Weight Gain With Clozapine Compared to First Generation Antipsychotic Medications

by Nancy H. Covell, Ellen M. Weissman, and Susan M. Essock

Abstract

Few studies have examined gender differences in the propensity to gain weight on clozapine. Weight gain increases risk for many medical illnesses and is of particular concern for people with schizophrenia who are more overweight than the general population. Long-stay patients in Connecticut state hospitals were randomly assigned to switch to open-label treatment with clozapine ($n = 138$) or to continue receiving first generation (conventional) antipsychotic medications ($n = 89$). Using survival and random regression models, we examined percentage of body weight gained during 2 years for patients assigned to clozapine versus those who continued taking first generation antipsychotic medications. We also examined the impact of gender on weight gain. Patients who switched to clozapine gained a greater percentage of weight (13 pounds, 7%) than did patients remaining on first generation medications (5 pounds, 4%) at the end of 2 years. Normal-weight patients on clozapine were more likely to become obese (body mass index [BMI] ≥ 30). Patients gained weight whether they switched to clozapine or remained on first generation antipsychotic medications, but weight gain was significantly greater (1 BMI unit) in the clozapine-treated group, particularly among women.

Keywords: Clozapine, weight gain, antipsychotic medication, gender, conventional antipsychotic.

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Weight gain is associated with most first generation (i.e., older or so-called conventional) antipsychotic medications (Doss 1979; Harris and Eth 1981; Bernstein 1987; Brady 1989) and second generation (so-called atypical) antipsychotic agents (Casey 1996; Brown et al. 1999; Tollefson and Kuntz 1999). Of the second generation antipsychotic medications, there is evidence that clozapine and olanzapine may produce the most weight gain (Sussman 2001; Vanina et al. 2002). In a meta-analysis,

Allison et al. (1999b) calculated standardized weight gain after 10 weeks of treatment with various antipsychotic medications at standard doses using a random effects model and found the following: clozapine 4.45 kg gain, olanzapine 4.15 kg gain, sertindole 2.92 kg gain, risperidone 2.10 kg gain, and ziprasidone 0.04 kg gain. Among first generation agents, thioridazine/mesoridazine was associated with the greatest weight gain, 3.19 kg, and haloperidol, 1.08 kg; molindone was associated with 0.39 kg weight loss. Placebo-treated patients lost 0.74 kg.

Converging evidence from studies using a variety of designs demonstrates a strong association between clozapine treatment and weight gain. These include nonexperimental studies (Cohen et al. 1990; Lamberti et al. 1992; Leadbetter et al. 1992; Umbricht et al. 1994; Heimberg et al. 1995; Frankenburg et al. 1998; Spivak et al. 1999; Henderson et al. 2000; Simpson et al. 2001), prospective studies using clinically based assignment to clozapine or other antipsychotic medications (Hummer et al. 1995; Kraus et al. 1999), and double-blind randomized controlled trials (Bustillo et al. 1996; Wirshing et al. 1999). Methodological issues determine the inferences we can draw from existing studies. Nonexperimental studies that lack comparison groups do not establish whether the weight gain associated with clozapine is greater than that associated with other antipsychotic medications or greater than that expected over time alone. In prospective studies examining outcomes associated with treatments selected by the prescriber (rather than random assignment to treatment condition), differences may result from selection bias (i.e., differences in the patients selected for the different medications) rather than differences in the effectiveness of the medications themselves. On the other hand, double-blind randomized controlled trials have high inter-

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nal validity but may lack generalizability for clinical populations that have a broad range of comorbid psychiatric and medical conditions.

Together, the evidence suggests that patients taking clozapine are at increased risk of weight gain compared to patients taking other antipsychotic medications (except possibly olanzapine). Few studies have examined whether this increased risk varies by gender. One study used clinically based decisions to assign individuals to a regular or restricted diet and found that, among dieting and nondieting inpatients taking clozapine, nondieting women gained the most weight during 6 months of clozapine treatment (13.5 pounds gained, $n = 9$), followed by nondieting men (4.5 pounds gained, $n = 21$), dieting women (1 pound gained, $n = 5$), and dieting men (16 pounds lost, $n = 5$) (Heimberg et al. 1995). Another study of 46 women and 50 men who had been diagnosed with chronic schizophrenia noted that weight increase while taking clozapine was related to clinical response in female but not in male patients, but it did not compare the relative weight gain for men and women. Female responders ($n = 17$) gained more weight (24 vs. 9.5 pounds) than female nonresponders ($n = 29$) (Bai et al. 1999).

Weight gain is problematic for patients with schizophrenia for several reasons. First, the most obvious concern about weight gain is an increase in health problems, most notably cardiovascular problems (Kannel et al. 1996; Solomon and Manson 1997), including hypertension, coronary heart disease, and stroke (Bakx et al. 1999; Kawachi 1999). Additionally, because a larger proportion of patients with schizophrenia smoke tobacco compared to the general population (Dalack et al. 1998) and tobacco use also increases cardiovascular risk (Jacobs et al. 1999; Price et al. 1999), weight gain represents a further increase of cardiovascular risk in an already high-risk cohort. Weight gain leading to overweight and obesity increases risk for diabetes (Sakurai et al. 1997; Solomon and Manson 1997; Kawachi 1999).

