USE OF PSYCHOTROPIC DRUGS IN CHILDREN AND ADOLESCENTS IN CATALONIA.

A cohort study with real world data from the electronic primary health care record from 2007-2017.

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PEPSICAT study.

Abstract

Objectives: This project has four main objectives: to describe the use of psychotropic drugs in children <18 years from Catalonia during the last decade, to describe the psychiatric diagnoses in the <18 years population consuming psychotropic drugs, to describe the characteristics of patients <18 years who start treatment with psychotropic drugs and, finally, to describe the consumption pattern of patients <18 years who start treatment with psychotropic drugs. Secondary objectives: to analyse factors associated with the use of different psychotropic drugs, to analyse factors related to the diagnosis of mental illness in patients under treatment with psychotropic drugs and to describe the adherence to psychotropic treatment. As exploratory objectives, an attempt will be made to correlate the maternal obstetric and psychiatric history with the consumption of psychotropic medication in the offspring and to analyse the reasons for the lack of a diagnostic record of mental pathology in patients with psychotropic treatment.

Methods: A descriptive observational study will be conducted from 2007-2017 in the population under the age of 18 with at least one prescription for a psychotropic drug. Two studies will be carried out: one to estimate the prevalence of psychotropic drug use in the <18 year population as well as diagnoses referring to psychiatric pathology and the second one will estimate the incidence of psychotropic drug use in the <18 year population. This second study will be carried out from a cohort consisting of the <18 year population presenting a first prescription of a psychotropic drug during the study period. This population will be followed until the end of the study or the impossibility to obtain information (death/transfer). The treatment period with this first psychotropic drug and the addition of other psychotropic drugs or the change of psychotropic treatment will be analysed during the follow-up. The data will be obtained from SIDIAP (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria) database, which contains anonymized clinical information on approximately 80% of the population of Catalonia. Information will be completed with data from the Basic Minimum Data Set for outpatient mental health care (CMBD-SMA). Data will be stratified by sex and age groups.

Expected results: According to the published literature of studies carried out in other European countries and conference papers with data from SIDIAP database, we expect to find an increase in psychotropic drugs consumption during the study period. With regard to the attention deficit hyperactivity disorder medication, the maximum consumption peak will be around 5-7 years of age and for antidepressants around 16-18 years of age. Most of the prescribed drugs will be out off label. We expect to find unique prescriptions without concomitant consumption of more than one psychotropic as well as, with the exception of the anxiolytics, a good persistence (>120%) to the treatment and in the case of the >16 years also a good adherence.

Keywords: Preschool, Child, Adolescent, Psychotropic Drugs, Maternal history, Obstetrical History.

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BACKGROUND

In the last decades, children affected by mental problems are 10-20% of the paediatric population, finding the Attention Deficit Hyperactivity Disorder (ADHD), followed by depression and anxiety, as the most prevalent disorders in the Western countries [1][2].

Consumption of psychotropic medication has increased in the paediatric population in recent years (children and adolescents, <18) in Europe[3][4][5]. However, during this stage of life, doctors often find themselves with few authorised drugs for these age groups, due to lack of evidence of safety and efficacy during the development of the drugs as these population groups are not included in clinical trials, as well as the lack of formulations adapted to paediatric dosage[6].

Although there is a large variation in the consumption of psychotropic medication at an international level in the paediatric population, this may be related to and influenced by multiple factors such as the cultural approach of each country towards mental diseases, the clinical practice, the health systems and health policy[7][8].

In the last two decades, studies have been carried out in several countries on the consumption of psychotropic drugs in children.
In the United Kingdom, the consumption of psychotropic medication in population <19 years showed an increase. For the stimulants group it went from 0.03 per 1,000 in 1992 to 2.9 per 1.000 in 2001, with the highest use in the 10-12 age group. Antidepressants also increased their use by 1.6 times, showing the highest prevalence of use the age group 16-18 years. The mean age at first psychotropic prescription was 12,6 years (SD 5,4) with an average of 1.2 prescriptions for different medications.
In Germany a study in children and adolescents (0-17 years) showed an increase in the psychotropic drug consumption from 19.6/1000 in 2004 to 27.1/1000 in 2012[10].
In France, 2.5% of children under 17 years of age had a psychotropic drug prescription in 2010, mostly anxiolytic (1.9%) and minority stimulants (0.2%)[11]. The most common association of psychotropic medications was antipsychotics with hypnotics or anxiolytics (30.4%). Anxiolytics were 77.5% of the unique prescriptions.
In Italy, the prescription prevalence of psychotropic drugs remained stable during 2006-2011, with a decrease in the incidence from 2006 to 2011 (from 1.15/1,000 children to 1.03/1,000 children)[12]. The most prescribed drug was risperidone (20.6% of those treated), followed by

