Published in final edited form as:

Schizophr Res. 2009 February ; 107(0): 134–138. doi:10.1016/j.schres.2008.10.020.

Cardiac-related findings at autopsy in people with severe mental illness treated with clozapine or risperidone

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Abstract

Clozapine is a superior agent for treatment-refractory patients with schizophrenia, but is underutilized in the US, likely due to the risk of side effects. This study examined all available autopsy data on cardiac disease and risk factors in people with schizophrenia in a sample of deceased persons with severe mental illness who had received clozapine ($N = 62$) or risperidone ($N = 42$). The mean body mass index (BMI) at the time of death was $31.4 \pm 8.8 \text{ kg/m}^2$ and $27.1 \pm 8.2 \text{ kg/m}^2$ in the clozapine and risperidone groups respectively ($t = 1.98$, $df = 60$, $p = 0.052$). Cardiac related measures examined included: abdominal wall thickness, heart weight, left ventricle thickness, right ventricle thickness, presence of notable cardiac involvement (atherosclerosis, fibrosis and hypertrophy) and number of cardiac arteries occluded. No significant differences in any of the cardiac findings were noted between patients in the clozapine and risperidone groups. Independent of treatment, cardiomyopathy deaths were associated with a higher abdominal wall thickness ($p = 0.042$) and a tendency towards higher BMI ($p = 0.051$) as

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Contributors

Deanna Kelly designed this study and data analysis, organized autopsy information and assimilation, wrote the protocol, and presented the results at the American College of Neuropsychopharmacology annual meeting in December 2007 and the College of Psychiatric and Neurologic Pharmacists in April of 2008. Additionally, she assisted in manuscript preparation. Mr. Linthicum assisted in data cleaning and analyzed the data using SPSS. He also assisted in manuscript preparation. Heidi Wehring drafted the information in manuscript form, coordinated manuscript preparation, and was involved in data collection. Stephanie Feldman coordinated data collection and assisted in manuscript finalization. Robert McMahon provided oversight for statistical analyses and assisted in manuscript preparation. Raymond Love coordinates the CAMP and atypical antipsychotic databases and provides oversight for state hospital coordination of data. He also assisted in manuscript preparation. Tara Wagner assisted in death identification, death record acquisition and the collection of autopsy records. She also assisted in the final version of the manuscript. Joo Cheol Shim assisted in study design and manuscript preparation. David Fowler provided autopsy records and assisted in the final manuscript.

Conflict of interest

Deanna L. Kelly, Pharm.D., BCPP has served on the advisory board for Bristol Myers Squibb and Solvay Pharmaceuticals.

Heidi J Wehring, Pharm.D., BCPP has nothing to disclose.

Jared Linthicum MS has nothing to disclose.

Stephanie Feldman LCSW MSW has nothing to disclose.

Robert P. McMahon, PhD has nothing to disclose.

Raymond C. Love, Pharm.D., BCPP has nothing to disclose.

Tara Wagner, MS has nothing to disclose.

Joo-Cheol Shim, MD, PhD has nothing to disclose.

David R. Fowler, MD, has nothing to disclose.

compared to the other causes of death. The results of this study suggest that while clozapine is associated with weight gain and metabolic abnormalities, there does not appear to be an increased occurrence of cardiac abnormalities in deceased persons who were treated with clozapine as compared to risperidone.

Keywords

Clozapine; Cardiomyopathy; Autopsy; Cardiovascular; Mortality

1. Introduction

Clozapine is the only antipsychotic medication currently available in the United States with established efficacy for treatment of refractory symptoms of schizophrenia. It has shown superiority over both conventional and second-generation antipsychotics for the treatment of these symptoms (Conley and Kelly, 2001; McEvoy et al., 2006). It may reduce hospitalizations and overall treatment costs (Buckman and Malan, 1999; Essock et al., 2000) and improve quality of life (Rosenheck et al., 1999) for patients with schizophrenia. In addition, clozapine is used in other psychotic illnesses such as bipolar disorder for which other treatments have failed (Gitlin, 2006). Clozapine has been shown superior to other antipsychotics for reducing suicide risk (Meltzer et al., 2003) as well as physical aggression and violence (Citrome et al., 2001; Krakowski et al., 2006).

