Self-monitoring: Awareness of Body Weight and What One Eats
Week 22: Phone reinforcement
Week 24: Revisit Burning Calories by Exercise
Week 26: Phone reinforcement
Week 28: Revisit Controlling Urges to Overeat and Snack
Week 30: Phone reinforcement
Week 32: Revisit Burning calories by Using Energy
Week 34: Phone reinforcement
Week 36: Revisit Decreasing Food Cues to Overeat and Snack
Week 38: Phone reinforcement
Week 40: Revisit Developing good eating habits
Week 42: Phone reinforcement
Week 44: Revisit Self-control of overeating
Week 46: Phone reinforcement
Week 48: Revisit Changing Snack habits
Week 50: Phone reinforcement
Week 52: Increasing success

3.7. STUDY VISITS

Subjects will attend visits at least once a month at which structured assessments will be conducted according to the study Schedule of Events in Appendix 1 and Appendix 2. During the first two weeks of study treatment, all subjects will be assessed clinically at weekly Visits 1 and 2.

3.8. PROCEDURES BY VISIT

The required procedures and assessments for subject evaluation are outlined in the Schedule of Events in Appendix 1 and Appendix 2.

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 10 or Visit 52/discontinuation visit. Fasting laboratory tests are required for subjects 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 Visit 13.

3.8.2. Screening Visit

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
- Other Medications Record

- Measure metabolic parameters including fasting laboratories (i.e., lipid profile, glucose, Hemoglobin A1C, insulin, and lipids, 2 hour OGTT)
- Blood draw for laboratory assessment
- Urine drug screen
- Collect specified demographic and medical data
- Assess each subject'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 0)

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 within 28 days of the screening visit.

The following assessments must be completed:

- Vital signs, weight (patient's weight at this visit will constitute baseline weight)
- Other Medications Record
- Clinical Global Impressions-Severity (CGI-S)
- Clinician Alcohol Use Scale and Drug Use Scale (AUS/DUS)
- Alcohol Use Questionnaire
- BPRS (Brief Psychiatric Rating Scale)
- C-SSRS (Columbia Suicide Severity Rating Scale)
- EDE-Q (Eating Disorder Examination Questionnaire)
- TFEQ (Three-Factor Eating Questionnaire)
- FCI questionnaire (Food and Craving Inventory)
- Behavioral Intervention
- DXA (Dual X-ray absorptiometry) (UNC ONLY)
- 24 hour food recall assessment, accelerometry
- 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 1 and 2 (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, adverse events/side effects, adherence, adjust dose as indicated) vital sign collection (including weight), and to provide the behavioral therapy intervention. The CGI-S will be completed at V1 and V2 and the BPRS and C-SSRS will be completed at V2 only.

3.8.5. Visit 3 (Week 4)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- 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 4 (Week 6)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- Study Medication Adherence and Dispensing Form

- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.7. Visit 5 (Week 8)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Substance Use Scale
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.8. Visit 6 (Week 10)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- Study Medication Adherence and Dispensing Forms
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.9. Visit 7 (Week 12)

This visit will include completing:

- Vital Signs, weight
- Blood draw for laboratory assessment (LFT (AST, ALT, GGT, total bilirubin), creatinine, eGFR, Lipid Profile, HbA1C, fasting glucose)
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS

- 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 8 (Week 16)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.11. Visit 9 (Week 20)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.12. Visit 10 (Week 24)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS

- C-SSRS
- Substance Use Scale
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms
- 24 hr food recall assessment, accelerometry
- EDE-Q (Eating Disorder Examination Questionnaire)
- TFEQ (Three-Factor Eating Questionnaire)
- FCI questionnaire (Food and Craving Inventory)
- Blood draw for laboratory assessment (chemistry, CBC w/diff, LFT (AST, ALT, GGT, total bilirubin), creatinine, eGFR, Lipid Profile, HbA1C, fasting glucose, insulin, leptin, Ghrelin, PYY3-36, GLP-1)
- Urine Drug Screen

3.8.13. Visit 11 (Week 28)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.14. Visit 12 (Week 32)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Substance Use Scale

- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.15. Visit 13 (Week 36)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.16. Visit 14 (Week 40)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.17. Visit 15 (Week 44)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS

- Substance Use Scale
- Alcohol Use Questionnaire
- Other Medications Record
- Study Medication Adherence Form
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms

3.8.18. Visit 16 (Week 48)

This visit will include completing:

- Vital Signs, weight
- Study Medication Dispensing
- CGI-S
- BPRS
- C-SSRS
- Study Medication Adherence Form
- Other Medications Record
- Adverse Events Form
- Behavioral Treatments and Behavioral Treatment Adherence Forms Global Behavioral Treatment Adherence Form
- Schedule DXA (Dual X-ray absorptiometry) (UNC ONLY) to be completed ideally by Week 52
- Setup 24 hr food recall assessment and accelerometry to be completed over the next 4 weeks before study completion

