Universitat de Girona
Facultat de Medicina

STUDY OF THE USE OF MEDICINES FOR THE TREATMENT OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CATALONIA

Final Degree Project

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Parc Hospitalari Martí i Julià

Salt

Author: Marta Vázquez Casar

Clinical Tutor: Dra. Sacramento Mayoral

Methodological Tutor: Dr. Xavier Castells

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INTRODUCTION:

Definition, history and epidemiology of ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is defined as a neuropsychiatric disorder that starts in childhood, and comprises a symptomatic triad characterized by hyperactivity, impulsiveness and/or lack of attention symptoms, more frequent and severe than what is usual for that age, and causing a significant impairment in school or work performance and in the activities of daily life (1).

History of ADHD

The first time someone talked about ADHD was in 1902, when George Still (2) described 43 children who had problems in sustained care and self-regulation, which he attributed a problem in the “moral control” of behaviour, owing to genetic problems or lesions pre or postpartum.

Between 1917 and 1918 there was an epidemic of encephalitis in North America that resulted in numerous cases of behavioural alterations that would be similar to what is known today as ADHD. As a result, it was generated the hypothesis that this could be associated with lesions in the cerebral parenchyma, using the terms "Minimum Brain Damage" or "Minimal Brain Dysfunction” (3).

In 1937, Bradley (4) accidentally discovered the therapeutic effects of amphetamines in hyperactive children.

Later, in 1968, the Diagnosis and Statistics of Mental Disorders Manual, second edition, known for its acronym in English as DSM-II (5) included this alteration as "Infantile Hyperkinetic Syndrome", which was characterized by excessive activity, restlessness and difficulty for the holding attention; subsequently, the DSM-III (1980) (6) used the

term “Attention Deficit Disorder”, insisting therefore on the importance of the attention problems. The specification of the number of symptoms required for diagnosis, the age of onset (7 years), the minimum duration of 6 months and the need to rule out other possible pathologies such as schizophrenia that could cause similar symptoms were also included.

In the DSM-IV (1994) (7), was again allowed the diagnosis in patients presenting only symptoms of inattention, and joined three subtypes of ADHD: inattentive, hyperactive / impulsive, and a combination of them, and they change the diagnostic criteria once more.

DSM-IV-TR (2000) (8) named it as “Attention Deficit and Hyperactivity Disorder”, and maintains the division in three subtypes.

Today there is a new version of the DSM (DSM-V) (2013) but the professionals are still using the DSM-IV-TR. Significant changes have been made in this area, such as an increase in the minimum age of presentation of the disease from 7 to 12 years old, the possibility to diagnoses with other psychiatric diseases as ASD (Autistic Spectrum Disease), and no requirement of social, academic and occupational impairment. Moreover, the disorder is included in the category of neurodevelopmental disorders (9). At the time that the new ADHD cases are diagnosed with the last manual, it is expected that the prevalence of the disorder will increase as the criteria are becoming less restrictive.

Epidemiology

This disorder has an important impact because of its high prevalence; it is one of the most frequent psychiatric disorders in the childhood. In 2012, Catalá-López and cols. (10) accomplished a meta-analysis that estimated that 6.8% of children and adolescents

in Spain met the criteria for diagnosis, with a variability between 4.9 and 8.8%, representing 361,580 children and adolescents (11). Wittchen et al. (12) estimated in 2010 that 3.3 million children and adolescents aged 6-17 years have ADHD in the European Union, with a prevalence of 5%, and the results by Polanczyk et al. (13) in 2007 yielded a world prevalence equivalent to 5.3%.

It must be highlighted that it has been found geographical differences in the prevalence of the disorder, varying between different regions of the world and even between different areas of the same country (1, 14).

Although ADHD symptoms severity decreases over time, it is estimated that half of patients continue to present the disorder in the adulthood, with predominance of inattention symptoms (15, 16), and hypotheses are beginning to be broached that there are cases that begin in adulthood (17). Specifically, Faraone SV et al (18) performed a meta-analysis that concluded the prevalence in adults of "persistent ADHD" and for "ADHD in partial remission" was 15% and 65%, respectively.

Classically ADHD has been considered to be predominant in males (13), but over the years it has been found that the prevalence is similar in both sexes, although there are differences in the main manifestations. Thus, it seems that in boys predominates hyperactivity, whereas attention deficit does it in girls, but the most frequent is the combinatied pattern (1).

Another characteristic that features ADHD and makes the diagnostic difficult is that comorbidities are prevalent in these patients (1).

Clinical symptoms:

As we mentioned in the definition, the classic ADHD clinic is composed by a triad of nuclear sympthoms. It consists in inattention, hyperactivity and impulsivity (1):

1- **Inattention**: represented by high distractibility, difficulty following orders and instructions and avoidance of activities in which attention is required (19).
2- **Hyperactivity**: children have problems to participate in quiet activities, they tend to be very restless children, and they are unable to respect some rules (19).
3- **Impulsivity**: characteristically recognized because they often interrupt conversations, talk excessively, blurt out answers before a question has been finished and have many problems to respect the environment (19).

However, not all cases are presented in the same way; there is a great variability in the combination of symptoms and in the severity of these symptoms (19). Moreover, as we said previously, many cases are usually accompanied by comorbidities and important consequences as oppositional defiant disorder, behavioral alterations, school failure, substance abuse and accidents (1). The alterations begin before 7 years old (12 in case of DSM-V) and it affects the correct child development (8, 9).

In adults, the clinic is lighter because the symptoms of hyperactivity and impulsivity diminish with age. Inattention refers to difficulties in organizing tasks or activities and hyperactivity and impulsivity can be detected as internal restlessness and excessive speech. In addition, comorbidities are also present, in this case in form of problems for emotional regulation and depressive profile disorders, increase of irritability, abuse of sustance and alteration of personality traits (1).

Diagnosis of ADHD

The diagnosis of ADHD is complex. It should be based on the clinical assessment confirmed by an expert on the recognition and treatment of it. There is no agreement about the instruments and criteria to be used for evaluating children with potential ADHD and there are no other techniques or tests that can support the diagnosis more

accurately. These difficulties in the detection, diagnostic process and methods originates some problems that can lead to under- or over-diagnosing ADHD.

Actually, DSM-IV/DSM-IV-TR (Annex 1) and ICD-10 (Annex 2) are the diagnostic criteria most commonly used. Both classifications describe the clinical condition of hyperactive children (ADHD/Hyperkinetic disorder) and use similar operative criteria for diagnosing it. However, as the ICD-10 diagnostic criteria are more restrictive, the diagnoses made with this tool are the most severe cases of ADHD according to DSM-IV-TR criteria. ICD-10 and DSM-IV-TR are also different when considering the subtypes of disorder.

Other clinical tests are SNAP-IV (Annex 3) and Conners Test (Annex 4). The Conners scale, the most used, scores the severity of symptoms with degrees from zero (none) to three (many). There is a short version that is less sensitive but more comfortable for the clinician. The SNAP-IV questionnaire also scores the symptoms from zero to three and has two versions - for parents and for teachers - with the DSM-IV criteria. Both of them are used as a tool to detect and measure the effectiveness of treatment (20).

The reality, as we said previously, shows that diagnosis criteria are becoming less restrictive, so that the cut-off point of the age of onset of the disorder has been raised, reducing the number of symptoms necessary for diagnosis and allowing diagnosis in the presence of comorbidities (1).

Ethiopathogenesis

ADHD has a heritability of 70-80%, higher to many other psychiatric disorders. (1). However, although numerous genes have been studied, the results are variable and therefore do not help us to obtain a clear conclusion, although we have found some that have revealed a greater relation between their alteration and the presence of risk of

ADHD. Some of these genes encode DRD4, DRD5, SLC6A3, SNAP-25 and HTR1B, that are related specially with dopaminergic system, and whit noradrenergic and serotoninergic systems too (21).

In addition, environmental factors have been associated with ADHD. These include: prenatal exposure to tobacco, prematurity and low birth weight, exposure to lead or extreme early social deprivation. Furthermore, dietary factors have been found, such as nutritional deficiencies or diets rich in fats and refined sugar or low in omega-3 fatty acids that may also have a role in the pathogenesis (1). Moreover, psychosocial factors such as low economic and social status, low parental education, maltreatment and institutionalization have been also associated with the development of ADHD (1).

Finally, there are hypothesis that demonstrate that these patients have some familiar predisposition to suffer from this disorder. It is frequent that a relative was diagnosed with ADHD or have had some behavioral disorder.

Therefore, we could deduce that there may be some genetic alteration that predisposes to suffering the disease, but in turn, certain environmental factors that trigger the clinic, what is known as epigenetics, are necessary (1).

