



abstract

Objective: to carry out a critical analysis of the evolution and management of Attention Deficit Hyperactive Disorder (ADHD), through a revision of its historical perspective, the aspects regarding drug efficacy and safety, alternative approaches to management and a focus from a social sciences perspective. **Methods:** a bibliographical research was carried out on ADHD and associated terms through Medline and the Cochrane Library, and extended to clinical practice guidelines (NICE, Spanish guidelines), independent drug publications (ISDB), data bases of regulatory agencies (Spanish Medicines Agency, EMA, FDA, Canada) and other complementary sources of information such as news media, websites or author correspondence. In addition, safety data were requested from the Centre for Pharmacovigilance of Navarra; data on diagnosis and prescription from the Drug Prescribing Service of the Navarra Health Services, and information on national drug consumption from the Department of Basic Common Services Portfolio (Ministry of Health). Lastly, contact was made with organizations such as EUNETHYDIS, FEAADAH or Rubió Laboratories with the aim of obtaining specific information. **Results and conclusions:** ADHD is a phenomenon of variable and increasing prevalence, with no consistent biological markers and questionable hypothesis in favour of an organic origin. Its diagnostic criteria have fluctuated enormously over time and rely on symptom-based scales insufficiently correlated with social, family or academic dysfunction. Non-pharmacological therapies require thorough research, and behavioural therapy plays a predominant role given its potential use. Pharmacotherapy shows some efficacy on symptoms in the short term with no clear continuity in relevant endpoints, and they should be considered only in exceptional circumstances. There are important cardiovascular, psychiatric and endocrine-related adverse effects related to pharmacotherapy (some rare and very lethal, while others are frequent but their clinical relevance is downplayed or ignored). ADHD drugs are substances of potential abuse and the current trend of initiating treatment in the adult population is a matter of concern, especially when the plurality of interests around the diagnosis makes it difficult for rational -objective, evidence-based treatment decisions to be made. **Key words:** ADHD, methylphenidate, atomoxetine, behavioural therapy, substance abuse, DSM-5.

Pay attention to the Attention Deficit Hyperactive Disorder (ADHD) Between an uncertain nature and a hyperactive prescription

"There is no greater power than the right to define the question"

John McKnight, 1995

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Available at: http://commons.wikimedia.org/wiki/File:H_Hoffmann_Struwel_20.jpg

This illustration has been obtained from the book entitled "Struwwelpeter" by Heinrich Hoffman (1844). The main character, Fidgety Phil, used to warn children about the consequences of slumping in their chair. This old story has been said to support the idea that ADHD is a real sickness, though the long-standing existence of a determined type of behaviour does not justify that it is labelled as a sickness. Instead of providing empirical evidence, paradoxically it is suggested that this behaviour's interpretation and classification depend on the historical and cultural context.

Introduction

It is not difficult to find controversy in health sciences, a field in which there is a confluence between the expected objectiveness of empirical evidence of treatment and subjective experience of the people who receive them. The extraordinary complexity of the human brain exacerbates this tension in the field of mental health, and clinical, ethical and social questions on any related issue multiply. Regarding children mental health, maximum prudence is necessary when considering medical interventions as the child's brain is in constant evolution and children are more vulnerable than adults.

Currently there is a paradigmatic example where a debate is open and ongoing, not only within the scientific community but also in education and among the general population. We refer to Attention Deficit Hyperactive Disorder (ADHD), where many interesting and unanswered questions converge: could the status of this disorder be challenged? If not, what is its ethiology? Are the diagnostic tools adequate? Can we confide in the pharmacological management options available in terms of efficacy and safety? Are we facing cases of suboptimal use of medication or are we overdoing it? And up to what extent does the particular interest of all parties implicated facilitate or make it more difficult to find a valid response to these questions? With no intention of leaving out any path of reflection on the issue, this paper will develop these questions taking into account two main principles: the best available evidence and above all, a focus on children as the centre of interest.

ADHD in large numbers

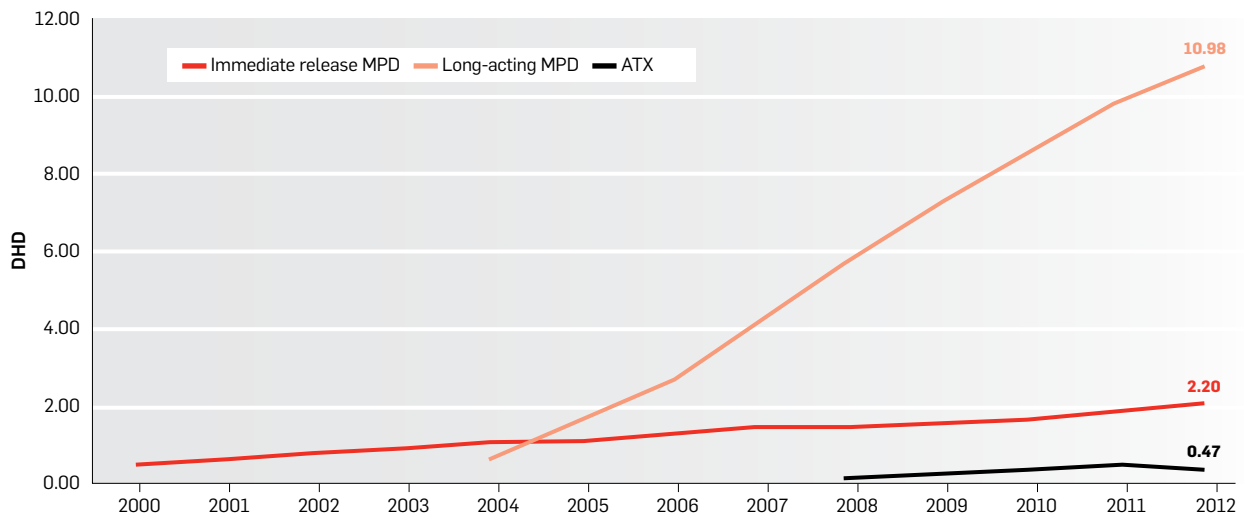
The global prevalence in children under 18 years old is estimated to be around 5%¹ with large variability in relation to sex (male: female = 3:1)², location (<5% in Asia, 5-20% in America)¹, ethnicity (greater consumption in Spanish nationals compared to immigrants),³ diagnostic criteria (5-fold more probable under criteria of the American Society of Psychiatry (DSM-IV) compared to the WHO criteria (ICD-10)⁴ and even in relation to the level of health care service (only 24% of children referred to the Child Mental health department from Primary care for a evaluation under diagnostic suspicion are confirmed to present ADHD).⁵