3.8.19. Visit 17 (Week 52) or Discontinuation Visit (if patient is discontinuing the assigned treatment condition early)

This visit will include completing:

- Vital Signs, weight
- Physical exam and medical history
- CGI-S
- BPRS
- C-SSRS
- 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
- DXA (Dual X-ray absorptiometry) (UNC ONLY)
- 24 hr food recall assessment, accelerometry
- EDE-Q (Eating Disorder Examination Questionnaire)
- TFEQ (Three-Factor Eating Questionnaire)
- FCI questionnaire (Food and Craving Inventory)
- Blood draw for laboratory assessment (chemistry, CBC w/diff, LFT (AST, ALT, GGT, total bilirubin), creatinine, eGFR, Lipid Profile, HbA1C, fasting glucose, insulin, leptin, Ghrelin, PYY3-36, GLP-1, 2 hour OGTT)
- Urine Drug Screen
- Reason for Assigned Treatment Discontinuation

If not completed between Week 48-Week 52 will need to:

- Schedule DXA (Dual X-ray absorptiometry) (UNC ONLY)
- 24 hr food recall assessment and accelerometry

3.8.20. 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, Vital signs, Alcohol Use Questionnaire, Substance Use Scale, Laboratory tests and/or Other Medication Record.

3.9. DETAILS OF PROCEDURES

3.9.1. Study Materials

Sites will use a stadiometer for measuring height and receive 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 accelerometers, 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 and Appendix 2.

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 52-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 5. The BMI for each patient will be calculated by the Data Management System to verify accuracy.

3.9.4. Clinical Global Impression Scale (CGI)

The Clinical Global Impression (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-S will be completed at all study visits.

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.

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 52 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

Laboratory testing will be conducted at the respective medical center laboratories at the 2 sites for this study: UNC Hospitals and Columbia University Medical Center for the routine laboratory tests. Appetite regulatory hormone testing will be conducted in the UNC Endocrine Laboratory. These hormonal samples will be collected and stored locally at -80°C and then shipped in batches to the UNC Endocrine Laboratory at intervals over the course of the study. 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 and Appendix 2. The following tests will be performed:

- Hematology: hemoglobin, hemoglobin A1C, hematocrit, RBC, WBC, differential white blood cell count, and absolute platelet count
- Serum chemistries: sodium, potassium, chloride, CO2, BUN, creatinine, fasting glucose, AST, ALT, alkaline phosphatase, total protein, albumin, total bilirubin, estimated GFR
- Lipids: total cholesterol, LDL-C, HDL-C, triglycerides
- Hormonal assays: Fasting insulin, leptin, ghrelin, PYY3-36, GLP-1
- 2 Hour oral glucose tolerance test (2 hour OGTT)
- Urine screen for drugs of abuse
- Serum pregnancy test for women who can become pregnant must be performed at the Screening Visit.

Values outside the normal range will be assessed for clinical significance by the site PI. If the accuracy of the result is in question, the test(s) may be repeated. 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 PI. (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 metformin-associated lactic acidosis in the setting of alcohol abuse, the goal is for the clinician to know how much alcohol each subject is drinking so as to help identify any individuals who may meet criteria for alcohol abuse or dependence after study randomization.

3.9.12. Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-point scale developed to measure changes in symptoms in people with schizophrenia participating in clinic trials. The BPRS is a clinician-based rating scale that emphasizes significant psychiatric symptoms including positive and negative symptoms of psychosis and general psychopathology. Ratings are made based on a 7-point Likert scale, from 1=“Not Present” to 7=“Extremely Severe.” The scale is administered in context of a clinical interview and includes observation of subjects’ behavior.

3.9.13. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale designed to assess suicidality in adolescents and adults. It rates suicidal ideation on a scale from “wish to be dead” to “active suicidal ideation with plan and intent.” The scale identifies behaviors that may be indicative of an individual’s intent to commit suicide. The scale is administered in an interview format by a trained clinician.

3.9.14. Eating Disorder Examination Questionnaire (EDE-Q)

The EDE-Q (Fairburn & Beglin, 1994) was designed to assess information on eating behavior in patients with eating disorders. It is composed of a total score and four subscales (Dietary Restraint, Eating Concern, Weight Concern, and Shape Concern); higher scores reflect greater severity or frequency. The EDE-Q also provides information on the frequency of objective and subjective binge eating and overeating episodes.

3.9.15. Three-Factor Eating Questionnaire (TFEQ)

The TFEQ (Stunkard & Messick, 1985) is used to assess psychological features of eating behavior **(**disinhibition, cognitive-restraint, and susceptibility to hunger).

3.9.16. Food Craving Inventory (FCI)

The FCI (White, Whisenhunt et al. 2002) was designed to measure specific food cravings, including a total score and four subscale scores (dietary fats, sweets, carbohydrates/starches, and fast-food fats).