Neurobiology

It is believed that there are two types of neuropsychological dysfunctions: on the one hand executive dysfunctions and on the other hand motivational dysfunctions. Executive dysfunctions altered maintained attention, planning, working memory and the ability to inhibit response. Motivational deficits refer to a preference for immediate, large rather than small rewards ("delay adversion") (1). These neuropsychological alterations correlate with two major neural systems: the fronto-striatal circuit, including

dorsolateral prefrontal cortex, anterior cingulated cortex and dorsal striatal nucleus (anterior attentional system) that regulate executive functions, and the mesolimbic circuit, orbitofrontal cortex and ventral striatal nucleus that regulate motivational functions (1). These functional alterations seem to be associated with alterations in the catecholaminergic neurotransmission. In subcortical areas, anomalies in dopaminergic neurotransmission may be found, especially in the reward circuit. In addition to this, alterations in dopamine (DA) and noradrenergic (NA) pathways that innervate the prefrontal cortex have been observed (22).

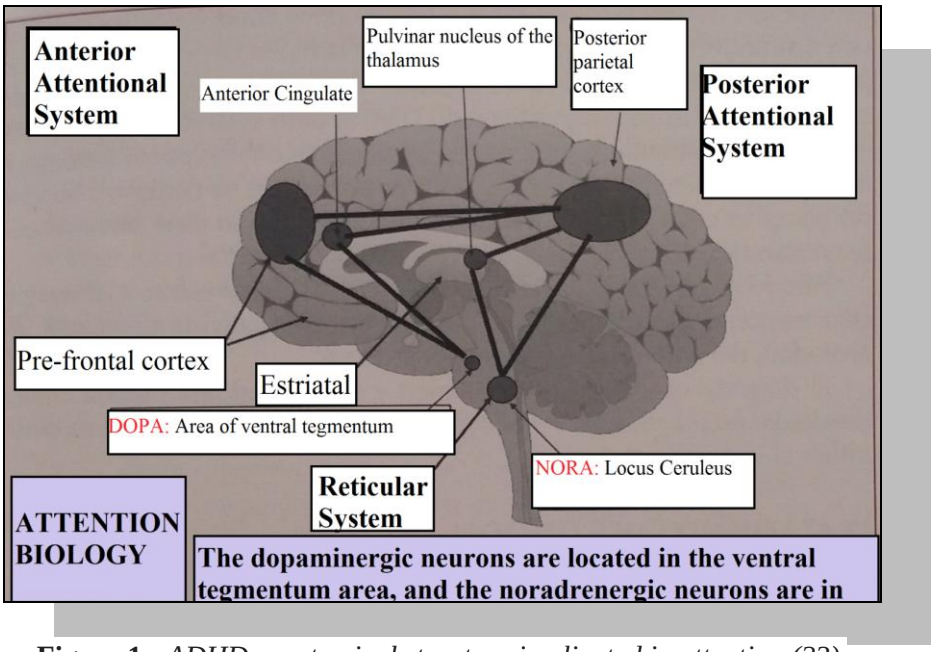

Figure 1: *ADHD: anatomical structure implicated in attention (23).*

What has been mainly seen in the different neuroimaging tests performed is that, compared to controls, ADHD cases have a generalized decrease in brain volume (24). It represents a delay in the cortical maturation, probably because, due to the symptoms of the disorder, learning is altered and new brain connections are not generated.

T**reatment of ADHD**

Management of patients with ADHD involves pharmacological and non-pharmacological strategies (1). A multimodal approach combining pharmacotherapy with psychological intervention is recommended.

Therapeutic recommendations

Both, the guide of clinical practice of National Health System (25), and NICE guideline (26) make recommendations to managing the disorder according to patients ADHD symptom severity. The DSM-IV-TR (8) considers that there are 15 items for the evaluation of a potentially ADHD patient. These items are divided into 9 inattention, 6 hyperactivity and 3 restlessness criteria. Depending on the number of items in each section as well as the experience of the clinician who diagnose them, these guideline recommend making different steps to treat these patients, that can be grouped in three subdivisions about the severity of the condition:

1- **Mild ADHD**: the therapy is based on psychological support, combining behavioural therapies or cognitive-behavioural therapy with school interventions (school adaptation, school reinforcement and teacher training) and parental training.

2- **Moderate ADHD (or lack of response):** in this case, the guideline recommends to continue with psychological therapy but adding pharmacological treatment. The first line of treatment will be Methylphenidate (MPH) or Atomoxetine (ATX), using one of them.

3- **Severe or Resistent ADHD**: in this case, the recommendations are continuing the treatment with psychological interventions with the possibility to change the

first line drug for other first line drug, use a second line drug or maybe, in the worst cases, we can think about the combination of two drugs.

Before beginning pharmacological treatment, it is important to have a complete examination of the patient, including height, weight, blood pressure and heart rate, and to assess family and personal history of cardiovascular disease (25, 26, 27).

However, the strength of these recommendations is not very high because, as we said, there is no homogeneous consensus on how to act with these patients.

Non pharmacological treatment

Several types of psychosocial interventions exist: psychological, psychoeducational and cognitive interventions. Cognitive interventions in turn consist in cognitive rehabilitation and executive function training. The psychological ones collect cognitive-behavioral therapies, the development of social skills and problem solving, and finally, psychoeducational therapies and training for parents and teachers are carried out.

1- **Cognitive training** seeks to teach the child to develop more planned ways of thinking, to allow him to have a better behavior. Maladaptive behaviors and cognitions are identified to find more appropriate ones. With this, these patients are allowed to be more resolute and have greater self-control (28).
2- **Cognitive-behavioral therapy** is based on the learning of behaviors considered correct through the use of punishment and reward, so that it seeks to reinforce those appropriate behaviors with positive reinforcements, and to avoid misconduct with the opposite (28).
3- **Parent education** seeks to inform and teach parents about ADHD. They learn to use techniques that allow better management of their children, strengthen

parental-filial trust and communication between both, favouring the correct development of the child (28).

4- **Teaching for the acquisition of social skills** conduct behaviors and capacities that allow establishing and maintaining constructive social relationships, through techniques such as maintaining eye contact or smiling. In this case it is preferred to perform a group therapy (28).

Pharmacological treatment

As we have seen previously, in 1937 Bradley discovered the pharmacological effects of amphetamines on patients who had a strange behavior considering what would be normal at their age (4). Today, this has evolved and we find the possibility of using 2 types of drugs specifically indicated for the treatment of ADHD (27).

1- **<u>Psychoestimulants:</u>** increase DA and NA in cortico-subcortico areas, through the inhibition of presynaptic reuptake (27).

- **Metylphenidate (MPH):** is the main pharmacological treatment, the most used in our country. Is found in 3 different pharmaceutical formulations (27).

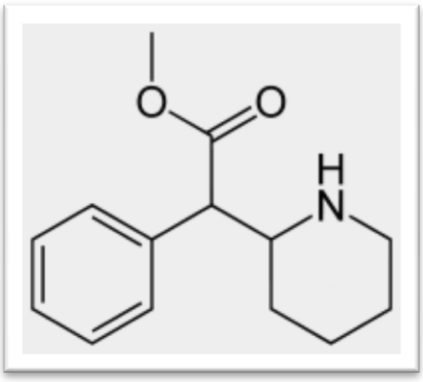

Figure 2: MPH molecule

<u>Immediate Release:</u> the effect begins between 30 – 60 minutes after taking it. Maxim effects are achieved 1-2 hours late, and the effect lastss 4-6h.

OROS (prolonged release with osmotic technology): the effect begins between 3-4 hours, and remains about 8-10 hours.

Pellets (prolonged release with concentration technology): It has a double effect. The effect begins between 1-2 hours (similar to immediate release) and it is maintained around 6-8 hours, similar to OROS formulation.

- **Lisdexamphetamine (LDX):** it is an amphetaminic derivate. It was marketed in Spain in 2014 (27).

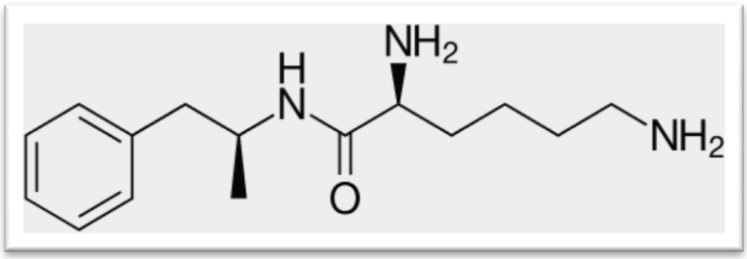

Figure 3: LDX molecule

The effect begins 30-60 minutes after taking it and it is maintained around 13h.