A second concern about weight gain for patients switched to clozapine is that weight gain may present a barrier to medication adherence (Fleischhacker et al. 1994). Being overweight may trigger patients' concerns about appearance and health and may produce physical discomfort. Patients who gain weight may also experience psychosocial stigma and discrimination (Kawachi 1999), and weight gain has been associated with reduced quality of life (Allison et al. 2003). Some researchers have noted that weight gain influences medication adherence (Fleischhacker et al. 1994). Medication nonadherence is predictive of increased relapse rates (Weiden and Olfson 1995). Increased relapse is associated with increased burden of illness on patients and their families and poorer long-term outcome for patients, as well as greater eco-

nomic and social costs (e.g., more disruptive behaviors) (Weiden et al. 1997). Furthermore, overweight individuals appear to sustain greater costs for health care than do non-overweight individuals (Gorsky et al. 1996), perhaps as a consequence of their increased risk for general health problems.

None of the studies cited above adequately address three important weight-related issues encountered when prescribing clozapine in routine clinical practice. First, given that nearly all antipsychotic medications have the potential to cause weight gain, do patients switched to clozapine gain significantly more weight than they would have gained had they continued treatment with other antipsychotic medications? Second, does gender play a role in susceptibility to clozapine-associated weight gain? Third, does baseline weight status influence susceptibility to clozapine-associated weight gain?

The present study analyzed data from a randomized clinical trial examining the cost-effectiveness of clozapine compared to usual care among long-stay state hospital patients (Essock et al. 1996*a*, 1996*b*, 2000). In this study, we examined differences in weight gain for patients randomly assigned to begin a trial of clozapine versus remain on the first generation medications typically used in state hospitals at the time of the randomized trial (hereafter referred to as "usual care"). We also examined the effect of gender on weight gain during treatment with clozapine or usual care. The study has a hybrid design; it is a randomized open-label study conducted in a routine practice setting. This design provides the advantages of random assignment (e.g., no selection bias) while maintaining features of routine practice such as no exclusions based on comorbid disorders or other illness features and no restriction on clinical decision making apart from the random assignment to clozapine versus usual care, thus ensuring broader generalizability.

Methods

Subjects and Procedures. All subjects were inpatients in Connecticut's state hospitals. Subjects were eligible to participate if they (1) had a chart diagnosis of schizophrenia or schizoaffective disorder, (2) had failed to respond to adequate trials on at least two different antipsychotic medications, (3) had a current hospitalization of at least 4 months, (4) had been hospitalized for at least 2 of the 5 preceding years, and (5) had no medical contraindication to clozapine (a detailed description of the eligibility and screening criteria and demographic characteristics of the sample appear in Essock et al. 1996*a*,1996*b*). These eligibility criteria were designed to capture those individuals for whom the U.S. Food and Drug Administration had approved use of cloza-

pine: "...severely ill schizophrenia patients...who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment" (Sandoz Pharmaceuticals Corporation 1991). Of the 227 eligible patients who provided written consent to participate, a biased-coin randomization strategy was used to assign 138 study participants to begin taking clozapine and 89 to continue receiving first generation antipsychotic medications (Essock et al. 1996*a*). Specifically, the first 84 study participants had a 50 percent likelihood of being assigned to clozapine, and patients 85 through 227 had a two-thirds likelihood. This unbalanced randomization was used to speed the rate at which people receiving care in state hospitals had access to a trial on clozapine while, at the same time, preserving randomization. (While the state had a limited number of clozapine "slots," the pressure to fill these slots quickly was enormous given that clozapine was the first new antipsychotic in decades; the increase in the likelihood of assignment to clozapine accomplished this more rapid filling of clozapine slots.) In each group, 39 percent of the study participants were women (Essock et al. 1996*a*). Two patients who were randomized to clozapine but who never began taking it were excluded from the analyses reported here. Of the remaining 225, 3 had no weight measure following baseline and were also excluded from the analyses.

The goal of the larger study was to examine clozapine's cost-effectiveness in routine practice settings. Therefore, treating psychiatrists were allowed to prescribe patients assigned to usual care any combination of first generation antipsychotic medications and ancillary medications available (those prescribed included haloperidol, chlorpromazine, thiothixene, fluphenazine, thioridazine, loxapine, perphenazine, mesoridazine, trifluoperazine, molindone, chlorprothixene, anxiolytics, antidepressants, lithium, carbamazeapine, valproic acid, and anti-extrapyramidal side effects [EPS] medications); none of the other second generation antipsychotic medications were available when this study began in November 1991. Similarly, for patients assigned to clozapine, treating psychiatrists could prescribe any first generation antipsychotic medication or ancillary medications in addition to clozapine.

