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Regional disease characteristics and comorbidities of patients with schizophrenia in the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC): Findings from an international large simple trial*

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ABSTRACT

Background: Using baseline data from the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), we assessed disease characteristics and prevalence of select comorbidities among subjects with schizophrenia in different clinical settings across 18 countries. ZODIAC was a randomized, open-label, one-year, large simple trial (LST) that enrolled 18,239 individuals with schizophrenia. Methods: Subjects were randomized to open-label treatment with ziprasidone (n = 9120) or olanzapine (n = 9119) in naturalistic (usual care) settings and followed for one year. Study sites (n = 749) applied minimal selection criteria in an attempt to make the study population as representative as possible of those receiving treatment in "real world" circumstances across the countries. Results: Mean patient age was 41 years, 55% were male, 34% were markedly ill or presented with more severe disease, and 66% of subjects had one or more select comorbid conditions [*i.e.* heart attack, stroke, hypertension, CAD/angina, high cholesterol/triglycerides, diabetes, or overweight (BMI ≥ 25)] at baseline. History of suicide attempt was greatest in the US (38%), compared with Sweden (34%), Brazil/South America (26%), Asia (23%), and Eastern Europe (20%). Overweight or obesity was the most prevalent comorbid risk factor, representing 60% of enrolled subjects, 70% of US subjects compared with 30% in Asia and 52% - 64% in the other regions studied. High cholesterol/triglycerides levels were found in 23% of US subjects compared with a relatively low prevalence in other countries (3% - 11%). History of cardiovascular or diabetes-related comorbidities was found in 31% of subjects. Current smoking (46.5%) and past smoking (11.8%) were common with men dominating the proportion of current smokers: US (61%); Asia (60%); Sweden (50%); Eastern Europe (49%); and Latin America (44%). Conclusions: Our findings indicate substantial baseline variations across countries in demographics, comorbid conditions, and psychiatric disease history. These data provide an international epidemiologic picture of schizophrenia and may help guide future research and treatment initiatives.

Keywords: Large Simple Trial; Schizophrenia; ZODIAC; Comorbidities

1. INTRODUCTION

Large simple trials (LSTs), with minimal selection requirements, are designed to assess the reliability, generalizability, and overall relevance of treatments in real world environments. As such, they verify and supplement findings from classical randomized controlled trials

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(RCTs) by providing robust, real-life safety and effectiveness based on observed patterns in naturalistic settings [1-3]. This is especially relevant for persons with psychotic disorders when baseline ethnic, health, and other risk factors are known to be potential moderators or mediators of psychiatric treatment outcomes [1,4].

The majority of clinical and observational data on schizophrenia published to date are derived from North American and West European populations. However, these data do not capture the full scope of disability given the high percentage of persons with psychiatric disorders residing in middle- or low-income countries [5]. This has prompted criticisms [6,7] and calls to address this imbalance [8,9].

The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) was a global, randomized, LST in schizophrenia that enrolled 18,239 subjects from 18 countries in North America, South America, Europe, and Asia [10]. It provided real-world data on outcomes for persons with schizophrenia from practice settings in diverse healthcare systems and cultures [10,11].

The aim of this paper is to highlight key demographic characteristics and assess the prevalence of psychiatric comorbidities among this large cohort. Data from international studies like ZODIAC offer the advantage of comparisons that could add important insight on diversities and challenges in treating this debilitating illness.

2. METHODS

2.1. Study Design

A total of 18,239 persons diagnosed with schizophrenia, schizophreniform, and schizoaffective disorder were enrolled in the ZODIAC LST between February 2002 and February 2006 (last patient last visit: April 2007). As described in detail elsewhere [11], participants were randomized to ziprasidone or olanzapine, after which no further protocol-mandated interventions were made. The primary study goal was to determine whether there was a statistical difference between ziprasidone and olanzapine for non-suicide mortality in typical clinical situations. Inclusion criteria were broad and exclusion criteria were minimal. While initial assignment of drug was done in a random fashion, neither the physician nor the subject was blinded to treatment allocation, consistent with routine medical care. Physicians and subjects were free to change regimens and dosing based on subjects' response to the assigned medication, and use of concomitant medications, including other antipsychotics, was permitted. Patients were followed for up to 1 year, regardless of duration on randomized treatment, to evaluate study outcomes. No laboratory testing or clinical monitoring was required by the protocol; rather, visits and tests were performed at the discretion of the treating physician.

