STUDY PROTOCOL

Descriptive analysis of schizophrenic disorders and their treatment in the Valencia Region, Spain

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RESEARCH TEAM

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Sponsor:

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INTRODUCTION

Schizophrenia is a chronic neuropsychiatric disorder with onset of symptoms usually during the second or third decade of life.[1,2] Disease occurrence may be associated with genetic, socio-demographic and environmental factors.[1,3,4] The main defining symptoms may include hallucinations, delusions, formal thought disorder, affective flattening, catatonic symptoms and inappropriate affects.[2] The global incidence of schizophrenia ranges from 8 to 43 per 100,000 individuals.[3] Antipsychotic medications (dopamine-receptor regulators, antagonist and partial agonists of dopamine and serotonin receptors) are currently the main pharmacological treatment of schizophrenia.[5] Although many schizophrenia patients have the potential to achieve long-term remission and functional recovery under proper treatment, most patients, throughout their life, suffer relapses characterized by an exacerbation of psychosis, which often require emergency rooms visits and hospitalizations.[6-9] Relapses may also cause subsequent refractoriness to antipsychotic treatment and loss of functional gains.[6] Schizophrenia causes a significant impact on the quality of life of patients and their families, the social environment and the healthcare system. [8] The aim of this study is to describe disease incidence and prevalence, progress, treatments received and healthcare utilization using the healthcare databases from the Valencia Region, Spain, a setting with universal (>98%) health coverage.

OBJECTIVES

Primary objectives

To estimate incidence rates and prevalence of schizophrenia and other schizophrenic spectrum disorders (SSD) among Valencia Region´s population aged 15 years and older

Secondary objectives

To describe antipsychotic use associated to schizophrenia and other SSD among Valencia Region´s population aged 15 years and older

To describe healthcare events associated to schizophrenia and other SSD among Valencia Region´s population aged 15 years and older

METHODS

Study design

A descriptive analysis of SSD including treatments received and subsequent health-care events will be performed using the region's health care databases from 1st January 2008 until the date of data extraction.

Study population

The population of interest will be Valencia Region's individuals aged 15 years and older during the study period:

(1) Covered by the public healthcare system at least one year
(2) Insured through the NHS (individuals not covered by HMO (Health Management Organizations) or fee-for-service insurance companies)

Study setting and data sources

The Valencia Region, one of the 17 Autonomous Regions of Spain, has a population of approximately 5,000,000 inhabitants. Approximately 98.3% of the population is covered by the public health system. The regional health system is divided into 24 Departments. It includes 32 public hospitals, 16 of them attending psychiatric patients.

Population-based administrative database

The regional population-based administrative database, SIP, collects and updates identification data, geographic location, assignment of health services, and access to public health services for both residents of the Valencia Community and non-residents with access to public health services. It includes APSI characteristic which is an identification code defined for each person at any time including: inhabitant's registration status, nationality (Spanish or not), sex, year of birth, health department assigned, health care

insurance, residence status, migrations, work activity, geopolitical group, and social exclusion. Since 2005, SIP can be linked with the hospital discharge database. All other healthcare databases are able to capture the demographic data from SIP as shown in Figure 1.

Hospital Discharge Database

The Spanish hospital discharge database, CMBD, collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases. Using CMBD is compulsory for all public hospitals, and over 95% of all discharges are included. According to the Spanish Ministry of Health, data are considered reliable since 2002.