Measures. We collected demographic data, a daily record of medication, and weights from information available via chart review. When more than one weight measure was available in a given month, we used the most recent weight for analysis purposes. We also computed body mass index (BMI—body weight in kilograms/square of height in meters). Patients were classified as normal weight if their BMI was < 25, as

overweight if their BMI was in the range from 25 to 29.9, and as obese if their BMI was ≥ 30 (Calle et al. 1999). Clinical research staff rated patients' psychiatric symptomatology every 4 months for 2 years using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1988).

Statistical Analyses

Baseline characteristics. To examine baseline group differences, we used *t* tests and one-way analyses of variance (ANOVAs) for continuous variables and chi-square for categorical variables. All probabilities reported are 2-tailed with a significance level of 0.05.

Weight gain over time. We examined weight gain through time using two methods. First, we used random regression models (Hedeker and Gibbons 1996). In contrast to repeated-measures ANOVA, random regression models retain individuals with missing observations and model more than one person-specific effect (Gibbons et al. 1988, 1993). We included the following covariates because they had a potential relationship to weight gain: age at randomization, gender, dosage, baseline BMI, and whether the patient's psychiatric symptomatology showed improvement during the course of the study (as suggested by previous research, e.g., Lamberti et al. 1992; Leadbetter et al. 1992; Bustillo et al. 1996), with improvement as defined by Kane et al. (1988) as a 20 percent or greater improvement in total BPRS score *and* either a total BPRS score of 17 or less (with items scaled 0 to 6) (Thompson et al. 1994) *or* a Clinical Global Impressions score of no more than "mildly ill." We included all group-by-covariate interactions—group by age, group by gender, group by dosage, group by baseline BMI, and group by BPRS response. Because weight gain can follow a nonlinear trend, we applied quadratic models to each analysis and used the highest-order model that represented a significant improvement in log likelihood over the lower-order model (e.g., using quadratic over linear). For the random regression models, we report the number of patients, rather than degrees of freedom, because the resulting *z* scores are based upon the standard normal distribution (which has no associated degrees of freedom).

Second, we applied survival techniques to examine whether there was a difference in the proportion of subjects with a minimum weight gain of 7 percent, 10 percent, 20 percent, 30 percent, and 40 percent above baseline over time between the two treatment conditions following methods used in a previous study (Umbricht et al. 1994). We ran separate analyses to test for significant differences between the clozapine and usual care groups using the Wilcoxon-Gehan chi-square test (Lee 1992) at each level of weight gain.

We performed regression analyses and survival analyses in two ways. First, we analyzed all data from the groups as randomized ("intent-to-treat analysis") for 6 months (during the period prior to the time physicians were free to prescribe clozapine outside of the study's protocol; see Essock et al. 1996*a* for a detailed description). Second, we repeated the analyses excluding data obtained from individuals who left their assigned treatment, subsequent to their changing treatment condition. Treatment-condition crossovers occurred for two reasons. First, 58 patients assigned to usual care began taking clozapine once clozapine was no longer rationed and physicians were free to prescribe it. Second, 46 patients assigned to clozapine stopped taking it during the 2-year period because of agranulocytosis or other low white blood cell counts (*n* = 8), medical concerns (*n* = 12; hypotension = 4, other cardiac problems = 4, other medical problems = 4), poor clinical response in the absence of medical problems (*n* = 7), poor clinical response in addition to medical issues (*n* = 8; hypotension = 3, seizure = 2, sedation = 1, other = 2), or patient/family preference (*n* = 11) (Essock et al. 1996*b*).

Groupings eliminating ("censoring") crossovers can be constructed several ways. For example, one could exclude all data from crossovers (i.e., examine only those patients who remained in their assigned condition for the duration of the study), or one could censor data from crossovers from the time of crossover onward. Eliminating crossovers entirely may be useful when examining symptom improvement (as a "best case" scenario including only medication responders). On the other hand, when examining potential adverse medication effects, as is the case in the present study, censoring data from the time of crossover onward allows one to retain as much relevant data as possible by permitting subjects to contribute observations as long as they remain in their assigned treatment condition. This is particularly important when there is an association between the outcome of interest and dropping out of treatment. For example, patients who stop taking clozapine may do so, at least in part, because of weight gain; analyses that use data from subjects up until the time they leave the assigned treatment condition capture weight gain data prior to crossover that would be excluded if data from such crossovers were censored entirely. Similarly, patients assigned to usual care may experience a change in their patterns of weight gain if they subsequently begin taking clozapine. Hence, in analyses that censor data following crossover, their data would be excluded once they began taking clozapine, but important information would be lost if their data were excluded entirely. Note that data from patients assigned to usual care were only censored when they began taking clozapine. There were 12 patients assigned to usual care who began taking another first generation antipsychotic medication. Because we were interested in comparing clozapine to the range of "usual care" medications available, we included these 12 patients in the analyses excluding data following crossover.

