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A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Naltrexone to Counteract Antipsychotic-Associated Weight Gain: Proof of Concept

Cenk Tek, M.D.,

Yale University School of Medicine, Department of Psychiatry

Joseph Ratliff, Ph.D,

Yale University School of Medicine, Department of Psychiatry

Erin Reutenauer, BA,

Yale University School of Medicine, Department of Psychiatry

Rohan Ganguli, M.D., and

University of Toronto, Centre for Addiction and Mental Health

Stephanie S. O'Malley, Ph.D.

Yale University School of Medicine, Department of Psychiatry

Abstract

Patients with schizophrenia suffer from higher rates of obesity and related morbidity and mortality than the general population. Women with schizophrenia are at particular risk for antipsychotic-induced weight gain, obesity, and related medical disorders such as diabetes and cardiovascular disease. Given preclinical studies revealing the role of the endogenous opioid systems in human appetite and the potential of antipsychotic medications to interfere with this system, we hypothesized that opioid antagonists may be beneficial in arresting antipsychotic-induced weight gain and promoting further weight loss in women with schizophrenia. In the present study, 24 overweight women with a diagnosis of schizophrenia or schizoaffective disorder were randomized to placebo (PLA) or naltrexone (NTX) 25mg/day for 8 weeks. The primary outcome measure was change in body weight from baseline. Patients in the NTX group had significant weight loss (−3.40kg) compared to weight gain (+1.37kg) in the PLA group. Mainly non-diabetic subjects lost weight in the naltrexone arm. These data support the need to further investigate the role of D2

Corresponding Author: Cenk Tek, M.D., Yale School of Medicine, Department of Psychiatry, Connecticut Mental Health Center, 34 Park Street, 267D, New Haven, CT 06519, T: 203-974-7484, F: 203-974-7691, cenk.tek@yale.edu.

Conflicts of Interest

Dr. Tek acknowledges the following sources of support: Grants/research support: NIH/NIDDK, Genentech; and is a member of the Genentech Inc. advisory panel.

Dr. Ratliff is currently employed as an Associate Nutrition Scientist at the Dr Pepper Snapple Group.

Ms. Reutenauer declares no conflicts of interest.

Dr. Ganguli currently has no relevant conflicts of interest, but has in the past received research grant support or honoraria from Jassen pharmaceutical, Lilly, Bristo Myers-Squibb, and Pfizer.

Dr. O'Malley received commercial research grant from NABI Biopharmaceuticals, Eli Lilly, Arkeo, and Pfizer, has ownership interest in Applied Behavioral Research, LLC and an abandoned patent on naltrexone, and is a consultant with Pfizer, Abbott, Alkermes, Ethypharm, GlaxoSmithKline, Lilly, Schering Plough, Lundbeck, Janssen, Gilead, and Hazelden Foundation.

blockade in reducing food reward based overeating. A larger study addressing the weaknesses of this pilot study is currently underway.

Keywords

Naltrexone; Antipsychotics; Obesity; Weight Loss; Schizophrenia

Introduction

Antipsychotic-induced weight gain is an important problem in the clinical care of schizophrenia. Obesity rates are very high in schizophrenia, which in turn contributes to morbidity and early mortality [1-4]. Obesity also contributes to lower quality of life, further stigma, and depression in this population [5]. Obesity among schizophrenia populations is in part an iatrogenic problem. Pre-antipsychotic era studies of body weight demonstrate overweight and obesity rates lower than general population [6, 7]. First reports of concern about antipsychotic-induced weight gain began a few years after the introduction of chlorpromazine [8, 9]. For successful holistic treatment of schizophrenia, it is clear that the weight gain problem needs to be resolved. The gold standard of obesity treatment for the general population is behavioral interventions that aim to incorporate healthy nutrition with realistic calorie restriction and physical activity into the daily lives of the participants through behavioral change [10, 11]. Such lifestyle interventions have consistently been shown to halt or reduce antipsychotic-induced weight gain and produce modest weight loss [12, 13]. However, when lifestyle interventions are used in the severe mentally ill population, the magnitude of weight loss achieved is much less than that of non-psychiatric samples. It appears that lifestyle intervention strategies may need to be supplemented by pharmacological strategies that have the potential to counteract the metabolic effects of antipsychotic medications