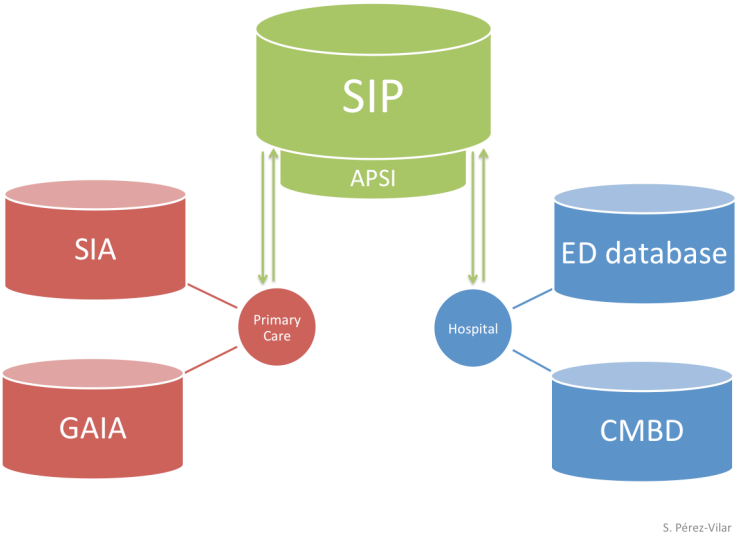
ED database

The ED database has been launched in 2008 and collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases. Over 45% of all ED visits during 2008-2014 include the main diagnosis codified (as of November 2014). Description of the diagnoses is available for all visits; therefore, data can be extracted using free text algorithms.

SIA-GAIA

SIA-GAIA is a primary care database used across the entire Valencia healthcare system. It was set up in 2006 and the percentage of the population included increased from 73.1% in 2007 to 88.8% in 2008 and to 95.7% in 2009. Currently, it is used in all Valencia´s Health Care System. This database contains primary care diagnoses (physician coded using the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM)) and all drug prescriptions (using Anatomical Therapeutic Chemical (ATC) Classification System). In addition, the recorded text about each episode and patient by the paediatrician, other physician, and by the nurse responsible is included. The database is also used at Specialty care Centres and is considered reliable since 2007. GAIA includes MDIS (Módulo de dispensación), which allows the registration of those prescriptions administered at the Primary Care or Specialty Centres.

Figure 1. Valencia Region´s health care databases to be used in this study



Case definition for events of interest

A schizophrenia disorder will be identified from SIA, CMBD or the ED database* through a search of the following ICD-9-CM codes:

295 Schizophrenic disorders

Other SSD will be identified from SIA or CMBD through a search of the following ICD-9-CM codes (including sub-codes, if any):

297 Delusional disorders
298.8 Other and unspecified reactive psychosis
298.9 Unspecified psychosis

Two cases definitions will be used: (1) a narrow definition including only codes codifying schizophrenic disorders (ICD-9-CM codes 295), and (2) a broader definition including schizophrenic disorders and SSD (ICD-9-CM codes 295, 297, 298.8 and 298.9).

*Since this database does not include codification of the diagnoses for all visits, an extraction using free text will be also requested

Exposure

Antipsychotic medication use will be identified from GAIA through the ATC code (including sub-codes) for antipsychotics, N05A.

Health care events

The following SSD-associated health care events will be identified from SIA, GAIA, CMBD and/or ED database through the following ICD-9-CM codes:

295 Schizophrenic disorders
297 Delusional disorders
298.8 Other and unspecified reactive psychosis
298.9 Unspecified psychosis

- Other treatments received by patients diagnosed with schizophrenia spectrum disorders will be extracted from GAIA

- Work absence among patients diagnosed with schizophrenia spectrum disorders will be obtained from SIA

- Hospitalizations among patients diagnosed with schizophrenia spectrum disorders will be extracted from CMBD

- ED visits among patients with schizophrenia spectrum disorders will be extracted from the ED database

- Specialty visits among patients with schizophrenia spectrum disorders will be obtained from SIA

- Primary care visits for schizophrenia spectrum disorders will be obtained from SIA

In addition, the following outcomes will be identified among patients diagnosed with schizophrenia spectrum disorders through the following ICD-9-CM codes:

- Psychotherapy: these interventions will be obtained from SIA and CMBD using the following procedure codes

94.3 Individual psychotherapy
94.4 Other psychotherapy and counselling
94.5 Referral for psychological rehabilitation

- Suicide: these events will be obtained from SIA and CMBD using the following codes:

E950-E959 Suicide and self-inflicted injuries

Variables

Data to be requested from SIP (including APSI):

Patient identifier within the health system (codified)
Birthdate
Identification*
Current location*
Assignation*
Exit of the health system*
Accreditation*
APSI codes as of 1st January 2008, 1st January 2012, and 31st December 2015

*As recorded in the current SIP´s data request form (See annex)

Data to be requested from SIA-GAIA:

Patient identifier within the health system (codified)
Birthdate
Date of diagnosis activation (diagnosis of interest)
Date of diagnosis deactivation (diagnosis of interest)

