Enhancing Quality and Utilization in Psychosis (EQUIP)

Wellness Program for Patients with Severe Mental Illness MANUAL

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Last Revised 6/04

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Executive Summary

The Wellness Program described in this manual was conceived as a direct result of the EQUIP research project (PI: Alexander Young, MD). The EQUIP project ("Evaluating Quality and Utilization in Psychosis") was funded by the Department of Veterans Affairs Health Services Research and Development Service (VA HSR&D) to develop, implement and evaluate a collaborative care model for schizophrenia. EQUIP has been implemented at the Greater Los Angeles Healthcare System and the Long Beach Healthcare System in close collaboration with the VA Desert Pacific Mental Illness Research, Education and Clinical Center (MIRECC; www.mirecc.org).

The EQUIP study

The collaborative care model which is being tested in EQUIP is designed to improve treatment though assertive management of care, involvement and education of caregivers, and feedback of clinical information to clinicians. The model extends proven illness self-management approaches to family members and other caregivers, since these individuals are a critical component of successful treatment for schizophrenia. It creates a collaborative environment within which psychiatrists are responsible for guideline-concordant prescribing, and case managers are responsible for ensuring access to needed treatment services. By implementing a collaborative care model, the project targets key problems in care identified in previous studies of treatment quality in schizophrenia (failure to coordinate and monitor care for individual patients, lack of attention to illness self-management skills, and a minimal availability of clinical information).

By the study mid-point, EQUIP revealed that obesity (a common side-effect of newer antipsychotic medications) was a serious problem. At Long Beach, the mean BMI was 28.7 and 45% of patients met criteria for obesity. At GLA, the mean BMI was 27.4 and 35% of patients were obese. Although local managers, mental health clinicians, and nutritionists believed strongly in the need for targeted services for obesity, there were no treatment resources available at these sites. As a result, the EQUIP team developed this standardized protocol for wellness services specifically designed for patients with severe mental illness (SMI). Wellness program sessions rely heavily on material from two sections of the Solutions for Wellness Group Program [1]: (1) Fitness and Exercise and (2) Nutrition, Wellness, and Living a Healthy Lifestyle.

Key Individuals in the Wellness Program

There are three key individuals who are the integral to the success of this Wellness Program: the patient's treating clinicians (psychiatrist and case manager), the clinical staff running the wellness groups, and the nutritionist. Psychiatrists should be alerted to address weight problems in their medication treatment and to utilize guideline-concordant approaches to switch to a medication with less weight gain liability or add medications that can reduce weight gain. A treatment guideline synopsis used in EQUIP and a full literature review which immediately follow this Executive Summary can both be of help in deciding the best medication treatment regime to address weight issues. Case managers can assist in lifestyle changes and ongoing support and encouragement. The clinical staff running the groups provides psychoeducation and social support in a group format. Nutritionists, trained to work with this specialized population, can assist in running groups, provide ongoing consultation to clinicians and clinical staff, and provide individualized interventions for particular patients (including food diaries, meal planning, etc.).

Treatment Guideline Synopsis for Weight Gain

Weight gain is the most important side-effect of the second generation antipsychotic medications. Being overweight places an individual at increased risk for diabetes, hyperlipidemia, morbidity and death. Given their high risk for obesity, all patients with schizophrenia should have their weight monitored. It is helpful to monitor Body Mass Index (BMI), which equals an individual's weight in kilograms divided by the square of their height in meters. A BMI calculator is available by clicking on www.nhlbisupport.com/bmi/bmicalc.htm . Normal BMI is between 18.5 and 25, overweight BMI between 25 and 30, and a BMI above 30 indicates obesity. People with a BMI between 19 and 22 live the longest.

Weight gain should be detected early so that action can be taken before the patient is very overweight. Antipsychotic medications differ in the severity with which they cause weight gain. The GREATEST potential for weight gain occurs with clozapine and olanzapine. These cause short-term weight gain that averages about 10 pounds, and long-term weight gain that can be much greater. MODERATE potential for weight gain occurs with risperidone, quetiapine, chlorpromazine and thioridazine. The LEAST potential for weight gain occurs with aripiprazole, ziprasidone, and other first generation antipsychotic medications.

