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Sudden unexpected death in schizophrenia: Autopsy findings in psychiatric inpatients



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ABSTRACT

Schizophrenia is associated with premature mortality and a high rate of sudden, unexpected deaths. Autopsy data are scant, and in studies using death certificates or root cause assessments, a majority of sudden deaths remained unexplained. In the community, post-mortem data indicate that the most common cause of sudden “natural” death is coronary artery disease. In this study, we used autopsy findings to determine the cause of sudden death in a consecutive cohort of 7189 schizophrenia patients admitted to a free-standing, psychiatric teaching hospital from 1989 to 2013. Medical record review identified 57 patients (0.79%) who died suddenly and unexpectedly during hospitalization. Autopsies were performed in 51 (89.5%) patients (55.9 ± 9.4 years, male = 56.9%). Autopsy-based causes of sudden death were most commonly cardiovascular disorders (62.8%). Specific causes included myocardial infarction (52.9%), pneumonia (11.8%), airway obstruction (7.8%), myocarditis (5.9%), and dilated cardiomyopathy, hemopericardium, pulmonary embolus, hemorrhagic stroke and brain tumor (2.0% each). The sudden death remained unexplained in 6 (11.8%) patients, 3 of whom had evidence of coronary arteriosclerosis on autopsy. Patients with and without myocardial infarction were similar regarding age, gender, smoking, body mass index and psychotropic treatment (*p* values ≥ 0.10). In conclusion, sudden cardiac death occurs at a 0.8% rate in a psychiatric hospital, well above general population rates. Autopsy findings indicate that sudden death in schizophrenia is caused by structural cardiovascular, respiratory and neurological abnormalities, with most cases due to acute myocardial infarction. Early recognition and treatment of coronary artery disease must become a clinical priority for all adults with schizophrenia.

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1. Introduction

The physical health of patients with schizophrenia is poor (De Hert et al., 2011a) and a large body of evidence has documented their shortened life expectancy (Osby et al., 2000; Rasanen et al., 2005; Colton and Manderscheid, 2006; Bushe et al., 2010). Suicides, accidents and cardiovascular disorders are considered the main reasons for the excess of premature, sudden and unexpected deaths in this population (Ruschena et al., 1998; Appleby et al., 2000; Colton and Manderscheid, 2006; Loas et al., 2008; Bushe et al., 2010; Manu et al., 2011). In patients treated with antipsychotic drugs, which include a large number of

individuals receiving psychiatric care for schizophrenia, sudden cardiac death has been the focus of large epidemiological studies in the United States (Ray et al., 2001; Ray et al., 2009). Using death certificates and complex algorithms to exclude patients who died from previously known noncardiac conditions and to adjust for co-morbid somatic disorders, the investigators established that the incidence-rate ratio of sudden cardiac death was doubled in individuals prescribed first- or second-generation antipsychotics in the last month of life (Ray et al., 2009). The findings were thought to reflect the dose-dependent antipsychotic drugs' inhibitory effect on phase 3 of the myocardial cell repolarization, which may lead to *torsades de pointes*, an arrhythmia that may lead to ventricular fibrillation and sudden death. However, the findings were disputed by the American Psychiatric Association's Council on Research, which has stated that “a retrospective analysis of death certificates to evaluate mortality by SCD [sudden cardiac death], ... may overestimate SCD incidence” (Lieberman et al., 2012). The American Psychiatric Association's position is supported by the methodology used to ascertain the sudden arrhythmic death syndrome

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(Behr et al., 2007). This diagnosis is made in cases of sudden death with no history of cardiac disease, no identifiable macroscopic cause of death at a complete autopsy, and no abnormal findings on microscopic examination of the heart by a cardiac pathologist.

Autopsy findings in patients with schizophrenia who died suddenly have been reported only a few times in the past two decades. In a study of 66 cases presented to the medical examiner in Maryland from 1994 through 1996, the majority of deaths not due to accidents or suicides were caused by atherosclerotic heart disease (Chute et al., 1999). In a 10-year review of 683 autopsies performed in people with a history of schizophrenia by the Department of Forensic Medicine in Sydney, Australia, the main cause of natural death was cardiovascular disease, present in 23% of a cohort in which 37% of deaths were attributed to suicide or voluntary overdose with prescribed or illicit drugs (Sweeting et al., 2013). In this Australian series, 72 (11%) of cases remained unexplained, and 30 of these patients were presumed to have primary arrhythmogenic disorders which may have been discoverable at a “molecular autopsy” (Semsarian and Hamilton, 2012). A study limited to 10 cases of clozapine-induced myocarditis diagnosed at autopsy included 3 patients with sudden and unexpected death (Ronaldson et al., 2011). The significance of these observations is limited by selection bias and incomplete clinical data.