Gender and weight gain. To identify any differential effect of gender on weight gain, we categorized men and women in each treatment condition (clozapine or usual care) by the maximum percent of weight gained: lost weight or gained nothing; gained greater than 0 percent and less than 10 percent of their baseline weight; or gained 10 percent or more of their baseline weight. The maximum percentage of weight gained is based on the highest recorded monthly weight compared to weight at baseline. We used chi-square analyses to determine whether the distribution of patients in each weight change category differed for men and women. We used two time frames for the analysis: 6 months and 2 years after treatment entry. For the 6-month analysis, we did an intent-to-treat analysis, because during this time there were only 16 crossovers, all of whom were individuals initially assigned to clozapine. For the 2-year follow-up, we censored data following crossover. We repeated all analyses using a 20 percent weight gain to define weight gain categories (i.e., lost weight or gained nothing; gained more than 0% and less than 20% of baseline weight; or gained 20% or more of baseline weight).

Change in weight status. We examined whether subjects assigned to clozapine or usual care were more likely to change their weight status (i.e., BMI categories: normal weight, overweight, or obese), comparing weight status at baseline and maximum weight status, using chi-square analyses. For example, are normal-weight patients more likely to become overweight when switching to clozapine as compared to continuing with usual care? We conducted similar analyses stratifying treatment group by gender (i.e., women assigned to clozapine, women assigned to usual care, men assigned to clozapine, and men assigned to usual care). Because reducing a continuous variable (BMI) to categories may attenuate group differences, we also examined the maximum change in BMI from baseline as a continuous variable. Using this variable, we applied *t* tests to examine differences in treatment assignment, and one-way ANOVAs to examine treatment assignment stratified by gender. We performed both intent-to-treat analyses and analyses where we excluded data following crossover (hereafter, "crossovers excluded").

We used SPSS statistical software for all analyses except the random regression modeling, which used MIXREG, a computer program for mixed-effects regression analysis with autocorrelated errors (Hedeker and Gibbons 1996).

Results

Baseline Information. The number of weights available per patient ranged from 2 to 27 (mean and median were 15 weight observations per patient) for the 2-year study period. Groups did not differ significantly with regard to baseline weight (clozapine: mean = 169 pounds [standard deviation (SD) = 41] and BMI mean = 26.7 [SD = 6], $n = 106$; usual care: mean = 175 pounds [SD = 40] and BMI mean = 27.3 [SD = 6], $n = 76$).

Weight Gain Over Time. The random regression analyses showed that patients who switched to clozapine gained more weight than patients who remained on first generation antipsychotic agents. The group-by-time interaction was not significant for the intent-to-treat analyses for the first 6 months of the study. However, when data from patients who discontinued their assigned treatment were censored following crossover to the other treatment condition, patients assigned to clozapine gained a significantly greater percentage of weight over baseline than did patients assigned to usual care (figure 1; $z = 3.1$, $n = 166$, $p < 0.005$ for the group-by-time interaction, and $z = -2.6$, $n = 166$, $p < 0.01$ for the group-by-time squared interaction). Among patients with weight data available at study month 24, patients assigned to clozapine had gained an average of 13 pounds (median = 10 pounds, SD = 18.6 pounds; mean and median 7% gain, SD = 12.4%; $n = 16$), whereas patients assigned to usual care had gained an average of 5 pounds (median = 6 pounds, SD = 14.7 pounds; mean 4% and median 5% gain, SD = 8.7%; $n = 13$). Comparable differences were found at study month 22, where the n's were larger ($n = 28$ for clozapine and $n = 18$ for usual care). Baseline BMI was significantly negatively related to weight gain in the quadratic model of intent-to-treat analyses and marginally related in both linear and quadratic models when data were excluded following crossover, with more weight gain seen among those with lower baseline BMIs. None of the other covariates was significant in any of the random regression models.

The survival analyses yielded similar findings. Figure 2 is a survival curve for patients in the clozapine and usual treatment groups showing the proportion of patients who gained less than 20 percent of their baseline weight over time, (i.e., proportion of patients maintaining a weight of less than 120% of their baseline weight). When we censored data following crossover, patients assigned to clozapine were significantly more likely to gain at least 20 percent of their baseline weight over time than patients assigned to usual care were (χ^2 [Wilcoxon] = 7.9, $df = 1$, $p < 0.005$). Patients assigned to clozapine were also significantly more likely to gain at least 30 percent of their base-

line weight over time than patients assigned to usual care were (χ^2 [Wilcoxon] = 6.7, $df = 1$, $p < 0.01$) in the crossovers-excluded analysis. At other levels of weight gain, there was a nonsignificant trend toward greater weight gain over time for the group assigned to clozapine in the crossovers-excluded analyses: 7 percent weight gain, χ^2 [Wilcoxon] = 2.5, $df = 1$, $p = 0.11$; 10 percent weight gain, χ^2 [Wilcoxon] = 2.8, $df = 1$, $p = 0.09$; and 40 percent weight gain, χ^2 [Wilcoxon] = 2.3, $df = 1$, $p = 0.13$. Four of the patients assigned to clozapine (4%) gained at least 40 percent of their baseline weight, while none of the patients assigned to usual care gained even 30 percent of their baseline weight (crossovers excluded). The groups did not differ under the intent-to-treat analyses at any level of weight gain, although there was a trend for patients assigned to clozapine to gain more weight than patients assigned to usual care. For example, using intent-to-treat analyses, 17 percent of patients assigned to clozapine compared to 9 percent of those assigned to usual care had gained 10 percent or more of their baseline weight by 6 months.