One of the most likely reasons for antipsychotic-induced weight gain is central histamine 1 (H1) receptor blockade as the antipsychotics which cause the most weight gain are strong blockers of H1 receptors [14, 15]. H1 receptors are involved in appetite regulation in the hypothalamus. Pure H1 blockers increase appetite and are associated with overweight/obesity [16]. Another obvious pharmacological action that might be responsible for weight gain is action on several serotonin (5-HT) receptors, particularly 5HT2c which is blocked by many second generation and several first generation antipsychotics. 5HT2c receptors are involved in appetite regulation [14, 17]. Lorcaserin, a 5HT2c agonist, was recently approved by the FDA as a weight loss agent. Blockade of H1 or 5-HT receptors, however, does not explain why a medication like haloperidol, an almost pure dopamine-2 (D2) blocker, would cause clinically significant weight gain [18, 19]. Weight gain associated with haloperidol is more pronounced for medication naïve first episode samples, where it has been shown to produce on average 7 kg weight gain over the course of a year [19, 20]. Most first episode patients are young, healthy, and have similar cardio-metabolic risk when they enter care to their non-SMI peers in the general population [3]. Their cardio-metabolic risk doubles within the first year of entry into psychiatric care [21].

D2 receptors do not appear to be directly involved in energy metabolism, at least in the appetite regulation component. On the other hand, the dopamine system is an integral part of the human reward system, and D2 receptors are particularly involved in food reward [22]. It can be said that food is a prime substrate for the human reward system. Endorphin release starts at chewing and is particularly pronounced for high sugar, high fat “palatable” foods [23]. These are efficient calories that are easily storable for lean times. Both animals and humans decrease their preference for palatable foods when central opioid receptors are blocked by an opioid receptor blocker [24, 25]. D2 receptors appear to be necessary for endorphin action for food reward [22]. Obese people have been shown to have down-regulated D2 action, and certain D2 receptor alleles, which result in decreased sensitivity of D2 receptors, have been reported to be associated with obesity [26-28]. D2 blockade in animals, when given in doses that simulate human clinical use, increases free food intake, which is reversed by opioid blockers, although opposite animal data exist as well [29]. D2 blockade appears to have an effect similar to reward dilution [30]. Because D2 blockade at various levels is the common property of all antipsychotics in clinical use, one simple explanation is that antipsychotics cause a curbing of the food reward, which in turn might cause patients to eat richer foods more frequently in order to reach similar levels of food reward. Increased circulating endogenous opioids shown to exist in obese females on antipsychotic medications provide partial support to this hypothesis [31]. If this is the case, D2 blockade may be partially responsible for the antipsychotic-induced weight gain. Perhaps, if the opioidergic reward is completely blocked, the compensatory reward eating will stop. Opioid receptor blockers, such as naltrexone, have been studied as weight loss agents and have not been shown to be consistently effective by themselves; however, they may be able to counteract the part of antipsychotic-induced weight gain that might be caused by D2 blockade. A recent study of add-on naltrexone treatment for subjects using olanzapine reported no significant change in weight, however a decrease of fat mass was reported [32].

Based on the above rationale, as a proof of concept, we conducted a double blind, randomized, placebo-controlled trial of the general opioid receptor blocker, naltrexone, as an add-on agent for continuing antipsychotic-induced weight gain among patients with schizophrenia. A low-dose strategy was employed to minimize side effects because higher doses did not produce any additional benefit in other populations [33]. Based on previous studies, we only recruited women to this pilot trial in order to maximize the signal [34]. We hypothesized that naltrexone would be able to stop the antipsychotic-induced weight gain, while subjects who receive placebo would continue the steady increase in their weight or show no effect.