sertraline (18%) and methylphenidate (7.1%). Of the 10 most prescribed active ingredients, 4 of them had no authorization in this group of age.
Denmark analysed a period of 15 years showing an increase in the prevalence of prescriptions for psychotropic medication in paediatric population from 1.34 to 12.35 per 1,000 persons-year (1996-2010)[13].

Most studies point to the fact that the age and sex with the highest prevalence of use change according to the therapeutic group. Stimulants and antipsychotics are more consumed by boys from 8 to 12 years and antidepressants are more consumed by girls from 14-16 years of age.

Maternal psychopathology has been linked to the risk of offspring suffering from mental illness. The possible relation between parents´ behaviour and/or mental illness and the risk of their children being diagnosed of a mental illness can be found in the literature [14][15].
In 1993, a study in the United States analysed the use of psychotropic medication in children (3.9% received psychotropic medication) and their relation with factors such as monoparental family and history of psychotropic drug use by parents.

In Spain we have not found any published studies on the use of psychotropic drugs in paediatrics. There is one study, with sales data from the IMS MIDAS, which observed a growth of 1,500 annual prescriptions for psychotropic medication in 2002 compared to 1,000 in 2000[8].

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HIPOTHESIS

1. The consumption of psychotropic drugs has increased in the paediatric population in the last decade.
2. The increase in the consumption of psychotropic drugs is reflected in an increase in diagnostic record of psychiatric illnesses in the paediatric population.
3. Maternal psychiatric history is related to the consumption of psychotropic drugs in the paediatric population.
4. Obstetric history is related to the consumption of psychotropic medication in the paediatric population.

OBJECTIVES

Main objectives

1. To describe the consumption of psychotropic medication (antipsychotic, antidepressant, stimulants, anxiolytic, hypnotic/sedative and antiepileptic drugs) in the population <18 years in Catalonia during the last decade: globally and stratified by age and sex.
2. To describe the diagnosis of psychiatric pathology in the <18 years population who consume psychotropic drugs in the last decade; globally and stratified by age and sex.
3. To describe the characteristics of the <18 years population starting treatment with psychotropic drugs.
4. To describe the pattern of consumption of patients <18 years who start treatment with psychotropic drugs.

Specific objectives

a) To analyse the relationship between psychotropic drugs prescribed and diagnoses registered.
b) To describe patterns of combinations of groups of psychotropic drugs in <18 years.
c) To describe the persistence of psychotropic treatment in new users of psychotropic drugs.
d) To describe adherence to psychotropic treatment in the subgroup of 16-18 years new users.
e) To analyse factors related to the use of different treatment groups in population <18 years.
f) To analyse factors related to the diagnosis of psychiatric illnesses in patients treated with psychotropic medication.
g) To conduct a bibliographic search.

Exploratory objectives

I. To analyse the maternal psychiatric history of patients <18 years with consumption of psychotropic drugs.

II. To analyse the maternal obstetric history of patients <18 years with consumption of psychotropic drugs.

III. To correlate maternal psychiatric/obstetric history and psychotropic drug consumption in children.

IV. To analyse the reasons for the lack of a diagnostic record of psychiatric illnesses in patients initiating psychotropic drugs (sample of 300 primary care patients).

V. To search for prevalence data on psychiatric pathology and consumption of psychotropic drugs in <18 years in Spain to make a comparison with our results.

METHODS

Two studies will be carried out to meet all the objectives:

1. Analysis of the prevalence of psychotropic drug use and psychiatric diagnostics in <18 years population in Catalonia by age and sex group in each year of the study.

2. Analysis of patients beginning treatment ("new users") with psychotropic drugs during the 10 years of the study. The population characteristics and the consumption pattern (prescription treatment duration, changes among the different psychotropic therapeutic groups or active substances and psychotropic drug associations). In this cohort a study analysing the relationship between drug consumption and psychiatric and obstetric maternal history will be carried out.

