Clozapine and Hypertension: A Chart Review of 82 Patients

David C. Henderson, M.D.; Tara B. Daley, B.S., M.P.H.; Laura Kunkel, M.D.; Myisha Rodrigues-Scott; Pamposh Koul, B.S.; and Doug Hayden, M.S.

Objective: Clozapine has been linked to significant weight gain and increase in serum lipids and appears to negatively impact glucose metabolism. In this retrospective chart review study, we examine changes in systolic and diastolic blood pressure and treatment for hypertension in clozapine-treated patients.

Method: Data on demographics and systolic and diastolic blood pressure were examined for up to 5 years (September 1987 to September 1992) in 82 patients treated with clozapine. Rates of hypertension treatment in clozapine-treated patients were compared with patients receiving conventional antipsychotics (N = 56) and other atypical antipsychotic agents (N = 102).

Results: The mean age of the 82 patients at the time of clozapine initiation was 36.4 ± 7.8 years, with 22 (27%) female, 75 (91%) white, 3 (4%) black, 3 (4%) Hispanic, and 1 (1%) Asian. The baseline weight was 175.5 ± 34.0 lb (79.0 ± 15.3 kg) and baseline body mass index was 26.9 ± 5.0 kg/m^2. There was a significant increase in systolic blood pressure (p = .0004) and diastolic blood pressure (p = .0001). Overall, 22 patients (27%) received treatment for hypertension following clozapine initiation. Only 2 (4%) of 56 patients in the conventional antipsychotic group and 9 (9%) of 102 patients in the other atypical antipsychotic group (olanzapine, N = 6; risperidone, N = 3) received treatment for hypertension.

Conclusion: Our findings suggest that long-term clozapine treatment is associated with increased rates of hypertension, which may have a significant impact on medical morbidity and mortality.

(J Clin Psychiatry 2004;65:686–689)

Received June 1, 2003; accepted Sept. 15, 2003. From the Schizophrenia Program, Department of Psychiatry, Harvard Medical School and the MGH Biostatistics Program, Massachusetts General Hospital, Boston, Mass.

This project was supported by a National Alliance for Research on Schizophrenia and Depression Young Investigator's Award (Dr. Henderson).

Dr. Henderson has served as a consultant for Janssen, Eli Lilly, Bristol-Myers Squibb, and Pfizer; has received grant/research support from Eli Lilly, Pfizer, Bristol-Myers Squibb, AstraZeneca, and Janssen; and has received honoraria from Pfizer, Bristol-Myers Squibb, and Janssen.

Corresponding author and reprints: David C. Henderson, M.D., Freedom Trail Clinic, 25 Staniford Street, Boston, MA 02114 (e-mail: dchenderson@partners.org).

Clozapine is an atypical antipsychotic that remains the most effective agent for the management of treatment-resistant chronic schizophrenia. Unlike conventional and other atypical antipsychotics, clozapine causes minimal extrapyramidal side effects. Despite the benefits, recent reports[1] have raised questions regarding clozapine's impact on medical morbidity and mortality. Clozapine is associated with significant weight gain, increase in serum lipids, and cardiomyopathy[2] and appears to negatively impact glucose metabolism.[3,4] Such metabolic abnormalities are leading to higher rates of diabetes mellitus than expected and raising concerns regarding cardiovascular disease.

Risk factors for cardiovascular disease include serum lipid abnormalities, smoking, a sedentary lifestyle, overweight/obesity, and hypertension. While a growing body of evidence related to serum lipid abnormalities, weight gain, obesity, and diabetes mellitus is emerging, there are few reports on the incidence of hypertension in clozapine-treated patients. Gupta and Rajaprabhakaran[5] reported a case of new-onset hypertension (blood pressure range, 124/90–164/116 mm Hg) that occurred within 1 week of initiating clozapine therapy. George and Winther[6] also reported a case of new-onset hypertension (160/108 mm Hg) that occurred with a clozapine dose of 62.5 mg/day. The hypertension resolved following clozapine discontinuation, only to return upon clozapine reinitiation.

Lund and colleagues[7] compared incidence rates of hypertension in patients receiving clozapine (N = 552) and conventional antipsychotic agents (N = 2461) using a medical and pharmacy claims database. They found no significant differences in overall incidence rates of hypertension in patients receiving clozapine versus conventional antipsychotic agents, with only 5.3% of conventional antipsychotic–treated patients and 4.1% of clozapine-treated patients receiving treatment for hypertension.