Methods

Twenty-four overweight women between the ages of 18-70 who met DSM-IV criteria for schizophrenia or schizoaffective disorder, based on SCID, were recruited. Subjects were defined as overweight if they had a BMI greater than or equal to 27 kg/m² and weight gain in the past year above 2% of previous year's body weight. Subjects were required to be on a stable dose of antipsychotic medication and deemed to be symptomatically stable by the clinical staff in the previous two months. All subjects gave a written informed consent to participate and the Yale HIC approved the protocol.

Subjects were excluded if they 1) Met criteria for current alcohol or other substance dependence, opioid use for any reason, or positive urine drug screen for opiates; 2) Had a history of dementia, mental retardation, or other neurological disorder that may interfere with study ratings; 3) Were not capable of giving informed consent for participation in the this study; 4) Ongoing pregnancy; 5) Known sensitivity to naltrexone; 6) A medical disorder known to cause obesity; 7) Use of sibutramine, topiramate, amphetamines, or over-the-counter weight remedies; or 8) Impaired liver function.

Study design

This was an eight week randomized, double-blind placebo-controlled, parallel, fixed-dose clinical study. Subjects who met inclusion criteria participated in a screening visit where blood and urine were taken and weight and BMI were measured. If laboratory results were within normal limits, the subject continued to a baseline visit where they were randomized to placebo or naltrexone 25 mg/day for eight weeks. Weight was measured with shoes off to the nearest 0.1 kg and height was measured to the nearest 0.1 cm to calculate BMI. At each visit, weight and blood pressure were obtained and subjects were asked about side effects and medication compliance. Questionnaires, interviews, and laboratory testing were performed at baseline, week 4, and week 8. No other behavioral or diet intervention was provided.

Study medicines were prepared by CMHC research pharmacy. Active and placebo capsules were identical. CMHC research pharmacy used a computerized randomization procedure to which investigators and subjects were blind. Compliance is monitored through pill counts.

Blood sampling and Analysis

All blood sampling was done via an indwelling catheter. Plasma glucose concentration was analyzed by the glucose oxidase method (Yellow Springs Instruments, Ohio)^[35]. Plasma immunoreactive insulin concentration was determined with a double antibody radioimmunoassay (Diagnostic, Webster, TX)^[36]. Serum cholesterol (Total-C, HDL-C) and Triglycerides (TG) were determined by standard enzymatic procedures (Sigma, St. Louis, MO). Assays of HbA1c were performed using an DCA Vantage analyzer (Siemens, Germany)^[37].

Interviews and questionnaires

The Positive and Negative Syndrome Scale (PANSS) was utilized to demonstrate that the intervention did not cause any worsening of schizophrenia symptoms^[38]. *Three Factor Eating Questionnaire (TFEQ)*^[39], also known as the Eating Inventory is a measure of eating behaviors with three factors: dietary (cognitive) restraint, disinhibition, and hunger. The TFEQ is a frequently used measure in obesity trials and has clinical utility to assess changes during treatment as well as treatment outcomes^[40]. *The Questionnaire on Craving for Sweet or Rich Foods (QCSRF)* is a two factor, nine item scale assessing the presence of cravings for rich and sweet foods and has been found to have good psychometric properties^[41]. The abbreviated *Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18)* is a brief, self administered questionnaire that was used to monitor quality of life outcomes^[42].

Statistical analysis

Analyses were performed with a modified intent-to-treat principle where every randomized participant who received at least one study pill was analyzed in the group to which they were randomized. Descriptive statistics were calculated for all participants at baseline to compare naltrexone and placebo participants using analysis of variance (ANOVA) for normally distributed covariates and chi-square tests for categorical covariates. Clinically relevant group differences were assessed using covariate adjustment in supportive analyses. All analyses were performed using SPSS, version 17.0 for Windows (SPSS, Chicago, IL).

