Modalities for effective weight loss in diabetics

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A. Questions

Is the addition of sibutramine to lifestyle modification able to induce more weight loss and maintain moderate weight loss in type 11 DM patients compared to lifestyle Modifications alone?

B. Background

Obesity has become a major health concern today with 60% of the adult population either overweight or obese. It is a major risk for many diseases including DM, HTN, CHD, hypercholesterolemia, musculoskeletal diseases and certain malignancies resulting in escalating health care cost with as much as 7% of national health care spending going to obesity related illnesses in 1995 [1]. The prevalence of obesity is far higher in diabetics who are at increased risk of CHD and stroke. Moderate weight loss (losing 5-10% of total weight) in this population has been shown to be beneficial. It leads to improved glycemic and BP control, decreases hyperlipidernia and may cause increased longevity [2]. Sustained moderate weight reduction may lead to a reduction or delay in micro and macrovascular complications in the long run. Most current interventions are able to achieve some degree of weight loss, however long term maintenance of weight loss continues to be problematic with most people regaining the weight after 1 yr. Lifestyle modifications- a combination of low caloric diet and exercise remain the mainstay of weight reduction. Certain new medications including orlistat and sibutramine have also been shown to be efficacious in long term weight management, and safe in diabetics [3]. There is no evidence whether there is an added benefit of addition of an anti- obesity agent to intense lifestyle modifications in the form of diet and exercise to see if there is increased weight loss and if this effect is maintained over time.

C. Hypothesis

Subjects assigned to Sibutramine plus lifestyle modification will loose significantly more weight and more would be able to maintain it compared to lifestyle modifications alone.

D. Conceptual and operational definitions

Primary outcomes: 2 major endpoints: Amount of weight loss (change from baseline) in each group. Whether patients are able to maintain weight loss in each group.

E. Study design

Randomized, double blind placebo trial, Intention to treat analysis

Prospective, interventional study. Study will be conducted over 18 months with 6 months dedicated with weight loss and the remaining 12 months to weight maintenance.

Study subjects to be recruited from ambulatory internal medicine clinics within the Columbia/ Cornell health care network. Subjects with Type II DM for <= 5 yrs with BMI 27-35, age 35-65 are eligible for the study.

F. Interventions

They will be randomized to 10-1 5mg of sibutramine or placebo. All subjects in the treatment group will be started on I Omg once a day. This dose would be increased to 15mg in participants who loose less than 2kg in the ls'month. Equal additional placebo will be given to control subjects that did not loose weight in first month. Both arms will receive a comprehensive lifestyle modification program -comprising of 12 weekly sessions with overall goals of achieving at least 7% wt loss (average weight reduction associated with beneficial effects in diabetics) through behavioral modification including low fat, low calorie diet and physical activity of moderate intensity at least 150 minutes a week. Each participant will meet with a nutritionist twice to help develop a 50OKcal deficit diet with <30% fat and < 10% saturated fat per day. Exercise part of the program will include both indoor and outdoor activities of moderate intensity. Participants will meet with case managers exercise instructors every 2 months for positive reinforcement. All subjects will keep activity logs to assess activity levels. Compliance with study drugs will be assessed through pill counts and structured interviews. Weight will be measured at baseline, once a week for the first 4 weeks and every 2 months thereafter.

G. Statistical analysis and Sample size

We will use tailed t tests to analyze changes in weight between the groups at baseline and at follow up. Chi square test will be used to compare the proportion of patients able to maintain weight loss in each group. The Finnish Diabetic Prevention Study Group looked at the effect of lifestyle changes among subjects with impaired glucose tolerance and diabetes. They found that on average, subjects in the intervention arm lost 4.2+/-5 Kg in I year [4]. If we assume a similar rate of weight loss in our control group and 10.2+/-9.3 Kg for the sibutramine group - which was the mean weight loss noted in a RCT comparing sibutramine to placebo [5], -this yields a sample size of 44 in each arm to achieve 80% power to detect a statistically significant difference in weight loss.

We assumed that only 1/3 of the control arm would be successful at maintaining weight loss at 12 months as opposed to 50% of patients in the intervention arm. This yields a sample size of 131 in each ann. Overall sample size will be 160 patients in each arm -accounting for 20% drop out rate.

H. Sample size

160 in each arm.

I. Subject selection

Population- Adults 35-65 with type 11 DM <= 5yrs. Patients will be recruited from all ambulatory clinics within Cornell/ Columbia medical centers.

Enrollment by PMDs./NP

a. Inclusion criteria/ eligibility

Type II DM, age 35-65, BMI 27-35, accept to be randomized, able to give informed consent.

b. Exclusion criteria

- Medical conditions and treatments that would contraindicate using diet and exercise
- Medical conditions and treatments that would contraindicate use of sibutramine - e.g. SSRIs, triptans, MAOIs,
- Diabetic on insulin
- Malignancy, physical immobility, known CAD, CHF, ESRD, uncontrolled HTN (SBP<160, DBP<100), hx of arrhythmia, smokers. Seizure disorder, psychiatric disorders,
- On weight loss meds currently or within the last 6 months.
- Any obesity related surgery, Body weight change> 10 pounds in the last 6 months.
- Pregnancy, breastfeeding or planned pregnancy

J. Adverse events

Increases in **blood** pressure and pulse have been reported with use of sibutramine [5, 6,7,8]. BP and Heart rate will be measured at each visit. Participants with systolic or diastolic BP increased from baseline by 10mmHg or > 20% increase in HR on 2 or more consecutive visits will have their dose decreased by 5mmHg decrements until acceptable blood pressure and heart rate is achieved. Participants will also be monitored for any exercise related injuries. They will submit their list of medications on each visit to be reviewed to ensure that they are not on any drugs that can potentially react to sibutramine.

