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ORIGINAL PAPER

Effects of Cigarette Smoking and Clozapine Treatment on 20-Year All-Cause & Cardiovascular Mortality in Schizophrenia

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Abstract
To estimate 20-year mortality risk in people with schizophrenia treated with second-generation antipsychotics (SGA) and examine the effects of cigarette smoking on mortality. Of the 1199 individuals with schizophrenia in the study, estimated 20-year all-cause mortality risk by Kaplan Meier Curve was 30% and leading causes of death included 27% cardiovascular disease, 13% cancer, 12% non-HIV infection, 5% respiratory causes, 20% other causes and 18% had unknown cause of death. For all-cause mortality, we found that white race and male sex were significant risk factors (HR = 1.5, $p = 0.002$ and HR = 1.33, $p = 0.033$, respectively). For cardiovascular mortality risk, we showed that cigarette smokers and white race were at higher risk (HR = 1.86, $p = 0.017$ and HR = 1.71, $p = 0.045$, respectively). Cardiovascular mortality risk at 20-years is 11%. Kaplan-Meier Survival Curve showed a statistical difference for smokers and non-smokers in cardiovascular mortality over the 20-year follow-up (Log rank chi-square = 5.35, df = 1, $p = 0.02$). 20-year all-cause mortality risk for individuals with schizophrenia was found to be 30% with cardiovascular disease as a leading cause. Cigarette smokers and white race were associated with an increased risk of death. Regarding cardiovascular mortality specifically, cigarette smoking increased risk by 86% over a 20-year period. Clozapine was neither a risk factor for all-neither cause nor cardiovascular mortality. This data suggests that long-term cardiovascular mortality continues to be increased in schizophrenia for those who are or have been cigarette smokers.

Keywords Schizophrenia · Mortality · Clozapine · Cigarette · Smoking · Cardiovascular

Introduction

Within the United States (US), approximately 0.9–1.5% of individuals are diagnosed with schizophrenia or a related psychotic disorder [1]. Schizophrenia has a profound effect on

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individuals' lives. It is rated by the World Health Organization (WHO) to be within the top 15 diseases for leading causes of disability. On average, the estimated life lost is 28.5 years per person [2, 3]. Previous schizophrenia mortality studies have reported that the most common cause of mortality is natural causes representing about 80–86% of deaths [3, 4]. Cardiovascular disease, specifically coronary artery disease, is the leading cause of natural death [5]. Other frequent causes include cancer (e.g. lung cancer), respiratory disease (COPD), and infection [3, 4]. Although deaths due to suicide or accidents only represents a minority of deaths, compared to the normal population, the risks are higher in patients with schizophrenia [3, 4].

The increased risk of mortality of individuals with schizophrenia is most likely attributable to a multitude of factors such as comorbidities, insufficient health services, poor diet and exercise, medication side effects, substance abuse, stigma about mental illness, and low economic status [4–11]. Metabolic syndrome and smoking are commonly associated with cardiovascular disease.

The metabolic syndrome, which is often exacerbated or caused by second generation antipsychotics (SGA), has been reported to increase the chance for cardiac risk factors such as weight gain, dyslipidemia, and diabetes [12]. Despite this evidence, studies have been inconsistent in demonstrating the effects of metabolic syndrome on mortality [12]. It is also unclear whether certain SGAs associated with higher rates of metabolic syndrome, such as clozapine, are associated with higher long-term mortality than other SGAs with lower liability for metabolic complications [12]. Because cardiovascular outcomes can take many years to develop and risperidone, the first SGA marketed after clozapine, only came to US market in 1994, there is a limited amount of data on long-term mortality.

Cigarette smoking rates are significantly higher among individuals with schizophrenia compared to general population (58–90%). Although patients with schizophrenia are more likely to smoke, rates of cancer mortality are lower than expected [13–16]. While there is an abundance of literature on mortality effects from cigarette smoking in the general population, there is a paucity of data specifically for the population with schizophrenia. Our earlier studies on 10-year mortality show that cigarette smoking is the highest risk factor for cardiovascular mortality in those with schizophrenia. However, with shorter life expectancy, the frequent presence of other comorbidities and life style issues, it is uncertain if cigarette smoking continues to carry a significant mortality risk in an aging population over a 20-year interval [15].

Objectives

To estimate the 20-year mortality risk of individuals with schizophrenia or other psychotic disorders, we examine the effect of cigarette smoking, clozapine use, and demographic variables on long-term mortality. We further examined the long-term impact of cigarette smoking and the use of SGAs risperidone and clozapine on all-cause and cardiovascular mortality.