Clozapine's efficacy makes it an agent of vital importance in the treatment of refractory psychotic symptoms. However, the rate of clozapine utilization in the U.S. is low (<5%), in spite of the estimation that 20% to 30% of patients with schizophrenia express symptoms that are refractory to first line antipsychotic agents (Conley et al., 2005; Fayak et al., 2003; Kelly et al., 2007a; Lieberman, 1998; Taylor et al., 2003). There are several factors that may contribute to the infrequent utilization of this medication. For example, clozapine underuse may in part be related to its comparatively intensive hematologic monitoring requirements, as well as the potential for serious side effects such as agranulocytosis, myocarditis, seizures, sedation, obesity, diabetes mellitus and other metabolic abnormalities (Kelly et al., 2007b; Lieberman, 1998). It has also been postulated that negative attitudes towards clozapine, lack of knowledge of its benefits, or its generic availability along with the more aggressive marketing of other second-generation antipsychotics may contribute to clozapine's underuse (Kelly et al., 2007b).

Recently, there has been an increasing focus on the cardiovascular health of patients with schizophrenia. People with schizophrenia are estimated to have a 1.5 to 2.0 times higher prevalence of risk factors for cardiovascular disease (CVD) (Casey, 2005). Emerging evidence suggests that patients with schizophrenia are more likely to die of CVD-related deaths as compared to the general population (Hennekens et al., 2005). Although many other factors are thought to contribute to this occurrence, antipsychotic medications have been examined for their potential role (Drici and Priori, 2007). Antipsychotic medications, particularly clozapine, have been associated with metabolic changes such as weight gain, hyperlipidemia, and glucose dysregulation, which may increase risk of cardiovascular disease. Clozapine has been associated with direct cardiovascular effects, such as tachycardia, bradycardia, hypotension, hypertension, QTc interval prolongation and other cardiac effects (Merrill et al., 2005). Clozapine-associated myocarditis and cardiomyopathy are rare adverse effects that are particularly worrisome to clinicians. Thought to be rare occurrences, the incidence of these adverse events has been difficult to determine (Wehmeier et al., 2005). However, the most recent published estimate of myocarditis incidence in clozapine-treated patients is 0.7–1.2% (Haas et al., 2007).

Because clozapine is such an important agent in the treatment of psychotic symptoms, and because possible antipsychotic-associated cardiac effects are being closely scrutinized, the concerns of possible cardiac complications and associated morbidity/mortality that may contribute to its underuse should be thoroughly investigated. A recent study by our group in a large schizophrenia population found that although the risk of CVD mortality in schizophrenia is increased over that of the general population, the risk did not appear to differ between clozapine (Standardized mortality ratio (SMR)=4.8, 95% CI: 3.2 to 6.8) and risperidone (SMR=3.1, 95% C.I: 1.3 to 6.1) ($\chi^2=0.81$, $p=0.37$) treatment (Kelly et al., under review). However, more information is needed about these patients, especially in situations where cardiac abnormalities may occur. This study examined cardiac related abnormalities upon autopsy inspection in people treated with clozapine compared to a sample who received risperidone treatment.

2. Methods

2.1. Study population

All patients who were treated with clozapine in the State of Maryland between 1990 and 2002, died between 1990 and 2004, and had an autopsy performed were included in the study. All clozapine treated patients were identified from a preexisting database maintained by the Clozapine Authorization and Monitoring Program (CAMP) in the State of Maryland.

The control group consisted of all patients who were treated as inpatients in State of Maryland psychiatric inpatient facilities, initiated on risperidone between 1994 and 2002, and died between 1994 and 2004. All control group patients were identified through the State of Maryland Antipsychotic Database. Risperidone-treated patients were chosen as a control group due to the relative differences in adverse effect profile between the two agents, as well as risperidone's comparable length of marketing in Maryland. The risperidone group was cross-matched with the CAMP database to identify for exclusion patients who were treated with clozapine before or after starting risperidone.