K. References

1. Thompson D. Lifetime Health and Economic Consequences of Obesity. Arch int Med 1999;159:2177-2183
2. Goldstein DJ Beneficial Effects Health Effects of Modest Weight Loss. Int J Obes Relat Met Disord. 1992; 16:397-415
3. N Finer et al. Sibutramine in effects for weight loss and diabetic control in obesity and type 11 DM-A RCT. Diabetes, Obesity and Metabolism2(2): 105-12, April 200.
4. Tuomilehto, J et al. The Finnish Diabetes Prevention Study Group. Prevention of Type 2 DM by Changes in Life style Among Subjects with Impaired Glucose Tolerance. NEJM. 2001;344(14):1343-1350
5. James JP, Astrup A. The STORM study group. Effect of Sibutramine on Weight Maintenance after Weight Loss: A RCT. Lancet 2000;356(9248):2119-2125
6. Berkowitz R et al. Behavior Therapy and Sibutramine for the Treatment of Adolescent Obesity. A RCT. JAMA 2003;289(14):1805-1812
7. Meridia (Sibutramine Hydrochloride) [package insert]. North Chicago, III Abbott Laboratories; 2002

IRB PROTOCOL

A. Study purpose and rationale

The aim of this study is to see if the addition of sibutramine, (a drug approved by the FDA for weight reduction) to standard of care lifestyle modifications will be beneficial in helping type 11 diabetics achieve and maintain modest weight loss. Type 11 diabetics have greater than 2 fold increased risk of CHD and stroke compared with non diabetics. About 80% of them are overweight and/or obese. Modest weight reduction (5-10%) in diabetics is associated with positive benefits including improved glycemic control, lipid profile and decreased blood pressure. Effective maintenance of weight loss in this high risk group may lead to a reduction in macrovascular complications.

B. Study Design and Statistical analysis

This will be a randomized double- blinded placebo trial. Overweight and obese diabetics (BMI 27-35) type Il diabetics who have had DM for < 5yrs and not on insulin, will receive a comprehensive lifestyle modification program geared towards exercise and diet, then subsequently randomized to either 10- 1 5mg sibutramine once a day or placebo. 160 subjects will be enrolled on each arm. Randomization will be computer generated. Proposed method of statistical analysis will be t tests to study amount of weight loss in each group at the end of 6 months and Chisquare analysis to compare proportion of patients able to maintain weight loss. Sample size calculated with 80% likelihood that differences found between the groups will be statistically significant.

C. Study procedure

Study will run for approximately 18 months- l't 6months for weight loss and then 12 months to observe maintenance of weight loss. No procedures will be performed.

D. Study Drug

Sibutramine- is FDA approved for the long term management of obesity in patients with BMI > =30 or >=27 with one risk factor (e.g. DM, hyperlipidemia.) It blocks re-uptake of serotonin, dopamine and noradrenalin - this result in increased satiety, decreased hunger and food consumption. It has also been shown increase basal energy expenditure which usually goes down as people loose weight. It has been demonstrated to be safe and effective in obese populations including diabetics and adolescents. Route of administration- oral Dose regimen- 10- 1 5mg- same as standard dose.

E. Medical Device

None

F. Study Questionnaires

None.

G. Study Subjects

Population- Adults 35-65 with type II DM <= 5yrs. Enrollment by PMDs. /NP Inclusion criteria/ eligibility- Type 11 DM, age 35-65, BMI 27-35, accept to be randomized, able to give informed consent. Exclusion criteriaMedical conditions and treatments that would contraindicate using diet and exercise Medical conditions and treatments that would contraindicate use of sibutramine - e.g. SSRIs, triptans, MA01s. Diabetics on insulin Malignancy, physical immobility, known CAD, CHF, ESRD, uncontrolled HTN (SBP<160, DBP<100), hx of arrhythmia, smokers. Seizure disorder, psychiatric disorders On weight loss meds currently or within the last 6 months. Any obesity related surgery, Body weight change> 10 pounds in the last 6 months Pregnancy, breastfeeding or planned pregnancy

H. Recruitment of Subjects

Subjects to be recruited from all ambulatory clinics within Cornell/ Columbia medical centers, advertisment on hospital website, flyers to be placed in clinics. PMDs, NPs will be informed of the study and encouraged to recommend patients.

I. Confidentiality of Study data

All study data will be coded anonymously and stored safely.

J. Potential conflict of interest

None

K. Location of the study

CPMC and Cornell

L. Potential Risks

Subjects in the placebo ann may not achieve as much weight reduction or maintenance as subjects in treatment arm. About 5% of patients in the treatment group may develop increases in blood pressure and heart rate, and may require and increase or addition of an anti-hypertensive to their medical regimen if increase in BP does not reverse after stopping the drug. There is a chance that some subjects may develop musculoskeletal injuries as a result of exercise.

M. Potential Benefits

All subjects will benefit from the structured comprehensive curriculum aimed at educating them about healthy eating habits and exercise- which has many beneficial effects that go beyond weight reduction alone.

N. Alternative Therapies

None.

O. Compensation and Cost to subjects.

No financial compensation. Subjects will receive discounts on gym membership (NYSQ if they choose to join a gym, and exercise equipment but will incur costs of regarding

P. Minors as research Subjects

Not applicable.

Q. Radiation and Radioactive substances

Not applicable.