Design

Population-based cohort observational study.

Study period

From January 1st 2007 to December 31th 2017.

Study subjects

For objectives 1 and 2 will be the patients <18 years by age group and sex with psychotropic drugs prescribed during the study period (2007-2017).

For Objectives 3-5, a cohort will be formed with patients <18 years who begin treatment with psychotropic drugs from January 1st 2007 to December 31th 2016. 2017 data will be used as follow-up data, allowing us to analyse the pattern of use for at least one year.

Inclusion criteria

Patients <18 years of age active in the database during the study period.

Patients <18 years initiating treatment with psychotropic drugs during the study period (new users cohort). The start of processing will be the date of the first invoice.

Exclusion criteria

Patients ≥18 years during the study period.

Sources of information

The data will be obtained from SIDIAP (Information System for Research in Primary Care) database. SIDIAP contains anonymized clinical information of all 279 PHC centers managed by

the Catalan Health Institute (ICS), covering a population of more than 5.8 million patients (about 80% of the total of 7.5 million population in Catalonia). The information contained in SIDIAP is registered by general practitioners (GP) from the primary care health sector, nurses and administrative staff in ECAP (electronic health records): comprehensive sociodemographic information, health conditions registered as ICD-10 codes, specialist referrals, clinical parameters, toxic habits, laboratory test results, GPs prescriptions and their corresponding pharmacy invoice data registered as Anatomical, Therapeutic, Chemical classification system (ATC) codes, date of sickness leave due to any cause, and date of death.

Data from consultations of the specialised Psychiatry Centres will be obtained from the Minimum Basic Data Set (Conjunto Mínimo Básico de Datos, CMBD) of Outpatient Mental Health Care (CMBD-SMA).

Prevalence Study (Objectives 1 and 2)

The prevalence of psychotropic drug use will be determined during each year of study by age groups (0-2; 3-5; 6-11; 12-15; 16-18) and sex, calculating patients treated per year according to active substance and pharmacological subgroup.

The prevalence of psychiatric disease diagnoses in the population <18 years old will be obtained by age group (0-2; 3-5; 6-11; 12-15; 16-18) and sex, for each year of study, establishing patients diagnosed per year according to the main pathologies in paediatric psychiatry classified in the CIE-10.

Drug use pattern (Objectives 3 and 4) "New users cohort"

Patients who start treatment during the study period (2007-2016) with psychotropic drugs will enter a cohort and will be stratified into age groups: 0-2; 3-5; 6-11; 12-15; 16-18 and sex and will be monitored until: completion of the study (December 31st, 2017), exit of the cohort by death, transfer or end of access to data for any reason.

The beginning of psychotropic medication treatment will be defined as having a prescription for psychotropic medication without any prior psychotropic prescription in the last 12 months. Each individual will enter the cohort once and will be followed to describe the pattern of use of psychotropic drugs: onset of more than one psychotropic drug, persistence to treatment and change of treatment. The results will also be stratified into groups of age and sex and expressed by active substance and pharmacological subgroup expressed as new users per year. For the assessment of persistence the analysis will be carried out by pharmacological groups/ active ingredients, establishing different persistence criteria according to the groups and the

pattern of persistence of the same described in the literature. The persistence to treatment will be assessed by the number of prescriptions per month by patient.

For the initiators in the age subgroup of 16-18 years old, , due to their similarity in doses to those of the adult population, the adherence to the treatment will be analysed by means of the proportion of days covered (PDC). No calculation of adherence will be made for the population <16 years of age because of their different doses (normally calculated by weight).

Mother-offspring linkage study (exploratory objective)

The SIDIAP database has linked almost 60% of the children to their mothers. The mothers of those patients included in the new users cohort having this linkage will be analysed by psychiatric and obstetric records (diagnosis and treatment) trying to establish a possible correlation of the maternal history with the psychotropic drug use in children.

Field Research (Exploratory Objective)

We expect to find a percentage of patients under treatment without a psychiatric diagnosis. A study to analyse the reasons for the lack of diagnostic record in the primary care records in patients under treatment with psychotropic pharmaceuticals will be carried out in 20 care centres by paediatricians, who will collect the information from the electronic health record from primary care (ECAP): psychotropic treatment, psychiatric diagnostic records or their lack and possible motives for it.