2.2. Study Assessments

Baseline questionnaires were completed by the treating clinicians or other study team members. Data on patient characteristics included age, height, weight, race (e.g. Caucasian/white, African-American/black, Asian/Pacific islander, Hispanic/Latino, other), smoking status (e.g. current smoker, past smoker, never smoked, unknown), age of onset and severity of schizophrenia (assessed using the Clinical Impression Scale [CIS], which is equivalent to the Clinical Global Impression [CGI] scale), number of previous psychiatric hospitalizations, history of suicide attempts, prior antipsychotic use (including ziprasidone or olanzapine), family and personal history of cardiovascular disease (CVD) and metabolic risks (e.g. heart attack, stroke, hypertension, coronary artery disease/angina, arrhythmia, high cholesterol/triglycerides), history of diabetes diagnoses and prior use of insulin or oral hypoglycemics, and other concomitant medication use and smoking status as reported by subject or caregiver.

The study follow-up form included questions on antipsychotic medication use, incidence of diabetes since last study visit, current diabetic therapy, height, weight, emergency room visit or hospitalization, and patient vital status since the last visit.

2.3. Statistical Methods

Pearson chi-square for categorical variables and F-test for continuous variables were used to compare patient characteristics and prevalence rates of comorbidities among subjects in different regions. Multivariate logistic regression models and ANCOVA were applied to evaluate cross-sectional associations of patient characteristics with comorbidities and polypharmacy (number of antipsychotic medications currently used >1). Patient characteristics collected included age, gender, race, duration of illness, smoking status, CIS score, psychiatric inpatient hospitalization experience, and history of suicide attempts. Duration of illness was derived as the time from date of diagnosis (self-reported) to the randomization date, or as "age-age of onset + 1". All reported p-values were 2-sided, and $p < 0.05$ was considered statistically significant. Multiplicity adjustment was not performed in this post-hoc, exploratory analysis. All analyses were performed with SAS/STAT, version 4.3 of the SAS system.

3. Results

3.1. Patient Characteristics

Subject demographics and baseline prevalence of comorbid conditions are presented in **Table 1**. Mean age was 41 years (range 18 - 96) and 55% of subjects were

Table 1. Prevalence of comorbid risk factors at baseline (ZODIAC).

