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Clinical Characteristics, Comorbid Medical Diagnoses, and Causes of Death of Individuals with Severe Mental Illness Who Died During Follow-up in Community Mental Health Centers: A Multicenter, Retrospective Study

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SUMMARY

Objective: In this study, it was aimed to define the clinical characteristics, causes of death, disease and treatment of patients who died while being followed for severe mental illness.

Method: The study was carried out in ten community mental health centers from six provinces. The clinical characteristics, causes of death, course of the illness and treatment characteristics of the patients who had a death report from the date the community mental health centers were opened until the start date of the study were analyzed by retrospective file scanning method.

Results: In an average of 52 months, files of 3715 patients were examined. There were death declarations for 106 patients. The diagnosis of most patients with death declarations was schizophrenia (78%), most of them were male (66%), mean age was 57, mean disease duration was 24 years. The rate of multiple antipsychotic medication use was 61%. The most common comorbidities were metabolic syndrome (36%), hypertension (22%), diabetes (18%) and chronic obstructive pulmonary disease (15%). The most frequently reported causes of death were cardiovascular diseases (39%), infectious diseases (14%) and cancer (11%).

Conclusion: Individuals with severe mental illness followed up in community mental health centers are mostly die due to preventable natural causes of death. Therefore, a sensitive approach should be taken to evaluate psychiatric and other medical conditions together. In our country, there is a need for natural follow-up studies investigating the average age of death and causes of death of individuals with severe mental illness.

Keywords: Schizophrenia, bipolar disorder, comorbidity, death, community mental health centers

INTRODUCTION

The life expectancy of individuals diagnosed with severe mental illness (SMI) such as schizophrenia, schizoaffective disorder and bipolar disorder is 9-20 years shorter as compared to the general population (Hoang et al. 2011, Laursen et al. 2014, Hayes et al. 2017, Cansız et al. 2018). Although this can be ascribed to high rates of suicide and accidents among individuals diagnosed with SMI, these unnatural causes account only for 40% of the incidences of death, the rest of the casues being preventable diseases including mainly cardiovaseular and cerebrovascular diseases, pulmonary system diseases, infections and cancer (Roshanaei-Moghaddam and Katon 2009, Baxter et al. 2016, Döngel et al. 2018).

Individuals with SMI have significant psychiatric, medical and social problems which complicate the diagnosis, treatment, and follow-up of the medical comorbidity as well as the psychiatric symptoms. They are under 1.5 fold higher risk for all medical diseases compared to healthy controls (Bahoriket al. 2017).

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The higher prevalence of medical diseases in SMI patients is caused by delayed and inadequate treatment, the side effects of the antipsychotic agents and also the unhealthy life style due to sedentary living, alcohol/substance use and improper eating behaviours (Laursen et al. 2014). The clinical condition of metabolic syndrome (MetS), involves multiple cardiometabolic risk factors for many medical conditions headed by diabetes and stroke. (Eckel et al. 2005). The International Diabetes Federation (IDF) bases MetS on meeting the obligatory criterion of increased waist circumference together with at least two criteria stipulated as high blood pressure, raised serum triglycerides, raised fasting blood glucose and and low level of high-density lipoprotein (HDL) (Alberti et al. 2006). Patients with SMI therefore constitute a high-risk group for MetS and need to be monitored regularly (Van Winkel et al. 2008, Cerit et al. 2008, Mitchell et al. 2013). It has been stated that individuals with SMI should be controlled for modifiable risk factors contributing to increased mortality, screened for comorbid medical diseases and assisted for access to healthcare services to be able to receive early diagnosis and treatment (Schoepf et al. 2014, Bahorik et al. 2017).

Although there are many international studies on the causes and the age of death among individuals with SMI, only few investigations made on the subject in Turkey have included data on the mean age of death as 59 years in schizophrenia (İpekçioğlu and Kendirlioğlu 2019), 51 years in bipolar disorder (Cansız et al. 2018), and as 50 years in cases of SMI (Böke et al. 2007) and reported the major causes of death as cardiovascular diseases, cancer, infections, and suicide (Böke et al. 2007, Cansız et al. 2018, İpekçioğlu and Kendirlioğlu 2019). Hence, it can be said that in Turkey, as also shown in other countries, the casuese of death for SMI cases are similar to those for the general public. It has been argued that individuals diagnosed with SMI cannot adequately benefit from the developments in the treatment of medical diseases that cause death and that the life expectancy gap observed between them and the general population may continue to increase over time (Laursen et al. 2014).