Results

Participant characteristics

Twenty-four women completed the initial screening and were randomized. Three participants (NTX=2, PLA=1) dropped out after randomization due to change of mind, leaving 21 (NTX=10, PLA=11) participants who started the intervention. All 21 subjects completed the study and comprise the evaluable sample. Table 1 presents the baseline characteristics of the sample. Two groups had similar demographics with no statistical difference. However, significantly more patients in the NTX arm had diabetes (6 vs. 1, $\chi^2=5.79$, $p=.016$), thus we performed additional analyses co-varying for diabetes.

Laboratory and anthropometric values

After eight weeks, participants randomly assigned to NTX had significant weight loss (-3.40kg , $\text{CI}=-5.16, -1.65$, $F=14.79$, $p=.001$) compared to weight gain in those assigned to PLA ($+1.37\text{kg}$, $\text{CI}=-.30, 3.03$), with diabetic status entered as a covariate. Subjects assigned to NTX had a significant reduction in BMI (-1.37 , $\text{CI}=-2.054, -0.68$, $F=15.86$, $p=.001$) vs. placebo ($+0.57$, $\text{CI}=-0.79, -1.22$) after the intervention. On post-hoc analysis weight change remained significantly different between the two groups, even when the analysis was not co-varied by diabetes (-2.45kg $\text{CI}=-4.86, -0.04$ vs. $+0.47\text{kg}$ $\text{CI}=-1.76, +2.70$; $U=27.00$, $p=0.049$). However, on average, only the non-diabetic subjects assigned to naltrexone lost weight (-4.98kg , $\text{CI}=-8.74, -1.22$), which was significant compared to baseline (Fig 1). Changes in BMI showed a similar pattern. Waist circumference on average was reduced by 3cm in the NTX arm and increased by 1cm in the placebo arm. However, this was not statistically significant between groups.

After eight weeks, there were no significant differences in metabolic laboratory parameters from baseline or between groups (Table 2).

QCSRF, TFEQ, PANSS, and Q-LES-Q 18

There were no differences in craving or reinforcement of sweet and rich foods at baseline. Between group analysis of change over 8 weeks did not show any statistical difference. In post-hoc analyses of the QCSRF subscales, NTX but not placebo resulted in a significant reduction in the craving of sweet and rich foods (-3.10 ± 3.92 vs. 0 ± 4.31 , $z=-2.25$, $p=.024$). Change in reinforcement was not different from baseline for either group after the intervention. There were no significant differences between the groups at any time point in

TFEQ cognitive restraint, disinhibition, and susceptibility to hunger subscales. Post-hoc analyses of change were not significant.

There were no differences in psychiatric symptoms or quality of life at baseline or in change over the 8-weeks of treatment.

Discussion

This pilot study demonstrated that naltrexone produced weight loss in a group of female schizophrenia patients who were acutely gaining weight while on antipsychotics. The effect was only seen in patients not currently diagnosed with diabetes mellitus. The medication did not produce any adverse change in psychiatric symptomatology and was well tolerated. All subjects who took at least one dose of study medication completed the study.

While there was significant weight loss in the active naltrexone group, this was not associated with corresponding change in metabolic parameters such as blood glucose and lipids. We might not have the power to observe this change. Also, improvement in metabolic parameters might require longer follow-up.

The mechanism of weight change seemed to be explained by decreased craving for sweet and rich foods. This is compatible with the working hypothesis that has driven this study; individuals on antipsychotic medications experience a reward dilution and eat more food to achieve the same reward. No other part of their eating behavior seemed to be changed. While it is not possible to exclude other mechanisms of weight loss with naltrexone, it is helpful to note that naltrexone alone does not produce appreciable weight loss in obese/overweight individuals who are not on antipsychotic medications^[43]. Also it is interesting to note that the partially negative study by Taveira et al recruited only subjects on olanzapine, an antipsychotic with relatively low D2 and very strong H1 blockade^[32]. This may indirectly support the working hypothesis of this paper, that naltrexone might counteract the D2 blockade-related portion of antipsychotic induced weight gain. On the other hand, Tavera et al showed a decrease in fat mass, and since both groups lost weight, presumably due to nutritional counseling provided, it might be hard to discern differences in naltrexone and placebo groups^[32]. Clearly studies with larger sample sizes are necessary.