This protocol was approved by the University of Maryland and State of Maryland Institutional Review Boards. Due to the low-risk nature of the study, and the fact that the included patients were deceased, a waiver was granted for informed consent.

Deceased patients were identified through matching patient records with the Social Security Death Index (SSDI). The Social Security Death Index Database records death dates and locations as reported for US citizens who received social security benefits or paid social security taxes. Death certificates were obtained from the State of Maryland Division of Vital Statistics. If an autopsy was requested, it was noted on the death certificate. Autopsy records were collected from the Office of the Chief Medical Examiner's (OCME) office in Baltimore, Maryland.

During the time period of study, 403 deaths occurred in 4434 (9%) patients treated with risperidone or clozapine. There were 194 (9%) deaths in the clozapine group ($n=2134$) and 209 (9%) in the risperidone group ($n=2300$). Of these deaths, autopsies were performed on 62/194 (32%) patients in the clozapine group and 45/209 (21%) of the risperidone group. All autopsies performed on patients in the clozapine group were located, and 42/45 (93%) of the autopsies performed on patients in the risperidone group were located.

2.2. Data analysis

Variables collected from the autopsy reports (clozapine, $n=62$ and risperidone, $n=42$) included: weight, height, abdominal wall thickness, heart weight, liver weight, brain weight, diagnosis of diabetes, left ventricle thickness, right ventricle thickness, presence of

atherosclerosis, fibrosis and hypertrophy, coronary artery occlusions (left main coronary artery (LMCA), circumflex artery (CX), left anterior descending artery (LAD), right coronary artery (RCA)), cardiomyopathy/myocarditis diagnosis and cardiac-related death. This report also details the number of coronary arteries with notable occlusions.

3. Results

3.1. Demographic information

Autopsy results of 104 patients, 62 clozapine treated and 42 risperidone treated, were included in the study. Seventy-seven percent of clozapine treated patients were Caucasian, as were 57% of those treated with risperidone ($\chi^2 = 4.98$, $df = 2$, $p = 0.08$). African American patients made up 21% and 38% of the clozapine and risperidone treated groups, respectively, with 1.6% and 4.8% Asian patients in the clozapine and risperidone groups. Male patients comprised 76% of the clozapine patients and 71% of the risperidone group ($\chi^2 = 0.25$, $df = 1$, $p = 0.62$). Diagnostic data were missing for twelve patients: five in the clozapine group and seven in the risperidone group. The majority of patients with available diagnostic data 69/92 (75%) were diagnosed with a psychotic disorder (schizophrenia, schizoaffective disorder, or other psychotic disorder); 49/57 (86%) clozapine-treated patients were diagnosed with a psychotic disorder, as were 20/35 (57%) of the risperidone treated patients ($\chi^2 = 9.61$, $df = 1$, $p = 0.002$). Three of the 57 clozapine-treated patients (5.3%) were diagnosed with an affective disorder, as compared to 11 of 35 risperidone-treated patients (31%) ($\chi^2 = 11.51$, $df = 1$, $p = 0.0007$). Other specific diagnoses reported included substance abuse (two patients in the clozapine group and one patient in the risperidone group, respectively) and dementia (one patient in the risperidone group). The mean age of death in the clozapine group was 44 ± 9.6 years compared to 45.4 ± 14.0 years in the risperidone group ($t = -0.61$, $df = 102$, $p = 0.54$).

3.2. Cardiac death

Seven of the 62 deceased patients whose autopsies were available (11%) in the clozapine-treated group died of cardiovascular disease, as did 3/42 (7%) in the risperidone group ($\chi^2 = 0.496$, $df = 1$, $p = 0.481$). Three (5%) patients and two (5%) patients died of cardiomyopathy in the clozapine and risperidone groups, respectively. There was one death from myocarditis in the clozapine group.

3.3. Cardiac findings

No significant differences in any of the cardiac findings were noted between patients in the clozapine treatment and the risperidone treatment group (See Table 1).