Methods

In this multicenter respective cohort study, unique patient records were included from individuals admitted to one of the seven public inpatient mental facilities in the State of Maryland between January 1, 1994 and December 31, 2000. Inclusion required that individuals be 19 to 69 years old, have a DSM-III or IV diagnosis of schizophrenia, schizoaffective disorder or psychosis not otherwise specified (NOS), and be prescribed either risperidone or clozapine.

January 1, 1994 was selected as the start date, because this was the first year risperidone was marketed in the US. Previously, clozapine had been the only SGA available. Patient data was identified and collected by two trained research staff (doctoral and predoctoral interns). Training included education on clinical charts, where to find objective information, and how to collect information using the standardized data collection forms. For the data collection and recording process, research staff used an algorithm. Patient records were not included if their records had incomplete information. This information from clinical charts confirmed diagnoses and provided history of cigarette use from the admission history and hospitalization records. This study was approved by State of Maryland IRB.

Mortality data were identified through utilization of the Social Security Death Index (SSDI). The SSDI is a national computerized database, which includes information on date of death, location, and date of birth. To confirm the identity of an individual on the SSDI, their name, date of birth, and social security number were matched to their patient record. Only individuals who died between January 1, 1994 and December 31, 2014 were included to avoid omission of patients who were not yet updated in SSDI. In some cases, it takes months to years to be added to the SSDI. To ensure that no records were missed, 3 team members independently examined SSDI information. After the identification and development of a list of deceased individuals through SSDI, a request for death certificates was sent to the Maryland Department of Health Vital Statistics Administration (VSA) in the Department of Health. From the death certificates, we verified dates of death and collected primary cause of death.

A total of 1213 patient records were identified and 14 were excluded due to nonmatching identifications. Thus 1199 were included in the analysis. Forms and data collection procedures were the same across each public inpatient mental health facility. For patients with multiple hospitalizations, data were used from the first hospitalization. The SGA prescribed at the time of first hospitalization during the study period was recorded; however, antipsychotic treatment during follow-up was unknown and may have changed through the course of treatment. Smokers were defined as subjects who currently smoked or who had ever been dependent on cigarettes. During the initial period of the study, patients could smoke in the hospital, however around 2007, the State of Maryland inpatient hospital facilities began to phase in a "tobacco-free" environment.

Cause of death was identified from death certificates and characterized into cardiovascular, infection (not HIV/AIDS), respiratory, cerebral vascular, cancer, other, and unknown. Cardiovascular disease deaths included: atherosclerotic cardiovascular disease, hypertensive cardiovascular disease, coronary artery disease, coronary vessel disease, coronary occlusion, congestive heart failure secondary to cardiovascular disease, myocardial infarction with underlying cardiovascular disease, myocarditis, dilated cardiomyopathy, and cardiac arrhythmia with underlying cardiovascular disease. Cardiovascular disease death did not include myocardial infarction secondary to other causes (e.g. cancer, asphyxia, infection), and cerebral vascular disorders (e.g. cerebral vascular attack, stroke, or cerebral hemorrhage).

Statistical Methods

All-cause mortality and cardiovascular mortality risk was estimated using the Kaplan-Meier method of survival analysis, with data included up to 12/31/2014. After 12/31/2014, mortality data was not included in the study. The Cox proportional hazards life regression model was used to estimate hazard ratios for mortality (age, race, sex, cigarette smoking and antipsychotic treatment) [17].

Results

A total of 1199 patient records were included and demographic variables can be seen in Table 1. 268 (22%) deaths occurred and the distribution can be seen in Table 2. Cardiovascular disease was the largest known contributor to death followed by cancer, non-HIV/AIDS infection, respiratory disease, and cerebral vascular disease.

Mortality Risk

The risk of all-cause mortality at 5, 10, 15 and 20 years are listed in Table 3. We also listed cardiovascular morality risk and distinguished risk between smoker and non-smoker groups. The risk of all-cause mortality and cardiovascular mortality was found to be 30% and 11%, respectively at 20 years. For smokers, 20-year all-cause and cardiovascular mortality risk was 32% and 13%, respectively. In comparison, non-smoker all-cause and cardiovascular mortality risk was 26% and 7%, respectively.

Predictors of Mortality

For all-cause mortality risk, white race and male sex were statistically significant risk factors (Table 4). For cardiovascular morality risk, white race and smoking were clinically significant risk factors. The comparison of cardiovascular mortality risk between cigarette smokers and non-smokers can be seen in Fig. 1. There was a significant difference noted on the Log-Rank Chi-square ($p = 0.02$).