	All subjects *		US		Eastern Europe		Latin America ‡		Asia		Sweden	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Number of subjects (%)	9801 (55)	8017 (45)	4949 (52)	4484 (48)	537 (53)	472 (47)	3776 (59)	2640 (41)	519 (57)	394 (43)	20 (43)	27 (57)
Mean age (95% CI)	39.1 (38.8, 39.3)	43.4 (43.1, 43.7)	42.5 (42.2, 42.9)	45.8 (45.4, 46.1)	37.0 (36.1, 38.0)	39.6 (38.5, 40.8)	35.4 (35.0, 35.8)	40.7 (40.2, 41.2)	34.4 (33.4, 35.3)	38.0 (36.8, 39.2)	48.3 (43.4, 53.3)	48.7 (42.0, 55.4)
Mena weight, lbs (95% CI)	81.5 (81.1, 81.9)	74.4 (73.9, 74.8)	88.5 (87.9, 89.1)	81.1 (80.5, 81.8)	81.0 (79.7, 82.3)	71.1 (69.8, 72.4)	74.7 (74.2, 75.2)	65.9 (65.3, 66.4)	65.5 (64.4, 66.6)	58.1 (56.9, 59.3)	84.2 (76.5, 91.9)	72.2. (66.4, 78.1)
Mean BMI (95% CI)	26.7 (26.6, 26.8)	28.5 (28.3, 28.6)	28.1 (28.0, 28.3)	30.4 (30.1, 30.6)	26.3 (25.9, 26.6)	26.5 (26.0, 27.0)	25.4 (25.2, 25.5)	26.3 (26.0, 26.5)	23.1 (22.7, 23.4)	23.6 (23.1, 24.0)	27.6 (25.0, 30.1)	26.3 (24.1, 28.5)
Smoking status												
Never smoked, n (%)	3271 (33)	3934 (49)	1204 (24)	1684 (38)	218 (41)	282 (60)	1704 (45)	1614 (61)	139 (27)	341 (87)	6 (30)	13 (48)
Current smoker, n (%)	5244 (54)	3042 (38)	3012 (61)	2068 (46)	261 (49)	158 (34)	1651 (44)	771 (29)	310 (60)	32 (8)	10 (50)	12 (44)
Past smoker, n (%)	1164 (12)	935 (12)	647 (13)	647 (15)	53 (10.0)	30 (6.4)	399 (11)	243 (9.2)	61 (12)	13 (3.3)	4 (20)	2 (7.4)
Unknown, n (%)	94 (1)	79 (1)	62 (1.3)	63 (1.4)	5 (0.9)	1 (0.2)	18 (0.5)	7 (0.3)	9 (1.7)	8 (2)	0 (0)	0 (0)
Mean duration of illness, years (95% CI)	12.8 (12.6, 13.1)	13.3 (13.0, 13.6)	14.4 (14.1, 14.7)	13.6 (13.3, 14.0)	10.0 (9.2, 10.8)	9.8 (9.0, 10.6)	12.0 (11.6, 12.3)	14.0 (13.5, 14.4)	8.1 (7.4, 8.8)	9.7 (8.7, 10.8)	15.5 (8.8, 22.2)	15.9 (9.7, 22.2)
Mean clinical impression score (96%CI)	5.23 (5.21, 5.25)	5.09 (5.06, 5.11)	5.17 (5.13, 5.20)	5.06 (5.03, 5.10)	5.03 (4.93, 5.14)	4.71 (4.60, 4.83)	5.39 (5.36, 5.43)	5.27 (5.23, 5.31)	4.82 (4.72, 4.92)	4.65 (4.54, 4.77)	4.5 (3.96, 5.04)	4.6 (4.15, 5.04)
Patient medical history												
Heart attack, n (%)	164 (1.7)	113 (1.4)	151 (3)	104 (2.4)	2 (0.4)	3 (0.6)	10 (0.3)	6 (0.2)	0 (0)	0 (0)	1 (5)	0 (0)
Stroke, n (%)	140 (1.4)	171 (2.2)	119 (2.4)	157 (3.6)	3 (0.6)	2 (0.4)	16 (0.4)	12 (0.5)	1 (0.2)	0 (0)	1 (5)	0 (0)
Hypertension, n (%)	1531 (16)	1600 (20)	1207 (25)	1223 (28)	44 (8)	52 (11)	258 (7)	301 (11.6)	18 (3.5)	21 (5.4)	4 (22)	3 (11)
CAD/angina, n (%)	223 (2.3)	211 (2.7)	185 (3.9)	176 (4.1)	13 (2.5)	11 (2.4)	23 (0.6)	23 (0.9)	0 (0)	0 (0)	2 (10)	1 (3.8)
Arrhythmia, n (%)	235 (2.5)	291 (3.8)	156 (3.3)	211 (4.9)	21 (4.1)	17 (3.7)	53 (1.5)	55 (2.2)	1 (0.2)	5 (1.3)	4 (20)	3 (11)
High cholesterol/ triglycerides, n (%)	1289 (15)	1322 (19)	959 (21)	988 (24)	55 (12)	36 (8.6)	266 (8.8)	280 (13)	9 (1.9)	16 (4.3)	0 (0)	2(9.5) (7.4)
Diabetes												
Diabetes therapy, n (%)	615 (6.4)	752 (9.5)	513 (10)	609 (14)	8 (1.5)	17 (3.6)	84 (2.3)	109 (4.3)	7 (1.4)	15 (3.8)	3 (15)	2 (7.4)
Current diabetic therapy, n (%)	453 (4.6)	528 (6.6)	380 (7.7)	436(9.7)	7 (1.3)	13 (2.7)	57 (1.5)	67 (2.5)	6 (1.2)	10 (2.5)	3 (15)	2 (7.4)