2- Non-Psychostimulants:

- **Clonidine**: is used as an antihypertensive drug. It affects alpha receptors (27).
- **Guanfancine**: it is expected to marketed yet in Spain within few weeks. It is another alpha agonist (27).
- **Atomoxetine (ATX):** this is the most important of the group. Selective inhibitor of noradrenaline presynaptic transporter. The effects begin between 15 days after taking it (27).

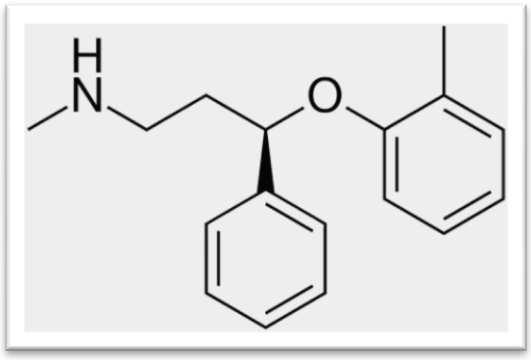

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Figure 4: ATX molecule

3- **Other Drugs:** tricyclic antidepressants and bupropion; although they do not have the indication for the treatment of this disorder, they have shown to improve the symptoms of ADHD in some studies (1).

MPH, LDX and ATX are authorized for the managed the symptoms in children above 6 years old and adolescents with ADHD (27). MPH and LDX are also authorized as a continuation treatment of adolescents whose symptoms continue through the adulthood (27). ATX is the only drug that can be initiated in the adulthood (27).

Other interventions

Currently, the tendency is to use dietary interventions as a possible treatment for symptom control. In studies compared with placebo, supplements with free fatty acids and the elimination of artificial diet dyes seem to have the capacity to decrease symptoms (29).

Efficacy of pharmacological interventions:

Since both EMA and FDA require new drugs to show short-term efficacy for reducing ADHD symptoms compared to placebo, the vast majority of studies investigating the efficacy of drugs to treat ADHD symptoms have a placebo-controlled design with a

duration of few weeks (4-12 weeks) and use ADHD symptom severity assessed with parent, patient or clinician rated scales as study outcomes (30). The relevance of these outcomes is arguable due to its subjective nature and because do not provide information on the clinical consequences of ADHD that is the main preoccupation of patients (31).

Pharmacological treatment has a moderate efficacy for reducing ADHD symptoms (32). It seems that symptomatic efficacy is slightly larger in children that adolescents or adults and when it is assessed by the clinician, instead of the patient or the parents (33). Furthermore, psychostimualnts seem to be more effective than non stimulants (33, 34), for these reasons, the former are recommended over the later (32, 35). It must be highlighted that there is a lack of long-term head to head studies using clinically relevant outcomes are lacking, and most information of this issue is available from few observational studies, some of which suggest that pharmacological treatment may reduce drug abuse (36, 37), criminality (38) and mortality (39). Nevertheless, such evidence is anecdotal, with a high risk of selection and confusion bias; therefore, these findings should be confirmed under controlled conditions (31).

Safety of pharmacological interventions:

Stimulants and non-stimulant drugs show important differences on the type of side effects caused, that make patients to discontinue the regimens. Among other adverse effects, the drugs registered in this study have hiporexic capacity, they help weight loss and cause less growth in children and adolescents, increase blood pressure and heart rate (27). In addition, because of their amphetamine characteristics, they are drugs of potential abuse, which can lead to dependence (40).

The following chart shows the adverse effects and recommendations for the use and contraindications of the drugs studied in this study.

Medication	Indications	Relevant side effects	Precautions and contraindications
Methylphenidate	START: Children over the age of 6 and adolescents CONT: adults	-Aggressiveness, hostility, anxiety, restlessness, depression, mood swings, irritability, psychomotor hyperactivity, tics -Decreased appetite, growth retardation -Insomnia, somnolence -High blood Pressure, tachycardia, palpitations -Ddizziness -Priapism	-Hypersensitivity -Pheochromocytoma -Glaucoma -Preexisting cardiovascular and cerebrovascular disorders -Hyperthiroidism -Diagnosis or history of severe major depressive disorder, severe bipolar disorder type I, psychotic disorder, anorexia, substance use disorder, suicidal thoughts - Pregnancy, lactation - Epilepsy or Seizures
Lisdexanphetamine	START: In children over the age of 6 and adolescents. CONT: adulst	-Anxiety, agitation, insomnia, irritability, mood swings, tremor, tics, dizziness -Decreased appetite; weight loss, growth alterations -Tachycardia and palpitations	-Hypersensitivity -Glaucoma; -Hyperthyroidism; -Moderate or severe high blood pressure, symptomatic cardiovascular disorders, advanced atherosclerosis -States of agitation, diagnosis or history of severe major depressive disorder, severe bipolar disorder type I, psychotic disorder, substance use disorder -IMAO´s -Pregnancy, lactation. -ISRS concomitant treatment. - Narcotic analgesics -Epilepsy

Atomoxetine	START:In children over the age of 6, Adolescents and adults. CONT: adults	-Aggressiveness, hostility; anxiety, agitation; depression, mood swings; suicidal thoughts; irritability; dizziness. -Cardiovascular disease	-Hypersensitivity; -Concomitant treatment with IMAO´s -Glaucoma; -Pheocromocitoma -Hepatic disease -Epilepsy -Growth alterations -ISRS antidepressive treatment. -β-Agonists treatment. -Lactation

Chart 1*: characteristics of ADHD treatment (27)*

JUSTIFICATION

In the last years, it has been generated a great mediatic echo that has allowed more people to know the existence of ADHD, however it is also generating misconceptions about this, wich is traduced in more naughty and restless children derivated to the specialist in order to find a diagnosis that explains their behaviour. Thus, we are witnessing an increase of the diagnosis of the disorder, which has been blamed of overdiagnosis. In fact, there are some references that affirm that the correct diagnosis of ADHD is only a 30-60% of cases derivated to Mental Health with the suspicion of a possible ADHD (41). This increase in the prevalence of the diagnosis of ADHD has lead to a continuous rise in the consumption of drugs to treat ADHD, coinciding with the marketing of new and expensive medicines.

Furthermore, the efficacy and safety of drugs to treat ADHD are controvertial. As we exposed, it is known that the adverse effects influence of neurological and cardiovascular system, and alter normal growth and development of the child. Moreover, as we have said, the drugs with indication for the treatment of ADHD have only shown short-term efficacy for the improvement of symptoms, while pharmacological treatment in the clinical practice is chronic. Finally, the efficacy has fundamentally been shown on the improvement of ADHD symptoms and quality of life, and it is known that the main problems of these patients are not the symptoms of inattention, hyperactivity and impulsivity, but the consequences derived from them.

For the reasons given above, it is necessary to know what the prevalence of the consumption of drugs to treat ADHD is, the characteristics of patients who consume these drugs and which the consumption trend of these drugs in the last years in Catalonia is.

METHODS:

Hypothesis

This is a descriptive study for which no hypothesis has been formulated.

Objectives

1- To determine the prevalence of consumption of drugs authorized for the treatment of ADHD in Catalonia.

2- To know sociodemographic and clinical characteristics of patients receiving treatment with drugs authorized for ADHD in Catalonia.

3- To evaluate the follow-up degree of the use recommendations these drugs to the recommendations of the technical file.

4- To study the drug consumption evolution for the treatment of ADHD in the period comprised between 2010 and 2015, in Catalonia and Girona.

Material and Methods

Two studies of drug use were carried out. The first one addressed the objectives 1-3 and the second one the number 4.

STUDY 1

Design:

A descriptive cross-sectional study was carried out.

Study population:

Patients receiving treatment with methylphenidate (MPH), lisdexamphetamine (LDX) or atomoxetine (ATX) sometime in 2015 was obtained.

Information source:

Information was obtained from the ICS Basic Health Data Database (DBS: Datos Básicos de Salud). This database includes information disassociated from patients treated at the Catalan Health Institute (Institut Català de la Salut) (ICS) and developed by the Primary Care Information System (SISAP) of the ICS (population served by ICS: 5,605,093 people in 2015). It does not include information from hospital data and is based on information recorded in computerized medical records (Historias Clínicas Informatizadas). It contains both socio-demographic data, as well as health problems, drugs and many clinical and laboratory variables. In this database is included those people who decide the health professional, doctor or nurse.

The data was provided by a database manager, completely anonymised by an encryption process whose decryption code is only known by the database managers, reason why we do not need Informed Consent.

Study variables:

Sociodemographic and clinical variables were collected.

The sociodemographic variables are age and gender.