3.9.17. Dual-Energy X-ray Absorptiometry (DXA)

DXA uses low- and high-energy photon beams to assess lean and fat tissue and bone mineral across the body. Subjects will undergo DXA scans at baseline and end-of-study. Radiation exposure from this procedure is minor, representing approximately one sixth of the unavoidable daily background radiation. DXA scanning will be conducted at the UNC site only.

3.9.18. Accelerometry

Primary estimates of sedentary and active behavior will be estimated via 7-day accelerometer monitoring at baseline, midpoint, and end-of-study. Accelerometers are small lightweight devices that measure acceleration and can be worn either on the wrist or at the waist to measure and record changes in body motion. This study will use the Actigraph GT3X+ accelerometer.

3.9.19. 24-hour dietary recall assessment

24-hour dietary recall assessments are administered as telephone questionnaires by trained personnel from the UNC Nutrition and Obesity Research Center. At baseline, mid- and end-of-treatment, each subject will complete two 24-hour nutritionist-assisted dietary recalls conducted during one random weekday and one weekend day. These assessments will provide a means for evaluating within-subject changes in dietary intake over the course of the study period. The

key measures of interest will be % macronutrient (fat, protein, carbohydrate) intakes.

4. DISCUSSION OF STUDY DESIGN AND APPROACH

There is a high comorbid prevalence of obesity and related metabolic disorders in people with schizophrenia. Given the fact that these comorbidities stem at least in part from established side-effects of antipsychotic medications, the relative paucity of pharmacological intervention research in addressing weight reduction in overweight people with schizophrenia is surprising. Current FDA-approved agents for obesity management include multiple sympthomimetic agents such as phentermine, phenylpropanolamine, and phentermine/topiramate combination treatment. Sympathomimetics have abuse potential, can contribute to hypertension and insomnia and also potentially exacerbate psychosis, making them less than ideal options for people with chronic psychotic disorders. Orlistat is a lipase inhibitor that is medically safer but it is often associated with unpleasant gastrointestinal side-effects and was found to be ineffective for antipsychotic-associated weight gain (Joffe et al, 2008).

In light of this background, several agents without sympathomimetic properties that are not FDA-approved for weight-loss have been studied for antipsychotic-associated weight gain in people with chronic psychotic disorders. Meta-analysis has identified metformin as the most effective adjunctive treatment studied to date, associated with approximately 3 kg weight reduction (Mizuno et al., 2014). Lorcaserin, a recently-approved 5-HT2C agonist for weight loss, represents another potentially important option for people with schizophrenia since it does not have sympathomimetic properties. In two large 52-week studies, mean weight loss for lorcaserin was 5.5-6 kg in overweight adults, with a differential weight loss for lorcaserin compared to placebo of 3-3.5 kg. The use of combination treatment with mechanistically distinct agents for weight loss (e.g. phentermine/topiramate, bupropion/naltrexone) and for other chronic disorders such as hypertension, epilepsy, and diabetes has been remarkably successful. The current study will seek to explore the combination of two non-symptathomimetic drugs – metformin and lorcaserin – for their effect on weight in overweight people with schizophrenia.

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 $\geq$ 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 medications is allowed with the exception of monoamine oxidase inhibitor (MAOI) class of antidepressants, given the theoretical risk of developing serotonin syndrome for people taking lorcaserin. 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.

Finally, the specific outcome measures were chosen primarily to assess the effects of metformin and lorcaserin on weight and selected metabolic parameters including measures of lipid and glucose metabolism. Additional outcomes will include effects on appetite regulatory hormones (e.g. leptin, grehlin, PYY3-36, and GLP-1), as well as information on appetite and feeding behavior (ie food intake assessments), fat distribution using DXA imaging, and accelerometry for assessing energy expenditure across the study. Evidence to support lorcaserin/metformin-associated benefits on measures of weight and lipid/glucose metabolism would provide generalizable information on a readily available weight-loss strategy for overweight patients with schizophrenia. Further assessments addressing mechanistic aspects of how metformin and lorcaserin may achieve weight loss will provide critical insights on how to design future studies using metformin and lorcaserin and also how to approach other novel interventions for antipsychotic weight gain.

5. STUDY MONITORING AND OVERSIGHT

5.1. SITE MONITORING

Representatives of the University of North Carolina at Chapel Hill will perform assessment 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 very important 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.

Dr. Jarskog (PI) will be available on pager and cell phone to all co-investigators to discuss any safety issue that emerges over the course of the study. All adverse events (AEs) occurring during the course of the study are to be documented and reported to the PI. All Serious Adverse Events are reported to the DSMB, IRBs and NIDDK as required. The occurrence of AEs will be assessed during the study and the PIs will follow all AEs to the point of satisfactory resolution. The PI will obtain additional input from Dr. Kirkman (Co-I, Endocrinologist) as needed for evaluating and managing any medical AEs.

