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Original article

Schizophrenia, antipsychotic drugs and cardiovascular risk: Descriptive study in primary care

M. Castillo-Sánchez [a,b,c,*], M. Fàbregas-Escurriola [a,d], D. Bergè-Baquero [e,f], Q. Foguet-Boreu [a,g,h], M.I. Fernández-San Martín [a,i], A. Goday-Arno [b,j,k]

[a] Institut Universitari d'Investigaciò en Atenciò Primaria (IDIAP) Jordi Gol, Barcelona, Spain
[b] Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
[c] Médico de familia, EAP Besòs, Barcelona, Spain
[d] Médico de familia EAP La Marina, Barcelona, Spain
[e] Institut de Neuropsiquiatria i Addiccions, Parc de Salut Mar, Barcelona, Spain
[f] Unitat de Recerca en Neurcociència Cognitiva, Universitat Autònoma de Barcelona, Barcelona, Spain
[g] Hospital de Campdevànol, Girona, Spain
[h] Departamento de Ciencias Médicas, Facultad de Medicina, Universitat de Girona, Girona, Spain
[i] Técnica de Salud ICS, Unitat Docent AFiC, Barcelona, Spain
[j] Servicio de Endocrinología y Nutrición, Hospital del Mar, Barcelona, Spain
[k] CIBER Obn, Centro de Investigaciones Biomedicas en obesidad y nutrición. Parc de Salut Mar, Barcelona, Spain

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1. Background

Patients affected by schizophrenia (SZ) have an increased cardiovascular morbidity and mortality [15,33]. Cardiovascular risk (CVR) has been extensively studied in the general population [34], but the aetiology in patients with SZ is extraordinarily complex [7], and has not been extensively studied.

There is an association between SZ and unhealthy lifestyles [5,13,37], but some studies suggest that it is the treatment with antipsychotic drugs (TAD) that leads to weight gain [28], consequently altering the metabolism of carbohydrates and lipids [10,29,32] and increasing the prevalence of metabolic syndrome and the expected CVR [3,17,20]. Similarly, a recent review [18] concluded that the increased CVR could be caused solely by the antipsychotics drugs' side effects.

However, some intrinsic factors of psychotic illness could also be involved. At the genetic level, SZ is associated with "classic" cardiovascular risk factors (CVRF) such as diabetes [22]. This association has been clinically confirmed [16,26,35]. Also, at the biochemical level, other markers suggest that a relationship exists between psychosis and "non-classical" CVRF such as differing levels of cortisol [35], interleukin-6 [16] or glutathione [1]; regardless of the TAD received.

TAD improves the control of psychotic illness and it could perhaps reduce the CVR that this illness could generate per se, decreasing overall mortality [6,38]. Furthermore, drugs such as clozapine, which leads to major alterations of lipid and carbohydrate metabolism as compared to other neuroleptics, does not possess a greater CVR than other atypical antipsychotic drugs [23]. This calls into question the relationship between true CVR and the alteration of CVRF generated by the TAD.

Finally, under-diagnosis and under-treatment of physical illnesses in patients with severe mental illness also seem crucial [14]. Differences can be found in both primary [2,36] and secondary [27,31] prevention in the management of these patients as compared to the general population. To mitigate this problem, various clinical guidelines and consensus-based recommendations have been developed [11]. However, there are few studies conducted in Spain and in primary care, even though they would fall within the ideal scope of these recommendations.

The objective of this paper was to describe the presence of CVRF in SZ patients and also in non-SZ patients receiving TAD (NS-TAD group), in the primary care population, without established cardiovascular disease (cardiovascular primary prevention).

* Corresponding author. CS Orihuela I, C. Madre Elisea 2b, cp 03300, Orihuela (Alicante), Spain. Tel.: +34966904053.
E-mail address: doctor.miguel.castillo@gmail.com (M. Castillo-Sánchez).

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2. Methods

Cross-sectional study from records stored in the digitized clinical historial in primary care. The data used came from six consecutive years (2006–2011).

2.1. Source of data

Individual morbidity data were obtained from the digitized clinical history (eCAP) of the Catalan Health Institute, which manages 274 of the 358 (76.5%) primary care centers in Catalonia (Spain), the remainder being managed by other entities. The Database from the Information System for the Development of Research in Primary Care (SIDIAP) [4] has eCAP's anonymous clinical information from 4,859,725 adults. Billing data from pharmacies were used for the analysis of treatments.