Overall, 27.9% of patients in both groups had either atherosclerosis, fibrosis, or hypertrophy present at autopsy. The percentage of patients with atherosclerosis at autopsy was 17.7% (11/62) for the clozapine and 23.8% (10/42) for the risperidone treated groups, respectively ($\chi^2 = 0.572$, $df = 1$, $p = 0.449$), presence of fibrosis 4.8% (3/62) and 4.8% (2/42), respectively ($\chi^2 = 0$, $df = 1$, $p = 0.986$) and hypertrophy was 3.2% (2/62) versus 2.4% (1/42), respectively ($\chi^2 = 0.064$, $df = 1$, $p = 0.801$). Upon autopsy, the number of patients in the clozapine and risperidone groups exhibiting coronary artery occlusion was 8.1% (5/62) and 9.5% (4/42) respectively for 1+ occlusion, 8.1% (5/62) and 7.1% (3/42) respectively for 2+ occlusion, and 3.2% (2/62) and 4.8% (2/42) respectively for 3+ occlusion. No significant differences were found in any of these measures.

3.4. Body mass index (BMI)

The mean BMI at the time of death was 31.4 ± 8.8 kg/m² and 27.1 ± 8.2 kg/m² in the clozapine and risperidone treated groups respectively ($t = 1.98$, $df = 60$, $p = 0.052$). In both

groups, cardiomyopathy deaths were associated with a tendency towards higher BMI (cardiomyopathy group BMI = $40.29 \text{ kg/m}^2 \pm 15.35 \text{ kg/m}^2$ ($n = 5$), sample without cardiomyopathy BMI, $28.39 \text{ kg/m}^2 \pm 7.38 \text{ kg/m}^2$ ($n = 57$) (Wilcoxon test, $\chi^2 = 3.81$, $df = 1$, $p = 0.051$). A significantly higher abdominal wall thickness was found in the cardiomyopathy group, at $3.45 \text{ in} \pm 2.80 \text{ in}$ ($8.77 \text{ cm} \pm 7.11 \text{ cm}$) ($n = 5$) as compared with abdominal wall thickness of $1.45 \text{ in} \pm 0.63 \text{ in}$ ($3.68 \text{ cm} \pm 1.60 \text{ cm}$) ($n = 47$) in the sample without cardiomyopathy (Wilcoxon test, $\chi^2 = 4.12$, $df = 1$, $p = 0.042$).

3.5. Diabetes

There was no difference in prevalence of diabetes between the clozapine and risperidone groups. Six of the sixty-two patients (9.7%) in the clozapine-treated group as compared to 1/42 (2.4%) in the risperidone-treated group (Fisher's exact test, $\chi^2 = 2.12$, $df = 1$, $p = 0.24$) carried a diagnosis of diabetes at time of death.

4. Discussion

The adverse effect profile of clozapine is thought to contribute to its underuse in patients with refractory psychotic illnesses (Casey, 2005; Kelly et al., 2007a,b). Although the antipsychotic medications as a class have been associated with various adverse effects, the potential effects of clozapine have been under increased scrutiny (Abidi and Bhaskara, 2003; Allison et al., 1999; Drici and Priori 2007; Iqbal et al., 2003). The metabolic and weight effects associated with clozapine, as well as other antipsychotics, have been of increasing concern, both because of primary effects on health and the potential for increase in cardiac risk factors (Drici and Priori, 2007). The knowledge that patients with schizophrenia are more likely than members of the general population to die of CVD further underscores the need to investigate the development of CVD in this population (Casey, 2005; Goff et al., 2005). Exploration of the comparative findings of patients treated with clozapine, as well as other antipsychotics, is important to assess and further target safety concerns and other areas of research. To our knowledge, this is the first study to examine the presence of cardiac-related abnormalities in deceased patients treated with clozapine. In the analysis of the autopsy findings from 104 deceased patients treated with clozapine or risperidone, we found no significant differences in coronary artery occlusions, heart weight, ventricular thickness and other cardiac findings.