Change in Weight Status. Intent-to-treat analyses did not yield any significant findings when maximum change in BMI was analyzed as a continuous variable. However, when we excluded data following crossover, patients assigned to clozapine showed an increase of about 1 BMI unit more than patients assigned to usual care ($t(161) = 2.5$, $p < 0.05$; mean maximum BMI increase = 2.33 [median = 1.27, SD = 3.11] for clozapine and 1.36 [median = 0.96, SD = 1.85] for usual care). About one-third of all patients with baseline BMIs in the normal range changed weight status (became overweight or obese) regardless of treatment assignment (clozapine vs. usual care). When we excluded data following crossover, we found a strong trend that patients with baseline BMIs in the normal range were more likely to become obese (BMI ≥ 30) when switched to clozapine compared to patients receiving usual care: 12 percent became obese in the clozapine group ($n = 6$ of 49), and 0 percent became obese (0 of 31) in the usual care group ($\chi^2 = 5.5$, $df = 2$, $p = 0.065$). Although the finding was not statistically significant, among patients who were overweight at baseline, a higher proportion of those who switched to clozapine became obese ($n = 8$ of 20, 40%) compared with those receiving usual care ($n = 5$ of 18, 28%). Intent-to-treat analyses yielded no significant findings, although again, there was a suggestion that beginning a trial on clozapine might be associated with weight gain (e.g., 23% of overweight patients who switched to clozapine compared to 17% of those remaining in usual care became obese in the first 6 months of treatment).

233

### Figure 1. Percentage of weight gained over baseline, crossovers excluded[1]
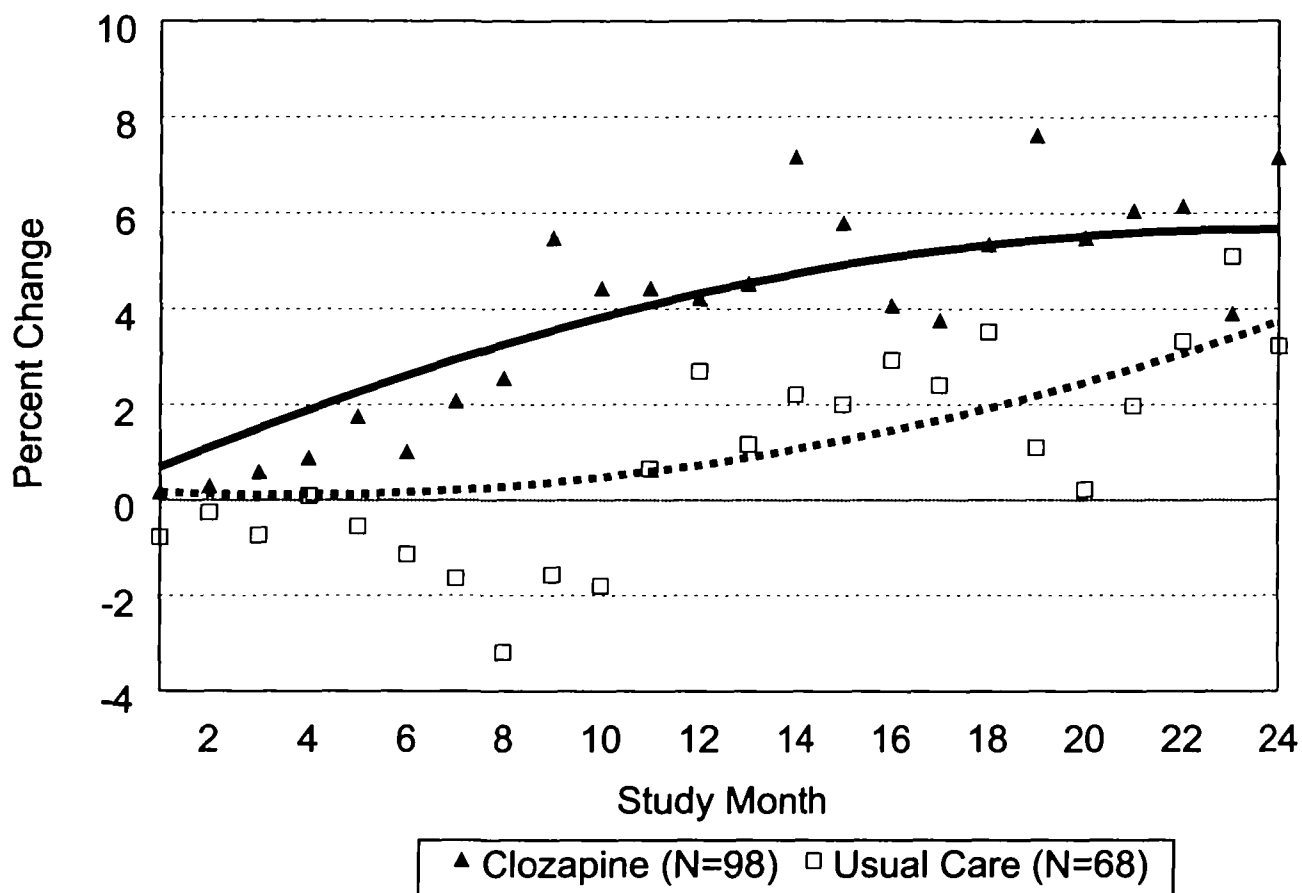
[1] Mixed regression lines showing changes in percentage of weight gained by study month. Points (closed triangles and open squares) represent actual group means. $z = 3.1$, $n = 166$, $p < 0.005$ for group by time, and $z = -2.6$, $n = 166$, $p < 0.01$ for group by time-squared.