Reported rates of sudden cardiac death in the general population range from 0.1 to 0.2% (Zipes and Wellens, 1998). In contrast with the limited data regarding the etiology of sudden death in patients with schizophrenia, autopsies have established that the majority of sudden and unexpected fatalities in the community are due to coronary artery disease. In a prospective study involving 692 individuals without history of cardiac disease autopsied in 83 coroner's jurisdictions in England, death was ascribed to coronary artery disease in 82.4% of cases, with acute ischemic changes in more than half of the subjects (Bowker et al., 2003). The proportion of coronary artery disease as the cause of sudden death was 63% in Ireland (Downes et al., 2010), and 80% in Hennepin County, Minnesota (Adabag et al., 2010). Similar findings have been reported in autopsies of adult hospital patients in Pittsburgh, Pennsylvania, who were presumed to have died of cardiac arrhythmia, but of whom 62% had >75% coronary artery stenosis and 53% had histological evidence of myocardial infarction (Nichols and Chew, 2012).

In this study, we present analyses of a consecutive cohort of patients treated for schizophrenia who died suddenly and unexpectedly in Romania, a country in which the public health legislation mandates autopsies for all patients dying during a hospital stay. We adopted a null hypothesis and postulated that the main cause of death in patients with schizophrenia is no different than in the general population, i.e., coronary artery disease with evidence of acute myocardial infarction.

2. Materials and methods

2.1. Setting

The patients described in this report were admitted to a 120-bed, free standing, public psychiatric hospital located in Brasov, Romania (population 277,000). The clinical care is provided by board certified psychiatrists affiliated with the local medical school. Patients deemed by their treating psychiatrist to have a significant medical deterioration are transferred the same day to the county hospital. The retrospective review of medical records was approved by the hospital's Ethics in Research Committee.

2.2. Patient population

From January 1, 1989 through December 31, 2011, the hospital admitted 7189 adult patients diagnosed with schizophrenia according to the contemporaneous version of the *Diagnostic and Statistical Manual* of the American Psychiatric Association. Public health legislation

requires a forensic evaluation of all inpatient deaths. The post-mortem examinations are carried out by board certified pathologists employed by the government at the local Institute for Legal Medicine. Autopsies are performed in all cases and the pathology report must include a summary of the findings. Exceptions from autopsy are granted only for narrowly defined religious or personal preference reasons.

2.3. Definition of sudden death

Hospital records over the 25-year period of the study identified 57 patients who died suddenly and unexpectedly. All of these patients died while being asymptomatic or within 1 h of new symptom(s) onset. None of these patients died of physical trauma, homicide, suicide or accidental drug overdose.

2.4. Data collection

Autopsies were performed in 51 (89.5%) of the 57 patients with schizophrenia who died suddenly and unexpectedly. Data extracted from their medical records and the post-mortem examination report included demographic information, duration of psychiatric disorder, length of stay prior to death, past medical history, medication regimen at the time of death, and autopsy findings. The chlorpromazine equivalent of the antipsychotic drugs received in 24 h preceding the sudden death was calculated according to published guidelines (American Psychiatric Association, 1997; Woods, 2003) and as previously used (Correll et al., 2009).

2.5. Statistical analyses

The autopsy findings were used to divide the sample into two groups of patients with or without myocardial infarction at autopsy. The significance of the differences between groups was assessed with χ^2 or Fisher's Exact tests for proportions and *t* test for continuous variables. All data were analyzed with JMP 5.0.1, 1989–2003, SAS Institute, Inc, Cary, North Carolina. All tests were two-sided, and alpha was set at <0.05.

3. Results

The study group comprised 29 males (56.9%) and 22 females (43.1%) with a mean age of 55.9 ± 9.4 years (Table 1). Patients had been diagnosed with schizophrenia for an average of 27.7 ± 10.3 years prior to their sudden death. The admitting diagnosis for the last hospitalization was paranoid subtype in 47 patients (92.2%), and catatonic and undifferentiated in 2 patients (3.9%) each. With the exception of one patient with pneumonia in whom the antipsychotic was stopped 2 days prior to death, all patients had received antipsychotic drugs in 24 h preceding their death, which had occurred after an average length of stay of 11.7 ± 7.6 days. The past medical history, as recorded by the admitting psychiatrists, was remarkable for congestive heart failure (4 patients, 7.8%), arterial hypertension (4 patients, 7.8%), bronchial asthma or chronic obstructive pulmonary disease (3 patients, 5.9%), diabetes mellitus (1 patient, 2.0%) and dyslipidemia (1 patient).

