Original

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Expert Recommendation: contributions to clinical practice of the new prodrug lisdexamfetamine dimesylate (LDX) in the treatment of attention deficit hyperactivity disorder (ADHD)

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·Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobiological disorders in childhood, and is characterized by inappropriate levels of inattention, hyperactivity and/or impulsiveness, with an estimated prevalence of 5.29%. ADHD can have a negative impact upon all areas of the life of the patient. The main clinical guides accept multimodal treatment, involving both pharmacological and psychological measures, as the best management approach in ADHD (psychoeducational, behavioural and academic). Lisdexamfetamine dimesylate (LDX) is a new drug for the treatment of ADHD. A multidiscipline expert document has been developed, compiling the scientific evidence referred to this new molecule. The study also addresses the existing shortcomings in current drug therapy for ADHD and the contributions of LDX to routine clinical practice, in an attempt to help and guide physicians in the use of this new treatment. This document is endorsed by the ADHD and Psychoeducational Development task Group of the Spanish Society of Primary Care Pediatrics (Grupo de TDAH y Desarrollo Psicoeducativo de la Asociación Española de Pediatría de Atención Primaria, AEPap), the Spanish Society of Pediatric Neurology (*Sociedad Española de Neurología Pediátrica*, SENEP) and the Spanish Society of Out-hospital Pediatrics and Primary Care (*Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria*, SEPEAP).

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Recomendación de expertos: aportaciones a la práctica clínica del nuevo profármaco lisdexanfetamina dimesilato (LDX) en el tratamiento del trastorno por déficit de atención con hiperactividad (TDAH)

El Trastorno por Déficit de Atención con Hiperactividad (TDAH) es uno de los trastornos neurobiológicos más frecuentes en la infancia, caracterizado por la existencia de unos niveles inapropiados de inatención, hiperactividad y/o impulsividad con una prevalencia estimada del 5,29%. El trastorno puede afectar negativamente a todas las áreas de la vida del individuo. Las principales guías clínicas aceptan el tratamiento multimodal como el más recomendable en el TDAH, lo que engloba la aproximación farmacológica y psicológica (psicoeducativa, conductual y académica). El dimesilato de lisdexanfetamina (LDX) es un nuevo tratamiento farmacológico para el TDAH. A fin de recopilar las evidencias científicas sobre esta nueva molécula se ha realizado un documento de expertos multidisciplinar. Este trabajo estudia además las carencias existentes en el tratamiento farmacológico actual en el TDAH y las aportaciones que presenta LDX en la práctica clínica diaria, intentando ayudar y guiar a los médicos en el uso de esta novedad terapéutica. Este documento está respaldado con los avales de las siguientes sociedades científicas: Grupo de TDAH

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y Desarrollo Psicoeducativo de la Asociación Española de Pediatría de Atención Primaria (AEPap), Sociedad Española de Neurología Pediátrica (SENEP) y Sociedad Española de Pediatría Extrahospitalaria y Atención Primaria (SEPEAP).

Palabras clave: Lisdexanfetamina, LDX, TDAH, Dimesilato

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobiological disorders in childhood, and is characterized by inappropriate levels of inattention, hyperactivity and/or impulsiveness. The estimated prevalence in school children is 5.29%, and the disorder can extend into adolescence in up to 60-85% of the cases, with symptoms also in adult life[1,2].

ADHD has a very strong negative impact upon all areas of the life of the patient. Because of the symptoms inherent to the disorder and to other frequently associated conditions, patients with ADHD are affected psychologically, in terms of academic performance, family and social relations, and in their work activities. Moreover, as has been demonstrated by a recent European epidemiological study, these patients are at an increased risk of suffering accidents[3], substance abuse or legal problems. As a result, their quality of life and self-esteem can be greatly affected. The economic costs associated to ADHD are important and are not only attributable to the medical or sanitary costs of the disorder but also to indirect costs resulting from productivity losses, legal problems or the educational repercussions of the disease.

Adequate treatment reduces and in many cases can even avoid the negative impact of ADHD upon these areas. The adoption of a personalized treatment strategy is therefore crucial in patients with ADHD.

CURRENT MANAGEMENT OF ADHD IN SPAIN AND IN OTHER COUNTRIES

The treatment strategy for ADHD must satisfy the needs of the patient and family, and must be designed on an individualized basis, making use of information referred to the patient, parents, teachers and other caregivers.