6.1.1. Serious Adverse Events

AEs will be assessed to determine if they meet criteria for an SAE. Serious adverse events (SAEs), as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE will be reported to the IRB, NIDDK, and the FDA. The initial SAE report will be followed by submission of a completed SAE report to all three institutions. In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will have appropriate follow-up and/or stabilization. Follow-up will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study procedures, or results in death. Outcome of SAEs will be periodically reported to NIDDK. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDDK.

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.

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 6 and 7.

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 other site will also have the opportunity to make contact with the PI for clarifying the event seriousness criteria.

A report of a SAE 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 PI 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 PI and sent to NIDDK 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 DSMB will evaluate issues of participant safety, the adequacy and integrity of accumulating data and study's ability to test the a priori 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.

A DSMB will be convened and will be comprised of three members including a biostatistician, one psychiatrist experienced in treating patients with schizophrenia and one internist with experience with management of obesity and diabetes. No members of the DSMB will be affiliated with any of the other institutions involved in the study.

During the initial meeting of the DSMB, the Board will formulate its operating procedures, including such issues as the Board's meeting schedule; the study monitoring process; the types and formats of reports it will receive from the study statistician; and how minutes will be taken and distributed.

Before the study is opened to subject accrual, the DSMB will meet to review the study protocol, particularly the specific outcome definitions, the analysis plan, the procedures for recording and reporting SAEs, and the monitoring proposal. The subject informed consent document/process also will be inspected to ensure that all required elements have been included in language understandable to a typical study subject to be enrolled in the trial.

The DSMB will monitor and evaluate the safety of the subjects throughout the course of the research study, through the following processes:

- Assess the performance of the trial with respect to subject recruitment, retention and follow-up, protocol adherence, and data quality and completeness, to help ensure the likelihood of successful and timely trial completion.
- Monitor interim data regarding the safety of the study regimens.
- Review and consider any protocol modifications or ancillary studies proposed by the study investigators after the main trial begins to ensure that these do not negatively impact on the main trial.
- Advise the Institutional Review Board as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

The DSMB will meet regularly (at least twice per year) to monitor the cumulative safety data during the period when participants are in the study. The DSMB will monitor the study according to the guidelines specified in the study protocol and the operating procedures established at the initial meeting, unless the DSMB determines during the course of the trial that modification of the guidelines is in the best interest of the study and its participants. Such a decision may be based on new information that emerges during the course of the study, realization of inappropriate initial study assumptions, or the occurrence of an unanticipated scenario.

Prior to each DSMB meeting the study biostatistician will prepare a report that summarizes study enrollment, progress and all adverse events including Serious Adverse Events. This will include specific tables for adverse events related to cardiovascular, metabolic, neurological and psychiatric system organ classes.

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 52 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 primary outcome is change in body weight at 52 weeks compared to baseline. The primary objective is to compare LOR/MET combination treatment with placebo. We will use a mixed model with treatment group, site and visit as factors, baseline as a quantitative covariate, and the treatment-by-visit and baseline-by-visit interaction terms. The unstructured (UN) variance/covariance matrix will be used for the analysis. The primary outcome will be a contrast examining the difference between treatment at the 52 week point for LOR/MET combination compared to placebo.

The secondary objective is to compare LOR treatment with placebo. This analysis will be performed similar to the comparison of LOR/MET combination treatment with placebo. This comparison will be declared significant if both, LOR/MET and LOR, comparisons are significant.

(We will also 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. In addition to the analyses above, we will perform sensitivity analyses using fasting glucose, insulin, appetite regulatory hormones, body fat distribution, smoking status, gender, and type of antipsychotic medication (low vs high liability for weight gain) as covariates in order to assess their impact on weight in this study.

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:

Based on our preliminary data with metformin for weight loss and on the published literature with lorcaserin monotherapy (Smith et al., 2010; Fidler et al., 2011; O'Neil et al., 2012), the following weight loss is hypothesized: 1.5 kg for placebo, 4.5 kg for lorcaserin monotherapy, and 6.5 kg for lorcaserin/metformin combination. Based on the literature and on our METS trial, the standard deviation of the change scores is expected to be 6 kg. We felt that a 3 kg change would be a clinically important change, and hence, a difference between treatment groups of 3 kg (or more) in change from baseline would represent a clinically important effect. The primary contrast of

interest will be the difference in weight change between the placebo and lorcaserin/metformin combination treatment. Although a mixed effects model will be used for data analysis, a one-way, three-group ANOVA on change scores was used as an approximation for estimating sample size, as use of a mixed model for such estimation would have required us to hypothesize a covariance structure, pattern of dropout, and a site effect. It is thus likely that our sample size estimates are conservative. In this model, for the primary contrast of placebo versus lorcaserin/metformin combination, to achieve power=0.85, with a two-tailed significance level of 0.05, will require 27 subjects per treatment group. A sample size of N=110 will be used in order to allow for ~25% dropouts.