Data from the USA are alarming where 11% of children between 4 and 17 years (6.4 million) are diagnosed at some point with ADHD and even though only 15% are categorized as very severe, up to 69% of those who actively present the disorder receive psychostimulant medication.⁶ In Spain, the prevalence is somewhat lower, between 1.2-4.6% in relation to the diagnostic criteria employed⁷ and today, there is still no reliable estimate in adults.¹ Nevertheless, these data are highly questioned, even when a relationship between the diagnosis of ADHD and the month of birth of a child suggests greater probability of being diagnosed in the less mature children in each school class.^{8,9}

The diagnostic circuit in Navarre is specified under a Protocol for the referral and transfer of information on ADHD in children and adolescents¹⁰ updated in 2012. When a family or school orientation department suspect ADHD, the child is referred to a pediatrician for confirmation and from here, in accordance with pre-defined criteria, the child is referred to either a Child Mental Health Centre or a Neuropediatrician.

Information from electronic clinical records reveals that 46% of 352 newly diagnosed children between 6-17 years between January 2012 and August 2013 were under stimulant medication. On the other hand, the data obtained from the Mental Health Department show a substantial increase in diagnosis over the last decade, from 215 children in 2001 (average age = 10.6 years, and ratio boys:girls = 4.5), to more than 1000 children in 2012 (average age = 14.1 and a ratio boys:girls = 3.4).

With regard to the employment of **drugs** in children diagnosed with ADHD, a steady increase has been observed in the USA since the 1990s.⁶ However, at present increasing drug use is even greater in other western countries.² In Spain, the introduction of drugs was delayed for 10 years,¹¹ coinciding with the commercialization in 2004 of long-acting methylphenidate (Figure 1). Currently, we find ourselves among the highest consumers of methylphenidate¹² in the world. Between 2000 and 2012, methylphenidate and atomoxetine consumption in the infant population has multiplied by nearly 30 times, maintaining a constant exponential growth.

Figure 1. Evolution of ADHD drugs use (DHD) in Spain in children and adolescents between 5 and 19 years.

MPD=Methylphenidate; ATX=Atomoxetine. DHD=Defined daily dose (DDD) per 1000 inhabitants per day. DDD MPD=30mg; DDD ATX=80mg. Data provided by the Department of Basic Common Services Portfolio (Ministry of Health)

Fragile theories, powerful treatments

ADHD can be diagnosed by employing either DSM or ICD criteria. According to the recent update of the ICD-10,¹³ the hyperkinetic disorder requires the unequivocal presence of abnormal levels of lack of attention, activity and impulsiveness, observed in different occasions and maintained over time, and which can be verified by direct observation and is not caused by other disorders such as autism, depression, mania or anxiety. As with cases related to difficulties in learning, motor control or substance abuse these problems also require a careful diagnostic differential.¹⁴

The etiology of ADHD is ultimately unknown, and opens up a world of speculation on the factors that intervene in its origin, and as a result, this decisively affects its management. Among the possible causes cited¹⁵ we find environmental causes (family, school, culture), diet (toxins, intolerances), individual psychological differences (cognitive, emotional), iatrogenia¹⁶ and even pre and perinatal factors. Some authors propose the origin as a result of a combined biological and environmental cause.² Nevertheless, the dominant scientific discourse considers these hypotheses in the best of cases to be secondary factors related to the main neurobiological^{17,18} explanation of ADHD's origin. According to the main theory, the real protagonists are the chemical neurotransmitter unbalances, a genetic component, and evidence from neuroimaging studies. Theoretically this vision would lead to medicalization

of the clinical condition as the first response in many cases,¹⁹ despite the fact that, as we shall see shortly, the evidence supporting this vision presents uncertainties.²⁰ But before we continue, we consider that elaborating a critical appraisal of the biological hypothesis does not necessarily mean denying attention-related or behavioural problems in some children. We only would like to point out the abstract nature of the ADHD concept as a disease and the undesirable consequences derived from this premiss.

The hereditary test

It is estimated that heredity accounts for 75% of the origin of ADHD.²¹ However, despite the enormous research effort dedicated to this task focussed lately on various genes related to the metabolism and transport of dopamine, no consistent marker has been identified for ADHD.²² Habitually referral is made to studies on twins to affirm that the condition represents a highly hereditary disorder, obviating that the assumption of an equivalent environment among twins and non identical siblings is highly problematic.²³ In 2010, the media affirmed that a specific genetic link had been discovered.²⁴ What is certain is that the range of potential candidates is even larger, the results obtained present high variability and when an association between certain genes and ADHD is found, the magnitude of this association is small. Certainly hereditary factors support the thesis of a chronic disorder.

However the large heterogeneity of the individuals diagnosed continues to be a relevant problem before any definitive conclusion can be made in this direction.² In any case genetic analysis is already available in Spain, which costs around 400 euros, mainly focussed on dopamine metabolism, and assures that it can predict a response to pharmacological treatment, discover the genetic predisposition to suffer from ADHD and inform on the risk of comorbidity.²⁵ The bibliographical references that support its commercialization recognizes that the results obtained from pharmacogenetic studies vary widely and at all times these genes are referred solely as candidates.²⁶

The neuroimaging test

Often neuroimaging studies are referred to in favour of the biological theory arguing that those affected present certain anomalies in the areas of the central nervous system involved in attention, inhibition, and motor response. However, structural and functional data from neuroimaging studies do not reveal any specific etiology of ADHD.²² Nor are they conclusive due to lack of consistency, in part because of the different techniques employed, scarce data in adolescents and adults, low statistical power or insufficient sample size. Even more important is the fact that the majority of the children evaluated by neuroimaging were medicated, and so the role of psychostimulants in the changes observed in brain volume and structure cannot be excluded.¹⁴ In any case, these so-called anomalies bear no information on whether they were present at birth or are a consequence of external agents.²⁷

The test of chemical imbalance

The habitual cycle employed in the development of drugs presumes basic research work of the disease under study, and the establishment of probable therapeutic targets derived from previous physio-pathological knowledge. In the case of ADHD, the road has been largely inverted, first the psychostimulants arrived modifying the behavioral pattern of hyperactive children and then a posteriori an attempt has been made to explain the dynamics of the disorder in terms of the effects of these drugs. Once said, it is obviously very different to affirm that methylphenidate acts by increasing dopamine levels than to assure that the cause of ADHD lies in a deficiency in neurotransmitters.²⁸