Clinical variables are: psychiatric disorders (personality disorders, depressive disorder, anxiety disorder, schizophrenia, psychosis, affective psychosis), drugs abuse (user of parenteral drugs, cocaine, cannabis, hallucinogens, stimulants, opioids), neurological disorders (dementia) cardiovascular diseases (hypertension, isquemic heart disease, cardiac insufficiency, auricular fibrillation, cerebrovascular disorders), endocrinological diseases (obesity, hyperthiroidism) and concomitant pharmacological treatments (ansiolytics, antidepressants, antiepileptics, antipsychotics).

Sample size:

The sample size has not been calculated because all available cases will be selected.

Statistical analysis:

The distribution of patients receiving pharmacological treatment for ADHD was determined according to their gender and age. Comorbidities and concomitant treatments were described. The prevalence of patients treated with ADHD drugs in Catalonia were calculated globally and by age. This analysis was done for all patients treated during 2015. To calculate the general prevalence of use we used the population assigned to the ICS in the denominator. The population served by the total ICS is about 5.600.000 inhabitants, which represents about 85% of the population of Catalonia.

STUDY 2

Design:

Longitudinal retrospective study.

Population of study:

It was not applicable as the information analysed was not based on patient or population data. We used data of purchase of MPH, LDX and ATX from 2010 to 2015, as an approach to assess their consumption.

Source of information:

Information was obtained from the ICS pharmacy database, which contains retail community pharmacy sales data of medicinal products reimbursed by the Spanish National Health Service and covers the whole Catalan population.

According to the information available in the web page of AEMPS (Centre of online Information of Medicines, CIMA), we made a list of drugs authorized in Spain for the treatment of ADHD in the interval of time under study (27). Annual dispensation data of the analyzed medications were obtained from the ICS Dispensing Drug Pharmacy database.

Study variables:

Drug consumption, expressed as Defined Daily Dose (DDD) per 1000 habitants/day for the treatment of ADHD dispensed by ICS from 2010 to 2015, both inclusive, was studied (see Annex 5 for DHD calculation). DDD is a standard dose used for the main indication of a medicine. DDD is stipulated by the WHO and it is: MP 30 mg / day, LDX 30 mg / day and ATX 80 mg / day) (42). The number of DDDs per 1000 inhabitants/day provides information on the region consumption of this drug and allows for time trends descriptions and between-region comparisons in drug use.

DDD per 1000 inhabitants/day were calculated for the entire Catalonia and for the basic health areas of the ICS which are: Alt Pirineu i Aran, Girona, Lleida, Catalunya Central, Barcelona, Camp de Tarragona and Terres de l´Ebre (see Figure 5).

Figure 5: *Basic Health Areas in Catalonia (43)*

Sample size:

Not applicable.

Statistical analysis:

DDD per 1000 habitants/day of the different pharmaceutical specialties of MP, LDX and ATX invoiced by Servei Català de Salut (CatSalut) of each of the years of study were obtained. DHD represents the DDD (Defined Daily Dose) per 1000 inhabitants per day. Information of the number of habitants of Catalonia was obtained from the data published by the INE/IDESCAT. The main DHD analysis was carried out using the annual population figures. Secondarily, we stratified the analysis by for each of the basic health areas by ICS.

ETHICS:

There are no ethical problems in this study since the DBS database has been provided with the ownership of each patient encrypted by a database manager, which is not among the researchers in our study.

On the other hand, the data used in study 2 are data of pharmaceutical dispensing, so they do not relate to any patient directly.

CEIC authorization has been obtained from the Doctor Josep Trueta University Hospital for the 2 studies and the classification of the EMA as EPA (Annex 6).

RESULTS

Study 1

The number of patients under treatment with drugs for ADHD in 2015 was 16,200. The prevalence of drug use stratified by 5-year interval of age is shown in Figure 6. It can be found that drugs to treat ADHD were fundamentally used in children, adolescents and young adults, with a peak of 2.3% in 10-14 year old children.

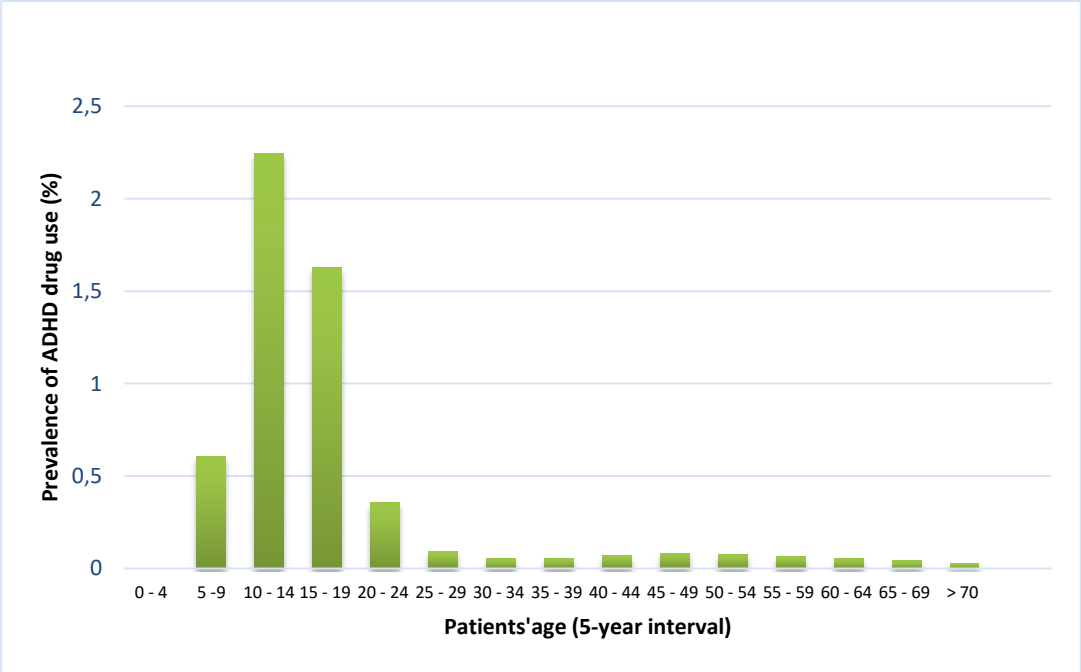

Figure 6: *prevalence of use of drugs indicated for the treatment of ADHD across patients´ age.*

Chart 2 show the characteristics of patients using drugs to treat ADHD. The sample was split in two groups (24 years or less and above) because younger patients were more likely to be using these drugs to treat ADHD (Figure 6), while in the older group it was likely that these drugs were used to treat other conditions.

Characteristics	All patients N= 16.200	< or = 24 yearss N=13.723	> 24 years N = 2.477
Sociodemographic:			
Age (Mean (SD))	18.8 (13.9)	13.6 (3.7)	47.6 (14.2)
Sex (Male %)	70.2	73.6	51.4
Comorbidities (%):			
Dementia	0.2	0.0	1.6
Hyperthyroidism	0.2	0.1	0.7
Hypertension	2.9	0.2	17.8
Cardiac Insufficiency	0.1	0.0	0.5
Ischemic Heart Disease	0.2	0.2	0.3
Auricular Fibrillation	0.1	0.0	0.9
Cerebrovascular Disorders	0.4	0.0	2.6
Obesity	8.9	7.2	18.2
Psychiatric comorbidities (%):			
Anxiety	8.2	4.9	26.4
Depression	8.0	1.8	41.9
Psychosis	0.7	0.5	2.0
Affective Psychosis	0.6	0.0	3.9
Schizophrenia	0.6	0.3	2.5
Personality Disorders	1.9	1.0	6.9
Drug misuse (%):			
Hallucinogens	0.0	0.0	0.2
Cannabis	0.5	0.3	1.5
Cocaine	0.5	0.0	3.0
Stimulants	0.0	0.0	0.2
Opioids	0.2	0.0	1.3
UPVD	0.0	0.0	0.0
Cocomitant drug use (%):			
Any Psychotropic Drug	23.9	17.3	60.2
Anxiolytics	7.5	1.7	39.9
Antidepressants	12.0	4.4	54.1
Antiepileptics	6.7	3.3	25.6
Antipsychotics	13.0	11.9	19.2

Table 2: *Characteristics of patients consuming ADHD drugs in 2015*

Overall, most patients were male and the prevalence of comorbidities was not frequent with the exception of obesity, depression, anxiety and personality disorder. Moreover, concomitant psychopharmacological treatment was frequent but the substance abuse

was not remarkable. There were important differences between patients of the two age groups. Older patients had more frequent comorbid conditions and shown a higher rate of concomitant psychopharmacological treatment. Indeed, the majority of them were receiving at least another psychopharmacological intervention in addition to drugs indicated for the treatment of ADHD. The prevalence of comorbid cardiac disease was low.