Antipsychotic medications in general, and clozapine in particular, have been associated with cardiomyopathy and myocarditis in rare cases. In the data mining study performed by Coulter et al. (2001), adverse events reported from 60 countries were scrutinized. A signal was detected for the association between clozapine and cardiomyopathy/myocarditis. A signal of association with cardiomyopathy/myocarditis was also found for antipsychotic medications as a group. In their report, risperidone was associated with cardiomyopathy but not myocarditis. In our study, three and two patients died of cardiomyopathy, respectively. There was one case of myocarditis death on clozapine. One in each group was not discovered until autopsy.

In our study, cardiomyopathy deaths were associated with a higher abdominal wall thickness, and a tendency towards higher BMI, as compared to the other causes of death. This finding was independent of drug treatment. Obesity-associated cardiomyopathy is becoming an increasing problem and has been found to occur independent of hypertension, coronary artery disease or other heart disease in the general population (Wong and Marwick, 2007a). Furthermore, insulin resistance may play a role in the pathophysiology of obesity-associated cardiomyopathy (Wong and Marwick, 2007b). Despite our results not being able to confirm if these cases were obesity related cardiomyopathy, obese patients on any antipsychotic may

be at risk for cardiomyopathy by nature of their obesity, whether or not the prescribed antipsychotic contributes additional independent risk.

Based on data at the time of death, clozapine patients in our study had a nonsignificant tendency to be heavier as compared to those treated with risperidone. Patients treated with certain antipsychotic medications may be at risk for becoming overweight (BMI ≥ 25 kg/m²) or obese (BMI ≥ 30 kg/m²). The potential for weight gain with the second-generation antipsychotics, especially clozapine and olanzapine, has been widely reported. Other second-generation and first-generation antipsychotics have also been associated with weight gain, to varying degrees. Clozapine and olanzapine have been the antipsychotics associated with the largest amount of weight gain, with 4 between 4 to 4.5 kg of weight gain at 10 weeks of treatment (Allison et al., 1999). Obesity is considered a risk factor for heart failure in the American College of Cardiology/American Heart Association ACC/AHA heart failure guidelines (Hunt et al., 2005). Efforts to prevent against and treat obesity in this population are of great importance. In addition to obesity, diabetes related variables might lead to greater mortality independent of coronary artery disease. Further study is needed to examine this relationship.

Our study is limited by the fact that it is retrospective in nature and lacking some data such as reason for autopsy, concomitant medications, underlying medical conditions, smoking status and lifestyle information. Also, due to limitations with available data, it cannot be guaranteed that all patients were actually taking clozapine or risperidone at the time of death. However, some of the potential changes that may be expected to occur as a result of medication exposure may be related to cumulative exposure and would not necessarily require medication be present in the body at time of death. Unfortunately, treatment duration could not be calculated consistently for all patients, so that information was not available for statistical analysis. However, due to the population from which this sample was drawn, it is likely that most patients had taken antipsychotic medication for a significant period of time. Likewise, doses of risperidone or clozapine were not reported. Although certain side effects of medications are likely dose-related, many of the adverse effects would be possible at all doses.

Nevertheless, it is the first report to examine autopsy data in this population. Despite these limitations, the existence of significant cardiac involvement in those treated with clozapine should have been apparent on autopsy. This study also included all diagnoses in order to have the largest sample possible. People with schizophrenia likely have a higher risk of cardiac complications as compared to other psychiatric diagnoses. Despite a larger number of patients diagnosed with a psychotic disorder in the clozapine group, no differences were noted in the autopsy findings. Lastly, the mean population in both antipsychotic groups is relatively young. This could be due to the tendency of individuals with schizophrenia to die at younger ages than the general population. An older sample with longer-term treatment may show more differences in cardiac abnormalities. However, the younger age of this sample allowed us to examine complications that may have occurred for reasons unrelated to older age. This sample also included a number of patients with diagnoses other than schizophrenia. For example, the risperidone group had more patients with an affective disorder diagnosis, at 31% versus only 5% of the clozapine group, and the clozapine likewise had more patients with a psychotic disorder diagnosis (85% versus 57%). The differences in diagnosis may be expected to equate to fundamental differences between patients, from concomitant medication exposure to lifestyle. In order to evaluate possible differences that diagnosis may play in the results, exploratory analyses were performed for patients in each group diagnosed with psychotic disorders. No statistical differences were noted between clozapine and risperidone patients with psychotic disorder diagnoses in cardiac death, fibrosis, hypertrophy, atherosclerosis, cardiomyopathy (3 in the psychotic

