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Course of weight change during naltrexone vs. methadone maintenance for opioid-dependent patients

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Abstract

Background—Mu opiate receptor agonism has been associated with weight gain, while mu antagonists have been associated with weight neutrality, or even weight loss.

Aim—This study examined the course of weight changes in opiate-dependent patients over the first six months of treatment in methadone (agonist) versus naltrexone (antagonist) maintenance.

Design—A retrospective chart review was conducted on 36 opiate-dependent patients maintained on methadone (n=16) or naltrexone (n=20).

Outcome measures and analyses—The primary outcome measure was change in body weight from baseline to 3 months and 6 months into treatment. ANOVA was used to compare mean weights between the methadone- and naltrexone-maintained patients. Secondarily, mean percent weight changes from baseline to 3 months, and baseline to 6 months into treatment were compared using Student's T-test.

Results—Weight at baseline, 3 months and 6 months into treatment did not differ significantly between the two groups, and neither did percent weight change from baseline to 3 months, and baseline to 6 months. At 3 months, n=16 methadone patients had a mean weight increase of 1.86% (SD 7.22%) compared to n=20 BNT patients with an increase of 4.63% (SD 6.49%),. At 6 months, n=16 methadone patients had a mean weight increase compared to baseline of 3.67% (SD 9.52%) compared to n=20 BNT patients, who demonstrated a mean increase of 6.69% (SD 7.56%). No association was found between baseline weight, defined as "low" or "high" relative to group medians, and percent gain within and between treatment groups.

Conclusion—This study did not detect a statistically different course of weight gain between methadone and naltrexone maintenance treatment for opiate-dependent patients.

Keywords

methadone; naltrexone; weight; opiate dependence

INTRODUCTION

Opiate addiction is a significant current public health problem in the U. S. that negatively affects patients' lives in medical, social, occupational and legal domains. It is estimated that 1 million Americans meet criteria for opiate addiction (1). Medically supervised treatment of these individuals with the opiate agonist methadone results in considerable reductions in

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morbidity and mortality (2). However, methadone-maintained patients have demonstrated significant weight gain while in treatment (3, 4). Preclinical trials have also found that chronic exposure to mu opiate agonism has been associated with weight gain (5–7). Naltrexone, a mu opiate antagonist, is an alternative treatment for less severely dependent opioid addicts, and has also demonstrated effectiveness in this population (8). Furthermore, mu antagonists have been associated with weight loss in preclinical (9) and clinical trials (5). Yet several clinical trials of naltrexone have failed to demonstrate either significant weight loss or significant weight gain (10–13). While the aforementioned studies were conducted in either normal or obese subjects, to date there are no published clinical data on the effects of naltrexone maintenance treatment on the weight of opioid-dependent subjects.

Weight gain is a significant health problem in the United States. According to the National Health and Nutrition Examination Survey (NAHANES) 2005–2006, 34.3% of US citizens 20 years old or older are considered obese, with body mass index (BMI) of 30 or more (14). Weight gain is a significant problem for opiate-dependent patients. An autopsy study of Swedish intravenous drug users found that 36% of heroin users were overweight (BMI>25), 43.1% of methadone treated patients were overweight, and that most of the obese (BMI 30.0 to 39.9) IV drugs users (27.5%) were methadone maintained patients (15). Being overweight or obese is associated with increased risk for developing coronary artery disease, insulin-resistant diabetes mellitus, osteoarthritis, various cancers (16). Given that drug abusers already face many health risks, these study findings highlight the importance of addressing weight management during the course of both agonist and antagonist maintenance for opioid dependence.

The aim of this study was to examine the possible association between naltrexone treatment and weight changes in patients being treated for opioid dependence. The hypothesis was that naltrexone maintenance treatment would lead to significantly less weight gain than methadone maintenance in opioid-dependent patients. A chart review was conducted comparing total weight during the first 6 months of treatment in methadone-maintained opioid-dependent patients (n=16) and naltrexone-maintained opioid-dependent patients (n=20). Baseline, 3-month, and 6-month data on weight status were obtained for comparison.