Study 2

Figure 7 shows the temporal trends of each drug marketed for the treatment of ADHD in Catalonia.

It is found that the consumption of drugs to treat ADHD between 2010 and 2015 was relatively flat. MPH is largely the most frequently consumed drug. ATX and LDX are infrequently used. Furthermore, important regional differences were also found with a higher drug consumption in the region of Pyreneess and lower in Girona (Figure 8). Moreover, drug use was flat in all regions with the exception of the Terres de l'Ebre were drug consumption reduced markedly throughout the study period.

Figure 9 show the trends of drug use in the region of Girona. Although, the overall drug use is lower than in other regions, it has increased by 60% in 5 years. MPH is the most frequently used drug.

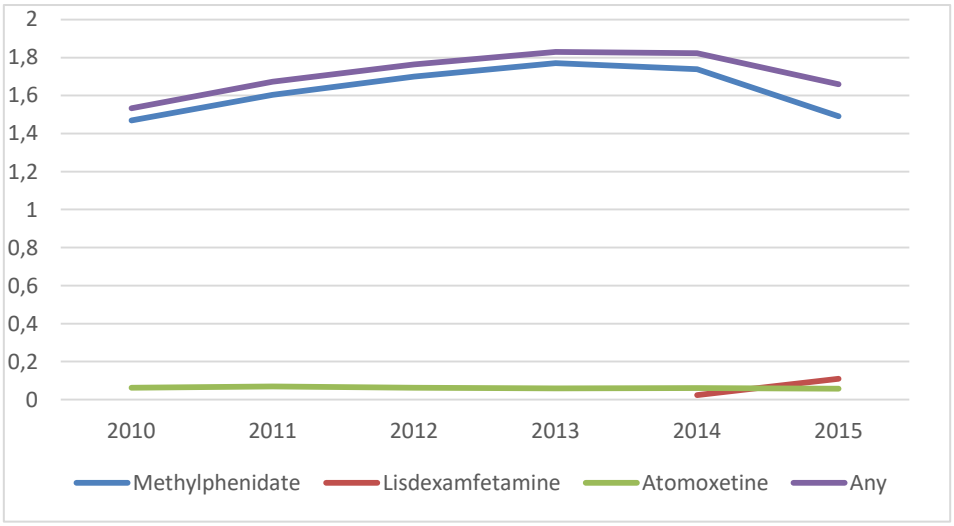

Figure 7: *evolution of the consumption of drugs to treat ADHD in Catalonia between 2010-15 expressed as DDDs per 1000 inhabitants/year.*

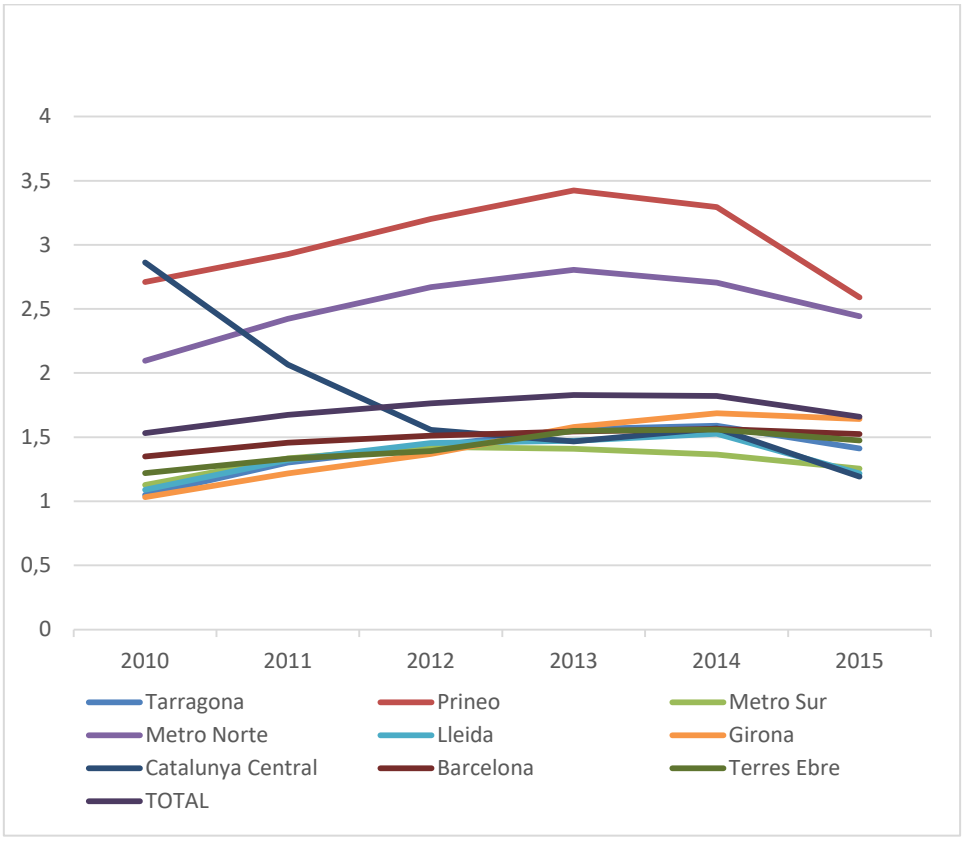

Figure 8: *Consumption of "any drug" to treat ADHD in all regions of Catlonia between 2010-15 expressed as DDDs per 1000 inhabitants/year.*

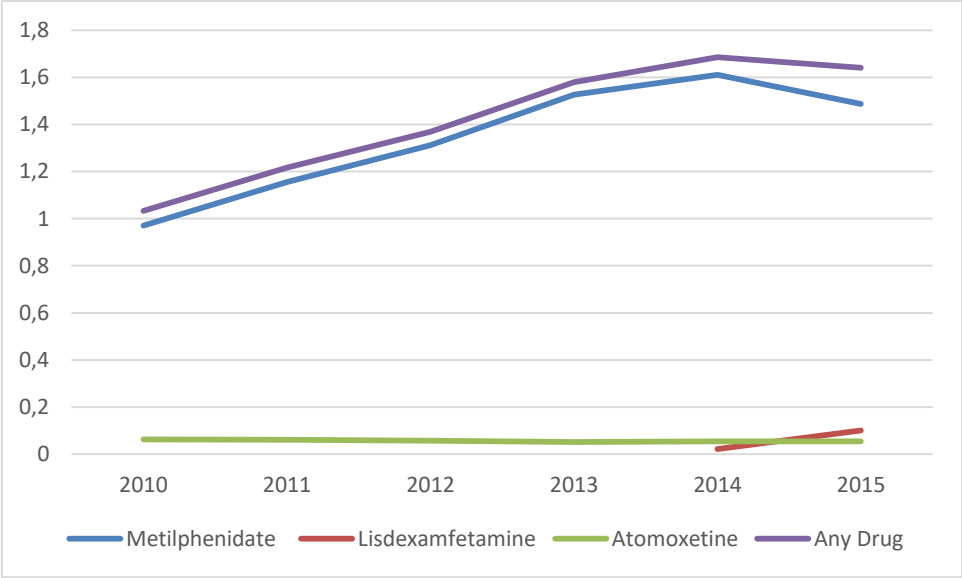

Figure 9: *evolution of the consumption of drugs to treat ADHD in Girona between 2010-15 expressed as DDDs per 1000 inhabitants/year.*

DISCUSSION

The results obtained in our study show that the majority of patients who consume drugs for ADHD are children, adolescents and young adults, being the maximum peak of consumption between 10 and 14 years, with a prevalence of 2.3%. Although we do not have the diagnosis for which these drugs are being prescribed, it is likely that most patients suffer from an ADHD because most patients using these drugs are young. The prevalence of consumption with respect to the population covered by the ICS in 2015 was 0.29%, being 1.66 if we set a limit in patients under 18 years. This consumption is lower compared to a prevalence of consumption of 6.1% in the US in 2011 (44), and similar to the obtained in the Nordic countries (2.1% in 2012) (45). Moreover, compared with the rest of Europe, data from France, Ireland, UK and Germany (46, 47, 48, 49), it reveals lower prevalences of drug treatment. We did not find significant consumption data in toddlers. Considering the ADHD prevalence is of 5-10%, overall, our data suggest that there is no currently overtreatment with drugs to treat ADHD in Catalonia.