For the defenders of this physio-pathological explanation, the alteration in executive functions (response inhibition, control of motivation –emotions– state of alertness, and working memory) is common in ADHD, a result of a delay in maturity of the brains fronto-subcortical pathways which are directly related to the functions of sustained and divided attention, as well as the inhibition of distraction.²¹ Stimulants like

The origin of ADHD is unknown and the criteria for diagnosis have constantly evolved in recent years

methylphenidate increase the release of dopamine and palliate the presumed deficiency, but only at an initial moment, because after a short period a mechanism of neuroadaptation occurs through a decrease in receptors in the postsynaptic neuron and in the dopamine released from the presynaptic neuron. To presume that the intake of psychostimulants produces stable effects in the long term has no biological basis besides the unpredictable consequences that these molecules can cause in the nervous system during active formation and development.²⁹ Another effect also described in children is the denominated "Discontinuation syndrome" according to which after a abrupt interruption of a stimulant, the amount of transporters of dopamine in the striate body increase by 50%. This is ultimately new compensatory activity carried out by the organism to reestablish the initial balance of neurotransmitters.²⁹

When the diagnosis does not remain stable: novelties from the DSM-5

To precisely callibrate the understanding of what today ADHD really means it is worth looking briefly at its history. There is consensus in that the British pediatrician Sir George Frederic Still in 1922 carried out the first medical consideration of this disorder, describing it as a defect of moral control.³⁰

During the 1920s it was linked to sequelae after encephalitis in children, many of them in institutional homes,³⁰ while in 1937 a determinant fact occurred when Bradley incidentally discovered the properties of the stimulant benzedrine in children with behavioural problems.³¹ However, these were times when psychoanalysis was at its peak and this discovery did not have any relevance until the pharmacological revolution occurred in the 1960s. Just before the disorder was known as "mimimum brain damage",²² with reference to a mild organic affectation which was certainly never proven.

In 1955, methylphenidate was commercialised in the USA. After Laufer described it in 1957, the hyperactive disorder was linked to behaviour patterns in children,

and in 1960 methylphenidate was approved in children (In Spain, approval came in 1981).³¹ Around the 1950s two systems of classifications of mental disease were established which have lasted up to today. On the one hand, the International Classification of Diseases (ICD-6, 1948) under the umbrella of the World Health Organization (WHO) and especially the Diagnostic and Statistical Manual for Mental disorders (DSM-I, 1952) under the patronage of the American Psychiatric Association (ASA). The evolution with respect to ADHD classification is clearly dominant with respect to the ICD in scientific literature⁵ and has presented large fluctuations worth looking at in detail (table 1).

The concept creation of ADHD has experienced a long history of profound changes, at times lacking any defined direction, and presenting inconsistencies between the two classifications. This entire process has led to recent modifications introduced in the DSM-5 (table 2), once again placing emphasis on the lack of attention as a dimension more attune with the diagnosis in adults. As a complement to the evaluation of these changes, it draws our attention that more than half of the working group of the APA in charge of the changes presented very important conflicts of interest.³⁶ Their transparency in relation to the conflicts of interest does not mitigate the bias and should always be avoided whenever possible.³⁷ We will now examine closely the major changes in DSM-5.

The scales apply scores with a poor correspondence to academic or social dysfunction

Greater relevance of symptoms rather than dysfunction

While the DSM-IV-TR explicitly required that certain symptoms be associated to dysfunction before 7 years of age (Criteria C), the DSM-5 raised the limit of age and only alluded the presence of symptoms. On the other hand, where the previous version required "clear evidence of significant dysfunction in the social, academic and occupational context" (Criteria D), the current version conforms with the symptoms "interfering or reducing" the quality in those contexts. The difference in degree between the mere interference and the provocation of a clinically significant dysfunction can cause in practice an increase of diagnosis in mild cases.

Table 1. ADHD evolution in the different versions of the DSM classification.

DSM-I	1952	No mention of the syndrome. 106 diagnostic categories. Predominance of psychoanalytic approach. In the USA, there was 1 mentally ill person /480 people. ³²
DSM-II	1968	The oficial nomenclature includes hyperkinetic reaction in children, similar to ICD-8. The notion of "minimum brain damage" persists. A typical childhood disorder that declines in adolescents. ³³
DSM-III	1980	Emphasis is made on lack of attention that is accompanied or not by hyperactivity, while the ICD-9 places priority on hyperactivity. For the first time, a cut off point is established, the need for the onset of symptoms before 7 years of age and the exclusion of other psychiatric disorders. Psychoanalysis gives way to a categorically biomedical approach. ^{32,33}
DSM-III-R	1987	Renamed ADHD, encompassing two sub-types in one (with or without hyperactivity). Symptoms are evaluated from scores and field trials.
DSM-IV DSM-IV-TR	1994 2000	357 diagnostic categories. ADHD is now divided into three subtypes (combined, hyperactive-impulsive and inattentive). The ICD-10 presents a list of similar symptoms, but with more requirements: ¹ <ul style="list-style-type: none"> • ICD requires a minimum of symptoms in 3 dimensions and dysfunction in at least 2 contexts. DSM only requires one dimension and "some alterations" in two contexts. • ICD requires a minimum of symptoms of 3 dimensions and dysfunction in at least 2 contexts. DSM only requires one dimension and "some alterations" in two contexts. • ICD considers humour, anxiety and development disorders as exclusion criteria. The DSM allows their inclusion in diagnosis classifying them as comorbidities.
DSM-5	2013	In the USA, 1 mentally ill person/50 people. Changes are introduced that facilitate the expansion of the prevalence of the disorder: ³⁵ <ul style="list-style-type: none"> • Relaxation of the need for significant clinical dysfunction associated with symptoms. • A reduction in adolescents (> 16 years) the number of symptoms needed per dimension from 6 to 5. • Raising from 7 to 12 years the age limit allowed for the onset of symptoms. • Considering autism as a comorbidity instead of an exclusion criteria. • Reducing the entity of subtypes. ADHD is understood as a disorder related to neurodevelopment.