Switching to an antipsychotic medication with less potential for weight gain is the most effective strategy. A number of pharmacologic strategies have been proposed that consist of adding an augmenting medication, such as topiramate or orlistat. This may be helpful in some patients. If a patient is taking a concomitant medication that causes substantial weight gain, such as valproate or paroxetine, one should consider discontinuing it.

A cornerstone of weight management is dietary control and exercise. Overweight patients should receive ongoing counseling regarding control of diet, plus consultation from a nutritionist. Simple approaches, such as low-carbohydrate diets, are likely to be more effective than complex approaches, such as calorie counting. A program for increasing activity and exercise should be strongly considered, with consultation from physical therapy and wellness programs.

References & For More Information:

NIH information: http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/profmats.htm
BMI calculator & tables: http://www.nhlbisupport.com/bmi/bmicalc.htm
General information: http://www.mirecc.org/resources.shtml

Overview of Weight Issues in Patients Treated for Psychosis

Weight Gain Associated with Antipsychotic Medications

There have been several well-documented studies showing a strong correlation between antipsychotic medications and weight gain. A comprehensive comparison of the weight gain experienced by patients while taking various antipsychotic medications was compiled (see Table 1), using a meta analysis of 81 studies that included data on weight change in antipsychotic-treated patients.

Table 1. Mean weight gain at 10 weeks on a standard dose (Random Effects Model) [2]

Medication	Weight (in kg)
Clozapine	4.45
Olanzapine	4.15
Thioridizine	3.19
Chlorpromazine	2.58
Risperidone	2.10
Nonpharmological control	1.33
Haldol	1.08
Fluphenizine	0.43
Ziprasidone	0.04
Molindone	-0.39
Placebo	-0.74

Most of the weight gain appears to occur during the first 6 months of treatment with an antipsychotic medication. However, there is still evidence of some weight gain, which may occur after this time period. Study data comparing approximate, longer-term (1 year) mean weight gain on atypical antipsychotic medications is shown in Table 2. [3, 4].

Table 2. Mean weight gain at one year

Medication	Weight (in kg)
Olanzapine	6.5
Quetiapine	3.0
Risperidone	2.0
Ziprasidone	0.5

Weight gain has been strongly associated with the development of type II diabetes. The prevalence of both obesity and diabetes among patients suffering from schizophrenia is approximately 1.5-2.0 times higher than in the general population [5], although some inpatients studies suggest that the prevalence of diabetes may be nearly 3 times higher than the general population from the same geographical area [6, 7].

Drug-induced hyperglycemia can be caused by insulin resistance, which in turn, may be due to weight gain, or by a direct effect on insulin-sensitive target tissues. Although much of the increase in diabetes in patients with schizophrenia may be due to weight gain, there is evidence that two medications in particular

(Clozapine and Olanzapine), appear to cause higher fasting and postprandial insulin levels than patients treated with first generation antipsychotics, even after adjusting for body weight [6].
In reviewing the available data on the atypical antipsychotic medications, it appears that Clozapine and Olanzapine consistently show an increased risk for diabetes [5, 8-10]. The risk for Risperdal and Quetiapine are less clear, as some studies suggest an increased risk, while others do not [8-10]. Ziprasidone and Aripiprazole has thus far not shown an increased risk for diabetes [5].

In reviewing the available information regarding lipid abnormalities associated with antipsychotic medications, these abnormal lipids appear to correlate with the propensity of the medication to cause weight gain. Among the atypical antipsychotic medications, Clozapine and Olanzapine appear to be associated with the greatest increases in total cholesterol and Triglyceride levels, and with the greatest decrease in HDL cholesterol [5]. The information on LDL is more controversial, as some studies appear to show in increase in LDL with these two medications, while others do not [5, 10]. Risperidone and Quetiapine appear to have less negative impact on lipid profiles [5, 10], and Ziprasidone and Aripiprazole appear to not have any significant impact on lipid profiles [5].