Patients diagnosed with SMI are expected to monitored regularly either in their own environment or in the CMHC premises within the scope of the community-based model of mental healthcare service designed to increase treatment quality and functionality with the aim to reintegrate the patients with the society. At the time of writing this article, the Ministry of Health data showed 177 CMHCs actively serving the population in their regions of responsibility (Ministry of Health 2020). It has been reported that healthcare facilities around the world equivalent to the CMHCs accomplish a more favorable contribution to the course of medical diseases in individuals with SMI (Druss et al. 2010, Vanderlip et al. 2017). Therefore, it is important to increase the knowledge and awareness of the healthcare professionals working in the CMHCs in Turkey about the comorbid diseases, MetS and all causes of death among individuals with SMI, who, according to the relevant planning, are to be registered and followed at the CMHCs in the long term on an outpatient basis.

Although there are data obtained from studies in different countries in the literature, there are only a few studies investigating the causes of death of individuals with SMI in our country. The research of CMHC is not available. In this study, it was aimed to determine the sociodemographic, clinical and treatment features and the causes of death of patients with SMI who have so far been followed up in CMHCs in Turkey.

METHODS

The study was carried out by the participation of 10 CMHCs actively providing service in 6 different provincial centers in Turkey. The patients who had ben issued with death certificates during follow up in these participating CMHCs, between the dates when they had been opened for public service and the date (18/07/2019) of starting this research, were determined by retrospective screening of the patient files. Age, gender, education level, marital status, socioeconomic level of the patients (defined as the low socioeconomic level of those who do not receive aid from the state), causes of death, all medical and psychiatric diagnoses, treatment characteristics, duration of psychiatric illness, CMHC registration periods, whether they came to CMHC within the previous six months before death, whether they were MetS according to the IDF criteria and other information related to the study were obtained from CMHC follow-up files and hospital information systems. The causes of death of the patients were learned from the hospital information system. The relatives of those whose causes of death could not be found in the hospital information system were contacted by phone to learn. The causes of death of some patients could not be determined. The study was conducted in accordance with the Declaration of Helsinki by obtaining the approval of the Non-Pharmaceutical Scientific Research Ethics Committee of the Health Sciences University Izmir Bozyaka Training and Research Hospital. dated and numbered as "SBÜİBEAHKAEK 17/07/2019-001" and written permissions from the chief physicians of the hospitals which the CMHCs are affiliated with.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 21.0 package program was used for data analysis. The data obtained from the CMCHs were expressed as percentage distribution, mean and standard deviation. Analyses by the One-sample Kolmogorov Smirnov test showed that the numerical data did not meet the assumptions for normal distribution. The Chi-square test was used to investigate the significance of the proportional differences between independent groups; and the Mann-Whitney U test was used to compare the continuous variables. The variables

were analyzed within the 95% confidence interval and p<0.05 value was considered statistically significant.

RESULTS

The CMHCs participating in this research had served in excess of 4 millian individuals throughout a mean period of 52.4±25.39 months, the service history of the earliest and the most recently opened centers being , respectively, 15 and 96 months. By retrospective scanning of the patient files kept after being registered at these centers, a total of 106 patients were found to have been issued with death certificate. The data on the participating CMHCs and the death certifications made by each are given in Table 1.

The 106 patients issued with death certificate comprised 36 (34%) females and 70 (66%) males with a mean age of 56.71±12.38 years and disease duration of 24.38±11.88 years. Of these, 62 (58.5%) had low level economic satus; 43 (40.6%) were married; higher number of males were single (p=0.025) and 81 (76.4%) had not attended the CMHC during the 6 months before the date of death. The sociodemographic and clinical data of these patients are given in Table 2.