METHODS

Design and Sample

A chart review was conducted on a total of 36 opiate-dependent former patients: 16 methadone-treated patients from the Addiction Institute of New York's Opioid Treatment Program, and 20 naltrexone-treated patients from the Behavioral Naltrexone Therapy (BNT) trial conducted at Columbia University's Substance Abuse and Treatment Service (STARS) outpatient research clinic. Patients treated at the Addiction Institute's Opioid Treatment Program received individual and/or group supportive counseling focused on relapse prevention and treatment compliance. Opioid-dependent participants enrolled in the BNT trial were inducted onto oral naltrexone for a 6-month maintenance course. Patients received twice-weekly BNT, a manual-based therapy incorporating elements of Motivational Interviewing, cognitive behavioral counseling, voucher incentives, and Network Therapy (17).

Charts were chosen for review among those which met the following criteria for patients: 1) were no longer attending and had been formally discharged from their treatment site, 2) had been in treatment for at least 6 months, 3) provided baseline, 3 month- and 6-month weights. While both facilities afford their patients regular clinical follow-up care, neither facility offers a treatment program or therapy specifically aimed at weight loss, diet or nutrition.

The research design and data collection plan were approved by the Institutional Review Boards of both New York State Psychiatric Institute and St. Luke's-Roosevelt Hospital. Waiver of consent for study participation was obtained from both IRBs, as the patients had been formally discharged, and were sufficiently de-identified. Charts reviewed from the Addiction Institute Opiate Clinic included patients treated between the years 1998 and 2009. Charts reviewed from STARS BNT clinical research program included patients treated in 2002 to 2007.

Facilities and Procedures

Addiction Institute—The Addiction Institute of New York's Opioid Treatment Program provides outpatient methadone treatment for up to 300 patients. The Opioid Treatment Program, located at Roosevelt Hospital in New York City, is a comprehensive treatment program for individuals with an opioid addiction. In addition to the administration of methadone or buprenorphine, a full range of clinical services are offered, including group and individual counseling, psychiatric services, medical and medication management, and vocational counseling for individuals with an opioid addiction.

STARS—The Substance Treatment and Research Service of Columbia University (STARS) is an outpatient research site. STARS consists of two outpatient locations where treatment is provided to participants enrolled in NIDA-funded trials for substance abuse or dependence. At any given time, approximately 4–7 trials are recruiting participants. Trials focus on state-of-the-art pharmacological and manual-based psychotherapeutic treatments of alcohol and other substances of abuse. Data for this study were collected from treatment-seeking opiate-dependent patients who were accepted into the BNT trial, then detoxified and inducted onto oral naltrexone and possibly intramusclular depot naltrexone as well.

Statistical Analyses

Chi-square analyses were used to compare proportional variables pertaining to the baseline demographics of the methadone-treated and naltrexone-treated samples. The Student's T-test was used to compare parametric baseline means between the two samples. ANOVA was used to detect significant differences at baseline and follow-up regarding weight between the methadone and naltrexone groups. Significance level was considered at $\alpha=0.05$, and all tests were 2-sided.

RESULTS

Baseline demographic data pertaining to the methadone-treated and naltrexone-treated cohorts are summarized in Table 1. Both groups were comprised predominantly of white or Hispanic men, who were domiciled, and had a high school education. When using Chi-square analyses to detect differences in proportions, only employment status ($p=0.05$) reached significance, revealing that the methadone-treated patients were less likely to be employed than the naltrexone-treated patients. There were no significant group differences regarding baseline amount of heroin or percentage using intravenous heroin, as well as baseline alcohol, cigarette, cocaine, or marijuana use.

Baseline diagnoses of diabetes, hypertension, mood disorder and psychotic disorder were explored, as all can be associated with weight gain. The two groups did not differ significantly with respect to these diagnoses. While diabetes, hypertension, and psychotic disorders are present in a small minority of the patients, mood disorders (major depressive disorder, dysthymia, and bipolar disorder) were more frequently diagnosed in the naltrexone-treated patients, but this difference did not reach statistical significance ($p=0.12$).