Discussion

The schizophrenia population is known to be at an increased risk of mortality in comparison to the general population, but current literature has yet to fully uncover the extent to which metabolic syndrome and cigarette smoking affect mortality in those with chronic schizophrenia

Table 1 Demographic information

Demographic Information		Total Sample = 1199
Mean Age (years)		41 (±11.4)
Sex	Male	745 (62%)
(1 missing)	Female	453 (38%)
Race	White	622 (58%)
(132 missing)	African American	445 (42%)
Medication	Clozapine	380 (32%)
	Risperidone	819 (68%)
Diagnosis	Schizophrenia	646 (54%)
	Schizoaffective	400 (33%)
	Other psychotic disorder	153 (13%)
Cigarette	Smoker	654 (55%)
	Non-smoker	545 (45%)

Demographic was collected from unique patient records from individuals admitted to one of the seven public inpatient mental health facilities in the State of Maryland between January 1, 1994 and December 31, 2000. Majority of data was male sex, white race, treatment with risperidone, diagnosis of schizophrenia, and smokers

Table 2 Causes of death

Causes of Death (total deaths = 268)			
Mean age at death	56 years (±11.7)	HIV/AIDS Infection	4 (2%)
Cardiovascular	72 (27%)	Diabetes	2 (1%)
Cancer	36 (13%)	Homicide	2 (1%)
Infection (not HIV/AIDS)	31 (12%)	Hepatic	1 (1 > %)
Respiratory	14 (5%)	Others	39 (15%)
Cerebral vascular	14 (5%)	Unknown	47 (18%)
Suicide	6 (2%)		

Cause of death data was collected from death certificates from the Maryland Department of Health Vital Statistics Administration. Death certificate were requested for individuals who were recorded as deceased in the Social Security Death Index

[3, 8]. In our study, we were able to provide additional insights into how these variables affect mortality. We observed that the 20-year mortality risk was 30%, and the most common cause of death was cardiovascular disease. We also found that white race and male sex were statistically significant risk factors for all-cause mortality and white race and cigarette smoking were statistically significant risk factors for cardiovascular mortality. These finding are mostly consistent with previous mortality studies in patients with chronic schizophrenia and contributes additional evidence [3, 4, 8].

Like studies on the prevalence of cigarette smoking in individuals with schizophrenia, smoking rates were high and more than half of the patient records indicated the patient smoked [16, 18, 19]. Our finding that cigarette smoking was statistically significant for increased cardiovascular mortality risk ($p = 0.017$) was unsurprising; however we only observed a numerical increase in mortality compared to non-smokers (32% vs 26%). In our previous 10-year mortality study on cigarette smoking, we reported that smoking increased both all-cause and cardiovascular mortality [15]. One reason for this difference may be attributable to the average lifespan of individuals with schizophrenia (56 ± 11.7 years) which is much earlier than the general population (78.8 years) [20]. Given the difference in lifespan, it is possible that the detrimental effects of cigarette smoking may have not had enough time to accrue and result in a lethal event. We did not have information on current smoking status, so it is also possible that people decreased cigarette smoking or had cessation in older years, contributing to less of an all-cause mortality difference in smokers. Harm reduction and cessation may lead to a decrease in mortality associated with smoking [21].

Our findings comparing clozapine to risperidone treatment showed there was no statically significant difference in all-cause or cardiovascular mortality risk between the two

Table 3 Mortality risk

Mortality Risk	5 years	10 years	15 years	20 years
All-cause mortality	6%	14%	21%	30%
Smoker	8%	15%	22%	32%
Non-smoker	5%	12%	19%	26%
Cardiovascular mortality	2%	4%	6%	11%
Smoker	3%	6%	7%	13%
Non-smoker	1%	2%	4%	7%

Mortality risk was analyzed using a Kaplan Meier Survival Curve over a 20-year period

Table 4 Predictors of mortality

Predictors of Mortality		Hazard ratio and 95% CI	Chi-square
All-cause mortality	White race	1.5 (CI 1.16–1.95)	0.002*
	Clozapine	0.93 (CI, 0.72–1.22)	0.611
	Male sex	1.33 (CI, 1.02–1.72)	0.033*
	Smoker	1.22 (CI, 0.95–1.56)	0.12
Cardiovascular mortality	White race	1.71 (CI 1.01–2.88)	0.045*
	Clozapine	1.16 (CI, 0.7–1.91)	0.574
	Male sex	0.94 (CI, 0.58–1.54)	0.811
	Smoker	1.86 (CI, 1.12–3.1)	0.017*