Relationship Between Gender and Weight Gain. Intent-to-treat analyses did not yield any significant findings when maximum change in BMI was analyzed as a continuous variable. However, when we excluded data following crossover, there were significant group differences $(F(3,162) = 3.3, p < 0.05)$. Post hoc Tukey tests indicated that women assigned to clozapine showed significantly greater increases in BMI than did men assigned to usual care (mean maximum BMI increase = 3.03, median = 1.62, SD = 3.72, for women assigned to clozapine and mean maximum BMI increase = 1.26, median = 0.77, SD = 1.48, for men assigned to usual care, $p < 0.05$). After 2 years, a significantly higher proportion of women taking clozapine gained 20 percent or more of their baseline weight in the crossovers-excluded analysis $(\chi^2 = 17, df = 6, p = 0.01)$ (table 1). Twenty-nine percent of women assigned to clozapine gained 20 percent or more of their baseline weight compared to men assigned to clozapine (13%), women assigned to usual care (8%), or men assigned to usual care (2%).

Intent-to-treat analyses and crossovers-excluded analyses with a 10 percent weight gain criterion yielded no significant findings.

We found a significant gender-by-treatment effect for change in weight status from normal BMI to obese (BMI ≥ 30) (crossovers-excluded analysis $[\chi^2 = 18.0, df = 6, p < 0.01]$). Among patients with normal baseline BMI, women assigned to clozapine were more likely to become obese (28%, $n = 5$ of 18) than were men assigned to clozapine (3%, $n = 1$ of 31) or women or men assigned to usual care (0%, $n = 0$ of 9 and 22, respectively). There was also a slight trend for women who were overweight at baseline to become obese if switched to clozapine (71%, $n = 5$ of 7) versus usual care (50%, $n = 3$ of 6) and compared to overweight men assigned either to clozapine (23%, $n = 3$ of 13) or to usual care (17%, $n = 2$ of 12) $(\chi^2 = 9.1, df = 6, p = 0.17)$. Obese individuals tended to remain obese in all groups. The intent-to-treat analysis showed no significant difference in weight gain among groups.

Figure 2. Time to 20 percent weight gain, crossovers excluded[1]
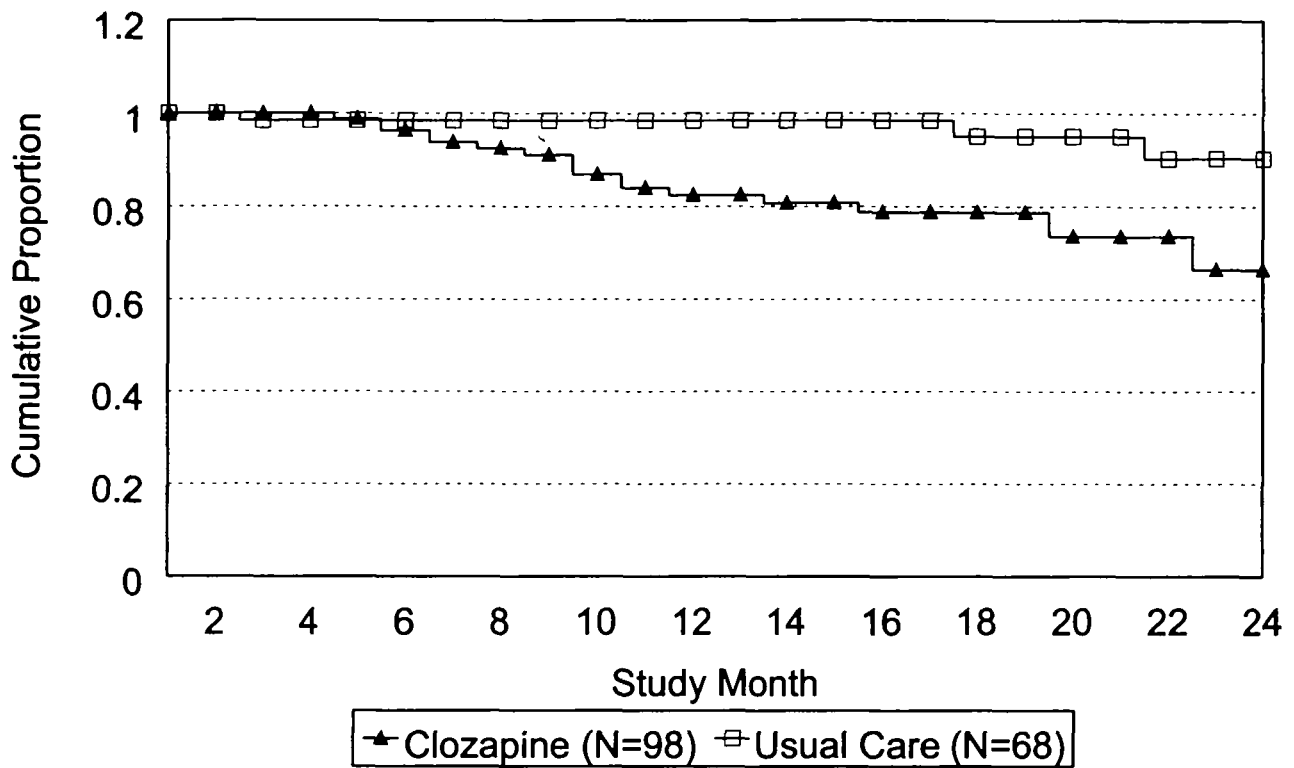
[1] Survival functions showing the proportion of patients who had not gained at least 20% of their baseline weight. $\chi^2 = 7.9$, $df = 1$, $p < 0.005$.