While the majority of patients in both groups were seeking treatment for heroin dependence, it should be noted that 4 of 16 methadone patients (25%) were using oral or IV opioids other than heroin at baseline (one was using an oxycodone product, two were using methadone purchased from the street, and two had transferred from other methadone programs). Of the naltrexone-treated patients, 2 of 20 (10%) were using hydrocodone products rather than heroin. However, these differences were not significant ($\chi^2 = 1.44$, $p>.05$).

Figure 1 demonstrates that weight at baseline, 3 months and 6 months into treatment did not differ significantly between the two groups, $F_{(1, 34)}=0.59$, $p=0.45$. A weight-by-treatment interaction was calculated using Huynh-Feldt correction due to lack of sphericity within the data. There was no significant interaction between treatment and weight, $F_{(1.37, 46.50)} = 0.79$, $p=41$. Percent weight change from baseline to 3 months, and baseline to 6 months, did not differ between the two groups. At 3 months, n=16 methadone patients had a mean weight increase of 1.86% (SD 7.22%) compared to n=20 BNT patients with an increase of 4.63% (SD 6.49%); $t_{(30.59)}=-1.19$, $p=0.24$. At 6 months, n=16 methadone patients had a mean weight increase compared to baseline of 3.67% (SD 9.52%) compared to n=20 BNT patients, who demonstrated a mean increase of 6.69% (SD 7.56%); $t_{(28.27)}=-1.03$, $p=0.31$.

To assess whether baseline weight would affect weight gain outcomes within and between treatment groups, patients were subdivided into “low weight” and “high weight” categories depending on whether their baseline weight measured below or above their treatment group’s median weight respectively. The median weight for the methadone-treated group was 164 lbs (74.4kg), and the naltrexone-treated group’s median weight was 167 lbs (75.7kg). The percentage of weight gained from baseline to 3 months, and from baseline to 6 months, did not differ between “low weight” and “high weight” patients within treatment groups. Furthermore, within weight categories, the percentage of weight gained from baseline to 3 months, and baseline to 6 months, did not differ between treatments.

Given the small differences in weight change over 6 months that was found between these treatment groups, a power analysis was undertaken to determine the number of patients that would be needed per group to observe a valid significant difference. Using the means and standard deviations between both groups at 6 months, such a study would have to include 232 patients per group to achieve adequate power (0.80) to detect these differences.

DISCUSSION

Both the naltrexone-maintained patients and the methadone-maintained patients were statistically similar across most baseline demographic, medical, psychiatric, and substance use items. At baseline, methadone patients were significantly less likely to be employed than the naltrexone patients. Furthermore, our hypothesis that there would be a significant difference in weight gain, with the methadone-maintained group demonstrating greater weight gain, was not supported. Notably, both groups gained approximately 10 pounds (add kg) of mean weight over 6 months of treatment.

This study has several limitations. The methadone maintenance treatment cohort used as a comparison, while statistically similar to the naltrexone-treated group regarding many variables, was comprised of an independent group of patients not originally recruited for research. Furthermore, one cannot account for differences in the facilities’ staff and procedures which may affect outcomes. Future studies might recruit patients clinically eligible for either agonist or antagonist maintenance and randomly assign individuals from the same recruitment cohort to either naltrexone or methadone maintenance. Body mass index (BMI) could not be measured in many cases due to absence of recorded height in the chart. In order to maximize data for analyses, weight in pounds and percent weight change

from baseline were used. The present analyses may have benefited from larger sample sizes with fewer missing data points.