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 LOR/MET, LOR monotherapy and placebo on 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 similar to those performed for weight.

7.2.4. Specific Aim #3

The response variable is the effect of lorcaserin/metformin, LOR monotherapy and placebo on appetite regulatory hormones, body fat distribution, food intake and energy expenditure. These variable are numeric and the analyses will be similar to those performed for weight

7.2.5. 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. If no more than 2 successive intermittent visits are missing, the data will be imputed. No more than 4 visits per subject will be imputed. 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 amount of missing data is informative or non-informative, 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.

Study personnel will have requisite education, training and experience for their assigned roles including training in the ethical conduct of research.

8.2. RISKS AND BENEFITS

8.2.1. Metformin 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. In the METS study, most GI symptoms resolved completely within the first week of treatment. If diarrhea or vomiting occurs, the usual approach is to hold study medication until symptoms resolve and then restart one capsule daily and titrate as tolerated.

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 $\geq$1.5 in males and $\geq$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. Lorcaserin Risks

Lorcaserin has a well-established and generally benign side effect profile. Trials to date that have included over 3,400 subjects exposed to lorcaserin for at least 1 year found the most common adverse events for lorcaserin compared to placebo were headache (17% vs 10%), dizziness (9% vs 4%), nausea (8% vs 5%), and fatigue (7% vs 3%). There were no differences in the occurrence of depression, anxiety or other psychiatric events, including suicidal ideation in studies of lorcaserin at lorcaserin doses up to 20 mg per day. At supratherapeutic doses from short-term Phase I safety studies in non-obese healthy volunteers, doses of 40 and 60 mg per day were associated with increased incidence of euphoria compared to placebo (up to 19% of subjects reported euphoria). In subsequent studies in obese individuals of lorcaserin up to 40 mg per day, reports of euphoria were low (<1%). In the large Phase III trials with lorcaserin limited to 20 mg per day, there was no increase in reports of euphoria or other symptoms of

mania, psychosis or physical/psychological dependence compared to placebo (Smith et al., 2010; Fidler et al., 2011). Because of the potential for lorcaserin to cause euphoria at supratherapeutic doses, it has been listed as a Schedule IV controlled substance. There are no data from animal or human studies demonstrating whether lorcaserin can induce physical dependence.

Lorcaserin has not previously been studied in people with schizophrenia. However, 5-HT2C agonists have previously been hypothesized to have potential antipsychotic efficacy by reducing mesocortical dopamine transmission in animal models of psychosis. To test this hypothesis, a recent 6 week RCT examined the safety and efficacy of vabicaserin, a selective 5-HT2C agonist versus olanzapine in 289 people with acutely exacerbated schizophrenia. Vabicaserin was found to produce similar improvements to olanzapine in positive psychotic symptoms, with no benefits on negative symptoms. There was no evidence of significant side effects associated with vabicaserin, including no evidence of psychotic exacerbation or exacerbation of other psychiatric symptoms (Shen et al, 2014). Although not directly testing lorcaserin, these data provide reassurance that 5-HT2C agonists do not pose a significant risk of psychotic exacerbation in people with schizophrenia, and that 5-HT2C agonists as a class may actually exert a therapeutic role for psychosis.

Given that lorcaserin is a serotonin receptor agonist, it has a potential risk of causing side effects associated with serotonin excess including the possible risk of serotonin syndrome. Serotonin syndrome is a rare but serious side effect that is characterized by a constellation of signs and symptoms that can include tachycardia, agitation, confusion, hypertension, rigidity, tremor, hyperpyrexia, and hyperreflexia (Boyer et al. 2005). It has been associated with agonism at the 5HT2A receptor (Nisijima et al, 2001; Isbister et al., 2001) and usually resolves quite rapidly following administration of a 5HT2A antagonist such as cyproheptadine. Because lorcaserin is a 5HT2C agonist, it does not normally induce serotonin syndrome. However, one of the 3,400 subjects exposed to lorcaserin in the registration trials developed symptoms consistent with moderate severity serotonin syndrome, and one subject developed mild symptoms judged possibly consistent with serotonin syndrome. Given that lorcaserin has not previously been studied in people with psychosis or depression, the safety of co-administration of other serotonergic agents has not been well established. The current study will take precautions by excluding patients taking pro-serotonergic agents including meperidine, buspirone, dextromethorphan, triptans, tramadol, ritonavir, tryptophan, ginseng, St. John’s wort. The current project provides an excellent opportunity to begin to collect data on the tolerability and safety of lorcaserin in clinically stable patients with schizophrenia taking antipsychotics. Subjects will be instructed in the signs and symptoms of serotonin syndrome and instructed to contact the research clinic or to seek emergency medical care. Side-effect monitoring aimed at psychiatric decompensation using the BPRS, C-SSRS and CGI will be administered regularly, especially during the first 3 months of the trial. Targeted side effect monitoring aimed at detecting serotonin

syndrome, or less fulminant serotonin excess, will be performed at each study visit. Furthermore, as part of the behavioral intervention, each subject will be contacted via telephone each week of the study to review the last behavioral lesson, and during these calls, subjects will be screened for evidence of serotonin syndrome.