Diagnosis description (diagnosis of interest)
Number of visits between date of diagnosis activation (diagnosis of interest) and the end of the follow-up
Date of the visits
Active diagnoses between 365 days prior to the date of diagnosis activation (diagnosis of interest) and the end of the follow-up
Date of diagnosis activation (Active diagnoses between 365 days prior to the date of diagnosis activation (diagnosis of interest) and the end of the follow-up
Date of diagnosis deactivation (Active diagnoses between 365 days prior to the date of diagnosis activation (diagnosis of interest) and the end of the follow-up
Description of active diagnoses between 365 days prior to the date of diagnosis activation (diagnosis of interest) and the end of the follow-up
Professional attendance (GP/Specialist)
Psychotherapy
Work absences (starting date)
Work absences (closing date)
Work absences (reason)
Clinical Risk Groups (CRGs)
Diagnosis associated with the prescription (ICD-9-CM code)
Medical prescription number
Dosage
Number of units prescribed
Starting date of the treatment
Closing date of the treatment
Type of dispensation
Number of units dispensed
Active principles (ATC code)
Active principles (description)
Date of prescription

Date of dispensation
Other medications prescribed during the same visit (ATC code)
Other medications prescribed during the same visit (description)
Dosage (other medications)
Number of units prescribed (other medications)
Starting date of the treatment (other medications)
Closing date of the treatment (other medications)
Type of dispensation
Date of dispensation of other medications
MDIS- Active principles administered (ATC code)
MDIS- Active principles administered (ATC code)
MDIS- Active principles administered (description)
MDIS- Date of administration
MDIS- Number of units administered
MDIS – Other medications received during the same visit

Data to be requested from CMBD - ED database:

Patient identified within the health system (codified)
Birthdate
Date of admission
Date of discharge
Diagnoses (ICD-9-CM codes)
Diagnoses (description)**
Procedures (ICD-9-CM codes)
Procedures (description)**
Discharge status

**Only for the ED database request

Statistical analysis

The incidence rate of schizophrenia and SSD will be calculated by dividing the total number of incident cases by the total number of person years at risk. 95% confidence intervals (CI) will be calculated assuming a Poisson distribution. Incidence rates will be calculated by age group, gender, calendar year, birth season, socio-economic conditions, environmental factors, and comorbidities.

Prevalence will be calculated over the entire study period by dividing the total number of patients diagnosed with schizophrenia and SSD in the database during the study period, divided by the total number of persons in the study population during the study period.

Descriptive analyses of baseline characteristics of the study population diagnosed with schizophrenia and SSD will also be carried out.

Descriptive statistics on frequency and patterns of antipsychotic drugs prescription and use and frequency of use, of other neuropsychiatric drugs among patients with schizophrenia and SSD will be assessed overall and for the main demographic and other important variables (age group, gender, calendar year, birth season, socio-economic conditions, environmental factors, and comorbidities).

Descriptive analyses on healthcare utilization among patients diagnosed with schizophrenia and SSD will be also undertaken, overall and for the main demographic and other relevant variables (age group, gender, calendar year, birth season, socio-economic conditions and comorbidities) and other relevant variables.

Analyses will be carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) or Stata/SE 13.1 (StataCorp LP Texas, USA). All tests will be two-sided with a significance level of 0.05.

Sample size

This is a population-based analysis to determine the incidence and prevalence of SSDs and describe the management of these disorders in the Valencia Region. To do so, electronic health records from the public healthcare system will be used. As described in the study proposal, >98% of

the population of Valencia is covered by the public health system, therefore, a sample size of 4.900.000 inhabitants will be considered to estimate the prevalence of SSDs. Given an expected prevalence of SSD of 1%, this sample size will ensure a margin error (precision) of ± 0.00008% to estimate the prevalence of SSD with a 95% confidence interval.

Limitations

Patients with schizophrenia could remain unnoticed since they might try to avoid psychiatric care or might be attended in private healthcare services.

Possible biases related to changes in diagnostic procedures throughout the study period. Positive predictive values of the ICD-9-CM codes to be used within Valencia´s databases have not been assessed.