clozapine group and 2 in the psychotic risperidone group, respectively), or diabetes. The one significant difference in the psychotic disorders group was the difference between BMI for the clozapine (31.9 kg/m²) and risperidone (25.3 kg/m²) groups (Kruskal–Wallis test, $p = 0.014$).

Due to concerns about the adverse effect profile of clozapine, clinicians should carefully consider the risks and benefits in their individual patients. However, clozapine continues to be an agent with great importance for the treatment of patients with refractory psychotic symptoms. Our findings that the clozapine-treated group did not differ from the risperidone-treated group in terms of cardiac abnormalities is consistent with the findings of a recent study that did not find a difference between cardiovascular disease mortality in patients receiving clozapine or risperidone (Kelly et al., under review). This reinforces the need for further research on antipsychotics and their potential direct and indirect effects on cardiovascular health. Finally, clinicians should remain vigilant about the potential increased cardiovascular risks of this patient population in general.

Acknowledgments

Special thanks to the Baltimore Office of the Chief Medical Examiner for the assistance in acquiring full autopsy reports.

Role of funding source

This work was supported by the National Institutes of Mental Health (R03 MH069871-01; Kelly, PI and the Advanced Centers for Intervention and Services Research (ACISR) (P50 MH40279; Carpenter, PI). The NIMH and ACISR had no further role in the design, collection, analysis, interpretation of data, in the manuscript preparation, and in submission of this study.

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Table 1

Demographic and autopsy data between treatment groups.

Characteristic	Clozapine <i>n</i> = 62	Risperidone <i>n</i> = 42	Test statistic
Age at time of death (years)	44.0 ± 9.6 ^a	45.4 ± 14.0	<i>t</i> = -0.61, <i>df</i> = 102, <i>p</i> = 0.54
Sex (male) (%)	76%	71%	$\chi^2 = 0.250$, <i>df</i> = 1, <i>p</i> = 0.62
Race (white)	48/62 (77%)	24/42 (57%)	$\chi^2 = 4.98$, <i>df</i> = 2, <i>p</i> = 0.08
Psychotic disorder diagnosis (%)	86%	57%	$\chi^2 = 9.61$, <i>df</i> = 1, <i>p</i> = 0.002
Affective disorder diagnosis (%)	5.3%	31%	$\chi^2 = 11.51$, <i>df</i> = 1, <i>p</i> = 0.0007
BMI ^a (kg/m ²)	31.4 ± 8.8	27.1 ± 8.2	<i>t</i> = 1.98, <i>df</i> = 60, <i>p</i> = 0.052
Abdominal Wall thickness (in)	1.8 ± 1.3 (4.6 ± 3.3 cm)	1.4 ± 0.9 (3.6 ± 2.3 cm)	<i>t</i> = 1.20, <i>df</i> = 50, <i>p</i> = 0.24
Liver weight (g)	2206.1 ± 862.6	1949.8 ± 698.9	<i>t</i> = 1.19, <i>df</i> = 54, <i>p</i> = 0.24
Heart weight (g)	458.4 ± 172.9	443.4 ± 139.0	<i>t</i> = 0.35, <i>df</i> = 55, <i>p</i> = 0.72
LV thickness (cm)	1.5 ± 0.3	1.7 ± 0.4	<i>t</i> = -1.31, <i>df</i> = 16, <i>p</i> = 0.21
RV thickness (cm)	0.4 ± 0.1	0.7 ± 0.9	<i>t</i> = -1.02, <i>df</i> = 5.03, <i>p</i> = 0.356

^aMean ± Standard deviation (SD).