Variables

Demographic:

Month of birth, sex, weight at birth, country of birth, adoption, rural/city primary health care, MEDEA index classification, Catalonian provinces.

Clinical variables

Number of visits (paediatrician, nurse, general practitioner), referrals to psychiatry/mental health, date of first visit, visits to social assistant, related problems to scholar dropout, psychotherapy, severe mental health program.

Birth related variables:

Gestational week at birth, APGAR, lactation.

Pharmacology treatment (22):

a) Antipsychotics (N05A)

b) Anxiolytics (N05B)
c) Hypnotics/sedative (benzodiazepines) (N05C)
d) Antidepressants (N06A)
e) Stimulants (N06BA)
f) Lithium (N05AN)
g) Antiepileptics (N03A)

Diagnosis: International Classification of Diseases (ICD), 10th version.

F00-F99: Mental and behavioural disorders.

Mother variables

Toxic habits, marital status, studies, MEDEA index, professional status, age at gestation, gestational week at deliver, weight (from the offspring), psychotropic medication invoice, psychiatric illness diagnosis, prenatal obstetric pathology registered.

Variables from CMBD- SMA:

Information about psychiatric diagnosis and visits to psychiatrist, psychologist, psychotherapist and social worker will be obtained from SIDIAP database and completed with the information of CMBD-SMA.

Sample

All SIDIAP <18 years with inclusion criteria and no exclusion criteria.

Data analysis

All data management, descriptive calculation and statistical analysis processes will be carried out using the statistical package R 3.3 (2016).

At the exploratory level, the demographic data and baseline characteristics of the population will be described by relative and absolute frequencies for the categorical variables and median standard deviation or median and interquartile range for the continuous variables.

In the bivariate analysis, we will consider the Chi-square test or the exact Fischer test for the categorical variables and the t-test of Student or the U-test of Mann-Whitney for the continuous variables according to their distribution.

Evaluation of psychotropic consumption based on psychiatric/obstetric maternal records, as well as the risk related to the persistence/adherence of these in patients with an age range of 16 to 18 years old, will be performed using multiple logistic regression models or proportional

risk models (Cox). Adjustment for risk factors will be determined based on the characteristics of the study population.

No imputation method is foreseen for the management of lost or missing data.

LIMITATIONS OF THE STUDY

I. Since this is an observational study of cohorts with data from a database, causation could not be established. However, the evaluation of these results are carried out under conditions of daily clinical practice with data from electronic records from PC through the SIDIAP database, which has proven its validity and representativeness of the population in previous studies[15-54-57].

II. Some of the limitations of this type of study are due to under-registration of some variables.

III. An inherent limitation of observational studies is the presence of possible confounding variables: Diagnosis-Treatment unbound.

IV. The calculation of the persistence of psychotropic treatment will be made using data from pharmacy invoice which are not always indicative of actual compliance with treatment.

V. Patients who present with psychotropic treatment years before the electronic record of the invoice data will be treated as new users, in order to minimise this bias, a 12 months period in the database with no invoice data for psychotropic medication will be needed.

VI. The mother-child bonding is not 100% and the mother's data during gestation is not 100% because their pregnancy and delivery assistance by private health insurances. This bias will appear in the exploratory objectives.

VII. As this is a drug use study in the paediatric population, it is not possible to analyse the consumption Defined Daily Doses in (DDD) so invoice data will be used. For the 16-18 years subgroup, adherence will be calculated according to DDD as doses in this age group are similar to those in adulthood.

ETHICAL AND CONFIDENTIALITY ASPECTS

The study will be carried out in accordance with national and international standards (Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects) on ethical aspects and standards of Good Research Practice principles and guidelines.

The protocol has been approved by the Research Ethics Committee of the 'Institute for Primary Health Care Research Jordi Gol (IDIAPJGol) ", reference institution for the Primary Health Care Research at ICS (Catalan Health Institute).

The appropriate level of security will be established (General Data Protection Regulation (EU) 2016/679 and Ley Orgánica 3/2018 de 5 de diciembre de Protección de Datos Personales y garantía de los derechos digitales). Data included in SIDIAP are anonymized and identified with an internal code that makes it impossible for the identification of the subjects included in the study, thus it is not necessary to ask for informed consent from the participants.