Finally, Fontaine and colleagues[8] estimated the effects of weight gain on the incidence of hypertension in patients treated with antipsychotics using raw data from 5209 respondents from the Framingham Heart Study's public use data set and national population demographic

statistics. Hypertension and weight gain were estimated to have a linear effect.

We reported a 5-year naturalistic study that examined clozapine-treated patients in whom high rates of diabetes mellitus, weight gain, and lipid abnormalities were observed.[4] This retrospective chart-review study examines the change in systolic and diastolic blood pressure in the same clozapine-treated patients over a 5-year period (September 1987 to September 1992). In addition, rates of hypertension treatment in clozapine-treated patients are examined and compared with patients receiving conventional antipsychotics and other atypical antipsychotic agents.

METHOD

This study was conducted in the outpatient clozapine clinic of an urban mental health center following approval by the Institutional Review Boards of the Massachusetts Department of Mental Health. Clozapine-treated patients' weight and vital signs were routinely monitored. Vital signs and clozapine dose were recorded from the clinical chart at 6-month intervals. When data were not available, additional information was sought in relevant inpatient and general medical records.

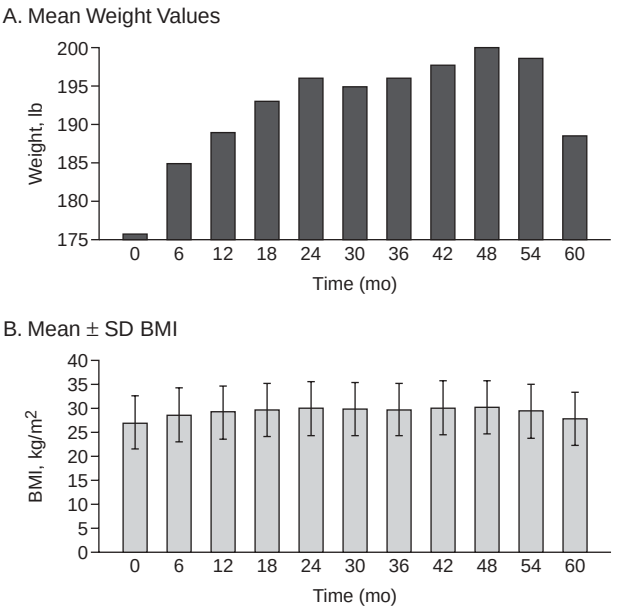
Additionally, all patients with a DSM-IV diagnosis of schizophrenia and schizoaffective disorder at the time of clozapine data collection were taken from an existing database and classified into 1 of 3 groups: clozapine, conventional antipsychotics, and other atypical antipsychotics (risperidone, olanzapine, quetiapine). Data on age, gender, race, and treatment for hypertension (while taking a particular antipsychotic agent) were collected. A research psychiatrist (D.C.H.) reviewed all records to confirm that antihypertensive agents were prescribed for the purpose of hypertension treatment and not for extrapyramidal symptoms or other medical or psychiatric conditions. A descriptive comparison is provided comparing the treatment for hypertension in the 3 groups.

Statistical Methods

Changes from baseline in systolic and diastolic blood pressure were analyzed using a mixed-effects model in the clozapine group. This model has fixed linear and quadratic terms for time and random intercept and linear and quadratic terms for time for each patient. The fixed effects estimate the mean parabolic trajectory of the change from baseline while the random effects allow a separate trajectory for each patient.

In order to test for an association of time-dependent covariates (change in cholesterol, triglycerides, clozapine dose, and weight gain) with changes from baseline, the mixed-effects model was augmented with a fixed and random covariate effect. This model tests for a dependency of change from baseline with the covariate beyond that already explained by passage of time. Two-sided p values $< .05$ were considered significant.