A prior concern with non-selective serotonin agonists for weight loss (e.g. fenfluramine, dexfenfluramine) had been cardiac valvulopathy, which led to the withdrawal of these agents by the FDA. The mechanism underlying valvular heart disease has been traced to agonism at 5-HT2B receptors which are expressed on cardiac valves (Rothman et al., 2000; Roth, 2007). As a selective 5-HT2C agonist, lorcaserin is not expected to produce similar cardiac valve problems and this was confirmed in the BLOOM and BLOSSOM studies (Smith et al., 2010; Fidler et al., 2011). Echocardiography was conducted on all participants and no evidence of lorcaserin-associated valvulopathy emerged.

Finally, the BLOOM-DM study demonstrated the safety of concurrent treatment with lorcaserin and metformin (O'Neil et al., 2012). Of the 604 enrolled participants, over 90% were taking stable doses of metformin at study entry. There were no significant safety signals that emerged, including similar rates of reported hypoglycemia between lorcaserin 10 mg BID (7.4%) and placebo (6.3%) arms.

8.2.1.2. 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. Given the increased theoretical risk of serotonin syndrome with lorcaserin, some pro-serotonergic agents have been added to the exclusion criteria, including all monoamine oxidase inhibitor (MAOI) class of antidepressants. Adjunctive medications are allowed to relieve specific clinical symptoms or manage study medication adverse events.

8.2.2. Potential Benefits to Participants

Study medication, 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. All subjects are likely to benefit from

the general medical advice on improved diet and increased physical activity that all subjects will receive during the study. They can also benefit from the medical monitoring that is performed at baseline and throughout the study. If physical conditions are detected during the study, then subjects will be referred to their local primary care providers for further evaluation and treatment. Furthermore, there is a growing database to support that metformin is associated with modest but significant weight loss in overweight patients with schizophrenia. Similarly, there is a good database to support the efficacy of lorcaserin for weight loss, but not yet in people with schizophrenia. If subjects are randomized to the lorcaserin/metformin combination treatment or to lorcaserin monotherapy, then they may benefit from the treatment, in addition to the behavioral intervention that all subjects will receive. 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 the first week of 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. The risk of serotonin syndrome may be increased with the use of lorcaserin. Serotonin syndrome is a rare but serious side effect that is characterized by a constellation of signs and symptoms that can include tachycardia, agitation, confusion, hypertension, rigidity, tremor, hyperpyrexia, and hyperreflexia. One probable case and one possible case of serotonin syndrome were identified among 3,400 subjects who received lorcaserin in the FDA registration trials. Targeted side effect monitoring aimed at detecting serotonin syndrome, or less fulminant serotonin excess, will be performed at each study visit. Furthermore, as part of the behavioral intervention, each subject will be contacted via telephone weekly or biweekly and subjects will also be screening for serotonin excess at those points of contact.

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. It is judged that 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, reasonably outweigh the risks to participating subjects.

8.2.4. Subject Payments

Participants will receive a payment ($45 for each visit, plus an additional $5 for visits when medication bottles are brought in) for each scheduled study visit attended to help compensate for effort and for transportation costs.

8.2.5. Costs to Patients

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 use confidentiality procedures consistent with the study protocol described herein. All study related documents, medical records and other identifying information will be kept in locked cabinets in locked offices. All study related documents (case report forms, source documents, lab requisition forms, test tubes etc.) will be coded using a study number and not the patient's name. Research participant's name or other identifying information will not be kept with their case report forms or source documents. The list linking study participants to their study numbers will be kept in a separate locked cabinet. All computerized records and schedules will 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 presented and

published in aggregate form with no personal identifiers.

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

Term	Definition
AE	Adverse event
BMI	Body Mass Index expressed in kilograms per meter squared (kg/m^2)
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CV	Cardiovascular (disease)
DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DXA	Dual X-Ray absorptiometry
FBS	Fasting Blood Sugar
GCP	Good Clinical Practices
HCG	Human chronic gonadotropin
HDL-C	High density lipoprotein – cholesterol
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MS	Metabolic syndrome
OAE	Other Significant Adverse Event
OC	Observed Case
2hr OGTT	Two hour Other Glucose Tolerance Test
OMR	Other Medications Record

SAE	Serious Adverse Event

Rating Scales

Acronym	Definition
BPRS	Brief Psychiatric Rating Scale
CGI-S	Clinical Global Impressions-Severity
C-SSRS	Columbia Suicide Severity Rating Scale
EDE-Q	Eating Disorder Examination Questionnaire
FCI	Food Craving Inventory
SCID	Structured Clinical Interview for DSM-IV
SF-12	Short Form Health Survey
SURFs	Service Utilization and Resources Form –Short Form
TFEQ	Three-Factor Eating Questionnaire