As shown in this section, weight gain associated with some atypical antipsychotic medications, can be significant, and may be interrelated with other risks factors for CHD, such as diabetes and abnormal lipid profiles. The most weight gain appears to be associated with Clozapine and Olanzapine, and these medications are also associated (independently), with abnormal glucose metabolism. Patients suffering from obesity, diabetes, hyperlipidemia, or other complications of being overweight (as listed in the next section), or are gaining weight on their current medication(s), should be evaluated very carefully when choosing or changing an antipsychotic medication. First line medications in the above patient population, should be those associated with the least risk for weight gain. As reported earlier, most of the weight gain associated with atypical antipsychotic medications, appears to occur during the first 6 months of use. Therefore, when antipsychotic medications are to be used, weight management interventions should be employed at the onset of antipsychotic therapy.

Medical Consequences of Being Overweight
Higher morbidity is associated with being overweight, and this increase rises as the body mass index (BMI) rises above 20 kg/m^2 [11]. The health risks for obesity include hypertension, diabetes type II, coronary heart disease, congestive heart failure, CVA, gallbladder disease, osteoarthritis, sleep apnea, colon cancer, breast cancer, and endometrial cancer. The specific increase in risk for each of these disease entities will be further explored in this section.

Blood pressure increases progressively with higher BMI values in both men and women. The prevalence of high blood pressure in men with a BMI >30 is 2.1 times higher than in men with a BMI <25 (38.4% vs 18.2%) [11]. The prevalence of hypertension in women with a BMI >30 is 1.9 times higher than in women with a BMI <25 (32.2% vs. 16.5%) [11]. Hypertension is a significant risk factor for the development of cardiovascular disease, with all its associated complications (i.e., coronary heart disease (CHD), cardiovascular accident (CVA), congestive heart failure (CHF)).

The development of diabetes type II, has been associated with weight gain after the age of 18 in both men [12] and women [13]. The relative risk of diabetes increases by approximately 25% for each additional $1kg/m^2$ increase in BMI above 22 kg/m^2 [14].

The risk of CHD and nonfatal myocardial infarction (MI) increase with increasing BMI levels. In the Nurses' Health Study, which controlled for age, smoking, parental history of CHD, menopausal status, and hormonal use, the risks for CHD were twice as high at BMIs between 25-28.9, and three times as high at BMIs at 29 or greater, as compared to BMIs less than 21[15].

The risk of CHF increases with weight in a number of studies, including the Framingham Heart Study [16]. This stems from several possible physiological changes associated with weight gain, including alterations in cardiac structure and function. These changes, such as ventricular dilation and eccentric hypertrophy, can result in both diastolic and systolic dysfunction.

The risk of ischemic, but not hemorrhagic strokes, correlates with increasing BMI. The ischemic stroke risk is 75% higher in women with BMI >27, and 137% higher in women with a BMI >32, as compared with women having a BMI <21 [10, 17].

The risk of gallstones increases in both men and women. For example, in women, the risk of either gallstones or cholecystectomy is as high as 20 per 1,000 women per year with BMIs >40, as compared with 3 per 1,000 women per year with BMIs <24 [18].

The risk of osteoarthritis increases with body weight, and is significantly associated with increased pain in weight-bearing joints. For example, in a study of twin middle-aged women, it was estimated that for each kg of weight gain, the risk of developing osteoarthritis increases by 9-13% [19].

Upper body obesity is a risk factor in the development of sleep apnea, and has been shown to be related to its severity. In particular, large neck girth is highly predictive of sleep apnea. Most people with sleep apnea have BMIs >30 [20]. The medical consequences of sleep apnea include arterial hypoxemia, interrupted sleep, pulmonary hypertension, systemic hypertension, and cardiac arrhythmias.

There appears to be a correlation between obesity and colon, breast, and endometrial cancer. The increased risk of colon cancer is somewhat controversial, and so will not be reported here. In postmenopausal women, there is a direct correlation between obesity and breast cancer. A gain of more than 20 lbs from age 18 to midlife doubles the risk of developing breast cancer [21]. The risk of endometrial cancer is three times higher among women with BMIs >30kg/m^2 as compared with women having BMIs <25 [22].

It is now clear that the medical consequences of being overweight are extensive. Given the severity of these medical complications, more aggressive measures should be employed by health care providers toward the treatment and prevention of weight gain and obesity.