At this point it is hard to explain why subjects who have already developed diabetes mellitus did not respond to naltrexone, however it is important to note that there was only one diabetic subject in the placebo arm. To our knowledge neither opioid receptors nor dopaminergic receptors are well studied in diabetic individuals in relation to food intake. This area clearly requires more study.

This study has some shortcomings. Due to the pilot nature of the study, the sample size was small, partly offset by large effect size. Another limitation is that we only recruited women. While women seem to suffer more from antipsychotic-induced weight gain, most people who receive antipsychotics for the treatment of schizophrenia are male. We also did not stratify the study randomization based on diabetes status; thus, we had to control for an uneven distribution statistically. Also, due to the sample size, we were unable to look at the effect of antipsychotic class on outcome in this sample. Finally, the naltrexone dose used

blocks about 70% of mu receptors, but may not block all delta and kappa receptors in the brain [44, 45]. It is not clear if a higher dose, such as that used in alcoholism, 50 mg per day, would have provided further benefit. We have recently started a larger NIH funded study to address all the weaknesses of the current study.

There is a need for interventions to address antipsychotic-induced weight gain to prevent morbidity and early mortality in the vulnerable population who have to use these drugs. We have hypothesized that antipsychotic weight gain is partly due to D2 receptor blockade induced dilution of food reward causing compensatory overeating. As a proof the concept we have conducted a randomized, double-blind, placebo-controlled study of naltrexone to block the food reward thus rendering compensatory overeating useless to achieve the same level of food reward. Naltrexone, as predicted, produced weight loss for a group of patients with schizophrenia who were acutely gaining weight, whereas subjects randomized to placebo continued to gain weight. However, the effect was observed only in patients who did not have diabetes. The results provide partial support for our working hypothesis. A larger study which addresses the weaknesses of this pilot study is currently under way [46].

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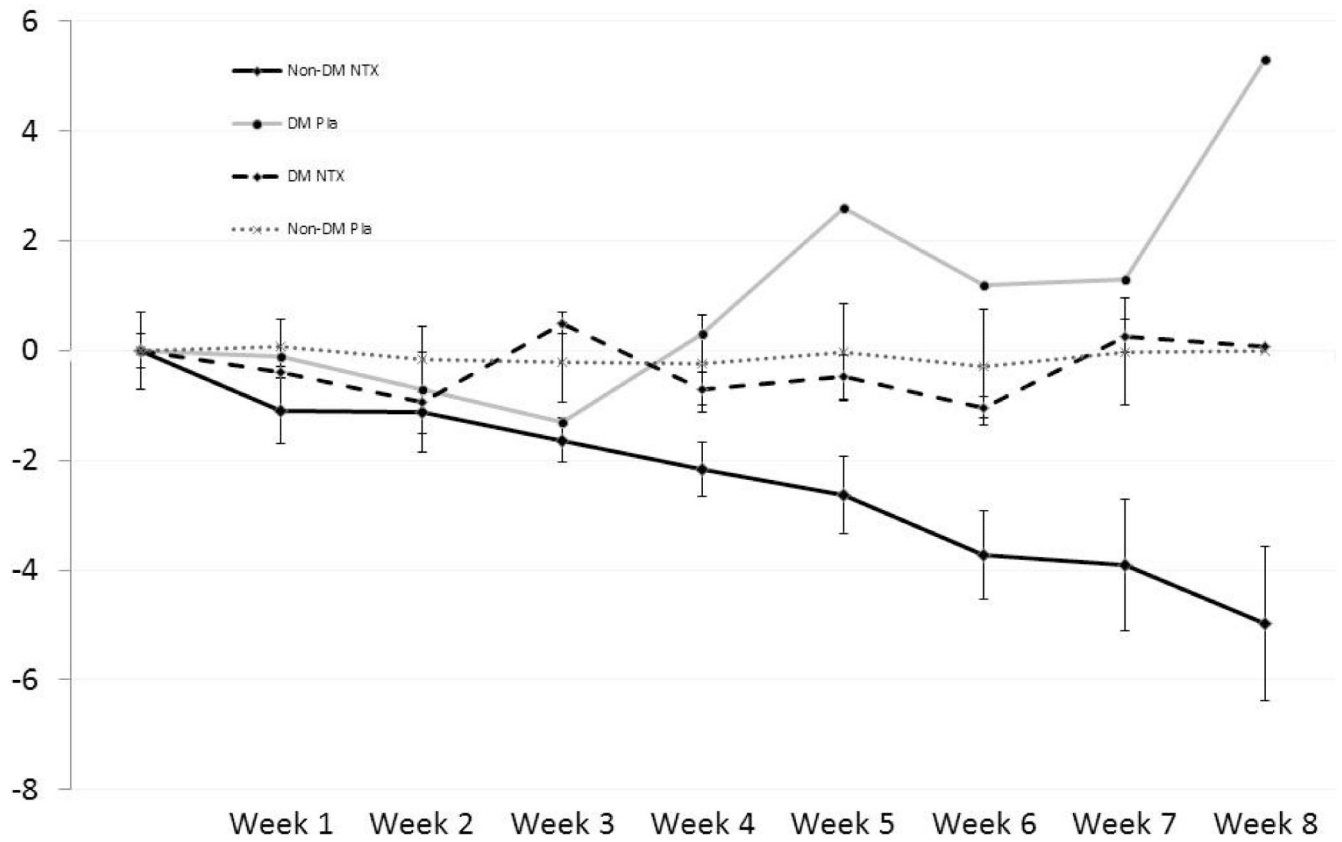