Table 1. CMHCs Participating in the Research and Their Features

	History of Service (months)	Total number of Population the CMHC is Responsible for	Total Number of the Patients Registered at the CMHC	After CMHC Registration Death Notification Number and Percent of Patients	
				(n)	(%)
İzmir Bozyaka CMHC[1]	64	500.000	367	6	5.7
İKCU ATRH CMHC[2]	56	558.000	479	12	11.3
Kemalpaşa CMHC[3]	27	102.000	210	3	2.8
Kuşadası CMHC[4]	15	120.000	526	8	7.5
Balıkesir CMHC[5]	96	183.084	617	37	34.9
Tuzla CMHC[6]	31	252.923	414	9	8.5
Konya Beyhekim CMHC[7]	72	1.289.450	317	13	12.3
Konya Selçuk CMHC[8]	40		180	3	2.8
Kayseri TRH CMHC-1[9]	65	1.389.680	755	15	14.2
Kayseri TRH CMHC-2[9]	39				
Total		4.395.137	3715	106	100

CMHC: Community Mental Health Center, IKCU ATRH: Izmir Katip Celebi University, Atatürk Training and Research Hospital, Kayseri TRH: Kayseri Training and Research Hospital.
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Table 2. Sociodemographic and Clinical Characteristics of Patients with Death Notifications During Follow-up in CMHC

	Female n=36 (34.0%)		Male n=70 (66.0%)		Total n=106 (%100)		*p*
Age (mean±SD)	57.42±11.41		56.35±12.92		56.71±12.38		0.631*
Marital Status (number, %)							0.025**
Single	6	16.7	24	34.3	30	28.3	
Married	13	36.1	30	42.9	43	40.6	
Widowed/Divorced	17	47.2	16	22.9	33	31.1	
Socioeconomic Level (number, %)							0.221**
Low	24	66.7	38	54.3	62	58.5	
Middle	12	33.3	32	45.7	44	41.5	
Disease Duration (Year) (mean± SD)	22.29±11.08		25.51±12.23		24.38±11.88		0.217*
Diagnosis (number, %)							
Schizophrenia	28	77.8	62	88.6	90	84.9	0.141**
Bipolar disorder	8	22.2	8	11.4	16	15.1	
CMHC follow-up duration (month) (mean± SD)	15.81±11.20		20.14±15.84		18.51±14.34		0.556*

*Mann-Whitney U test **Chi-square test

Table 3. Characteristics of Psychotropic Agents Used by Patients with Death Notifications While Being Followed up in CMHC

	Number	Percent
Combination Antipsychotic Use		
Single antipsychotic	38	35.8
Two or more antipsychotics	68	64.1
Long-acting antipsychotic use		
Not using	53	50.0
Long-acting antipsychotic only	32	30.2
Long-acting and oral use together	21	19.8
Antipsychotic Agents		
Quetiapine	40	37.7
Olanzapine	33	31.1
Aripiprazole	21	19.8
Risperidone	18	17.0
Clozapine	17	16.0
Paliperidone	13	12.3
Amisulpride	13	12.3
Haloperidol	10	9.4
Zuclopenthixol	5	4.7
Chlorpromazine	2	1.9
Mood Stabilizers		
Valproic acid+ Sodium valproate	16	15.1
Lithium	5	4.7
Carbamazepine	2	1.9
Lamotrigine	1	0.9
Other Psychotropic Agents		
Antidepressant	24	22.6
Biperiden	7	6.6
Cholinesterase enzyme inhibitors	2	1.9

Table 4. Medical Comorbidities Diagnosed and Causes of Death Among Patients While Being Followed up in CMHCs

	Number	Percent
Diagnosed Medical Comorbidities		
Hypertension	23	21.7
Diabetus Mellitus	19	17.9
Chronic Obstructive Pulmonar	16	15.1
Disease	12	11.3
Cancer	11	10.4
Congestive Heart Failure	6	5.7
Epilepsy	5	4.7
Chronic Renal Failure	4	3.8
Dementia	3	2.8
Coronary Artery Disease	2	1.9
Cerebrovascular Disease	1	0.9
Tuberculosis	1	0.9
Parkinson's Disease	52	49.1
Not known		
Cause of Death		
Cardiovascular disease	41	38.7
Infections	15	14.2
Cancer	12	11.3
Accident	7	6.6
Stroke	5	4.7
Other reasons	5	4.7
Suicide	4	3.8
Unknown	17	16.0