*statistically significant ($p < 0.05$)

medications. Despite clozapine being associated with a higher incidence of metabolic syndrome compared to other antipsychotics, these finding were not surprising and are consistent with previous studies [22–27]. The results are important because clozapine is a useful treatment option for treatment-resistant schizophrenia (TRS) and fear of metabolic syndrome may be a barrier to its use for some healthcare providers. Although clozapine has not been found to increase the risk of mortality, the effects of metabolic syndrome and the development of cardiac risk factors are still clinically relevant. Cardiovascular mortality in schizophrenia is likely complex and attributable to many factors besides metabolic syndrome. Possible contributing factors may include an inherent physiologic risk with schizophrenia, poor lifestyle habits, substance abuse, and preexisting comorbidities.

Our study found that white race and male sex were risk factors for all-cause mortality and white race for cardiovascular mortality. These findings are consistent with previous mortality studies of individuals with schizophrenia and our 10-year mortality studies [3, 4, 15, 25]. The enhanced risk in all-cause mortality in males and white race may be due to higher rates of suicide in males and white race which may be masked by the unknown cause of death category [3, 4]. Although our results are consistent with previous studies, our study did exclude 132 patient records due missing info on race, so these findings should be interpreted cautiously.

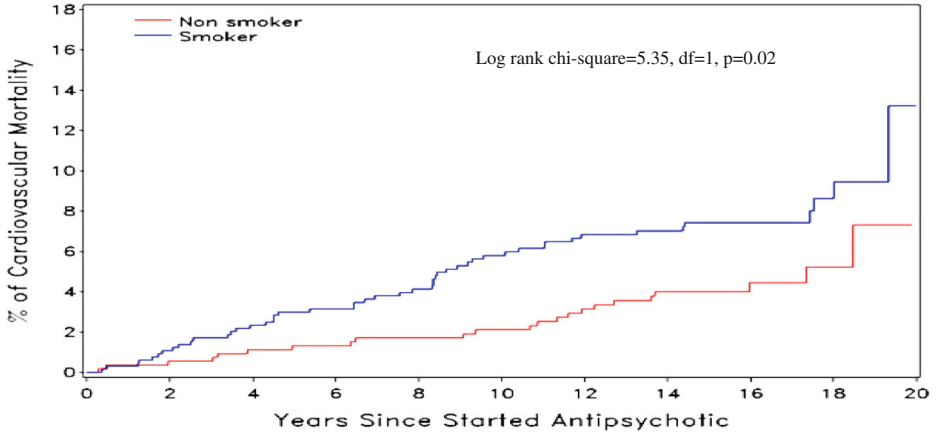

Fig. 1 Cardiovascular Mortality Difference Between Non-smokers and Smokers. Analyzed by Cox Proportional Hazard Regression model for cardiovascular mortality in a cohort of smokers and non smokers. Generated by SPSS

Strengths of our study included its large sample size, extended duration, and use of patient hospital admission and treatment records instead of claims or administrative data that may be less accurate and incomplete [28–30]. For example, previous studies have reported that as much as 25% of the time, medical record diagnoses did not match the administrative diagnosis [30].

Limitations of our study included the retrospective design, lack of knowledge about previous and future treatments, and possible inaccuracies in death records. Also, the study size could have been too small to demonstrate a difference in some of the more uncommon causes of death. Lack of information on previous and future treatments is a limitation, because changes in medication or previous treatments may have affected mortality.

This study contributes further evidence that opportunities exist to improve the lives of those with schizophrenia. Thirty percent of our chronic patients are at risk of death in 20 years following their first antipsychotic treatment. Future research should examine the best methods to improve cardiovascular health among this specific population.

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Compliance with Ethical Standards

Conflict of Interest Deanna L. Kelly: Advisory board for Lundbeck and a consultant for HLS Therapeutics. Raymond C. Love: Speaking fee for Nevada Psychiatric Association, received honorarium for Advisory Board on Pharmacist Administration of Medication, and is part of the National Alliance of State Pharmacy Association. All other authors declare they have no conflicts of interest.

Ethical Approval All procedures performed were done so in accordance with the ethical standards of the University of Maryland and Maryland Department of Health Institutional Review Boards and with the 1964 Helsinki declaration and its later amendments.

Informed Consent A waiver of informed consent was approved by the University of Maryland-Baltimore and the Maryland Department of Health Institutional Review Boards for this retrospective study.

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