Potential lack of record on administration of antipsychotics within the healthcare system might occur since the corresponding instruction (*Instrucción de 2 de septiembre de 2013, del Director General de Farmacia y Productos Sanitarios, sobre productos de prescripción, preparación, transporte, recepción y admnistración de jeringas precargadas de metotrexato subcutáneo, antipsicóticos parenterales y extractos estabilizantes*) was published and implemented in late 2013. Nevertheless, drug prescription and administration place (health center) would need to be done using SIA-GAIA.

Certain demographic characteristics such as race and familiar history of schizophrenia will not be available in the databases.

ETHICS AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with all applicable ethic and regulatory requirements, including all applicable subject privacy requirements, the guiding principles of the Declaration of Helsinki, and Ethical Guidelines for Epidemiological Investigations.

In order to maintain dissociation of the data, personal data in the original datasets will be dissociated: the database´s managers will perform a

reversible transformation of the unique identification number and they will store the seed for each individual.

The study will be submitted for approval to the Ethics Research Committee of the Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública (CEIC DGSP/CSISP). As per internal operational rules of the mentioned Ethics Committee and Databases Management systems, a waiver of informed consent according to the article 32 of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) will be also requested.

The study will be informed to the Spanish Medicine Agency (AEMPS) in order to request its classification (as 'Estudio No-EPA') according to the existing local legislation (Orden SAS/3470/2009).

PHARMACOVIGILANCE

As per Good Vigilance Practices, Module VI (8 September 2014 EMA/873138/2011 Rev 1*) and Orden SAS/3470/2009 about observational post-licensure studies, this study meets the criteria to be considered as a retrospective observational (non-interventional) post-licensure study based on secondary use of data. Therefore, and according to the mentioned regulation, the reporting of suspected adverse reactions is not required. On the other hand, it is not expected in this project that explicit information related to causal relationships between adverse events and a specific product is included in these databases. No free texts will be retrieved for the purpose of this study, and no additional analyses in order to find adverse reactions with a possible, probable or very probable causal relationship will be performed. Information related to the patient will not be available in order to perform causality assessment. Therefore, no information about adverse drug reactions is expected to be collected. Nevertheless, in the hypothetical case that an adverse drug reaction to a Janssen product was found, this will be reported within 24 hours to Janssen-Cilag as described in the following section (see also definitions section).

Procedures for reporting adverse drug reactions and pregnancies (or pregnancies in partners of patients) with Janssen products.

During the database analysis, all ADRs -whether serious or not- and all special safety situations and exposures during pregnancy (or partner pregnancy)

hypothetically documented AND RELATED to a Janssen Drug in the source data (database) must be recorded in the study report. The database must include information to confirm that the adverse event is specifically stated (verbally or in a document) as at least possibly related to the use of a Janssen product (see definitions of causal relationship).

The investigator will directly report by fax all serious ADRs and exposures during pregnancy (or partner's pregnancy) with an abnormal outcome occurring during treatment with a Janssen product, within 24 hours of becoming aware of them, to Janssen (by FAX to number 917228520, see Annex), using a serious adverse reaction reporting form or a pregnancy reporting form as applicable. This notification will be done in parallel also to Health Authorities as the Investigator sponsor has this responsibility. (See Adverse Drug Reaction definition section and Serious Adverse Drug Reaction definition sections)

Procedures for reporting serious adverse reactions and pregnancies (or partner's pregnancies) with non-Janssen medicinal products.

With regard to serious ADRs and exposures during pregnancy (or partner's pregnancy) documented in the database after exposure to a non-Janssen investigational product, the investigator must report them as soon as possible to the relevant authorities www.notificaram.es (or to the manufacturer of the medicinal product in the absence of adequate local regulations).

Special circumstances

Safety issues of interest related to a Janssen product that require reporting or safety assessment include:

- Drug exposure (maternal and paternal) during pregnancy (see section 10.3; pregnancy exposure form should be submitted)
- Overdose of a Janssen product
- Exposure to a Janssen product through breastfeeding
- Suspected abuse/misuse of a Janssen product
- Inadvertent or accidental exposure to a Janssen product (e.g. during drug administration)
- Absence of the expected drug activity (i.e. lack of effect) of a Janssen product (not due to treatment noncompliance, but to suspected lack of

efficacy)
- Medication error with a Janssen product (with or without the patient's exposure to the investigational Janssen product; for example, name confusion)
- Suspected transmission of any infectious agent through the administration of a medicinal product
- Unexpected clinical or therapeutic benefit with use of a Janssen product.