Continued

Past diabetic therapy, n (%)	249 (2.5)	297 (3.7)	193 (3.9)	224 (5.0)	2 (3.7)	5 (1.1)	50 (1.3)	62 (2.4)	2 (0.4)	5 (1.3)	2 (10)	1 (3.7)
Psychiatric inpatient hospitalization, n (%)	7369 (75)	6070 (76)	3901 (79)	3489 (78)	496 (92)	431 (91)	2578 (68)	1841 (70)	376 (72)	282 (72)	18 (90)	27 (100)
Number of psychiatric hospitalizations												
0	2425 (25)	1934 (24)	1041 (21)	983 (22)	41 (7.6)	41 (8.7)	1198 (32)	798 (30)	143 (28)	112 (28)	2 (10)	0 (0)
1 - 5	4882 (50)	4124 (52)	2400 (49)	2259 (51)	294 (55)	298 (63)	1903 (50)	1333 (51)	277 (53)	218 (55)	8 (40)	16 (59)
6 - 9	1004 (10)	865 (11)	587 (12)	546 (12)	92 (17)	69 (15)	266 (7)	207 (7.9)	57 (11)	37 (9.4)	2 (10)	6 (22)
10+	1473 (15)	1068 (13)	904 (18)	674 (15)	110 (20)	64 (14)	409 (11)	298 (11)	42 (8.1)	27 (6.9)	8 (40)	5 (19)
History of suicide attempts, n (%)	2594 (28)	2744 (35)	1517 (33)	1787 (42)	102 (20)	89 (19)	853 (23)	772 (30)	113 (22)	90 (23)	9 (45)	6 (22)
Overweight/obese, BMI, n (%) [+]	5509 (57)	5011 (63)	3254 (67)	3188 (72)	307 (58)	246 (52)	1793 (48)	1441 (55)	141 (28)	121 (32)	14 (70)	15 (58)
Family medical history												
Heart attack, n (%)	2599 (30)	2502 (35)	1653 (38)	1737 (44)	65 (13)	72 (16)	850 (25)	671 (29)	23 (5)	16 (4)	8 (44)	6 (24)
Stroke, n (%)	1915 (22)	1862 (26)	1142 (27)	1243 (32)	49 (10)	45 (10)	690 (20)	534 (23)	31 (6)	35 (9)	3 (18)	5 (21)
Hypertension, n (%)	4494 (53)	4035 (58)	2190 (53)	2306 (60)	179 (38)	166 (39)	1988 (58)	1449 (61)	128 (26)	105 (29)	9 (60)	9 (43)
Coronary artery disease/angina, n (%)	2061 (26)	2046 (31)	1216 (31)	1333 (37)	96 (21)	94 (24)	709 (22)	584 (27)	33 (7)	30 (8)	7 (41)	5 (22)
arrhythmia, n (%)	897 (12)	870 (14)	470 (13)	526 (16)	33 (8)	25 (7)	391 (13)	310 (15)	2 (0.4)	7 (2)	1 (9)	2 (12)
High cholesterol/ triglycerides, n (%)	2315 (32)	2184 (37)	1181 (33)	1324 (40)	66 (19)	58 (18)	1040 (36)	772 (40)	24 (5)	27 (8)	4 (40)	3 (20)

[*]Data included for subjects with completed gender information (n = 17,818); [‡]Combining South America and Brazil; [+]Body Mass Index (BMI) calculated using ZODIAC subject weight and height.

male. US subjects were older (mean age: 43 years), compared with other regions (mean ages 34 - 40 years). Age (age deciles < 20, 20 - 29 through 60 - 69, ≥70), and gender distributions varied significantly across regions ($p < 0.001$ for age by region; $p < 0.001$ for gender by region; $p < 0.001$ for age by gender by region).