Table 2. Diagnostic criteria of ADHD specified in the DSM-5. Source: <http://www.cdc.gov/ncbddd/adhd/diagnosis.html>

A	People with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development characterised by (1) and (2):
(1)	<p>Inattention: six or more symptoms of inattention for children up to age 16, or five or more for adolescents (17 and older) and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level Inattention.</p> <p>(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities. (b) Often has trouble holding attention on tasks or play activities. (c) Often does not seem to listen when spoken to directly. (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked). (e) Often has trouble organizing tasks and activities. (f) Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework). (g) Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones). (h) Is often easily distracted (i) Is often forgetful in daily activities.</p>
(2)	<p>Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity for children up to age 16, or five or more for adolescents aged 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level.</p> <p>(a) Often fidgets with or taps hands or feet, or squirms in seat. (b) Often leaves seat in situations when remaining seated is expected (c) Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless). (d) Often unable to play or take part in leisure activities quietly. (e) Is often "on the go" acting as if "driven by a motor". (f) Often talks excessively. (g) Often blurts out an answer before a question has been completed. (h) Often has trouble waiting his/her turn. (i) Often interrupts people or interferes with others' activities.</p>
B	Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
C	Several symptoms are present in two or more settings (e.g., at home, school or work; with friends or relatives; in other activities).
D	There is clear evidence that the symptoms interfere with, or reduce the quality of social, school, or work functioning.
E	The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder).

Note: The disorder should be specified depending on the predominance of an inattentive presentation, hyperactive/impulsive presentation or a combined presentation, or if in partial remission and if the degree of current affectation is mild, moderate or severe. In any case the distinction among the degrees of dysfunction are still confusing.

Flexibility with age in relation to the onset of symptoms

There is no empirical evidence to determine one or any other age with regard to the onset of symptoms,³⁸ so the possibility of arbitrariness is always open. The limit of 7 years was determined when the disorder was typical and proper of childhood. According to a revealing study, only 50% of the adults diagnosed with ADHD recalled having symptoms before they were 7 years old, compared to 95% who did so before they were 12 years.³⁹ On the other hand, a cohort study concluded that neither the prevalence of children diagnosed, nor the clinical repercussion varied when the limit was modified, obviating the fact that it is not the prevalence in childhood that is under stake, but that in adults as we shall see later on.⁴⁰ In this sense, it is quite alarming to note the temporal coincidence of the publication of DSM-5 criteria and the

approval in various European countries of the new indication for atomoxetine (Strattera, Lilly)⁴¹ in adults, with the additional knowledge that important collaborators in the elaboration of these criteria showed clear links to the drug manufacturer.^{42,43}

A lower number of symptoms for diagnosis.

Up to now the starting point indicated that adults were being diagnosed through symptom-based scores validated in field studies carried out in children.⁴⁴ The novelty of the DSM-5 suggests that adults do not need to fulfil the threshold in the number of current symptoms despite persistent dysfunction, although it is not known if symptoms, prevalence or severity decline is somewhat real or an artefact of the scale score used. The reduction

in the number of symptoms required is proposed with the idea of limiting false negatives, based on statistical premises with debatable cut off points and despite the admission that the evidence in favour is weak.³⁹ On the other hand, the possible scenario of an increment of false positives is not contemplated.

Widening the scope of comorbidities

The consideration of autism as an exclusion criteria in the diagnosis of ADHD, currently present in the ICD-10 criteria, no longer appears in the new update of the DSM-5. Concomitant treatment of both is considered beneficial, minimizing both the importance of the adverse effects that psychostimulants entail and the greater inherent difficulty for these patients to communicate these adverse effects.³⁹

Reliability of diagnostic scales

Beyond these considerations involving the DSM-5, a reflection is warranted on the suitability and thresholds of the different scales employed, as any clinical judgement should be based on the aspects contemplated by the scales. In clinical practice, these are not an exclusive source of information to establish diagnosis. In fact, they are integrated with data proceeding from the clinical interview and evaluations from a clinical, social, and psychological perspective. The scales score clinical symptoms with a poor correlation with academic and social dysfunction^{28,45} and often rest on the interpretation of what parents or teachers understand as "abnormal" behaviour,³⁷ in which case there is discrepancy in the evaluations.²² However, what is crucial is that neither the DSM nor the ICD classification capture the heterogeneous phenotype of the disorder, in great measure by using a categorical system instead of a dimensional approach.⁴⁶ The categorical spectrum requires a clear distinction between what is normal and pathological, what does not occur in the case of ADHD.² On the other hand, the gold standard employed to validate the scales is, after all, a clinical judgement of the evaluator with no other references.⁴⁴ This may lead to wide variability in diagnosis.

In any case, on referring to studies carried out in our context, we find that both the premiss of significant dysfunction and the use of well defined diagnostic tools by clinicians are not employed in the majority of cases. According to a questionnaire given to neuro-pediatricians and child psychiatrists, 64% initiated pharmacological treatment based solely on symptoms. In another study with pediatricians, more than half did not recur to diagnostic criteria to establish ADHD in a patient,⁵ and a significant percentage of clinicians showed a tendency towards diagnosing ADHD despite not fulfilling criteria.⁴⁷

The stimulants are substances that are susceptible to recreational use, under special regulation in many countries, and their abuse is increasing

With or without drugs? No evidence in the long term

In 1998, the American Medical Association declared ADHD as "one of the best studied disorders in medicine".⁴⁸ However, as far as drug research is concerned there is a substantial amount of poor-quality short-term studies. Let us start then by talking about how these studies address efficacy of drugs used to treat ADHD.

Methylphenidate acts as a stimulant of the central nervous system inhibiting the uptake of dopamine and noradrenaline in presynaptic neurons and increasing the release of these neurotransmitters in the extraneuronal space. One meta-analysis has shown its qualities in the **short-term**:⁴⁹ the child's motor activity is reduced, classmates suffer less from interruptions, the child's level of attention is increased and he/she is able to concentrate on simple routine or repetitive tasks given the greater sustained attention.²⁹ From this perspective the scales show that these children are "better responders" which on the other hand is a fact that is produced independent of the diagnosis of ADHD (remember student attachment to Centramine). Therefore, the impression given is that there is a pretence to certify a disease on the basis of very low specific pharmacological action and the capacity to improve performance without the need of a psychopathological disorder.⁵⁰