3.1. Causes of death

Cardiovascular disorders, identified in 32 (62.8%) of the cases, were the most common cause of sudden death in this cohort of inpatients with schizophrenia. The cardiovascular disorders included 27 patients (52.9%) with acute myocardial infarction, and 3 patients (5.9%) with myocarditis. None of the cases of myocarditis had been treated with clozapine. One patient (2.0%) had dilated cardiomyopathy and acutely decompensated heart failure with pulmonary edema. The cause of death was identified in one patient (2%) as cardiac tamponade due to hemopericardium. This patient was the only one restrained just before

Table 1
Demographic features and psychotropic drug treatment of schizophrenia inpatients who died suddenly and unexpectedly and had a post-mortem examination.

Characteristic	Total (N = 51)	Myocardial infarction on autopsy (N = 27)	No myocardial infarction on autopsy (N = 24)	p
Age (years ± S.D.)	55.9 ± 9.4	53.9 ± 9.0	58.3 ± 9.9	0.10
Male gender, N (%)	29 (56.9%)	16 (59.3%)	13 (54.2%)	0.71
Duration of schizophrenia (years ± S.D.)	27.7 ± 10.3	25.6 ± 10.0	30.1 ± 10.5	0.13
Length of stay (days ± S.D.)	11.7 ± 7.6	10.5 ± 7.0	13.0 ± 8.2	0.26
Antipsychotic drugs at the time of death, N (%)				
First generation antipsychotics	43 (83.4%)	23 (85.4%)	20 (83.3%)	0.85
Haloperidol	38 (74.5%)	19 (70.4%)	20 (83.3%)	0.28
Levopromazine	19 (37.3%)	9 (33.3%)	10 (41.7%)	0.54
Chlorpromazine	5 (9.8%)	4 (14.8%)	1 (4.2%)	0.20
Thiopropazine	2 (3.9%)	2 (7.4%)	0	0.17
Second generation antipsychotics (%)	8 (15.7%)	4 (14.8%)	4 (16.7%)	0.85
Clozapine	3 (5.9%)	1 (3.7%)	2 (8.3%)	0.48
Amisulpride	3 (5.9%)	2 (7.4%)	1 (4.2%)	0.62
Olanzapine	1 (2.0%)	1 (3.7%)	0 (0.0%)	0.25
Quetiapine	1 (2.0%)	0 (0.0%)	1 (4.2%)	0.28
Number of antipsychotic drugs ± S.D.	1.43 ± 0.58	1.41 ± 0.64	1.46 ± 0.51	0.76
Antipsychotic polytherapy, N (%)	20 (39.2%)	9 (33.3%)	11 (45.8%)	0.36
Chlorpromazine equivalent (mg/day ± S.D.)	420.1 ± 187.1	410.2 ± 198.3	431.3 ± 173.6	0.69
Other psychotropics at the time of death, N (%)				
Benzodiazepines	38 (74.5%)	19 (70.4%)	19 (79.2%)	0.47
Mood stabilizers	18 (35.3%)	12 (44.4%)	6 (25%)	0.15
Antidepressants	2 (3.9%)	0 (0.0%)	2 (8.3%)	0.13

the sudden death. He had a ruptured left ventricular wall, and may have had an early myocardial infarction, but the report of microscopic findings could not be located for this retrospective analysis.

Among the 11 (21.6%) patients who died of a respiratory disorder, 6 (11.8%) had pneumonic consolidations, 4 (7.8%) had airway obstruction (laryngeal or tracheal) with food boluses, and one (2.0%) died of a massive pulmonary embolus. In two cases (3.9%), the death was due to a neurological disorder, a hemorrhagic stroke and a brain tumor (Table 2).

The post-mortem macroscopic and histological examination did not identify a specific cause of death in 6 (11.8%) patients. Structural abnormalities of the heart were identified in 5 of them, i.e., extensive coronary arteriosclerosis in 3, dystrophic myocardial changes and chronic pericarditis in one patient each (Table 3). The patients with coronary atherosclerosis had no evidence of coronary thrombosis or myocardial necrosis. The patient with myocardial dystrophy had fibrofatty replacement, similar to findings reported in cases of sudden death produced by arrhythmogenic cardiomyopathy (Basso et al., 2009), but no pre-mortem evidence of ventricular rhythm disturbance. No additional virological, toxicological or biochemical studies were performed.