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Appendix 1. Schedule of Events (Baseline to Week 24)

Assessments	SCR	BL V0	WK1 V1	WK2 V2	WK4 V3	WK6 V4	WK8 V5	WK10 V6	WK12 V7	WK16 V8	WK20 V9	WK24 V10
Demographics	X											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
SCID/Psych + Med Hx/PE	X											
Incl/Excl Criteria	X											
Study Drug Disp + Adherence		X	X	X	X	X	X	X	X	X	X	X
CGI - Severity	X	X	X	X	X	X	X	X	X	X	X	X
BPRS, C-SSRS		X		X	X		X		X	X	X	X
Substance Use Scale		X			X		X		X			X
Alcohol Use Questionnaire		X			X		X		X			X
Other Meds Record	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/Side Effects	X	X	X	X	X	X	X	X	X	X	X	X
Behavioral Intervention		X	X	X	X	X	X	X	X	X	X	X
DXA (Dual X-ray absorptiometry) (UNC ONLY)		X										
24 hr food recall assessment, Accelerometry		X										X
EDE-Q, TFEQ, FCI questionnaires[c]		X										X
LABS												
Pregnancy test[b]	X	X			X		X		X	X	X	X
Chemistry	X											X
CBC w diff	X											X
TSH	X											
LFT[d], creatinine, eGFR	X								X			X
Urine Drug Screen	X											X
Lipid Profile, HbA1c, fasting glucose	X								X			X
2hr OGTT	X											
Post OGTT insulin	X											
Insulin, Leptin, Ghrelin, PYY3-36, GLP-1	X											X

[a] V17 assessments are performed at Wk52 or at any earlier visit at which a subject discontinues for any reason.

[b] For female subjects of childbearing potential.

[c] Eating Disorder Examination Questionnaire (EDE-Q), Three-Factor Eating Questionnaire (TFEQ), and Food Craving Inventory (FCI)

[d] LFTs = AST, ALT, GGT, and total bilirubin

Appendix 2. Schedule of Events (Week 28 to End-of-Study)

Assessments	WK28 V11	WK32 V12	WK36 V13	WK40 V14	WK44 V15	WK48 V16	WK52 V17[a]
Demographics							
Vital Signs	X	X	X	X	X	X	X
SCID/Psych + Med Hx/PE							X
Incl/Excl Criteria							
Study Drug Disp + Adherence	X	X	X	X	X	X	X
CGI – Severity	X	X	X	X	X	X	X
BPRS, C-SSRS	X	X	X	X	X	X	X
Substance Use Scale		X			X		X
Alcohol Use Questionnaire		X			X		X
Other Meds Record	X	X	X	X	X	X	X
Adverse Events/Side Effects	X	X	X	X	X	X	X
Behavioral Intervention	X	X	X	X	X	X	X
DXA (Dual X-ray absorptiometry) (UNC ONLY)						X	X*
24 hr food recall assessment, Accelerometry						X	X*
EDE-Q, TFEQ, FCI questionnaires[c]							X
LABS							
Pregnancy test[b]	X	X	X	X	X	X	X
Chemistry							X
CBC w diff							X
LFT[d], creatinine, eGFR			X				X
Urine Drug Screen							X
Lipid Profile, HbA1c, fasting glucose							X
2hr OGTT							X
Post OGTT insulin							X
Insulin, Leptin, Ghrelin, PYY3-36, GLP-1							X

[a] V17 assessments are performed at Wk52 or at any earlier visit at which a subject discontinues for any reason.
[b] For female subjects of childbearing potential.
[c] Eating Disorder Examination Questionnaire (EDE-Q), Three-Factor Eating Questionnaire (TFEQ), and Food Craving Inventory (FCI)
[d] LFTs = AST, ALT, GGT, and total bilirubin
*****DXA Scan, 24 hour food recall assessment, and accelerometry are ideally completed at Week 48 but if not done by Week 52 can be done at end of study visit.

Appendix 3. 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 4. 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 5. BMI Calculation Chart

Body Mass Index Table

	Normal						Overweight					Obese										Extreme Obesity																
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body Weight (pounds)																																			
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

Source: Adapted from *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.*

Appendix 6. 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 7. 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 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

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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 (eg watching TV)

6. Excessive eating of candy, cake, ice cream, and potato chips, etc
   Solution: Decrease the amount of each by half (eg. 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).

Week 2

Burning Calories by Exercise

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

~ <u>Weekly:</u>

► 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

~ <u>Target:</u>

► Current weight = _____ lbs.

► Total weight loss = _____ lbs.

► Target weight = _____ lbs.