However, even though this issue is under debate, *a priori* this newly attained change in behaviour though socially more acceptable is associated with a lower quality and spectrum of emotional expression, less exploratory desire and cognitive flexibility, less capacity for wonder and reflection, less spontaneity and initiative, plain mood and a more passive attitude,^{34,51} though this issue remains controversial.⁵² Besides, these drugs are ineffective in potentiating shared and divided attention. In order to know whether it is worth to bet on the pharmacological approach, it is necessary to focus on what the drug is

capable of offering in **the long run** in terms of relevant endpoints (improvement in learning parameters, school failure and dropouts, family and social behaviour, substance abuse, criminality, etc.). Unfortunately there are very few and ambiguous studies in this field.⁵³

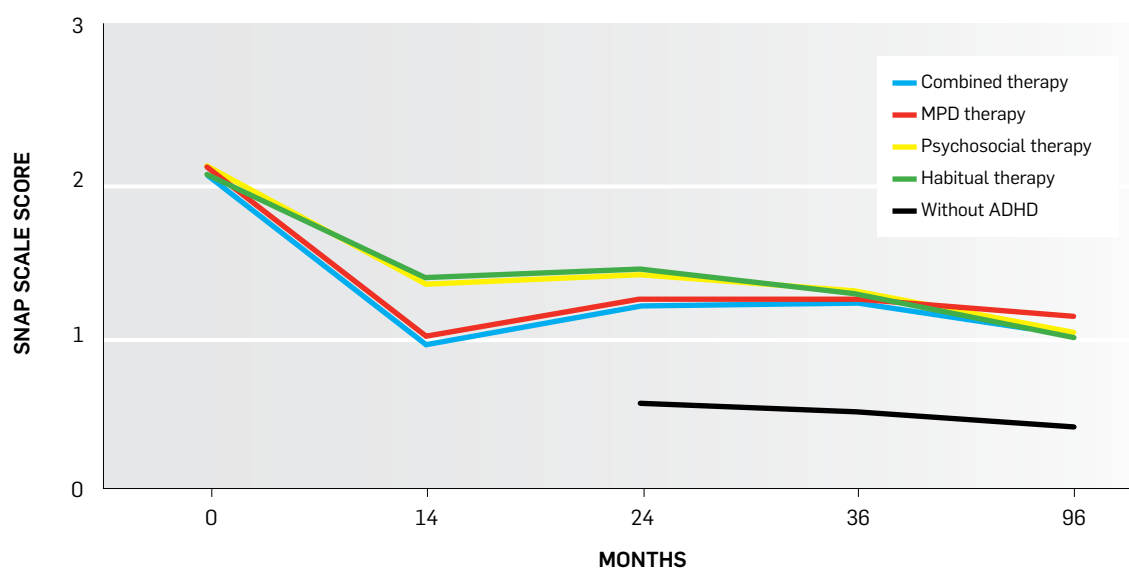
Methylphenidate: MTA study as the main reference trial

A Cochrane review on the efficacy of methylphenidate in children and adolescents diagnosed with ADHD including more than 300 studies is pending publication in late 2014.⁵⁴ Meanwhile, among individual trials, the start of the MTA⁵⁵ study is understood as the most serious attempt up to now to clarify the long-term effects of psychostimulants, specifically methylphenidate in ADHD. The MTA included 579 children between 7 and 10 years (80% male) who all fulfilled criteria for combined ADHD. They were randomly assigned to four arms of treatment (medication, psychosocial treatment, combined treatment and standard practice). The follow-up was 14 months and as many as 19 endpoints were measured on aspects such as ADHD symptoms, aggressiveness, social skills, anxiety and depression, relationship with parents and academic performance.⁵⁶ Sample size calculation was based on the "nuclear ADHD symptoms" endpoint, and this was evaluated with the SNAP scale for parents and teachers.⁵⁷ The trial suffered from important limitations, especially the absence of a necessary placebo group. At the same time,

blinding was revoked and follow-up was more intense in the pharmacological arm, 23% of the subjects under behavioural therapy received medication as well, the inclusion of cognitive elements was not contemplated, a third of the participants were already under treatment, and the switch from methylphenidate to another stimulant due to inadequate response was allowed.

After **14 months**⁵⁶ all groups improved the scales score with small differences between them. It is worth mentioning that 75% of the subjects under psychosocial therapy were successful without medication throughout the study. In comparison the group under medication showed higher scores than the psychosocial group in only 3 of 19 variables (specifically there was a better score in attention deficit, contradictory results between parents and teachers in hyperactivity, and no differences among the rest of the variables). Combined treatment scored higher in 6 of 19 variables, in addition to the three above mentioned, the best parents score in anxiety/depression, aggressiveness (with no differences for teachers) and the reading test (no differences in mathematics or spelling). Compared to behavioural therapy, drug use or combined treatment showed some improvement of scarce magnitude in just a few variables (figure 2). With the exception of attention deficit, no coherence was found between teachers and parents. The validation of the data from the SNAP-IV scale suggest an acceptable internal coherence, while the clinical relevance remains unknown in terms of the dysfunction implied since there

Figure 2. Evolution of the SNAP scale scores for symptoms of ADHD in the MTA study.



MPD=Methylphenidate. In the SNAP scale, the 18 items referred to as ADHD symptoms were scored according to the degree in which they occurred (3=Very much; 2=Quite a bit; 1=Just a little; 0=Not at all), and the global average was calculated. The first 14 months refer to the randomised clinical trial, while the rest represent the prospective follow-up period.

was only a 0.5-point difference between the medication and psychotherapy groups at the end of the study.^{58,59}

After the 14-month period there was freedom to choose a management approach and a prospective cohort follow-up was initiated.

After **2 years**,⁵⁹ the medication and the combined groups maintained an advantage in comparison to the rest, but the size of the effect was reduced to half, and therefore its clinical significance is questionable. After **3 years**,⁶⁰ the groups showed no differences in any way and it could be said that the use of medication was a predictor of worsening symptoms.²⁹ A similar trend was found after **8 years**⁶¹ of follow-up. Another cohort study (RAINE) did not find any variable that improved in the long-term in children under drug therapy for ADHD.⁶²

DSM-5 does not give any recommendation about treatment duration. In clinical practice, this is often prolonged, and studies in Spain show an average length of 4 years.⁶³

The conclusion is that neither the type or intensity of treatment reduces dysfunction at the end of follow-up and the association between symptoms and dysfunction is only modest.⁶¹ Moreover, the scale employed to measure primary symptoms of ADHD is not useful in adolescence, given that only 30% of the initial participants fulfilled the DSM-IV criteria.⁶¹ The National Institute of Mental Health itself, promoter of the study recognizes that there are no data in favour of employing methylphenidate in the long term.⁶⁴