Figure 1. Weight and Body Mass Index (BMI) in Clozapine-Treated Patients (N = 82) Observed During a 60-Month Period



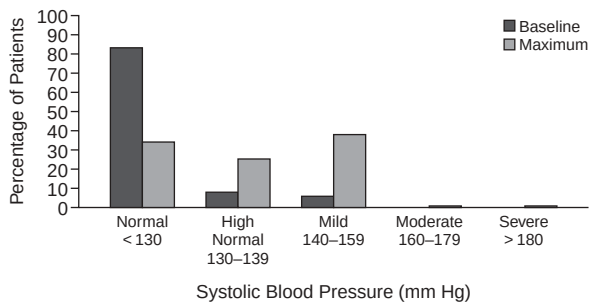
The maximum systolic and diastolic blood pressures were tabulated into categories recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[9]

RESULTS

Data were obtained on 82 patients treated with clozapine for at least 1 year and up to 5 years. The mean age at the time of clozapine initiation was 36.4 ± 7.8 years, with 22 (27%) female, 75 (91%) white, 3 (4%) black, 3 (4%) Hispanic, and 1 (1%) Asian. Fifty-five (67%) of the patients had a diagnosis of schizophrenia and 27 (33%) of schizoaffective disorder. The baseline weight was 175.5 ± 34.0 lb (79.0 ± 15.3 kg) and body mass index (BMI) was 26.9 ± 5.0 kg/m^2. The baseline systolic blood pressure reading was 113.74 ± 11.75 mm Hg, and the baseline diastolic blood pressure reading was 76.98 ± 9.57 mm Hg.

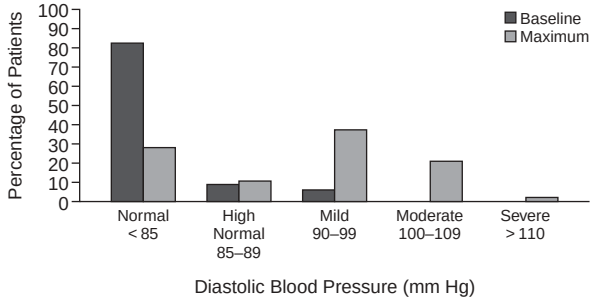
For clozapine-treated patients, there was a significant increase in systolic blood pressure (linear coefficient = 0.27 mm Hg per month, SE = 0.07; mixed-effects model, $t = 3.84$, $df = 49$, $p = .0004$), which was associated with an increase in body weight (linear coefficient = 0.18 mm Hg per pound of body weight, SE = 0.7; mixed-effects model, $t = 2.61$, $df = 49$, $p = .0120$) (Figure 1A and 1B). There was a nonsignificant association with change in systolic blood pressure and change in total se-

Figure 2. Classification of Adult Systolic Blood Pressure in Clozapine-Treated Patients[a,b]



[a]Based on the classifications recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[9]
[b]Comparing baseline to the maximum systolic blood pressure value observed during a 60-month period.

Figure 3. Classification of Adult Diastolic Blood Pressure in Clozapine-Treated Patients[a,b]



[a] Based on the classifications recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[9]
[b]Comparing baseline to the maximum diastolic blood pressure value observed during a 60-month period.

rum cholesterol (linear coefficient = 0.05 mm Hg/mg/dL of total serum cholesterol, SE = 0.03; mixed-effects model, t = 1.76, df = 42, p = .086). At baseline, more than 80% of patients' systolic blood pressure was normal (< 130 mm Hg). Over the 60-month period, more than 40% of patients' maximum systolic blood pressure reading was in the hypertensive range (≥ 140 mm Hg) (Figure 2).

There was a significant increase in diastolic blood pressure (linear coefficient = 0.20 mm Hg per month, SE = 0.04; mixed-effects model, t = 4.84, df = 49, p = .0001), which was not associated with a change in weight or clozapine dose, despite increases in both weight and BMI (Figure 1A and 1B). At baseline, more than 90% of patients' diastolic blood pressure was < 90 mm Hg. Over the 60-month observation period, more than 60% of patients' maximum diastolic blood pressure readings were in the hypertensive range (≥ 90 mm Hg) (Figure 3). Race, age, and gender had no significant effects on systolic and diastolic blood pressure over the 60-month period.

Six months after initiating clozapine therapy, 6 (7%) of 82 patients had a systolic blood pressure reading > 140 mm Hg, and 5 patients (6%) had a diastolic blood pressure reading > 90 mm Hg. After 1 year of clozapine treatment, 6 (7%) of 82 patients had a systolic blood pressure > 140 mm Hg, and 15 (18%) had a diastolic blood pressure > 90 mm Hg. Overall, 22 (27%) of 82 clozapine patients received treatment for hypertension following clozapine initiation.

Of the 30 clozapine patients diagnosed with diabetes mellitus, 16 (53%) were treated for hypertension. In comparison, 16 (73%) of 22 patients who were treated for hypertension were also diagnosed with diabetes mellitus.