Pharmacologic Approaches which May Assist with Weight Loss

The use of medications for the treatment of obesity are generally recommended only as an adjunct to dietary measures, exercise, and behavioral modifications. Recently published APA practice guidelines on the treatment of patients with schizophrenia, recommend that in patients with a BMI>18.5, "an increase in BMI of 1 BMI unit would suggest a need for intervention by monitoring weight more closely, engaging the patient in a weight management program, using an adjunctive treatment to reduce weight, or changing the antipsychotic medication." [23]. Medications which may assist with weight loss, are recommended under the following circumstances:

1. In those patients with a BMI of > 30kg/m^2, or with a BMI of >27kg/m^2 when combined with medical comorbidities (diabetes, CHD, hyperlipidemia, history of CVA, hypertension (HTN)).

2. Patients who have met the above criteria, and have not lost at least 8-10% of baseline weight after more than 6 months in spite of diet modification with an adequate exercise program [24].

FDA approved medications which assist with weight loss generally fall into two main categories: Those that decrease food intake by suppressing appetite, and those that decrease nutrient absorption. Each category of medications will now be examined in more detail.

Medications which reduce appetite

Most appetite suppressants work by increasing anorexigenic neurotransmitters, such as serotonin, norepinephrine, and dopamine. Medications which increase serotonin only, notably, Fenfluramine and dexfenfluramine, were withdrawn from the market in the United States because of associations with valvular heart disease and pulmonary hypertension.

The most well studied noradrenergic medication used for weight loss to date is phentermine. This medication is approved by the FDA for short-term use only (i.e., less than 12 weeks for the treatment of obesity)[25]. The usual recommended dose of phentermine is 18.75-37.5mg PO QAM. The average amount of weight loss in the general population has been 4-20 lbs (2-10 kg) compared to placebo in the short term (6 months) [25]. The side effects of phentermine include insomnia, dry mouth, constipation, euphoria, palpitations, and hypertension. Unfortunately, phentermine is generally not recommended in patients suffering from schizophrenia, as its dopaminergic effects may worsen psychosis. Phentermine is contraindicated in patients suffering from hypertension, advanced cardiovascular disease, hyperthyroidism, glaucoma, and those having a history of substance abuse. Phentermine should not be used in patients taking MAOIs, guanethidine, tricyclic antidepressants, sibutramine, CNS stimulants, or EtOH [25].

Sibutramine is a medication which inhibits norepinephrine reuptake, serotonin reuptake, and to a lesser extent, dopamine reuptake. It is approved by the FDA for long-term use for weight loss and weight maintenance in conjunction with dietary measures involving caloric restriction. The recommended dose for sibutramine is 5-15mg PO QD. In several studies, patients taking sibutramine while following a reduced calorie diet, lost 5-8 percent of their preintervention weight, as compared with 1-4 percent among patients receiving placebo [26-29]. Sibutramine appeared to help maintain reductions in weight as compared to placebo for at least a year in one study [30]. The side effects of sibutramine can include hypertension and tachycardia, although these appear to be mild. Other side effects include insomnia, headache, constipation, and dry mouth. Sibutramine is contraindicated in patients suffering from uncontrolled hypertension, severe hepatic dysfunction, severe renal impairment, narrow-angle glaucoma, coronary artery disease, arrhythmias, congestive heart failure, history of CVA, and those having a history of substance abuse. Sibutramine should not be used in patients taking MAOIs, SSRIs, centrally active anorexiants, sumatriptan, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, tryptophan, and lithium [25].