The Product Fact Sheet includes a warning stating that the "long-term safety and efficacy of methylphenidate has not been evaluated systematically in controlled trials" and that "regular reassessment of the drug's usefulness in the long term should be carried out for every patient". The drug should be discontinued temporarily "at least once a year to evaluate the child's status".⁶⁵

Studies in children comparing the efficacy of long-acting vs immediate release formulations present a follow-up of just a few weeks.⁶⁶

Atomoxetine and lisdexamphetamine: evidence of little relevance

Atomoxetine is a selective norepinephrine reuptake inhibitor that indirectly increases dopamine in the prefrontal cortex. In the short term, it is more effective than placebo on improving primary symptoms of ADHD in children, with a mild to moderate size of effect.¹⁴ A comparison was made with methylphenidate OROS for 6 weeks, where the latter showed some superiority but only after excluding patients with intolerance or with low response to methylphenidate.⁶⁶ There are no long-term randomised trials on this drug, except for one placebo-

controlled trial that had previously selected responders to the drug in a 3-month open run-in period.⁴¹

Lisdexamphetamine is dexamphetamine pro-drug, indicated in children over 6 years when there is no adequate response to methylphenidate.⁶⁷ In the USA its use is far more extensive than atomoxetine,⁶⁸ while in Europe an ongoing pre-marketing campaign highlights the unattended needs in the management of ADHD.⁶⁹ Supportive studies are either short-term or open design.

Paying attention to the "other side" of drugs

All drugs present adverse reactions, and just as psychostimulants do, atomoxetine does not fall short. The main side effects are listed below:^{29,41,65,70-75}

Cardiovascular effects

Increase in blood pressure (≈ 4 mmHg) and heart rate (3-6 bpm), a fact that produces concern especially if treatment extends to adults. Sudden death in children has been reported even in those with no previous congenital defect.

Effects on growth

Long-term treatment involves weight loss and height loss, perhaps related to the anorexic effect and the uncertain recovery when treatment is discontinued. The MTA study showed a loss after 3 years of about 3 cm in height and 2.7 kg weight.

Effects on the nervous system

Insomnia or headaches are very frequent but also cases of tics (especially methylphenidate), emotional disorders, hallucinations, psychotic and maniac reactions, even in case of no previous history. In animals, neurotoxicity, discontinuation syndrome and action potential alterations have been detected by neuroimaging.

Endocrine-related effects

Studies are needed regarding the impact on puberty, that confirm or reject the hormonal imbalances recorded in preclinical trials.

Gastrointestinal effects

Abdominal discomfort and pain are frequent.

Other effects

The medication is related to suicide ideation and bipolar disorder.

The Spanish Pharmacovigilance data base (FEDRA) registered up to September 2013 a total of 264 adverse reactions (185 severe) with methylphenidate and 104 suspicions (85 severe) with atomoxetine. The most common effects reported for both drugs corresponded to the psychiatric sphere, 22 cases of hallucinations with

methylphenidate, and 11 cases of suicide ideation with atomoxetine.⁷⁶

The Spanish Medicines Agency has recommended a cardiovascular and psychiatric evaluation prior to initiating treatment with methylphenidate in addition to follow-up during treatment, weight and height monitoring of patients and, most importantly a review of the adequacy of the indication at least once a year.⁷⁷ In the case of atomoxetine, a greater focus on cardiovascular safety has been placed.⁷⁸ In clinical practice, blood pressure and heart rate monitoring should be carried out in addition to an ECG (especially if family history of sudden death and personal history of congenital arrhythmia or congenital cardiac disease).

Safety is a key issue when drug therapy is applied to children and long-term studies on adverse effects are necessary. Currently there is one ongoing project (www.ADHD-ADDUCE.org) focussed on addressing these issues with European public funding and leadership from the EUNETHYDIS network researchers, a group that presents a high potential for bias to be taken into account as we shall see later.

Substance abuse and antisocial behaviour: a complex debate.

Stimulants are substances that are susceptible for recreational use,⁷⁹ are under special regulations in many countries and while their prescription rates are increasing so are those of substance abuse.^{80,81} Young people with psychiatric comorbidities or in prison present a greater risk of abuse.¹⁴ On the other hand, there is a long-standing debate on whether the use of stimulants in children can provoke abuse-related behaviour with other substances (tobacco, cocaine, etc.). There are studies supporting this hypothesis⁸² and also recent studies that do not seem to confirm this.^{83,84} Although it is estimated that immediate release presentations are the most dangerous, in France 100 cases of abuse, dependency or inadequate prescriptions were detected between 2000 and 2011. These also included long-acting presentations.⁸¹ Given its different molecular structure, atomoxetine may be suggested as elective,^{14,85} but there is still concern about the possible massive incorporation of adults in the treatment of ADHD.

With regard to the relationship between drugs employed in ADHD and delinquency there is also literature on this topic presenting contradictory results. A Scandinavian study⁸⁶ on ADHD patients over 15 years of age with a follow-up period of 4 years showed a protective effect that disappeared when treatment was discontinued. Patients evaluated did not appear representative of the average population with ADHD as they presented a high tendency to commit crime. This issue was also addressed by the MTA study,⁸³ which found that children with higher rates of delinquency after 24 and 36 months were associated with having taken medication a year before.

Teachers establish a suspicion of ADHD and can be influenced by health information lacking scientific rigour

Non pharmacological management: uncertainty due to lack of research

There are various Cochrane reviews on the effects of non-pharmacological treatment, concluding that the evidence to recommend some techniques such as **acupuncture**,⁸⁷ **homeopathy**,⁸⁸ **meditation**,⁸⁹ **fatty acid supplementation**,⁹⁰ or **family therapy**⁹¹ is far from compelling. There is also little evidence to support or reject **social skills**,⁹² given the high risk of these studies, and **neurofeedback**⁴⁵ lacks studies with adequate design to correctly evaluate clinical improvement. The **exclusion of colorants** has shown some positive effects but often in individuals with previous food sensitivity.⁹³

With respect to **behavioural interventions**, a Cochrane⁹⁴ review concluded that parent training can have a positive effect on ADHD. However, the methodology of the studies is of poor quality, the risk of bias is high, and there is lack of information on relevant variables such as school performance or adverse effects. One meta-analysis⁹⁵ found efficacy on behavioural therapies, but this was not confirmed by another meta-analysis⁹³ later on when only the probably blinded evaluations were analysed. The MTA study⁵⁵ lacked a placebo group that would have permitted the assessment of the real effect of psychological treatment.