Enrolled subjects were diagnosed with schizophrenia on average for 13 years; only 10% (1814 of 17,904 subjects) had duration of illness less than 6 months (from the date of diagnosis). Average duration of illness was long in the US (14.0 years, 95% CI: 13.8 to 14.3 years) and the shortest was in Asia (8.8 years, 95% CI: 8.2 to 9.4 years).

Current smoking (46.5%) and past smoking (11.8%) were common among this study population (**Table 1**) with men dominating the proportion of current smokers: US (61%); Asia (60%); Eastern Europe (49%); and Latin America (44%) ($p < 0.001$, smoking status by region; $p < 0.001$ smoking status by gender; smoking status by gender by region, $p < 0.001$).

Mental illness severity as assessed by CIS score differed among regions after adjusting for age, gender, and race ($p < 0.001$, ANCOVA). The percentages of markedly ill or more severe subjects varied by country as follows: Brazil (45%), the US (32%), Asia (24%), and the other regions studied (31% - 35%). History of psychiatric inpatient hospitalization was highest in Eastern Europe (92%), compared with the US (78%) and the other regions studied (69% - 72%). The majority of subjects took one antipsychotic medication regardless of geographic region (**Table 2**). Subjects in the US had the highest prevalence of concomitant medication use (81%), compared with Eastern Europe (52%) and the other countries (72% - 75%).

3.2. Comorbidities and Family Medical History

The majority of subjects (66%, 11,989/18,239) entered the study with one or more select comorbid conditions [*i.e.* heart attack, stroke, hypertension, CAD/angina, high cholesterol/triglycerides, diabetes, or overweight (BMI ≥ 25)] as shown in **Table 1**. Overweight or obesity (defined as BMI ≥ 25) was the most prevalent comorbid risk factor, representing 60% of enrolled subjects. ZODIAC subjects had a mean weight of 81.5 kg (95% CI: 81.1 to 81.9) for men, and 74.4 kg (73.9 to 74.8) for women. Overweight or obesity (BMI ≥ 25) was seen in 69% of US subjects compared with 30% in Asia and other regions (51% - 63%) (**Table 1**).

History of cardiovascular or diabetes-related comorbidities was found in 31% of subjects. Simultaneous presence of multiple CVDs were present in 12% of subjects, 14% (1143/8007) of women and 11% (1035/9787) of men. Hypertension was the most common cardiovascular comorbidity (16% men vs. 20% women) and prevalence was highest in the US, followed by Sweden, Eastern Europe, Latin America, and Asia. Prevalence of high cholesterol/triglycerides was also reported in 15% of subjects, ranging from 8.8% in Latin American men to 24% in US women. History of Coronary Artery Disease (CAD)/angina and arrhythmia was approximately 3.0%, and was comparable between the US and Eastern Europe; estimates were lower in remaining regions. History of heart attack or stroke was about 3% in the US but less than 1% in other regions.

Family medical history of select comorbidities were collected with US subjects reporting a higher prevalence of a family history of heart attack (41%), high cholesterol/triglycerides (37%), CAD/angina (34%), stroke (30%), and arrhythmia (15%) compared with other regions (**Table 1**).

3.3. Correlations between Comorbid Conditions, and Polypharmacy

Table 3 shows selected comorbidities by duration of illness (<5 years vs. ≥5 years). The likelihood of having at least one of these comorbid factors increased with duration of illness (or age) ($t = 4.14$, $p < 0.001$), number of antipsychotic medications currently used ($t = 4.12$, $p < 0.001$), and smoking ($t = 6.36$, $p < 0.001$), independent of gender, race, regions, and severity of illness (multivariate logistic regression analysis). There was a positive association between the duration of mental illness and likelihood of being overweight/obese ($t = 2.64$, $p < 0.008$), after adjusting for region, race, gender, severity of mental illness, and other cardiovascular/diabetes comorbidities.