Week 1 Homework

Daily Weight and Pedometer Record

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							

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

Date	Meal	Meat, Fish, Eggs	Bread, Cereal, Pasta, Rice, Potatoes/ Fries	Vegetables	Fruit	Cake, Cookies, Candy, Ice Cream	Chips (1bag= 1oz.)	Popcorn, crackers	Soda	Tea, coffee	Milk, Cheese	Other
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
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	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											

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

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							

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

Date	Meal	Meat, Fish, Eggs	Bread, Cereal, Pasta, Rice, Potatoes/ Fries	Vegetables	Fruit	Cake, Cookies, Candy, Ice Cream	Chips (1bag= 1oz.)	Popcorn, crackers	Soda	Tea, coffee	Milk, Cheese	Other
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
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	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											
	Breakfast											
	Lunch											
__/__/__	Dinner											
	Snack											

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

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
10 min. exercise am							
10 min exercise pm							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
10 min. exercise am							
10 min exercise pm							

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

Week 4 Homework

Daily Weight and Pedometer Record

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							
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	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
10 min. exercise am							
10 min exercise pm							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
10 min. exercise am							
10 min exercise pm							

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

Eating Habit Record
Resisting Urges through Self-talk

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Resisted Urge to Overeat							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Resisted Urge to Overeat							

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

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							
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	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
15 min. exercise am							
15 min exercise pm							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
15 min. exercise am							
15 min exercise pm							

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

Activity Habit Record
Choosing to Use More Energy

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Get off bus early							
Take stairs instead of elevator							
Walk instead of driving							
Walk fast up hills							
Walk the long way							
Stand instead of sitting							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Get off bus early							
Take stairs instead of elevator							
Walk instead of driving							
Walk fast up hills							
Walk the long way							
Stand instead of sitting							

Mark an "X" for each time you use this strategy

Week 8 Homework

Daily Weight and Pedometer Record

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							
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	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
20 min. exercise am							
20 min exercise pm							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
20 min. exercise am							
20 min exercise pm							

Mark an "X" for each time you complete your exercise

Activity Habit Record
Choosing to Use More Energy

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Get off bus early							
Take stairs instead of elevator							
Walk instead of driving							
Walk fast up hills							
Walk the long way							
Stand instead of sitting							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Get off bus early							
Take stairs instead of elevator							
Walk instead of driving							
Walk fast up hills							
Walk the long way							
Stand instead of sitting							

Mark an "X" for each time you use this strategy

Week 10 Homework

Daily Weight and Pedometer Record

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							
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	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
25 min. exercise am							
25 min exercise pm							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
25 min. exercise am							
25 min exercise pm							

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							
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 12 Homework

Daily Weight and Pedometer Record

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Weight							
Pedometer							
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							
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

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

Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Resist Urge through self-talk							
Limit eating to 1 or 2 locations							
Limit to 1 serving							
No other activities at meal time							
Chew food completely							
Put utensils down before next bite							
Leave food on plate							
Date	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Resist Urge through self-talk							
Limit eating to 1 or 2 locations							
Limit to 1 serving							
No other activities at meal time							
Chew food completely							
Put utensils down before next bite							
Leave food on plate							

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.

From the American Dietetic Association. Accessed at http://www.eatright.org/cps/rde/xchg/SID-5303FFEA-4134E4E1/ada/hs.xsl/home_4367_ENU_HTML.htm. November 17, 2005

Food Groups	One Serving Size Equals...
Breads, Cereals, Rice, Pasta, and other Grains Group	• 1 slice bread or 1/2 bagel the size of a hockey puck. • 1/2 cup cooked rice equals a cupcake wrapper. • 1/2 cup pasta equals an ice cream scoop.
Fruit and Vegetable Groups	• 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.
Meat, Chicken, Fish, Dry Beans and Peas, Eggs, and Nuts Group	• 3 ounces lean meat, chicken, or fish measures up to a deck of cards or a check book.
Dairy Group	• 1 ounce cheese equals about 4 dice.
Fats, Oils, and Sweets Group	• Use sparingly. For a teaspoon of fat, look to the tip of your thumb.

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

Accessed at http://nhlbisupport.com/chd1/Tipsheets/sevenways.htm, November 17, 2005

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

TYPE OF EXERCISE	CALORIES BURNED PER HOUR
Sleeping	55
Eating	85
Sewing	85
Knitting	85
Sitting	85
Standing	100
Driving	110
Office work	140
Housework	160
Golf, with trolley	180
Golf, without trolley	240
Gardening, planting	250
Dancing, ballroom	260
Walking, 3mph	280
Table Tennis	290
Gardening, hoeing	350
Tennis	350+
Water aerobics	400
Skating, rollerblading	420+
Dancing, aerobic	420+
Aerobics	450+
Bicycling, moderate	450+
Jogging, 5mph	500
Gardening, digging	500
Swimming, active	500+
Cross country ski machine	500+
Hiking	500+
Step Aerobics	550+
Rowing	550+
Power walking	600+
Cycling, studio	650
Squash	650+
Skipping rope	700+
Running	700+