Table 2
Causes of sudden, unexpected death in schizophrenia inpatients who had a post-mortem examination.

Cause of death	N (%)	95% confidence interval
Cardiovascular disorders	32 (62.8%)	49.5–76.0%
Myocardial infarction	27 (52.9%)	39.2–66.6%
Myocarditis	3 (5.9%)	0–12.3%
Dilated cardiomyopathy	1 (2.0%)	0–5.8%
Hemopericardium	1 (2.0%)	0–5.8%
Respiratory disorders	11 (21.6%)	10.3–32.9%
Pneumonia	6 (11.8%)	2.9–20.6%
Airway obstruction	4 (7.8%)	0.5–15.2%
Pulmonary embolus	1 (2.0%)	0–5.8%
Neurological disorders	2 (3.9%)	0–9.2%
Hemorrhagic stroke	1 (2.0%)	0–5.8%
Brain tumor	1 (2.0%)	0–5.8%
Unexplained	6 (11.8%)	2.9–20.6%

3.2. Chronological distribution of sudden and unexpected death

The 5-year intervals with the lowest and highest rates of sudden and unexpected death were 1999–2003 (0.569%) and 2004–2008 (1.085%), respectively (Fig. 1).

3.3. Comparison of patients who died of myocardial infarction with the other patients

Patients who died of myocardial infarction (n = 27) and those who died of another cause (n = 24) were similar with regard to age, gender, duration of illness, length of stay, psychotropic treatment during their last admission (Table 1) and past medical history.

A majority of patients in both groups were cigarette smokers (63.0% vs 66.7%, p = 0.78). The groups with and without myocardial infarction had similar body mass index (25.0 ± 3.3 vs. 25.9 ± 4.5 kg/m², p = 0.40) and proportion of patients with fasting glucose levels ≥ 100 mg/day (18.5% vs. 16.7%, p = 0.86). Low-density lipoprotein cholesterol levels were not assessed.

4. Discussion

In this study, we used autopsy findings to determine the cause of sudden death in a cohort of 7189 patients admitted for the treatment of schizophrenia to a free standing teaching psychiatric hospital over a 25-year period (1989–2013). Medical record review identified 57 (0.79%) patients who died suddenly and unexpectedly during the hospital stay. Autopsies were performed in 51 patients. The post-mortem examinations indicated that 27 (52.9%) patients had myocardial infarction, 6 (11.8%) pneumonia, 4 (7.8%) airway obstruction, 3 (5.9%) myocarditis, and 1 (2.0%) each dilated cardiomyopathy, hemopericardium, pulmonary embolus, hemorrhagic stroke and brain tumor. The sudden death remained unexplained in 6 (11.8%) patients, 3 of whom had evidence of coronary arteriosclerosis on autopsy. Patients with and without myocardial infarction were similar with regard to age, gender, smoking, body mass index and psychotropic drug therapy. The rate of myocardial infarction identified in this study is greater than that in community samples (Kannel and Thomas, 1982; Waller et al., 1992) and, if confirmed in larger samples of patients with schizophrenia, may represent a specific vulnerability of patients with this psychotic disorder.

Table 3
Demographic features and autopsy findings in schizophrenia patients with unexplained sudden death.

Patient #	Age (years)	Gender	Body mass index	Smoker	Length of stay (days)	Autopsy findings
1	32	Male	29.0	Yes	11	Interstitial pulmonary fibrosis
2	49	Male	20.1	Yes	6	Coronary arteriosclerosis
3	60	Male	27.3	Yes	10	Myocardial dystrophy
4	66	Male	32.7	Yes	6	Coronary arteriosclerosis
5	58	Female	21.1	Yes	2	Coronary arteriosclerosis
6	66	Female	25.5	No	4	Chronic pericarditis

The data are limited by the lack of toxicological evaluation of cases without a clear cause of death, incomplete pre-mortem assessments of risk factors for coronary artery disease, and absence of information regarding the prevalence and etiology of sudden death in the community from which the psychiatric hospital receives its patients. Nevertheless, this is the first study in which all sudden deaths in patients with schizophrenia have been witnessed and an autopsy was carried out without delay in a near-totality (89.5%) of cases.