Table 2. Antipsychotic Medication Use History.

	All subjects	US	Eastern Europe	Latin America	Asia
Number of subjects	**18,229**	**9735**	**1022**	**6504**	**921**
Current antipsychotic medication use, n (%)	14,404 (79%)	7207 (74%)	797 (78%)	5543 (85%)	823 (89%)
Number of antipsychotic medications currently used					
None	3825 (21%)	2528 (26%)	225 (22%)	961 (15%)	98 (11%)
1	10,679 (59%)	5724 (59%)	638 (62%)	3770 (58%)	519 (56%)
≥2	3725 (20%)	1483 (15%)	159 (16%)	1773 (27%)	304 (33%)

Table 3. Comorbidities in ZODIAC by illness duration.

	Duration		
	<5 Years	**≥5 Years**	**p-value**
Number of subjects	**5897**	**12,016**	
Number of comorbid factors[†]			
1 Comorbid factor	2316 (40%)	4869 (41%)	<0.001
2 Comorbid factors	687 (12%)	2037 (17%)	
≥3 Comorbid factors	269 (5.4%)	909 (9.1%)	
None	2378 (41%)	3515 (30%)	
Psychiatric inpatient hospitalizations	3430 (58%)	10,065 (84%)	<0.001
History of suicide attempts	1660 (29%)	3724 (32%)	<0.001
Number of antipsychotic medications currently used			
None	1702 (29%)	2017 (17%)	<0.001
1	3339 (57%)	7191 (60%)	
≥2	851 (14%)	2803 (23%)	
Smoking status			
Never smoked	2723 (46%)	4524 (38%)	<0.001

[†]Comorbid factors: cardiovascular (heart attack, stroke, hypertension, CAD/angina, high cholesterol/triglycerides), diabetes, or overweight (BMI ≥ 25).

Polypharmacy was more frequent in men (23%) than in women (18%) ($t = 6.50$, $p < 0.001$), in overweight subjects ($t = 6.13$, $p < 0.001$), persons with more severe mental illness as assessed by CIS score ($t = 18.20$, $p < 0.001$), and longer duration of illness (or age) ($t = 14.05$, $p < 0.001$). No association was found between antipsychotic polypharmacy and the prevalence of other cardiovascular or diabetes comorbidities ($t = 0.84$, $p = 0.401$) after adjusting for race and regions (logistic regression analysis).

3.4. Early Phase Patient Subgroup Analysis

Only 1814 subjects reported duration of illness less than 6 months. Among this subgroup, the prevalence of comorbid conditions was: 51% for overweight/obesity, 22% for obesity, 23% for one or more cardiovascular morbidities, and 8.1% for the presence of multiple (≥2) cardiovascular comorbidities. Estimates were all significantly lower than those observed in subjects with 6 months or longer duration of illness (all $p < 0.001$), independent of region and gender.

4. DISCUSSION

ZODIAC is the largest prospective, randomized study of subjects with schizophrenia conducted to date [10]. Since procedures and data collection were greatly simplified compared with RCTs, this study elucidates the demographic profile of persons with schizophrenia in naturalistic clinical settings. There are, however, similarities/differences in patient demographics and characteristics across regions and countries.

There are few, but notable examples of cross-national observational studies of comparable scale including the W-SOHO (Worldwide-Schizophrenia Outpatient Health Outcome) study, which pooled data from the SOHO (Schizophrenia Outpatient Health Outcome) observational study in 10 Western European countries and the IC-SOHO (Inter-Continental SOHO) study in 27 other countries [1,12,13]; the METEOR study in 16 European countries [14]; and the randomized SCoP safety trial on schizophrenia subjects across Europe and Asia [15]. However, due to the paucity of published data summarizing cross-national information on comorbidities and risk factors prevalent in schizophrenia subjects, we highlight key country and region-specific comparisons from other schizophrenia trial populations whenever available.