Table 5. Comparison of Causes of Death and the Use of CAPM of Patients with Death Notification During Follow-up in CMHC, According to Whether They Have Additional Diseases or Not

	Comorbidity No (n=52)		Comorbidity Yes (n=54)		*p*
Cause of Death (number, %)					
Unknown	10	(19.2)	7	(13)	0.531*
Cardiovascular disease	21	(40.4)	20	(37)	
Other	21	(40.4)	27	(50)	
CAPM (number, %)					
No	20	(38.5)	18	(33.3)	0.582*
Yes	32	(61.5)	36	(66.7)	

CAPM: Combination of antipsychotic medication
*Chi-square test

Table 6. Comparison of the Causes of Death of Patients with a Death Report While Being Followed up in CMHC According toTheir Combination Antipsychotic Use

	CAPM (-) (n=38)		CAPM (+) (n=68)		*p*
Age (mean±SD)	56.05±13.61		56.87±17.76		0.747
Cause of death (number, %)					
Unknown	4	(10.5)	13	(19.1)	0.391
Cardiovascular disease	14	(36.8)	27	(39.7)	
Other	20	(52.6)	28	(41.2)	

CAPM: Combination of antipsychotic medication

While 53 (50%) of the patients were on depoantipsychotic agents, 68 (64.1%) were on combination therapy with 2-3 agents. The most prescribed antipsychotics were quetiapine (n=40, 37.7%), olanzapine (n=33, 31.1%) and aripepriazole (n=21, 19.8%). Biperiden was prescribed for 7 (6.6%) cases; and valproic acid (n=16, 15.1%) was the most prescribed mood stabilizer. The details of the pharmacotherapy given to the patients during follow up at the participating CMHCs are given in Table 3.

Medical comorbidities had been found during follow up in 54 (50.9%) of the patients with 38 (35.8%) having been diagnosed with MetS on the IDF criteria. The most frequently reported medical comorbidities were hypertension (HT) (n=23, 21.7%), diabetes mellitus (DM) (n=19, 17.9%), and chronic obstructive pulmonary disease (COPD) (n=16, 15.1%). The first three reported causes of death were cardiovascular diseases (n=41; 38.7%), infection (n=15; 14.2%), and cancer (n=12, 11.3%). There were 17 cases (16%) with unknown cause of death. Data on the comorbidities and causes of death are given in Table 4.

Statistically significant differences were not determined between the incidences of death with and without medical comorbidities (p=0.531) or with and without the use of combination antipsychotic therapy (CAPM) (p=0.582) (Table 5). Also significant differences were not found wih respect to mean age and the use of single or combination antipsychotic therapy (Table 6).

DISCUSSION

This study demonstrated that death certificates were issued mainly for single male patients with SMI and a mean age of 57 years, during follow up at 10 different CMHCs in 6 different provincial centers of Turkey. The most frequently reported cause of death was cardiovascular disease and the most prevalent medical comorbities were HT, DM and COPD.

The higher incidence of death seen among the male patients is consistent with the results of international follow-up studies (Brown 1997, Ran et al. 2007, De Mooij et al. 2019). This was attributed to a higher effect of SMI on mortality in males (Chang et al. 2010) or the possibility of lonely life being a higher risk of mortality for the single male members of the general popıulation (Franke and Kulu 2018). Although SMI diagnosis in lonely single males can increase the risk of mortality, this explanation may not be valid for Turkey given the sociocultural background that allows single men to live together with their families. The factors of loneliness/ lack of social support has not been evaluated in this study as the relevant data on the family background of the patients were not available. Long term follow up studies are needed to validate this assumption in our country.