The autopsy findings support the hypothesis that the causes of sudden death in schizophrenia are not different than in the community-dwelling populations (Thomas et al., 1988; Bowker et al., 2003; tavora et al., 2008; Adabag et al., 2010; Downes et al., 2010) and patients admitted to general hospitals (Heriot et al., 2010; Nichols and Chew, 2012) without severe mental illness, in whom unexpected deaths are primarily due to coronary artery disease that has produced a myocardial infarction. Coronary artery disease is highly prevalent as a cause of sudden death (42%) even in subjects aged 30–40 years old (Shen et al., 1995). Advances in genetic testing aimed at discovering mutations associated with the long QT syndrome have not changed the etiological hierarchy of sudden death, as demonstrated by a recent study of 71 patients aged 25–60 who died suddenly in Minneapolis (Adabag et al., 2010). Acute coronary lesions were found in 27% of patients and previous silent myocardial infarction was discovered in 34% of cases, while only 5 subjects (7%) had possibly deleterious mutations of the ion channel genes.

The data generated by the autopsies in this cohort of patients with schizophrenia expand the observations previously reported by us on 100 consecutive sudden deaths (18% with autopsy) in psychiatric patients in a New York psychiatric institution (Manu et al., 2011). Using structured, multidisciplinary root cause analyses, the cause of death was identified in 48 cases (48.0%). Fifteen of those (31.3%) had evidence of an acute coronary syndrome, while the unexplained cases were predicted by the presence of diabetes and dyslipidemia, i.e., the main risk factors for coronary artery disease (Manu et al., 2011). The utilization of antipsychotic drugs was similar in the explained and unexplained groups, a finding echoed by the finding of similar chlorpromazine equivalent dosages of antipsychotics administered during the last day of life to patients with and without myocardial infarction presented in our current report. Likewise, the other causes of death discovered at autopsy in this study were not different from those frequently reported in our previous survey of psychiatric patients (Manu et al., 2011), in which we have found a similar prevalence of myocarditis, upper airway obstruction, pneumonia, pulmonary embolization and hemorrhagic

strokes. The one case of sudden death caused by rapidly expanding brain tumor is unusual and the proposed mechanism of death includes herniation due to mass effect, acute hemorrhage and seizures (Vougiouklakis et al., 2006). Taken together, the data do not support a construct implying that an antipsychotic-related arrhythmia is the primary event responsible for a significant proportion of sudden deaths in patients with schizophrenia receiving antipsychotic drugs.

The presence of upper airway obstruction with undigested food (choking) among the causes of death in this group of schizophrenia patients reflects the high risk of dysphagia in patients with severe mental illness. In a 400-bed Massachusetts hospital 4 patients died in 1 year from asphyxia. Prospective studies have identified bradykinetic dysphagia secondary to neuroleptic-induced extrapyramidal syndrome (Bazemore et al., 1991) and fast eating syndrome (Fioritti et al., 1997) as the most common causes of life-threatening choking episodes. The risk of deep venous thrombosis, leading to pulmonary embolism, is also increased in patients treated with antipsychotic drugs (Shulman et al., 2013).

Our findings suggest that a substantial decrease in the prevalence of sudden death in schizophrenia can be obtained only through programs aimed at the primary prevention of coronary artery disease and secondary prevention of myocardial infarction. In the Framingham Heart Study, from 1950 to 1999, such programs have proven their effectiveness among individuals without psychotic disorders by decreasing the risks of sudden death and non-sudden mortality related to coronary artery disease by 49% and 64%, respectively (Fox et al., 2004). Reductions of this magnitude will require not only early detection and treatment of coronary and diabetogenic risk factors in psychiatric settings, but also parity in access and quality of medical care for patients with schizophrenia. In order to achieve these important goals that have been highlighted for at least a decade now, provider, patient and system level barriers must be identified and addressed (De Hert et al., 2011b).

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None.

Contributors

1. Petru Ifteni designed the study and collected the clinical and autopsy data.
2. Christoph Correll designed the study and performed the data analyses.
3. Victoria Burtea designed the study and collected the clinical data.
4. John Kane provided advice during study design, data collection and data interpretation.
5. Peter Manu designed the study, collected autopsy data and wrote the paper.

Conflicts of interest and source of funding

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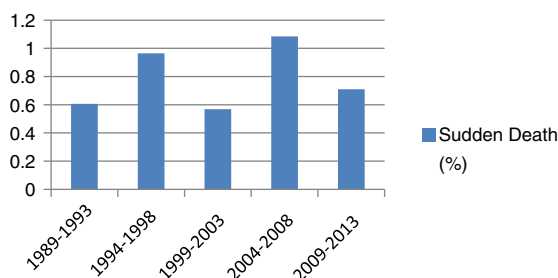


Fig. 1. Frequency (%) of sudden unexpected death among schizophrenia inpatients.

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