A recent study has shown the superiority of parental training over methylphenidate in children under 6 years.⁹⁶ **Cognitive therapy** which includes self-directed learning and self-control skills has lost importance compared to behavioural therapy.⁴⁵ Despite the support received from clinical guidelines, such as those from Scotland and Spain, **psycho-pedagogical interventions** still present very limited evidence on their real value in ADHD.⁷

In summary, among all non-pharmacological therapies, behavioural intervention is worth paying attention to, and is also recommended by the NICE guidelines independently of the severity of the disorder. Certainly further research on this field is required, and should be adapted to the characteristics of psychotherapy. Taking into account the available data along with the interest on safety issues, many clinicians confide in this therapy as a reasonable option in the management of behavioural

problems, without forgetting that they are not exempt of financial and organizational costs, and the evidence to support them is rather insufficient.

Some comments on clinical practice guidelines

If Clinical Practice Guidelines (CPG) are to be really useful in orienting clinicians, they should be designed with the highest possible methodological rigor and prevention of avoidable bias. According to the GRADE classification, medication use in children and adolescents with ADHD is rated as 2A,⁹⁷ which is a weak recommendation that depends on the context of the patients or the values of the society at hand.

The Spanish CPG (2010),⁹⁸ financed by the Ministry of Health presents some important limitations. There is great concern about the composition of the collaborating group, the search strategy, the (in)consistency between evidence and recommendations or the inadequate management of conflicts of interest, where a great majority of participants are linked to ADHD drugs manufacturers. In general, recommendations are similar to those of NICE and SIGN, where only a moderate degree of ADHD is required to recommend the use of drugs in addition to non-pharmacological measures (Recommendation 7.4.2.1).⁹⁹ Of the 73 recommendations issued, only 2 related to treatment present "grade A evidence level" according to SIGN, and this is because of considering MTA as a high-quality study with low risk of bias (1++). However, as mentioned above, the trial presented significant limitations that challenge the high qualification received.

The NICE CPG (2013)¹⁴ whose president has participated in the Steering Committee of the EUNETHYDIS¹⁰⁰ network has a great influence among clinicians and clinical guidelines. In this CPG, a combination of biological and environmental factors is said to lie in the origin of ADHD. From data after 14 and 24 months of the MTA trial, combined therapy involving parental training and methylphenidate is recommended in cases with severe symptoms and functional deterioration (for diagnosis, at least moderate dysfunction is required, and in this case, psychotherapy would be sufficient). Nevertheless, in the same CPG it is acknowledged that the symptoms score threshold to treat adults is not evidence-based, and even more so when symptoms manifest in a different way with age. The CPG has received criticisms in many aspects such as the greater importance given to biomedical factors compared to psychological factors, unconvincing management of the different prevalence of ADHD in relation to gender, culture or social class, complacency in the absence of long-term results on relevant variables, resignation with regard to the deficient design of the MTA study, or an excessively optimistic interpretation of outcomes after 3 years.¹⁰¹ A key point is the reference to the recommendation of pharmacological treatment in severe ADHD. The main reference cited by the NICE guidelines in favour of medication is a paper¹⁰²

authored by the same president of the working group on data of the MTA study at month 14th. Results beyond 14 months and good-quality systematic reviews where the absence of relevant data is documented are simply ignored.¹⁰³

ADHD in adults, the second-to-last frontier?

We initiated our reflection on ADHD in adults given the modifications introduced in the DSM-5 regarding the age for initiating pharmacological intervention and the reduction of the number of symptoms required. In the 1970s various cohort studies suggested that some children with ADHD could still have problems in adulthood, while even in the 1980s it was maintained that all diagnosis of ADHD in adulthood should unconditionally originate from childhood, with no initial diagnosis existing from adulthood. This idea changed during the 1990s with the development of the DSM-3-R and the influence from the Children and Adults with Attention-Deficit/Hyperactivity Disorder Organization (CHADD), and was finally consolidated in the DSM-4. Lastly, by the end of the 1990s a debate on the possibility of suppressing the requirement of reconstructing ADHD from childhood for diagnosis in adults was started. Among others, this proposal was defended by David Shaffer, the president of the ADHD group for the DSM-5.³³ Today it has been affirmed that between 50-70% of the children with ADHD maintain the diagnosis partially at 25 years while 15% retain all symptoms,¹⁰⁴ drawing great attention to the public media.¹⁰⁵

This approach can be challenged because of the following facts: 1) Diagnosis of all adults with ADHD is carried out with criteria validated only in children.⁴⁴ 2) Symptom-behaviour profile is not the same in children as in adults, with greater hyperactivity in children compared to adolescence and adulthood, where lack of attention predominates.⁷ 3) The comorbidity reported in adults is very high, reaching up to 90%.¹⁰⁶ 4) The risk of potential stimulant dependence and a greater repercussion regarding cardiovascular effects would be predictably higher in the adult age. Only short-term data in children are currently available.^{71,107}

Some studies lasting 6 months have been proposed to evaluate the usefulness of pharmacological treatment in adults. One of them employed methylphenidate, where statistically significant reductions in ADHD symptoms were found, but with a high rate of both premature dropouts (24% methylphenidate, 43% placebo) and response in the control group (61% methylphenidate, 42% placebo).¹⁰⁸ Atomoxetine is clearly positioned for adult management. Marketing approval for adults is supported by 3 six-month studies with a high rate of dropouts, uncertain clinical significance and contradictory results. Two studies found an improvement in ADHD symptoms, while a third did not show advantages on "work dysfunction" (primary endpoint).^{41,109} Lastly, a recent cohort

study published suggested that the risk of suffering a traffic accident in men with ADHD could be reduced by pharmacological treatment. However, this association is no longer significant when participants involved in criminal activities or substance abuse are excluded, far from the majority that characterizes patients diagnosed with ADHD.¹¹⁰

In summary, all this indicates that the current anecdotal prescription of drugs for adults with ADHD will increase soon, despite the still feeble evidence of its usefulness.¹¹¹ This leads us to the last section of our review where we will discuss on whether our society prudently employs drugs, or on the contrary, medicalizes the "non-pathological difference."