Table 1. Number and percentage of men and women whose maximum gain over 24 months was greater or less than 20% of their baseline weight ($\chi^2 = 17$, $df = 6$, $p = 0.01$)

	Assigned to Usual Care		Assigned to Clozapine	
	Men, n (%)	Women, n (%)	Men, n (%)	Women, n (%)
Weight loss or no change	8 (19%)	6 (24%)	15 (25%)	11 (29%)
0% < gain < 20%	34 (79%)	17 (68%)	37 (62%)	16 (42%)
Gain ≥ 20%	1 (2%)	2 (8%)	8 (13%)	11 (29%)

In the regression model when data were censored following crossover, the gender-by-group term was not statistically significant above and beyond the significant group-by-time interaction and other model variables (baseline BMI, dosage, age, and response as defined using the BPRS). Although not significant, there was some suggestion that gender influenced weight gain on clozapine (e.g., the group-by-gender estimate indicated that women assigned to clozapine were expected to gain an additional 1.7% of their baseline weight compared to individuals in other groups).

Discussion

Patients randomly assigned to switch to clozapine treatment gained significantly more weight than patients assigned to continue with usual care, which consisted of treatment with first generation antipsychotic medications. The difference in weight gain between the two groups began shortly after randomization and continued to grow throughout the 2-year study, with patients assigned to clozapine gaining an average of 1 BMI unit more than those assigned to usual care. Most patients entered the study already overweight (BMI 25–29.9) but not yet obese

(BMI ≥ 30). Among these individuals, there was a nonsignificant trend for sufficient weight gain to cross the threshold into obesity for patients who began a trial with clozapine. Among individuals who began the study at a normal weight, 12 percent of those who switched to clozapine but none of the patients who continued taking first generation agents gained sufficient weight to be categorized as obese within 2 years.

Women who switched to clozapine were more likely to experience significant weight gain, with an average increase of 3 BMI for women assigned to clozapine. Among patients who began the study at normal weights and were switched to clozapine treatment, women were significantly more likely to become obese. To date, there has been little information to guide physicians when considering gender differences in drug effects on weight (Sussman 2001). These data provide the first empirical evidence of a gender difference in susceptibility to weight gain when switching to clozapine treatment from other antipsychotic medications.

Regardless of the underlying mechanism, significant weight gain is cause for concern because of the health risks associated with it (see Casey and Zorn 2001 for a review of the pharmacology of weight gain with clozapine and other antipsychotic medications). Nearly one-third of women taking clozapine gained a significant amount of weight (20% or more of their baseline weight). Nearly two-thirds of patients with schizophrenia were already overweight before beginning clozapine treatment, a finding consistent with other studies (Umbricht et al. 1994; Allison et al. 1999*a*).

Our results, taken together with reports that clozapine is associated with increases in serum triglyceride levels (Gaulin et al. 1999), and with reports of increased risk of diabetes (Henderson et al. 2000), hyperglycemia (Lindenmayer et al. 2001), and insulin resistance (Melkersson et al. 1999), suggest the need for preventive and ongoing interventions for individuals switching to clozapine treatment. This appears to be especially important for women and for patients who are overweight prior to initiating clozapine treatment.