The conventional antipsychotic comparison group (N = 56) had a mean age of 49.54 ± 10.63 years, with 26 (46%) female, 46 (82%) white, and 10 (18%) African American. Thirty patients (54%) had a diagnosis of schizophrenia and 23 (41%) of schizoaffective disorder.

The other atypical antipsychotic group (N = 102) had a mean age of 44.63 ± 11.54 years, with 36 (35%) female, 84 (82%) white, 14 (14%) African American, 3 (3%) Hispanic, and 1 (1%) Asian. Fifty-four patients (53%) had a diagnosis of schizophrenia and 48 (47%) of schizoaffective disorder. Only 2 (4%) of 56 patients in the conventional antipsychotic group and 9 (9%) of 102 patients in the other atypical antipsychotic group (olanzapine N = 6; risperidone N = 3) received treatment for hypertension.

DISCUSSION

Overall, the data suggest that clozapine therapy may be associated with elevations in systolic and diastolic blood pressure, resulting in treatment for hypertension. Additionally, a significant positive correlation exists between weight gain and an increase in systolic blood pressure. A positive linear relationship exists between BMI and mortality rate as well as relative risk of developing cholelithiasis, hypertension, coronary heart disease, and, especially, type 2 diabetes mellitus.[10]

The significance of more than 60% of clozapine patients' maximum diastolic blood pressure in the hypertensive range is unclear (Figure 2). The tremendous amount of variability in blood pressure readings may be influenced by many factors, including stress, anxiety, cigarette smoking, caffeine, alcohol, or sodium intake. Therefore, we relied on treatment for hypertension to obtain a more accurate assessment of incidence in clozapine-treated patients.

The lower rates of hypertension treatment in the comparison groups may reflect the quality of medical follow-up for non–clozapine-treated schizophrenia patients.

Hematologic screenings and vital signs were conducted on a regular basis in our clozapine program. There was no such system in place for patients receiving treatment with conventional or other antipsychotic agents. Patients with psychiatric disorders, particularly those with severe mental illnesses, have high rates of undetected and untreated medical problems and substantially elevated mortality rates.[11] Thus, access, use, and quality of medical care may increase the impact of hypertension in patients with schizophrenia.

The effects on elevated systolic and diastolic blood pressure occurred relatively soon after initiation of clozapine treatment. Blood pressure in the hypertensive range was observed just after 6 months. Therefore, blood pressure should be monitored frequently after clozapine therapy begins. While weight and BMI increased over time, neither measurement correlated with an increase in systolic or diastolic blood pressure or treatment for hypertension. However, there was a clear association with treatment for hypertension and treatment for diabetes (73%), which is consistent with hypertension as a risk factor for diabetes mellitus.[10]

We are concerned about cardiovascular disease in clozapine-treated patients. Adding hypertension to prolonged obesity, diabetes mellitus, and lipid abnormalities may place clozapine-treated patients at greater risk of cardiovascular disease and early death. We recommend that all patients treated with clozapine undergo routine medical screening for weight gain/obesity, lipid abnormalities, diabetes mellitus, and hypertension on a regular basis. Cardiovascular risks should be calculated and systematically tracked. Reliance on the primary care medical system for this population may result in significant undertreatment of these medical disorders. Mental health providers must play an active role in monitoring and instituting appropriate interventions and referral for clozapine-treated patients.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004;64:701–723
2. Coulter DM, Bate A, Meyboom RH, et al. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ 2001;322:1207–1209
3. Henderson DC, Cagliero E, Borba C. Atypical antipsychotic agents and glucose metabolism: Bergman's Minimal Model analysis. Presented at the 40th annual meeting of the New Clinical Drug Evaluation Unit; May 30–June 2, 2000; Boca Raton, Fla
4. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
5. Gupta S, Rajaprabhakaran R. Paradoxical hypertension associated with clozapine [letter]. Am J Psychiatry 1994;151:148
6. George TP, Winther LC. Hypertension after initiation of clozapine [letter]. Am J Psychiatry 1996;153:1368–1369
7. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001;58:1172–1176
8. Fontaine KR, Heo M, Harrigan EP, et al. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. Psychiatry Res 2001;101:277–288
9. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154–183
10. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427–434
11. Cradock-O'Leary J, Young AS, Yano EM, et al. Use of general medical services by VA patients with psychiatric disorders. Psychiatr Serv 2002;53:874–878