Epilogue: on the right to define the question

The ADHD along with some other conditions have served sociologists to raise important questions: how and who should elaborate the concept of what we understand as disease? To what extent should we employ psychoactive drugs to facilitate social control within what is culturally accepted? Is it convenient to focus mainly on the individual when dealing with problems that could reveal more complex dysfunctions, in the family, academic or social structure?²¹ Traditionally childhood was a considerably protected period from pharmacological intervention but times are changing. Even the UNICEF has drawn attention to the trend of increasing use ADHD drugs in Spain.¹¹²

Numerous actors on stage with many different interests

The stand we take on any issue depends to a great extent on the sources we trust. Those who underline the validity of ADHD as a disease insist that the prevalence is variable based on different methodologies of measurement and the degree of cultural tolerance,²¹⁴ and could increase by better detection. Detractors however respond that the weight of heredity in ADHD is completely overestimated.¹¹³ Despite, or perhaps because of ADHD being an inadequate and unspecific category, its incidence rate has not stopped growing, first in male and later in female children, adolescents and adults.¹¹⁴

In this process it is fundamental to consider who investigates, and how ADHD is investigated, because this will condition to a great extent the rest of the factors. On one hand, it has been denounced that the National Institute of Mental Health has financed with greater ease projects employing an organic and physiological approach to ADHD rather than the rest of the approaches.²⁷ In addition, there is little research on those social factors that could contribute to finding a diagnosis of ADHD.² Moreover, many of the leading research groups who generate evidence and opinion on ADHD, especially from

The pharmacological option should be the last alternative to turn to, and employed for the shortest possible time

North America, present important conflicts of interest, where there have been instances of sanctioned scandals involving concealment of million dollar payments by pharmaceutical companies¹¹⁵ and support for reaching specific commercial objectives.¹¹⁶

In Europe the EUNETHYDIS network is based in universities and counts with intense collaboration from the pharmaceutical industry leading their clinical trials, interpreting and presenting their general results.¹¹⁷ Its influence on European regulatory marketing applications is relevant and, despite the expressed declaration on transparency,¹¹⁸ their main commitments still have to be materialized. Sources from EUNETHYDIS assure that it has not been possible to create a web site to publish the conflicts of interest of the members due to lack of funding for this concept, which vividly contrasts with the celebration of international congresses which receive substantial support from manufacturers involved in the management of ADHD.^{119,120}

Many times these same experts will collaborate in the elaboration of CPGs, even holding positions of high responsibility,¹⁴ and later these CPGs will be endorsed by scientific societies, used by the public administrations, or included as reference documents in the Patients' Associations website. The latter also face the great challenge of maintaining independence and transparency. In this sense, we regret that the Spanish Federation of Associations to Aid in ADHD (FEAADAH)¹²¹ has not been able to facilitate the information we asked for on their activities, budget and sources of funding.

Lastly, it is necessary to mention the mass media, usually on alert about news on ADHD that emphasize the pharmacological approach.¹²² Most of these news items have been refuted or have faded out over time. Is this the model we really desire, despite the obvious "secondary effects"?

Only by strengthening independent research can we address the crying need of patients and society as a whole, because this way relevant questions can be addressed without prejudicial attitudes.

Centered (this time for real) in the interest of the child

And what do the children think about all this? There are certainly not many studies that consider children's opinion. One of them (ADHD VOICES),¹²³ of little statistical robustness consisted of 151 interviews to children and showed some acceptance of medication with a clear demand for other therapeutic alternatives. However, other publications have outlined children's rejection of medication,^{29,34} indirectly manifested by a high rate of non-compliance with treatment in adolescence regardless the pathology considered.

Despite the evident trend in increasing costs of drugs, which will reach approximately 4200 million dollars in 2015,¹²⁴ the nature of our main concern should not be economic, but rather social and ethical. Perhaps the current dynamism of western society does not favour the development of sustained attention in children, postponement of compensation, reflection or emotional intelligence and maturity that we demand from them.¹²⁵ In this context families and schools often feel overwhelmed by cases of complex behaviour involving multiple factors: lack of time, lack of specific skills, difficulty in personalizing educational pathways, breakdown of moral authority, competitive pressure, etc.² Once a child is labelled as sick, this leads to a partial liberation on the part of the involved parties' responsibility, the drug presents itself as a comfortable option with visible short-term results, even much cheaper than other non-pharmacological therapies.

The pill arrives to reinforce and perhaps reformulate the identity of the young child.³³ No doubt punishments, school expulsions, and family conflicts are avoided, but we should be conscious of the fact that the price consists of a subordination and conditioning of their autonomy and abilities to the whim of a drug. The attitude adopted by the education realm is a key issue because it actively intervenes in the detection of diagnosis and there is a risk of becoming instrumentalized through biased information.¹²⁶

Children diagnosed with ADHD even when fulfilling DSM or ICD criteria, can require different therapeutic approaches because attention is a very sensitive function of diverse causes.¹²⁷ In fact even focusing on the primary signs does not seem to produce good results in the long term. That is why some authors, certainly with good criteria, propose the pharmacological management as the last option for specific situations, limited in time while the case is rigorously evaluated and in an environment that is organized in favour of the child.²⁹ This is the goal we propose to work for, whereby the impact of medication is minimal, and a thorough and paused process of evaluation is carried out,³⁷ with a multifactorial perspective and a serious implication of children, families and the educational community, all leading to a range of alternative solutions.¹²⁸ This is because the objective is clear: "All for the children, but **with** the children".

Conclusions

ADHD is a phenomenon of variable and increasing prevalence of unknown origin and with no consistent biological markers.

Its diagnostic criteria have enormously fluctuated over time, and are based on symptoms scales insufficiently correlated to social, academic and family dysfunction.

Non-pharmacological management require further research, although behavioural therapy shows potential usefulness.

Medication presents some efficacy on symptoms in the short-term with no clear continuity in relevant variables, and should therefore be considered as an exceptional resource.

Drugs cause cardiovascular, psychiatric and endocrine-related adverse effects usually downplayed or ignored. They can also produce dependence and abuse.

Acknowledgements

We are grateful to José Antonio Inchauste (psychiatrist) and Miguel Ángel Valverde (clinical psychologist) for reviewing this article and for their remarks and suggestions. We also appreciate the Basic Common Services Portfolio (Ministry of Health) and the Drug Prescribing Service of the Navarra Health Services for the invaluable data provided for the elaboration of this article.

We thank Dr Clint Jean Louis, of the Emergency Department of the Navarra Regional Health Service in Spain, for translating the original manuscript into English.

Note

The author has no conflicts of interest to declare.

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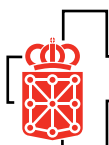
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ISSN

1138-1043

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