Given the clear deleterious effects of weight gain, clinicians should provide counseling and medical care to support the modifications in behavior and diet (e.g., increased exercise, decreased caloric and fat intake) necessary to control weight gain. Evidence from several studies suggests that dietary interventions may attenuate antipsychotic-associated weight gain. For example, in one study, 31 individuals with severe and persistent mental illness who were residing in a residential center and taking atypical antipsychotic medications were provided with a low-fat, low-calorie diet and followed for 1.5 years (Aquila and Emanuel 2000). The average body weight for

this group did not increase significantly through the 1.5 years of followup, although 12 (43%) of the 28 individuals available for followup at 18 months had experienced some weight gain (Aquila and Emanuel 2000). For the general population, one commercial weight loss program that targeted increased exercise coupled with decreased caloric and fat intake was found more effective than brief counseling and self-help for weight loss (Heshka et al. 2000). Some evidence suggests that this same commercial program may also be effective for individuals with schizophrenia (Ball et al. 2001; Aquila 2002), particularly men with schizophrenia (Ball et al. 2001).

The additional weight increase of about 8 pounds over 2 years for patients switched to clozapine compared to usual care should not dissuade psychiatrists from considering suggesting a trial on clozapine. Depending upon the individual, the benefits associated with clozapine may override the risks associated with the weight gain. Risk/benefit statements can be difficult to quantify because the value of the potential outcomes (e.g., reduction in psychotic symptoms and negative symptoms, weight gain) varies across individuals. However, given that approximately one-third of otherwise treatment-refractory patients do respond well to clozapine (Kane et al. 1988; Breier et al. 1994; Essock et al. 1996*a*; Rosenheck et al. 1997), it appears that, for many patients, the potential benefit is worth the risk of weight gain, particularly if weight gain is addressed preventatively. Our results also underscore the fact that, despite significantly greater weight gain for patients switched to clozapine, about one-quarter experience weight loss or no weight gain, and about one-half experience only moderate weight gain (between 0% and 20% of baseline weight). Although some patients, particularly women, do gain substantial weight after switching to clozapine, not all do so.

We note the following limitations of this study. First, we relied upon weights recorded in patients' medical records; therefore, the data were less complete than if a weight measure had been obtained at every research interview. It is possible that in addition to weights taken routinely, some patients may have been weighed selectively (e.g., when weight change was noticed or when the patient was medically ill). We also recognize that weight and BMI alone are not sufficient predictors of health risk. Future studies should also include measures of abdominal adiposity, which has shown a relationship to increased health risks, including increased risks of high blood pressure, type 2 diabetes, dyslipidemia, and metabolic syndrome (Janssen et al. 2002). Measures of waist circumference, although less accurate than computed tomography and magnetic resonance imaging, are the most accurate assessment of abdominal adiposity

that can be practically carried out in routine practice settings (National Institutes of Health 1998). Second, based on our methodology, we cannot compare whether clozapine and other agents differ in their inherent propensity to cause weight gain (i.e., if given to antipsychotic-naïve patients). Patients in this study had been taking antipsychotic medications for several years, and most were already overweight, so we could not isolate whether the additional weight gain was due to a particular medication or the cumulative effects of years of treatment with antipsychotic medications. To help address this issue, future studies of individuals in their first psychotic episodes should monitor weight gain. Our methodology does address questions more commonly encountered in routine clinical practice: Are patients who switch to clozapine treatment likely to gain more weight than they would have if they stayed on their current treatment? Who is at greatest risk for weight gain? Finally, we did not have access to information on exercise and nutritional intake for this sample. Such information would have been useful in comparing those who gained weight to those who did not.

Strengths of the study were as follows: (1) randomization minimized concerns about nonequivalent groups that hampered some earlier studies, and (2) by comparing clozapine to a range of first generation antipsychotic medications, we addressed the concern about using haloperidol as the sole comparison agent. However, we recognize that by comparing clozapine to a variety of conventional antipsychotic medications, we may not have estimated closely the expected weight gain with clozapine compared to any particular agent. The 2-year study design also provided an opportunity to examine weight gain over a relatively long medication trial.

In conclusion, switching to clozapine appears to increase the risk for weight gain over and above that expected from remaining on first generation antipsychotic medications, especially among women. This weight gain has the potential to increase health problems and pose barriers to adherence. Clinicians should discuss the risk of weight gain with their patients who are considering taking clozapine and offer dietary and other interventions, particularly for female patients. However, clinicians should also bear in mind that many patients do not gain weight when switched to clozapine, or gain only modest amounts. This suggests that, except for rare patients, the potential for weight gain should not preclude a clozapine trial when it is clinically indicated. Simultaneously, clinicians should be proactive in prescribing dietary changes and exercise to minimize potential weight gain. The present study was conducted when clozapine was the only available second generation antipsychotic medication. Because some of the other

second generation antipsychotic medications also appear to be associated with weight gain (Umbricht and Kane 1996; Song 1997; Zimbroff et al. 1997; Osser et al. 1999), future studies should continue to monitor weight to determine the relative liability for weight gain among all of the first and second generation antipsychotic medications. Future studies also should gather information about exercise and dietary intake to help inform behavioral interventions that may minimize weight gain and thus reduce medical morbidity and improve adherence.

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