In ZODIAC, most subjects were diagnosed with schizophrenia for over ten years and 10% were diagnosed within 6 months of study enrollment. Longer dura-

tion of illness appeared to be associated with poorer clinical outcomes evidenced by more reported comorbidities, e.g. heart attack, stroke, and heavy antipsychotic medication use (*i.e.* more reliance on polypharmacy) in those with five or more years of illness compared with less than five years (**Table 3**). A subgroup analysis of subjects with duration of illness less than 6 months also confirmed these findings.

History of psychiatric inpatient hospitalization was higher (92%) in Eastern Europe, compared with the US (79%) and the other regions studied (69% - 72%). This finding is consistent with use of long-term institutionalization as an acceptable local practice in psychiatric treatment and management in this region [16-20].

It is known that persons with schizophrenia also have a high burden of comorbidities that may be manifestations of the illness itself, poor diet and lifestyle, poor access to healthcare, or the propensity to develop CVD and other health problems [21-23]. As a result, mortality rates are two to three times higher among persons with schizophrenia than that of the general population [24-27] and corresponding elevated risks of dying from a wide range of somatic conditions and risk factors three to ten times higher [26]. Excess CVD mortality may be attributed to prevalence of risk factors commonly referred to as metabolic syndrome [28,29], a problem that is compounded by increased use of second-generation antipsychotics, as several agents are associated with excess, undesirable weight, and metabolic side-effects [30-33].

Metabolic and related risks, e.g. hypertriglyceridemia, overweight/obesity, were common among ZODIAC subjects. Sixty percent of subjects were considered overweight or obese (with a BMI ≥ 25) compared with 29.4% of European subjects with schizophrenia (obesity = BMI > 30) in the METEOR study [14], 32.8% in a physician-based survey in Europe [34], 76% of Brazilian subjects (overweight or obese = BMI > 25) [35], and 33.3 to 39.8% in Taiwanese subjects (obese = BMI ≥ 26.4 or 27) [36,37]. Overall, Asian subjects reported better cardiovascular and metabolic profiles compared with the other cohorts, possibly owing to Asian culture, lifestyle, and diet [38,39]. Rates of hypertension and diabetes in ZODIAC, at 16% and 6.4% respectively, are corroborated by other trials in this patient population [34,37,40-41]. Metabolic and associated risks were highly prevalent among ZODIAC subjects, underscoring the severe public health challenge they pose to this at-risk population.

Although anti-smoking campaigns have made health risks associated with tobacco use clear to the general public, high rates of smoking are reported among individuals with schizophrenia [42,43] compared with the worldwide current smoker prevalence rate of 26% [27]. Evidence suggests that some persons with schizophrenia might smoke as a form of self-medication, to ameliorate the positive and negative symptoms, cognitive (memory/attention) deficits, mood changes and stress associated with the disease, or the side-effects produced by antipsychotic medications [44-48]. Regardless, the prevalence of smoking among persons with schizophrenia is two to three times higher than in the general population and approximately 50% higher than similar, elevated rates of smoking in people with other psychiatric diagnoses [49-54]. ZODIAC rates were consistent with these findings (>40% of subjects were reportedly current smokers) with prevalence highest among US (61%) and Asian (60%) men. Male smokers outnumbered female smokers in each region perhaps due, in part, to cultural norms regarding smoking behaviors [55-57]. Further, patients with schizophrenia who smoke have a multi-fold increase in risk of dying from CVD even when compared to those who are nonsmokers [58], and also shown in ZODIAC, heavy addiction to cigarettes is clearly an important factor contributing to elevated mortality and morbidities in schizophrenia [44,59-60].

Given the high prevalence of health risks and family history of CVD observed in ZODIAC, personal history was expected to corroborate these data. Instead, investigators reported relatively low prevalence in personal history of heart attack, diabetes, and other cardiovascular ailments across all regions. This, however, might reflect the common phenomenon of under diagnosis of these comorbidities among psychiatric subjects. The awareness of, and hence diagnosis and monitoring of these comorbidities have been low among mental healthcare providers [61], and psychiatrists were the source of these data in this study. Despite repeated calls for attention, the under diagnosis and under monitoring of medical comorbidities, either as baseline conditions or as treatment emergent side-effects, persist among mental health professionals [62,63]. A related but more ominous possibility is the possibility of a "weeding-out" process; given the elevated risks from comorbidities mentioned above, under treatment and diagnosis, few schizophrenia patients survived to leave a history [64,65].