The latest published figure on the mean life expectancy in the general population of Turkey was 78.3 years (TurkStat 2019). In our study, the mean age of death for the 106 patients with SMI and certified death during follow up at a CMHC was 57 years. Recently the lowered life expectancy of individuals with SMI has been ascribed to multiple factors including their inability to monitor comorbid medical diseases with regularity due to cognitive impairment and adverse psychiatric symptoms; the possible prevention of receiving adequate medical service by the stigmatizing attitudes of healthcare professionals and attribution of the physical symptoms and complaints of the comorbidity to the psychiatric disorder and the adverse contribution to the prognosis of the medical comorbidity by the side effects of the multidrug therapy for the psychiatric and the medical conditions (Laursen et al. 2014, Bitter et al. 2017). We found out that the majority of the deaths certified by the CMHCs were due to preventable natural causes and half of the cases did not involve medical comorbidites. The World Health Organization (2015) called for increased awareness by the physicians working in the field of the shortened life expectancy of individuals with SMI which is a public health problem yet to be corrected despite the prolongation of life expectancy with the recent developments in medicine. Not having included a control group in this research, has prevented the comparative evaluation of the life expectancy of patients with SIM, but we can say, on the basis of the data given in the literature, that the CMHC employees attending individuals with SIM should be careful about this fact.

CAPM is defined as the use of multiple antipsychootics. A common reason for the use of CAPM is the expectation of a greater or faster therapeutic response than can be achieved with a single agent (Barnes and Paton 2011). However, there is not any evidence based effectiveness of using CAPM in the maintenance treatment for SMI (Langan and Shajahan 2010). Even if the use of CAPM is preferred for certain clinical indications on the basis of the treatment guidelines, careful monitoring and evaluations of clinical efficacy and side effects are recommended (Goodwin et al. 2009, Baandrup 2020), There are arguments that the use of CAPM increases the risk of death in individuals with SMI, and that the use of more than one medication may pose the risk of severer side effects and treatment noncompliance (Goodwin et al. 2009,Langan and Shajahan 2010, Kadra et al. 2018). In our study, 64% of the patients with SMI were on combined antipsychotic therapy and the percentage of patients on clozapine was low. These results are similar to those reported by others on patients followed up in CMHCs (Tabo et al. 2012, Aydın et al. 2020). The use of CAPM was found to be high (62%) with notably low (3%) use of clozapine in patients with psychotic disorders living in institutions in Turkey (Ersan and Yıldız 2015). Treatment guidelines recommend the use of CAPM in the limited cases resistant to clozapine with the warning for awareness by physicians of the possibility for increased risk of mortality (Kadra et al. 2018). In this study, the age of death and cause of death were not different between the cases with and without the use of CAPM. Also, the use of CAPM was not sifgnificantly different in the cases with and without comorbidity. An explanation for these results may be related to the limited number of the cases which prevented comparison of numbers of cases on the basis of death cause. Statistical analysis of the data was possible by grouping on the basis of cardiovascular diseases, other causes and uknown causes of death. Even though the results on differences were statistically insignificant, observation of CAPM use as high as 64% was remarkable. It is recommended that our results should be repeated on larger numbers of cases.

In our study, the incidences of HT, DM and COPD were the highest among the medical comorbidities diagnosed with SMI; and the distribution frequencies were similar to those seen in previously reported studies on individuals diagnosed with SMI in Turkey (İpekçioğlu and Kendirlioğlu 2019, Döngel et al. 2018, Cansız et al. 2018). The 35.8%. prevalence of MetS observed in our study was similar to the those reported among schizophrenia (41%) and CMHC patients (46.5%) in Turkey (Cerit et al. 2008, Delibaş and Erdoğan 2019). As reported in the literature, the prevalence of MetS seen in patients with SIM followed up in CMHCs are above that determined in the general population (McEvoy et al. 2005) and can be attributed to the lifestyle, diet, inadequate medical care, smoking and using psychotropic medications (Casey et al. 2011). Quetiapine and olanzapine observed in our study as the most frequently used antipsychotics, are both risky agents for developing MetS (Meyer and Nasrallah 2009). Antipsychotic agents may have adverse effects on some of the modifiable risk factors related to MetS and, therefore,