There are several additional comparisons that can be made between methadone- and naltrexone-treated opioid dependent cohorts in future studies. The current study could have benefited by comparing other secondary outcomes regarding weight gain in addition such as changes in blood pressure, hemoglobin A1c, cholesterol and triglycerides, as well as abdominal girth. We considered examining data on blood pressure as a secondary outcome to weight gain; however, too many data points were missing from the methadone-maintenance group to allow for adequate statistical comparison. Literature suggests that opioid dependence is associated with derangements in glycemic control similar to that of non-insulin dependent diabetes mellitus (18–20). Furthermore, naltrexone administration has been associated with decreased hemoglobin A1c in obese human subjects (21). The clinical literature associating opiate antagonists with weight loss is somewhat tenuous, with several clinical trials failing to observe significant weight loss (22–25). However, there is stronger evidence in the literature pertaining to changes in dietary preference. Preclinical (26–34) and clinical (35–38) data suggest that exposure to mu-opiate agonists is associated with a predilection for fatty and sweet (“palatable”) foods. Additionally, exposure to mu-opiate antagonists such as naltrexone is associated with a reduction in intake of fatty and sweet foods without necessarily leading to weight loss in both preclinical (27–30, 39–40) and clinical (41–43) trials. Further studies in this area may benefit from examining changes in dietary habits among opioid-dependent patients initiating methadone maintenance treatment versus naltrexone maintenance treatment. There is already a literature describing methadone-maintained patients’ shift in dietary preference toward sweet and fatty foods and away from more nutritious options (35, 44). In one study, gender influenced weight loss in obese subjects randomized to daily placebo, 50mg or 100mg of naltrexone. Female subjects lost a mean of 1.7 kg (3.7 lb) by the end of the study, while no effect was found in male subjects (45). The present study included too few female subjects to allow for adequate statistical comparison to control for gender.

Naltrexone maintenance therapy represents a viable alternative treatment to methadone maintenance for opiate dependence, especially for opioid addicts presenting for treatment early in the course of addiction and for those addicted to prescription opioids. Preclinical and clinical data suggest that maintenance on mu opiate agonists such as methadone is associated with weight gain, possibly due to changes in diet with increased preference for sweet and fatty foods. Preclinical and clinical data (in non-opiate-dependent human subjects) suggest that antagonist maintenance is typically a weight-neutral, or even weight-diminishing, treatment condition. The present study could find no significant difference in mean weight change among opiate dependent patients treated with either methadone or naltrexone maintenance therapy without any specific dietary counseling.

The negative results of this study may be explained by neurobiological and psychosocial factors. In addition to mu opiate receptor activity, agonism of kappa and delta opiate receptors have also been associated with hyperphagia (46–47). Naltrexone is an antagonist at the mu receptor (Ki 0.5nM), the kappa receptor (Ki 0.9nM) and at the delta opiate receptor (Ki 10nM) (48). Perhaps patients undergoing naltrexone maintenance treatment experience comparable weight gain to their methadone maintained counterparts because they receive hedonic effects from palatable foods through the kappa and delta opiate receptor pathways due to differential receptor blockade. Studies exploring the effects of naltrexone on weight change have used non-opiate-dependent lean or obese subjects (5, 10–13). It has been demonstrated that opiate-dependent individuals generally maintain poor diets, and often lead peripatetic lifestyles, constantly on the move from “fix” to “fix” (49). Perhaps stabilization in a structured clinical setting leads to a diversion of resources to food rather than drugs, and

a diminution of “exercise” spent wandering for drugs and an increase in sedentary activities. These psychosocial changes may have a greater effect on weight changes in opiate dependent patients than the differential effect of mu agonists or antagonists on the central nervous system.

Opiate dependent patients in treatment may have few supportive resources and coping skills. “Fast food” and sweets may be used for comfort during abstinence, and may also be used for primary subsistence. High-calorie foods tend to be less expensive to healthier food options. Treatment providers focus on opiate addicts’ path toward, and maintenance of, abstinence. Emphasis should also be placed on this vulnerable population’s primary medical care, including maintenance of proper weight.

Lastly, potential weight gain associated with chronic use of mu-opiates has special implications for pain management providers, since chronic opioid therapy is an acceptable strategy for management of noncancer pain (50). Providers should be wary when treating pain secondary to both osteoarthritis often associated with obesity (51) and peripheral neuropathy associated with Type-2 diabetes (52). Potential weight gain from chronic mu-opiate administration to treat these pain conditions may eventually compound the severity of the pain, necessitating a cycle of escalating doses of opiate medication. This is particularly dangerous for obese patients, who may be more susceptible to respiratory suppression from mu-agonists as they are already prone to developing sleep apnea (53).