Figure 1. Weight Change (Mean kg \pm SE) for Diabetic (DM) and Non-Diabetic (Non-DM) subjects on naltrexone (NTX) and Placebo (Pla)

Table 1

Baseline Characteristics of The Sample

	Naltrexone (n=11)	Placebo (n=12)
Age (years)	50.0 ± 9.6	41.4 ± 11.6
Weight (Kg)	116.8 ± 27.8	102.0 ± 27.1
Diagnosis	7- Schizophrenia 4- Schizoaffective	5- Schizophrenia 7- Schizoaffective
Atypical antipsychotic	7	8
PANSS Total Score	64.7± 17.2	56.0± 16.7
Diabetes	6	1
Race	4- White 7- African American 0- Hispanic	7- White 4- African American 1- Hispanic
Education (years)	13.4 ± 4.1	13.7 ± 3.9

Table 2
Baseline vs. Week 8 Laboratory Values Between Placebo (Pla) and Naltrexone (NTX) groups

	Pla		NTX	
	week 0	week 8	week 0	week 8
Weight	104.66 (26.8)	105.14 (28.1)*	110.51 (19.2)	108.06 (17.7)*
BMI	40.14 (12.0)	40.32 (12.5)**	41.95 (8.4)	41.0 (7.7)**
Glucose (mg/dl)	93.82 (7.9)	94.11 (7.5)	113.40 (28.2)	129.22 (45.2)
Insulin (uIU/ml)	13.84 (10.8)	12.36 (4.4)	26.42 (40.0)	35.51 (42.0)
Triglycerides (mg/dl)	137.80 (48.1)	121.44 (57.1)	117.40 (49.4)	121.22 (49.7)
Total Cholesterol (mg/dl)	193.09 (28.1)	189.78 (41.2)	158.0 (32.2)	175.33 (41.3)
HDL Cholesterol (mg/dl)	48.73 (10.1)	53.56 (10.1)	47.5 (5.5)	49.22 (8.0)
LDL Cholesterol (mg/dl)	123.18 (41.3)	111.22 (33.5)	86.80 (26.2)	104.11 (39.9)
Hemoglobin A1c (%)	5.72 (0.2)	5.71 (0.2)	6.41 (0.8)	6.65 (1.1)

* (p = 0.049)

** (p = 0.041) All others not significant between groups