This study was achieved by using a sub-sample of clinical logs from the SIDIAP, the SIDIAPQ, consisting of 1,936,443 adult patients (40% of the population in the SIDIAP database). SIDIAPQ integrates the records of 1365 general practitioners, whose records obtained the highest score (relative to expected prevalence values) in a matching process validated for clinical research [19]. In this validation process, a prevalence of SZ, obesity and diabetes (among other pathologies) similar to that expected according to the studies of reference was described.

This manuscript has not been prepared in collaboration with the institutions holding these records, so the quality and accuracy of the results are the responsibility of the authors of the manuscript alone.

2.2. Study population

Patients over 18 years of age, assigned to the SIDIAPQ medical teams and attended to at some point during the study period were used. Three groups were established: SZ, NS-TAD subjects and control group. The inclusion criteria were:

- SZ group: prevalent SZ and diagnoses of schizophrenic instances during the period of study. Selecting the ICD-10 (*International Statistical Classification of Diseases and Related Health Problems, tenth version*) codes included in F20 (''Schizophrenia'') and subtypes. They could or not have a prescription for TAD;
- NS-TAD group (no SZ, but TAD): patients that had withdrawn at least three prescriptions for any antipsychotic drug from the pharmacy during the study period were considered to be receiving TAD. We discarded sulpiride and lithium, which, although classified as antipsychotic drugs according to the ATC classification (*Anatomical, Therapeutic Chemical classification system*), had different recommendations for use in psychosis treatments. This group is miscellaneous (Table 1), although the prevalence of some disorders related to the consumption of psychotropic substances, affective disorders and disorders of neurotic nature are highlighted. At no time during the study period did the patients of this group present SZ (F20 and subtypes) diagnoses;
- control group: non-exposed group (without SZ or TAD), randomly chosen from the rest of the study population (simple randomization). Formed by patients without SZ or TAD, randomly chosen from the rest of the study population. A sample that was twice as large as the total exposed population (SZ and NS-TAD) was generated before selecting the SIDIAPQ sub-sample.

2.3. Exclusion criteria

People with F28 (''other psychotic disorders not organic'') or F29 (''non-organic psychosis without specifying'') codes without SZ ($n = 8593$) were excluded from the three groups at the early stage of study. Patients with dementia (F0 and subtypes) were also excluded.

To determine the CVR without established cardiovascular disease, those people with a prior diagnosis of ischemic heart disease (I20, I21 I22, I23, I24 and subtypes), cerebrovascular disease (I25, I61, I63, I64, I65 and subtypes) or intermittent claudication (I73.9) were excluded.

2.4. Study variables

For each patient, age, sex, and the health problems of interest that were active at some time during the period of study were collected. These problems were defined according to codes found in the ICD-10, such as those related to consumption of alcohol (F10 and subtypes), cocaine (F14 and subtypes), and tobacco (smoker or non-smoker, as well as code F17). The following CVRF were collected: type 1 and 2 diabetes mellitus (E10, E11, E12, E13, E14), obesity (E66 and subtypes or BMI greater than 30), dyslipidemia (E78.0, E78.5, E78.1, E78.3, E78.4) and arterial hypertension (I10, I11, I12, I13, I15); and the average number of individual, modifiable CVRF (from 0 to 5, including smoking).

The Framingham-Regicor equation [30] was applied, and expressed as a percentage of CVR after 10 years. This equation is

Table 1
Diagnoses found in the ICD-10 classification that could justify the prescription of antipsychotic drugs in the NS-TAD group (patients without schizophrenia but in treatment with antipsychotic drugs).

ICD-10 codes	Mental and behavioral disorders	Total number in the NS-TAD group[a]	%
F10-19	Mental and behavioral disorders due to psychoactive substance use	9180	30.7
F20-29	Schizophrenia[b], schizotypal and delusional disorders	1772	5.9
F30-39	Mood (affective) disorders	6739	22.5
F40-49	Neurotic, stress-related and somatoform disorders	6456	21.6
F50-59	Behavioral syndromes associated with physiological disturbances and physical factors	2275	7.6
F60-69	Disorders of adult personality and behavior	1288	4.3
F70-79	Mental retardation	965	3.2
F80-89	Disorders of psychological development	122	0.4
F90-98	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	654	2.2
F99	Unspecified mental disorder	460	1.5
F10-99	Total[c]	29,911	100

[a] Diagnoses included have been active at some time during the period; some of them may be developmental diagnoses (in which case the initial diagnosis as well as the evolved recounts diagnosis).
[b] By definition, in NS-TAD group the diagnoses of schizophrenia (F20 and subtypes) are excluded.
[c] Total of diagnoses from ''Mental and behavioral disorders'' in ICD-10, excluding ''organic mental disorders, including symptomatic disorders'' (whose presence is exclusion criterion).