Although most patients who consume these drugs probably have an ADHD, there are some data that make us think of a possible off-label use. In figure 6 we see that, although the majority of sample is younger than 25 years, there is consumption that lasts until the 70 years, age very unlikely to have an ADHD. In patients older than 24 our data indicate that these drugs are likely to be used to treat dementia (prevalence of 1.57% in older than 24 years). It must be noted that some studies suggest that these drugs increase cognitive function of patients, improving the concentration and improve them day by day (50). These drugs may also be used to treat depression (prevalence of 41,93% in older than 24 years). This off-lable use may be justified by the mood enhancing effects of these drugs, particularly of psychostimulants (51). However, in the

case of depression, especially if this is severe, the technical file contraindicates the use of MPH (27). Another fact that is striking is the high prevalence of obesity in these patients, with a prevalence of 18.23% among those over 24 years old. One of the effects of these drugs is hyporexia, which may explain that these drugs are be used as therapy in cases of important obesity (50).

It is remarkable the low prevalence of use of medicines to treat ADHD in patients with a history of ischemic heart disease, heart failure, stroke or hypothyroidism. This finding may indicate that these drugs are not prescribed to patients with comorbid condition that contraindicate their use or in whom these drugs should be used with caution (27).

Treatment for ADHD is often used in conjunction with other psychotropic drugs (prevalence of 23.9%). In general, this may be because in patients with ADHD the existence of comorbidities, such as depression, anxiety or challenging opposition disorder is prevalent, and therefore in these cases other drugs that can improve the derived symptomatology are used (1, 50). Moreover, some drugs without indication for ADHD treatment are used in order to improve ADHD symptoms (1).

Taking into account drug consumption of medicines to treat ADHD, in the period 2010-2015, our data show that it is relatively stable. Some increase is suggested in some regions, fundamentally those with the lowest consumption. Our finding contrasts with those in the US and other European countries, where the drug consumption trend that has followed since the 1990s is on rise. The stabilization of drug consumption seen in Catalonia may reflect an increased awareness of the risks associated. In this sense, it is of note that recently, the Catalan ombudsman issued a statement warning about the risks associated with the risks of these medicines (52). It is also possible that campaigns warning about the possibility that ADHD is overdiagnosed and overtreated in other

countries may have contained the increase of sales on drugs to treat ADHD in Catalonia (53).

The evaluation of the number of DDDs 1000 inhabitants/year throughout the study period shows that MPH is largely the most consumed drug. This may be due to the fact that the other drugs offer little advantages over this drug. The second place is in dipute. During the years 2010-2013 the ATX followed in second place since it was the other drug that had with indication for treatment of ADHD. However, in 2014 with the commercialization of the LDX this second place is under discussion, getting it last in 2015.

If we compare the trend of total consumption of all of these drugs, we obtain a small increase of 0.3 DHD between 2010 and 2013 (1.53 and 1.83 DHD respectively), followed by a small decline afterwards (1.65 DHD in 2015). Our results contrasts with those of Castilla-La Mancha where an uninterrupted increase of drug consumption has been observed since 1992 from 0.03 DHD to 2.07 in 2015 (11). Similarly, In Castilla - León drug consumption has increased from a DHD of 0.1 in 1992, to 1.5 in 2009 stimating 2.5 DHD in 2013 (54). Therefore, we conclude that our data of reflect a lower consumption of drugs to treat ADHD Catalonia than in other regions of Spain.

Our study shows notable between-region differences in the consumption of drugs to treat ADHD. Our data do not permit to draw any explanation to this finding. Nevertheless, it must be noted that such geographical variability has also been described in the United States, and may reflect social and cultural differences in the understanding of what ADHD is and how it should be treated (54).

LIMITATIONS

Our study is not free of limitations. The main one is that we do not know whether the patients treats actually have an ADHD because information of this diagnosis is not available in the dataset used, therefore we cannot determine the prevalence of this disorder in our environment. On the other hand, we do not have knowledge about the practice that is taking place in mutual, private consultations or all those services that are not in charge of the ICS. Moreover, the DBS database that has been provided to us only collects primary care data, which is included by the nursing staff or the doctor who cares for the patient, so we also lack data from the hospital setting. The characteristics studied in study 1 do not refer to current diagnoses in 2015, at which point we evaluate the consumption of drugs for ADHD, but to lifetime diagnosis. Therefore, we cannot infer that patients with, for instance, depression suffer from this condition at the moment of data collection thus; establishing a relationship between drug use and diagnosis is highly speculative.

Finally, in study 2 the main limitation we find is that the time series studied is very short. Furthermore, the data collected indirectly represent the drug sales, since they are data of pharmaceutical dispensation. Therefore, we are making an assumption that once bought at the pharmacy, the drug is consumed.

CONCLUSIONS

- The prevalence of drug use for ADHD in 2015 in the population in charge of ICS was 0.29%. If we consider that those who actually have this disorder are those under 18, we obtain a prevalence of 1.66%. The peak of consumption occurred in the range of 10 to 14 years of age, with a prevalence of 2.3%.
- The majority of patients receiving drugs to treat ADHD are young and men. Psychiatric comorbidities as well as concomitant treatment with other psychotropic drugs are common.
- It is likely that drugs to treat ADHD are being used as off-label medication to treat depression, dementia and obesity.
- The use of drugs to treat ADHD in patients with contraindication for their use is low.
- While the consumption of drugs for ADHD in the study period has remained relatively stable in Catalonia between 2010-15, there are important geographical differences across regions, and it has raised in Girona.

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ABBREVIATIONS

- ADHD: attention deficit and hyperactivity disorder
- AEMPS: Agencia Española del Medicamento y Productos Sanitarios
- ASD: Autistic Spectrum Disease
- ATX: atomoxetine
- CatSalut: Servei Català de la Salut
- CEIC: Comité de Ética e Investigación Clínica
- CIMA: Centro de Información sobre Medicamentos Online
- DA: dopamine
- DBS: Datos Básicos de Salud
- DHD: Dose/Habitant/day
- DRD 4: dopamine D4 receptor gene
- DRD 5: dopamine D5 receptor gene
- DSM-II: Diagnostic and Statistical Manual of Mental Disorders, second edition
- DSM-III: Diagnostic and Statistical Manual of Mental Disorders, third edition
- DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
- DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised
- DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
- EMA: Agencia Española del Medicamento
- EPA: Estudio Postautorización
- FDA: Food and Drug administration (USA)
- HTR1B: serotonin 1B receptor gene
- ICD-10: International Statistical Classification of Diseases and Related Health Problems, 2010
- ICS: Institut Català de la Salut
- INE/IDESCAT: Instituto Nacional de Estadística/Instituto de Estadística Catalán
- LDX: lisdexamphetamine
- MPH: metilphenidate
- NA: noradrenaline
- SISAP: Sistema de Información sobre Salud en Atención Primaria
- SLC6A3: dopamine transporter gene
- SNAP – IV: questionnaire of Swanson, Nolan y Pelham, IV version
- SNAP – 25: synaptosomal-associated protein 25 gene

ANNEXES

Annex 1: DSM-IV-TR

Criteria for the diagnosis of Attention Deficit Hyperactivity Disorder.

A. **(1)** or **(2):**

(1): six (or more) of the following symptoms of inattention have persisted for at least 6 months with an intensity that is de-adaptive and incoherent in relation to the level of development:

Inattention:

(A) often does not pay enough attention to details or makes mistakes by carelessness in schoolwork, work or other activities.

(B) often has difficulty maintaining attention in tasks or play activities.

(C) often seems not to hear when spoken to directly.

(D) often does not follow directions and does not complete homework assignments, assignments, or duties in the workplace (not due to negative behavior or inability to understand instructions).

(E) often has difficulty organizing tasks and activities.

(F) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as slanderous or domestic work).

(G) often misplace objects necessary for tasks or activities (eg, toys, school exercises, pencils, books, or tools).

(H) is often easily distracted by irrelevant stimuli.

(I) is often neglected in daily activities.

(2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months in relation to the level of development:

Hyperactivity:

(A) Often shakes hands or feet, or stirs in his / her chair.

(B) Often leaves his or her seat in the classroom or in other situations where he or she is expected to remain seated.

(C) Often runs or jumps excessively in situations where it is inappropriate to do so (in adolescents or adults it may be limited to subjective feelings of restlessness).

(D) Often has difficulty playing or quietly engaging in leisure activities.

(E) Is often "on track" or often acts as if it had a motor.

(F) Often talks in excess.

Impulsiveness:

(G) Often precipitates answers before questions are completed.

(H) Often has difficulty keeping shift.

(I) Often interrupts or intrudes on the activities of others (eg, meddles in conversations or games).