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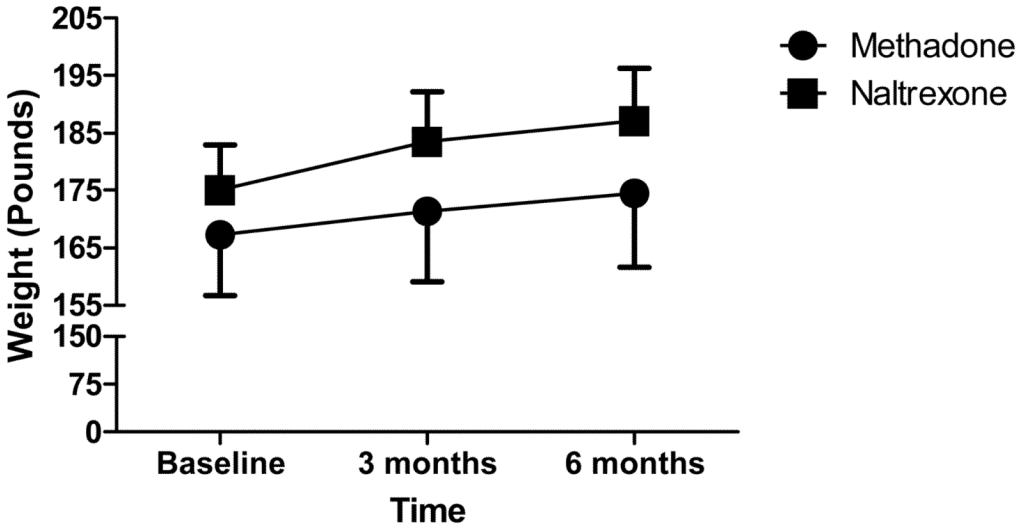

Figure 1.
Weight Across 6 Months of Opioid Maintenance
Note: Error bars depict the standard error of the mean.

Table 1

Baseline demographics and drug use

	Naltrexone n=20	Methadone n=16
Age in years (SD)	37.45 (9.25)	41.18 (9.49)
Male n(%)	16(80.0)	11(68.7)
Race n(%)		
White	10 (50.0)	9 (56.2)
Hispanic	5 (25.0)	5 (31.3)
African-American	4 (20.0)	2 (12.5)
Other	1 (5.0)	0 (0.0)
Employed* n (%)	10 (50.0)	3 (18.8)
Domiciled n (%)	20(100)	16(100)
Highest level of education n (%)		
grade school	6 (30.0)	3 (18.8)
high school	5 (25.0)	7 (43.7)
at least some college	9 (45.0)	6 (37.5)
Diabetes n (%)		
no diagnosis	19 (95.0)	16 (100.0)
Diagnosed, untreated	0 (0.0)	0 (0.0)
Diagnosed, treated	1 (5.0)	0 (0.0)
Hypertension n (%)		
no diagnosis	18 (90.0)	13 (81.2)
diagnosed, untreated	0 (0.0)	2 (12.5)
diagnosed, treated	2 (10.0)	1 (6.3)
Mood disorder n (%)		
no diagnosis	11 (55.0)	11 (68.8)
diagnosed, untreated	8 (40.0)	2 (12.5)
diagnosed, treated	1 (5.0)	3 (18.7)
Psychotic disorder n(%)		
no diagnosis	19 (95.0)	15 (93.7)
diagnosed, untreated	1 (5.0)	0 (0.0)
diagnosed, treated	0 (0.0)	1 (6.3)
Daily heroin bags^ (SD)	6.03 (3.59)	8.18 (5.76)
IV heroin ^ n(%)	9(45.0)	11(68.8)
Daily drinks of alcohol (SD)	0.50 (1.00)	0.56 (1.63)
Daily packs cigarettes(SD)	0.68 (0.44)	0.57 (0.51)
Daily $'s on cocaine (SD)	3.80 (10.82)	2.06 (7.48)
Daily marijuana joints (SD)	0.42 (0.99)	.13 (0.34)

* significance of difference between groups p<=0.5

^n=11 methadone and n=18 naltrexone patients used heroin at baseline