psychiatrists have been recommended to be aware of the potential metabolic side effects of antipsychotic medications (De Hert et al. 2009). It has been stressed that physicians are held responsible for the inadequacies in following up comorbid medical diseases underlying the increased mortality among individuals with SMI (Bitter et al. 2017). Given the increased risk of early mortality in cases of SIM comorbid with HT, DM and/or COPD, follow up at CMHCs is recommended to include primary interventions for weight management, cessation of cigarette smoking and health screening for assessment and optimal treatment of DM, hyperlipidaemia and cardiovascular diseases. It was noticed in this study that more than half of the patients who died during follow up had not attended the CMHCs for minimally 6 months, suggesting that the psychiatric as well as the medical follow ups did not have regularity. Patients not attending their follow up appointments should be actively chased for on site close follow up by the CHMC mobile teams.

In our study, 52 (49.1%) patients with a death report did not have a known medical disease. This result is consistent with the literature reporting that the frequency of overlooked medical disorders is high in individuals diagnosed with SMI (Döngel et al. 2017). It has been suggested that the prevalence of comorbidities associated with the causes of death and their fatal course may indicate that individuals diagnosed with SMI, despite medical advances, may not receive therapies that will benefit the same as individuals without a diagnosis of SMI (Laursen et al. 2014, Piotrowski et al. 2017) Psychiatrists should be trained well enough in the detection and treatment of physical diseases, be aware of common comorbidities, play a more active role in diagnosis, prevention and treatment, anti-stigmatization training for practitioners and physicians in other specialties to ensure that individuals diagnosed with SMI can receive equal healthcare services with other segments of the society suggested (Leucht et al. 2007, Döngel et al. 2018). Sudden death has long been known to be common among psychiatry patients using antipsychotic agents (Appleby et al. 2000) which raise the risk of sudden cardiac death (Ray et al. 2009) by 2-3 fold in cases with SIM as compared to the general population (De Hert et al. 2011). In our study we determined 17 (16%) cases with cause of death unkown. Statistically significant differences were not determined when comparing the patients with and without known cause of death on the use of CAPM. Much as unknown cause of death and death without a medical comorbidity suggest sudden cardiac death, the only explanation may not be this and our results also do not support this possibility. It is concluded that in future studies care should be given to the outcome of cardiac death and follow ups and data collection should be made accordingly.

Our results indicated that the most common causes of death of patients with SMI under healthcare follow up were cardiovascular diseases, infections and cancer. These results are in agreement with those on the causes of death in individuals with SMI diagnosis (Saha et al. 2007, Roshanaei-Moghaddam and Katon 2009, İpekçioğlu and Kendirlioğlu 2019). Also, the two leading causes of death in the Turkish population were reported as circulatory system diseases and malignant tumors with incidences of, respectively, 36.8% and 18.4% (TurkStat. 2019). As reported in the literature (Brown 1997), death is caused by similar medical conditions in the members of the general population and the individuals with SMI, but occurs at an earlier age in the latter group. In our study, the incidence of death by suicide among patients with a mean disease duration of 25 years was lower than that reported for the patients in the initial years of SMI diagnosis (Çetin and Eker 2011). This may be explained by the difference in the years of disease duration.

The data of this research, based on retrospective file investigations, may include the erroneous data entries in the patient files. For example, data on the cause of death, diagnosis of any medical illness, the place of living and whether alone or with company could not be found for some of the cases. Also, a limitation has been caused by not being able to compare the data with those on patients with SMI diagnosis not registered at CMCHs and on healthy controls. There are a limited number of studies in Turkey regarding the causes of death in individuals diagnosed with SMI, our study being the first multi-center retrospective study in this field. Despite these limitations, we believe that our study will contribute to the literature by presenting data from the CMCH services in our country.

CONCLUSION

Generally, the most frequent causes of death among individuals followed up for SMI are cardiovascular diseases, infections and cancer. It was seen in this study that HT, DM, COPD and MetS were also common causes of death in the patients registered with CMHCs in Turkey. The results indicate for more active role in early diagnosis, treatment, and uninterrupted medical follow-up for comorbidites. It is recommended to develop the needed healthcare policies and precautionary measures by conducting natural follow-up studies on the population members diagnosed with SMI in order to determine their mean age of death and the causes of death in comparison to the general population.

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