B. Some symptoms of hyperactivity-impulsivity or inattention that caused alterations were present before 7 years of age.

C. Some disturbances caused by symptoms occur in two or more environments (eg, at school, work, and at home)

D. There must be clear evidence of clinically significant impairment of social, academic or work activity.

E. Symptoms do not appear exclusively in the course of a generalized developmental disorder, schizophrenia, and other mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or personality disorder)

Based on the type:
- *Attention deficit hyperactivity disorder, combined type*: if criteria A1 and A2 are met during the last 6 months.
- *Attention deficit hyperactivity disorder, type of predominant attention deficit*: if Criterion A1 is met, but not Criterion A2 in the last 6 months.
- *Attention deficit hyperactivity disorder, type of hyperactive-impulsive predominance:* if Criterion A2, but not Criterion A1, is fulfilled during the last 6 months

Annex 2:ICD-10

F90 hyperkinetic disorders

G1. *Attention deficit*. At least six of the following symptoms of attention deficit persist for at least six months, to a degree that is maladaptive and inadequate to the level of development of the child:

1) Frequent inability to pay attention to details along with careless mistakes in school work and other activities.

2) Frequent inability to maintain attention on tasks or play.

3) He often pretends not to listen to what is being told.

4) Persistent inability to complete assignments assigned to them or other assignments assigned to them at work (not caused by deliberate opposition behavior or difficulty in understanding the instructions).

5) Decreased ability to organize tasks and activities.

6) Often avoids or feels markedly uncomfortable with tasks such as homework that require sustained mental effort.

7) Often loses necessary objects for tasks or activities, such as school supplies, books, pencils, toys or tools.

8) Easily distracted by external stimuli.

9) Often forgetful in the course of daily activities.

G2. *Hyperactivity*. At least three of the following hyperactivity symptoms persist for at least six months, to a maladaptive grade and inadequate to the child's developmental level.

1) Frequently shows restlessness with movements of hands or feet or moving in the seat.

2) Leave the seat in the classroom or other situations in which you are expected to remain seated.

3) Often runs or climbs excessively in inappropriate situations (adolescents or adults may manifest only by feelings of restlessness).

4) He is generally inadequately noisy in the game or has difficulty in quietly entertaining in play activities.

5) Persistently exhibits a pattern of excessive motor activity that is not substantially modifiable by the requirements of the social environment.

G3. *Impulsiveness.* At least one of the following symptoms of impulsivity persists for at least six months, to a maladaptive grade and inadequate to the developmental level of the child.

1) He often exclaims or responds before full questions are asked.

2) Often unable to keep a turn in queues or other group situations.

3) Often interrupts or intrudes on the affairs of others (for example, bursts into the conversations or games of others).

4) Often talks excessively without holding back from social considerations.

G4. The onset of the disorder is not later than 7 years of age.to

G5. *Generalized character*. The criteria must be met for more than one situation, ie the combination of attention deficit hyperactivity disorder must be present in the home, school, or other settings where the child can be observed, such as (Evidence of such outsourcing usually requires information from a number of sources) Parents' information about behavior in a child's school is not usually sufficient)

Annex 3: SNAP-IV test:

For each item, select the box that best describes this child. Put only one check per item.		Not at all (0)	Just a Little (1)	Quite A Bit (2)	Very Much (3)
1.	Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities				
2.	Often has difficulty sustaining attention in tasks or play activities				
3.	Often does not seem to listen when spoken to directly				
4.	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties				
5.	Often has difficulty organizing tasks and activities				
6.	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework)				
7.	Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)				
8.	Often is distracted by extraneous stimuli				
9.	Often is forgetful in daily activities				
10.	Often fidgets with hands or feet or squirms in seat				
11.	Often leaves seat in classroom or in other situations in which remaining seated is expected				
12.	Often runs about or climbs excessively in situations in which it is inappropriate				
13.	Often has difficulty playing or engaging in leisure activities quietly				
14.	Often is "on the go" or often acts as if "driven by a motor"				
15.	Often talks exessively				
16.	Often blurts out answers before questions have been completed				
17.	Often has difficulty awaiting turn				
18.	Often interrupts or intrudes on others (e.g., butts into conversations/games)				
		Total	Total	Total	Total
	Average score for ADHD-Inattention (sum of items 1-9/ # of items)				
	Average score for ADHD-Hyperactivity-Impulsivity (sum of items 10-18/ # of items)				
	Average score for ADHD-Combined (sum of items 1-18/ # of items)				

Annex 4: Conners test

Parent´s test

Activity	**NO**	**- -**	**-**	**Without changes**	**+**	**++**	**YES**
Your child prepares to start the day (he gets up, gets dressed, etc.)							
Your child prepares things well from school (books, arrive on time, etc.)							
The control and monitoring notes of the school are positive							
The family meal runs smoothly (if you eat at home)							
Extra afternoon school activities run smoothly							
Your child performs assigned tasks at home (make your bed, etc.)							
Family dinner runs smoothly							
No sleep problems (sleep well all night)							
In general, consider the day as positive							
Your child has breakfast well							
Your child has eaten the food he takes to school for recess							
Your child has a good lunch							
Your child snacks well							
Your child's behavior is stable throughout the day							
Your child's behavior gets worse at noon							
Your child's behavior gets worse in the afternoon							
Your child completes homework correctly (showering, dressing, etc.)							
Your son takes time to sleep							
Your son sleeps well all night							
Has your child forgotten or not taken part or all of the treatmen							
No problems in the leisure activities of home (games, TV, etc.)							
Your child is assigned homework assignment							

Teacher´s test

Activity	NO	- -	-	Without changes	+	++	YES
The child arrives on time to school							
The child arrives prepared to the school (brings his books, tasks, etc.)							

The child follows the instructions in class							
The child remains seated in class and does not interrupt or disturb							
The child waits his tirno in the situations that require it							
Child interacts well with peers at recess							
The child maintains an appropriate behavior between class and class							
No more problems in the school dining room (if you eat at school)							
Extra-school activities (soccer, etc.) run smoothly							
In general, consider the day as positive							

Annex 5: Calculation of the DOSE / INHABITANT / DAY indicator

DDD / 1000 inhabitants / day (DID):

$$\frac{Nº\ of\ cont\ \mathbf{X}\ Nº\ of\ FF\ /\ cont\ \mathbf{X}\ c\ /\ FF\ X\ 1000}{DDD\ \boldsymbol{X}\ Nº\ of\ inhabitants\ \mathbf{X}\ 365\ days}$$

Where:

Nº of cont: number of containers dispensed in a year.

FF / cont: number of pharmaceutical forms per container

C / FF: content of active ingredient per dosage form

DDD: defined daily dose

Nº of inhabitants: number of people in the study population

For example:

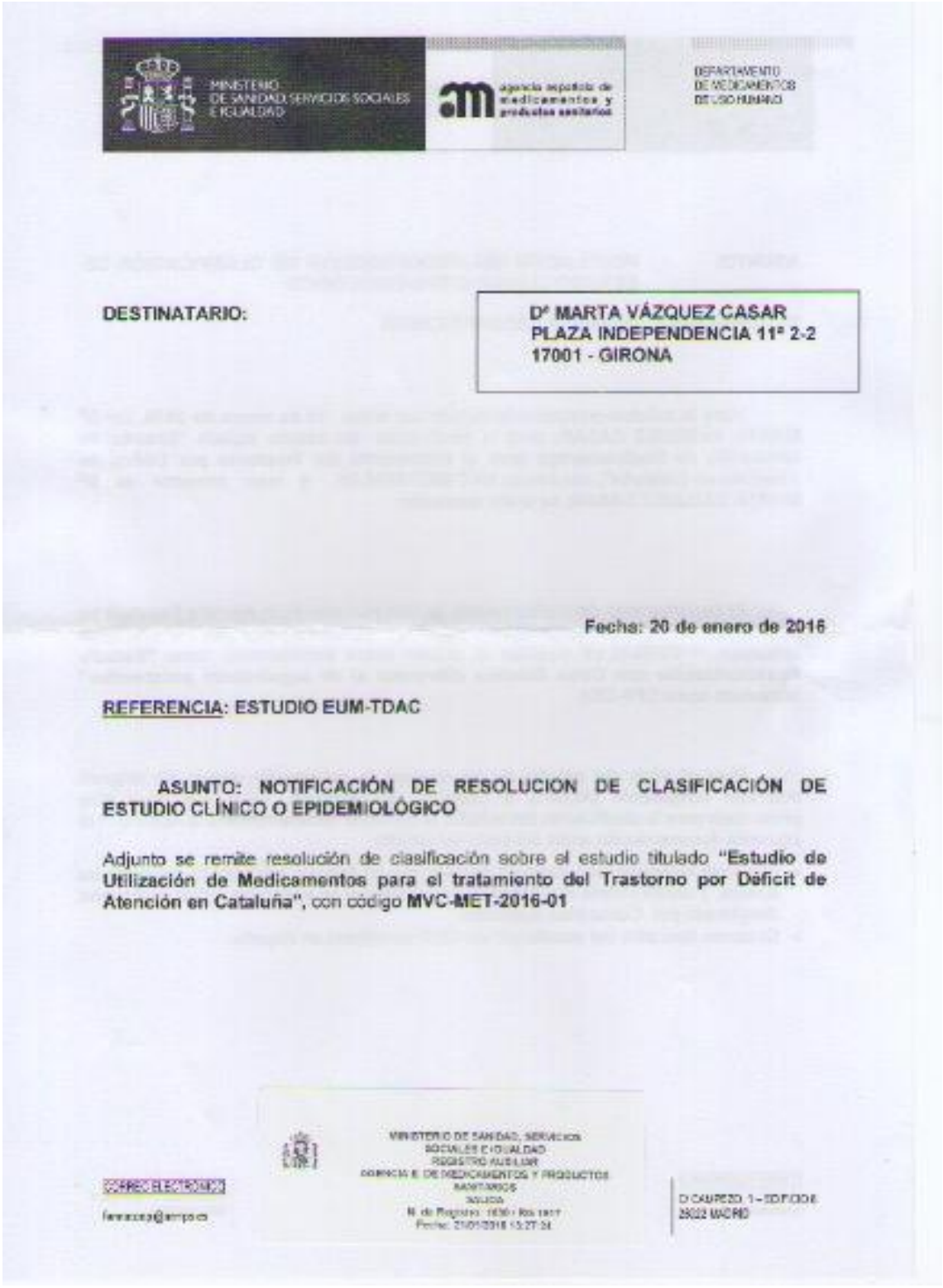
Suppose that in Catalonia in a year 100,000 packs of 10 tablets of 18mg MPH and 45,000 packs of 20 tablets of 36 mg were sold. The population studied is 5,600,000 people. The DDD of MPH is 30 mg / day.