These safety events may not comply with the definition of an adverse reaction; however, from a regulatory standpoint, they are treated the same way. The special circumstances should be included in the report. Any special circumstance that meets seriousness criteria must be recorded in a serious adverse reaction reporting form and reported to Janssen within 24 hours of becoming aware of it.

DEFINITIONS

Causal relationship

An adverse event will be considered not associated to use of the treatment when the attribution is "unrelated" or "doubtful" according to the following definitions:

Unrelated: An adverse event that is not related to use of the medicinal product. This is thus not an adverse reaction.

Doubtful: An adverse event for which an alternative explanation, such as concomitant drugs or disease, is more likely, or whose temporal relationship suggests that a causal relationship is unlikely. This is not an adverse reaction.

Possible: An adverse event that could be due to use of the medicinal product. There are no conclusive alternative explanations, such as concomitant medicinal products or diseases. The temporal relationship is reasonable; therefore, a causal relationship cannot be excluded. It is an adverse reaction.

Probable: An adverse event that could be due to use of the medicinal product. The temporal relationship suggests a relation (this is confirmed, for instance, on product dechallenge). An alternative explanation, such as concomitant medicinal products or diseases, is less probable. It is an adverse reaction.

Very probable: Adverse event listed a potential adverse reaction and that cannot be reasonably explained by an alternative explanation, such as concomitant medicinal products or diseases. The temporal relationship is highly suggestive (for example, it is confirmed by drug dechallenge and

rechallenge). It is an adverse reaction.

Adverse drug reaction

An adverse drug reaction (ADR) is defined as any harmful, unintentional response to a medicinal product (whether investigational or not). The term "response to a medicinal product" means that there may be a causal relationship between the drug and the adverse event, i.e. that the relationship cannot be ruled out.

ADRs, unlike adverse events, are characterized by the suspicion of a causal relationship between the medicinal product and the episode. All adverse events that the reporting investigator or sponsor considers to have a reasonable causal relationship with the medicinal product meet the requirements for ADRs.

Serious adverse drug reaction

According to the ICH and the European Guidelines on Pharmacovigilance for medicinal products for human use, a serious adverse event (or serious ADR) is any harmful medical episode (or "response to a medicinal product" as defined below) that, at any dose:

- Results in death
- Is life-threatening (The subject was at risk of dying at the time of the event; this does not refer to events that might hypothetically have caused death had they been more severe)
- Requires hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Raises suspicion of the transmission of an infectious agent through a medicinal product
- Is medically important*

*Medical and scientific judgement should be used to decide whether other situations should be considered serious, such as important medical episodes that may not be life-threatening or cause death or an immediate hospitalization, but may endanger the subject or require intervention to prevent any of the above outcomes or any condition that the investigator considers medically important.

In terms of the hospitalization reports, the sign, symptom or diagnosis that led to the hospitalization constitutes the serious event whose details must be reported.

TIMELINES

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Study design															
IRB approval + Spanish Medicines Agency classification															
Contract signature															
Statistical analysis plan design*															
Acquisition of data*															
Data cleaning+analysis*															
Discussion of results*															
Manuscript + report*															

*** These activities would start once the contract has been signed**

DISSEMINATION STRATEGY

The dissemination actions will comprise at least:

- Publication of a scientific paper in an indexed scientific journal

BUDGET

ACTIVITIES	COST
Study design	3,000 €
Statistical analysis plan design	1,000 €
Ethical and regulatory processes IRB submission, IRB dispenses, Spanish Medicines Agency classification	1,000 €
Study coordination	3,000 €
Data management Data request, data extraction (5 databases), data cleaning, data merging and tabulation, data quality review	34,000 €
Data analysis and study results Statistical analysis plan implementation, preparation and presentation of study results	3,000 €
Manuscript and final report Preparation and submission	5,000 €
Publication fee Publication in an indexed open access journal	2,000 €
SUBTOTAL	52,000 €
MANAGEMENT AND ADMINISTRATIVE EXPENSES (15%)	7,800 €
TOTAL BUDGET	**59,800 €**

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