Medications that decrease nutrient absorption

Orlistat is a medication which binds to gastrointestinal lipases in the lumen of the small intestine, which prevents hydrolysis of dietary triglycerides into absorbable free fatty acids and monoacylglycerides. It is approved by the FDA for long-term use for weight loss and weight maintenance. Patients taking orlistat will excrete approximately one third of the dietary fat that is ingested, thereby reducing calorie absorption. The usual dose is 120mg PO TID within 1 hour of a meal. It is recommended that patients should also take a

daily multivitamin at least 2 hours before or after taking orlistat, as this medication can reduce the absorption of fat-soluble vitamins. Patients taking orlistat lost approximately nine percent of their preintervention weight as compared with 5.8 percent of those who took placebo [31]. In longer-term studies (i.e., longer than one year), orlistat appeared to decrease diastolic blood pressure, lower fasting insulin levels, and reduce total cholesterol and LDL cholesterol, in a manner which was independent of weight loss [32, 33]. The side effects of orlistat include fecal urgency, fecal incontinence, steatorrhea, and flatulence. These side effects led to discontinuation in approximately nine percent of patients, as compared with five percent taking placebo [31]. Orlistat is contraindicated in patients suffering from chronic malabsorption syndromes and in cholestasis. Orlistat should not be taken with cyclosporine, as this may impair its absorption.

Non-FDA approved medications/off-label use

Topiramate has been used as an anticonvulsant, and as a mood stabilizer. However, there have been a number of case reports involving patients with mental illness, who have lost weight with topiramate. The weight loss ranged from 7 to 33 kg over the course of 2 to 8 months [34-38]. Topiramate is usually started at 25mg PO BID and then titrated up to 400mg /day. The side effects of topiramate include cognitive slowing, sedation, dizziness, fatigue, leukopenia, and kidney stones. Topiramate should be used with caution in patients suffering from dementia or other cognitive impairments, and in patients who are taking other medications which have a propensity to cause bone marrow suppression, such as Carbamazepine. There have also been case reports involving Topiramate-induced leukopenia in patients taking Clozaril, although this data has not been as clearly demonstrated [39].

Metformin is an oral hypoglycemic medication that has also been shown to have weight reducing effects in some patients. There has been one open-label study on the use of metformin for weight gain due to antipsychotic use. Metformin at 500mg PO TID was added to existing antipsychotic medications (olanzapine, quetiapine, risperidone, or valproic acid) in patients who had gained more that 10% of their baseline weight. In a period of 12 weeks, these patients showed a statistically significant decrease in BMI of 2.22kg/m^2 and an average weight loss of 2.93kg [40].
The side effects of metformin include nausea, vomiting, diarrhea, and lactic acidosis. Lactic acidosis is estimated to occur at a rate of 3 cases per 100,000 patient-years of exposure. Metformin should be used with caution in patients with a history of EtOH abuse, and is contraindicated in patients with hepatic dysfunction, renal insufficiency, congestive heart failure, and pulmonary disease, due to a higher risk of lactic acidosis [41].

Amantadine is an antiviral and anti-Parkinsonian medication, that acts by stimulating dopamine release, and by inhibiting dopamine reuptake. In a recent study, patients who had experienced an average weight gain of 15 lbs while being treated with Olanzapine, were then treated with amantadine 100-300mg/day for a 12 week period. The average weight loss at week 4 was 1.1 kg, and 2.2 kg by the end of the study [42]. Amantadine should be used with caution in schizophrenic patients, as this medication can be associated with worsening psychosis.

Nizatidine is an H2 antagonist, which may assist with weight loss by reducing appetite or by suppression of gastric acid secretion [43]. A prospective, randomized, double blind study was conducted to evaluate the potential for nizatidine to limit the amount of weight gain in patients receiving olanzapine. It was found that patients receiving nizatidine at 300mg BID gained 25% less weight over 16 weeks as compared with the placebo group (3.9kg vs 4.8kg). However, this difference was not statistically significant [44].

General comments regarding pharmacotherapy for weight loss

It is recommended that medications used for weight loss be used singly rather than in combination. Combination drug therapy may increase the risk of adverse events. These medications should only be used as part of a comprehensive program that includes behavior therapy, dietary measures, and an increase in physical activity. After starting medications, patients need to return for follow-up in 2-4 weeks, then once a month for the first 3 months, and then once every 3 months for the first year. During these visits, it is important to monitor their weight, blood pressure, pulse, and for the appearance of any adverse side effects.

Herbal medications, although highly popular, are not recommended as part of a weight loss program. These preparations have unpredictable amounts of active ingredients, and unpredictable amounts of other additives, which may cause serious side effects.