This study also has some inherent limitations that deserve attention. Despite its large-scale and global design, ZODIAC findings may be skewed by its imbalanced country and regional samples. Of course, it is prudent to always exercise caution when extrapolating from regional findings to specific countries, especially those in large, diverse regions such as Asia [66,67]. Moreover, Sweden's study sample, the only participating country from Western Europe, was too small to serve as an adequate surrogate for the entire region. In addition, systematic training was not done in order to achieve inter-rater reliability on clinically subjective measure like illness severity across countries and regions. Finally, the ZODIAC study was not designed to test regional differences

in study outcomes. Of particular importance to this paper, the methods used to enroll patients were not the same in all countries [10,11].

ZODIAC provides valuable cross-country and regional information on schizophrenia disease history and manifestations, related risks, and comorbidities, which have important implications for clinical research, patient management, and mental healthcare policy in the 18 countries studied. Further, it provides important insights on conduct and interpretation of international trials, as well as, adaptation of clinical practice and customization of guidelines for mental healthcare management to specific regions.

5. CONTRIBUTORS

Dr. Siu wrote the first draft of the paper. Statistical analysis was performed by Dr. Siu. Drs Reynolds, Geier, Karayal, and Mrs Kolitsopoulos are full-time employees and shareholders of Pfizer.

6. CONFLICT OF INTEREST AND AUTHOR DISCLOSURE

Dr. Kane served as a consultant to Pfizer in connection with the scientific oversight of the study and served as a consultant or advisory board or speakers bureau for Alkermes, Amgen, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pierre Fabre, Proteus Biomedical, Roche, and Sunovion, and is a MedAvante shareholder. Dr. Fleischhacker receives research grants from Otsuka, Pfizer, Janssen, Alkermes, Eli Lilly; consulting honoraria from Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, Unitedbiosource, MedAvante, Sunovion, Merck; speaker honoraria from Lundbeck, Sunovion, Janssen, Eli Lilly, Otsuka, Astra Zeneca; and owns MedAvante stocks. Dr. Strom is an employee of the University of Pennsylvania, which received financial support from Pfizer in connection with the scientific oversight of the study and the development of this manuscript. He also served as consultant to Pfizer on topics not related to this study and has consulted for Abbott Laboratories, American College of Neuropsychopharmacology, American Medical Association, Astra-Zeneca, Berlex, Biogen, Blue Cross Blue Shield, Bristol-Myers Squibb, Boehringer Ingelheim, Centocor, Cephalon, CV Therapeutics, Cygnus Corporation, Daichii, Eli Lilly, Forest, GlaxoSmithKline, Hoyle Consulting, Johnson & Johnson, Medco, Mediwound, Novartis, NPS Pharma, NUVO Research, Ocient, Pfizer, Pharm Research, PhRMA Foundation, Sanofi-Aventis, Shire, TAP Pharmaceuticals, Teva Neuroscience, and Wyeth. Dr. Ruskin served as a consultant to Pfizer in connection with the scientific oversight of the study and has served as a consultant or scientific advisory board member for Astellas, AstraZeneca, Bristol-Myers Squibb, Cardiome, Epix, Forest Labs, Genzyme, Javelin, Lundbeck, Millennium, Myriad, Novartis, NovoNordisk, Portola, Purdue, Sanofi-Aventis, Sequel, Sunesis, and Theravance. Dr. Faich is an employee of United BioSource Corporation, which received financial support from Pfizer in connection with the scientific oversight of the study and the development of this manuscript. Dr. Siu is a paid consultant to Pfizer Inc. and Sunovion. Drs. Reynolds, Geier, Karayal, and Mrs Kolitsopoulos are full-time employees and shareholder of Pfizer.

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