$$\frac{(100{,}000\ \mathbf{X}\ 10\ \mathbf{X}\ 18\ +\ 45{,}000\ \mathbf{X}\ 20\ \mathbf{X}\ 36)\ \mathbf{X}\ 1000}{30\ \mathbf{X}\ 365\ \mathbf{X}\ 5.600.000}$$

DID = 0.82

That is, 0.82 people out of 1000 were treated with MPD DDD. It can also be interpreted as that 1000 inhabitants use 0.82 DDD of treatment per day.

Annex 6: classification of the EMA and CEIC authorization



MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS DE USO HUMANO

DESTINATARIO:

Dª MARTA VÁZQUEZ CASAR
PLAZA INDEPENDENCIA 11º 2-2
17001 - GIRONA

Fecha: 20 de enero de 2016

REFERENCIA: ESTUDIO EUM-TDAC

ASUNTO: NOTIFICACIÓN DE RESOLUCION DE CLASIFICACIÓN DE ESTUDIO CLÍNICO O EPIDEMIOLÓGICO

Adjunto se remite resolución de clasificación sobre el estudio titulado **"Estudio de Utilización de Medicamentos para el tratamiento del Trastorno por Déficit de Atención en Cataluña"**, con código **MVC-MET-2016-01**

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
REGISTRO AUXILIAR
AGENCIA E. DE MEDICAMENTOS Y PRODUCTOS SANITARIOS
SALIDA

CORREO ELECTRONICO

D CALPREZO 1 - EDIFICIO E
28022 MADRID

ASUNTO: **RESOLUCIÓN DEL PROCEDIMIENTO DE CLASIFICACIÓN DE ESTUDIO CLÍNICO O EPIDEMIOLÓGICO**

DESTINATARIO: **Dª MARTA VÁZQUEZ CASAR**

Vista la solicitud-propuesta formulada con fecha **19 de enero de 2016**, por **Dª MARTA VÁZQUEZ CASAR**, para la clasificación del estudio titulado **"Estudio de Utilización de Medicamentos para el tratamiento del Trastorno por Déficit de Atención en Cataluña"**, con código **MVC-MET-2016-01** y cuyo promotor es **Dª MARTA VÁZQUEZ CASAR**, se emite resolución.

El Departamento de Medicamentos de Uso Humano de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), de conformidad con los preceptos aplicables, [1] **RESUELVE** clasificar el estudio citado anteriormente como ***"Estudio Posautorización con Otros Diseños diferentes al de seguimiento prospectivo"*** (abreviado como EPA-OD).

Para el inicio del estudio no se requiere la autorización previa de ninguna autoridad competente (AEMPS o CCAA)[2]. No obstante, salvo que haya sido presentada para la clasificación del estudio, el promotor deberá remitir a la AEMPS [3] la siguiente documentación antes del inicio del estudio:

- Protocolo completo (una copia en papel y otra en formato electrónico), incluidos los anexos, y donde conste el número de pacientes que se pretenden incluir en España, desglosado por Comunidad Autónoma.
- Dictamen favorable del estudio por un CEIC acreditado en España.

CORREO ELECTRÓNICO
farmacoep@aemps.es

C/ CAMPEZO, 1 - EDIFICIO
28022 MADRID

Contra la presente resolución que pone fin a la vía administrativa podrá interponerse Recurso Potestativo de Reposición, ante la Directora de la Agencia, en el plazo de un mes a contar desde el día siguiente a aquel en que tenga lugar la notificación de la presente resolución. [4]

Madrid, a 20 de enero de 2016

EL JEFE DE DEPARTAMENTO DE
MEDICAMENTOS DE USO HUMANO

César Hernández García

[1] Son de aplicación al presente procedimiento la Ley 30/1992, de 26 de noviembre, de Régimen Jurídico de las Administraciones Públicas y del Procedimiento Administrativo Común; la Ley 12/2000, de 29 de diciembre, de medidas fiscales, administrativas y de orden social; Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios; Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos; el Real Decreto 1275/2011, de 16 de septiembre, por el que se crea la Agencia estatal "Agencia Española de Medicamentos y Productos Sanitarios" y se aprueba su estatuto; el Real Decreto 577/2013, de 26 de julio, por el que se regula la farmacovigilancia de medicamentos de uso humano y la Orden SAS/3470/2009, de 16 de diciembre, por la que se publican las directrices sobre estudios posautorización de tipo observacional para medicamentos de uso humano.

[3] De acuerdo con la Orden SAS/3470/2009, de 16 de diciembre

[2] Los documentos se enviarán a la siguiente dirección postal: Agencia Española de Medicamentos y Productos Sanitarios. División de Farmacoepidemiología y Farmacovigilancia. Parque Empresarial "Las Mercedes", Edificio 8. C/ Campezo, 1. 28022 Madrid.

[4] De conformidad con lo dispuesto en los artículos 116 y 117 de la Ley 30/1992, de 26 de noviembre, o Recurso Contencioso-Administrativo ante el Juzgado Central de lo Contencioso-Administrativo de Madrid, en el plazo de dos meses contados desde el día siguiente al de la notificación de la presente resolución, de conformidad con la Ley 29/1998, de 13 de Julio, reguladora de la Jurisdicción Contencioso-Administrativa, sin perjuicio de poder ejercitar cualquier otro recurso que se estime oportuno. En caso de interponerse recurso de reposición no podrá interponerse recurso contencioso-administrativo hasta la resolución expresa o presunta del primero.

[CORREO ELECTRÓNICO]

farmacovigi@aemps.es

C/ CAMPEZO, 1 - EDIFICIO 8
28022 MADRID

Hospital Universitari de Girona
Doctor Josep Trueta

Avinguda de França s/n.
17007 Girona
Telèfon 972 940 200
www.gencat.net/ics/trueta

Marta Riera Juncà, Secretària del Comitè d'Ètica d'Investigació Clínica CEIC GIRONA, amb domicili a Av. de França s/n 17007 Girona

CERTIFICA

Que el Comitè d'Ètica d'Investigació Clínica CEIC GIRONA, segons consta en l'acta de la reunió celebrada el dia 23/11/2015 ha avaluat el projecte: **Estudio de Utilización de Medicamentos para el Tratamiento del Trastorno por Déficit de Atención con Hiperactividad en Cataluña. Cod UDGMTF201501**, amb la Sra. MARTA VÁZQUEZ CASAR com a investigadora principal.

Que els documents s'ajusten a les normes ètiques essencials i per tant, ha decidit la seva aprovació.

I, perquè consti, expedeixo aquest certificat.

Hospital Universitari de Girona
Doctor Josep Trueta
Comitè Ètic
d'investigació Clínica
Institut Català de la Salut

Girona, a 26/01/2016