An integral approach to the management of ADHD encompasses pharmacological, psychological and psychoeducational measures, among others. The decision to prescribe drug treatment must be based on an adequate diagnostic process, with special assessment of the symptoms causing functional deterioration and the patient environment. Par-

Table 1	Drugs used for the treatment of the symptoms of ADHD
Pharmacological Class	**Drug**
Stimulants	Metilphenydate* Lisdexamphetamine*
Noradrenaline Selective Reuptake Inhibitors	Atomoxetine*
Adrenergic agents	Clonidine** Guanfacine**
Antidepressants	Bupropion** Tryciclic antidepressants** MAOI (monoamine oxidase inhibitors)** Reboxetine**
Dopaminergic agents	Modafinil

*Labelled in Spain for the treatment of ADHD
**Not labeled in Spain for the treatment of ADHD. Its use is regulated by RD 1015/2009 regarding the use of not authorized drugs in special situations

ticipation by the patients and parents, as well as information and collaboration on the part of the teachers, are important elements in establishing the best treatment option according to the individual circumstances, and in facilitating adherence to therapy.

Drug treatment must be associated to psychosocial therapies that contribute to lessen residual dysfunction[4]. The combination of both treatment approaches is referred to as *multimodal therapy*, and is more effective than psychosocial treatment alone. In this regard, multimodal therapy affords beneficial effects upon the symptoms of ADHD and their functional repercussions[5].

In the last 50 years, the most widely used drug treatments have been stimulating agents such as methylphenidate (MPH) and dextroamphetamine (currently not available in Spain). Non-stimulating drugs are also used to treat ADHD, including atomoxetine, which is the only substance authorized in Spain. Use is also made of molecules belonging to other pharmacological groups, such as noradrenergic antidepressants or alpha-adrenergic agonists. However, these drugs are prescribed outside the indications contemplated in the Summary of Product Characteristics (SPC), and are limited by their potential adverse effects and restricted efficacy[6]. (Table 1).

Methylphenidate is the standard treatment in Europe, as evidenced by a recent study comparing the ADHD management strategies used in different European countries. In Spain, almost 70% of the patients receive long-acting

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Table 2	ADHD treatment use and standards

	France		Germany		Italy		Netherlands		Spain		UK		Total (Europa)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total number of patients (N)	130		151		144		74		134		146		779	
Lines of treatment														
One	85	65.4	77	51.0	81	56.3	46	62.2	69	51.5	64	43.8	386	49.6
Two	37	28.5	45	29.8	60	41.7	19	25.7	48	35.8	55	37.7	295	37.9
Three	7	5.4	24	15.9	3	2.1	7	9.5	15	11.2	17	11.6	73	9.4
Four	1	0.8	3	2.0	0	0.0	1	1.4	1	0.8	7	4.8	18	2.3
Five or more	0	0.0	2	1.3	0	0.0	1	1.4	1	0.8	3	2.1	7	0.90
Current treatment type[a]														
No treatment[b]	12	9.2	14	9.37	9	6.3	2	2.7	2	1.5	7	4.8	46	5.9
Pharmacotherapy only	71	54.2	84	55.6	33	22.9	45	60.8	48	35.8	93	63.7	374	48.0
BT only	10	7.7	10	6.6	59	41.0	1	1.4	9	6.7	1	0.9	90	11.6
Pharmacotherapy and BT	37	28.5	43	28.5	43	29.9	26	35.1	75	56.0	45	30.8	269	34.5
Current treatment class[c, d]														
Short-acting MPH	39	34.2	56	36.8	43	54.4	25	31.7	0	0.0	16	10.2	179	25.1
Long-acting MPH[e]	73	64.0	82	54.0	0	0.0	45	57.0	91	68.9	107	68.2	398	55.8
Short acting AMP	0	0.0	1	0.76	7	8.9	1	1.3	0	0.0	2	1.3	11	1.5
Atomoxetine[f]	1	0.9	13	8.6	29	36.7	8	10.1	13	9.9	32	20.4	96	13.5
Others	1	0.9	0	0.0	0	0.0	0	0.0	28	21.2	0	0.0	29	2.1

N total number of patients, BT behavioural therapy, MPH methylphenidate, AMP amphetamine

[a] Percentages are based on the total number of patients reporting treatment type
[b] Not included in any analyses
[c] Percentages are based on the total number of patinets reporting treatment class
[d] Treatment could be monotherapy or combination therapy
[e] Long-acting MPH is not approved for use in Italy
[f] Atomoxetine is not approved for use in France

MPH as treatment. The rest of the patients receive atomoxetine or other treatments (Table 2)[7].
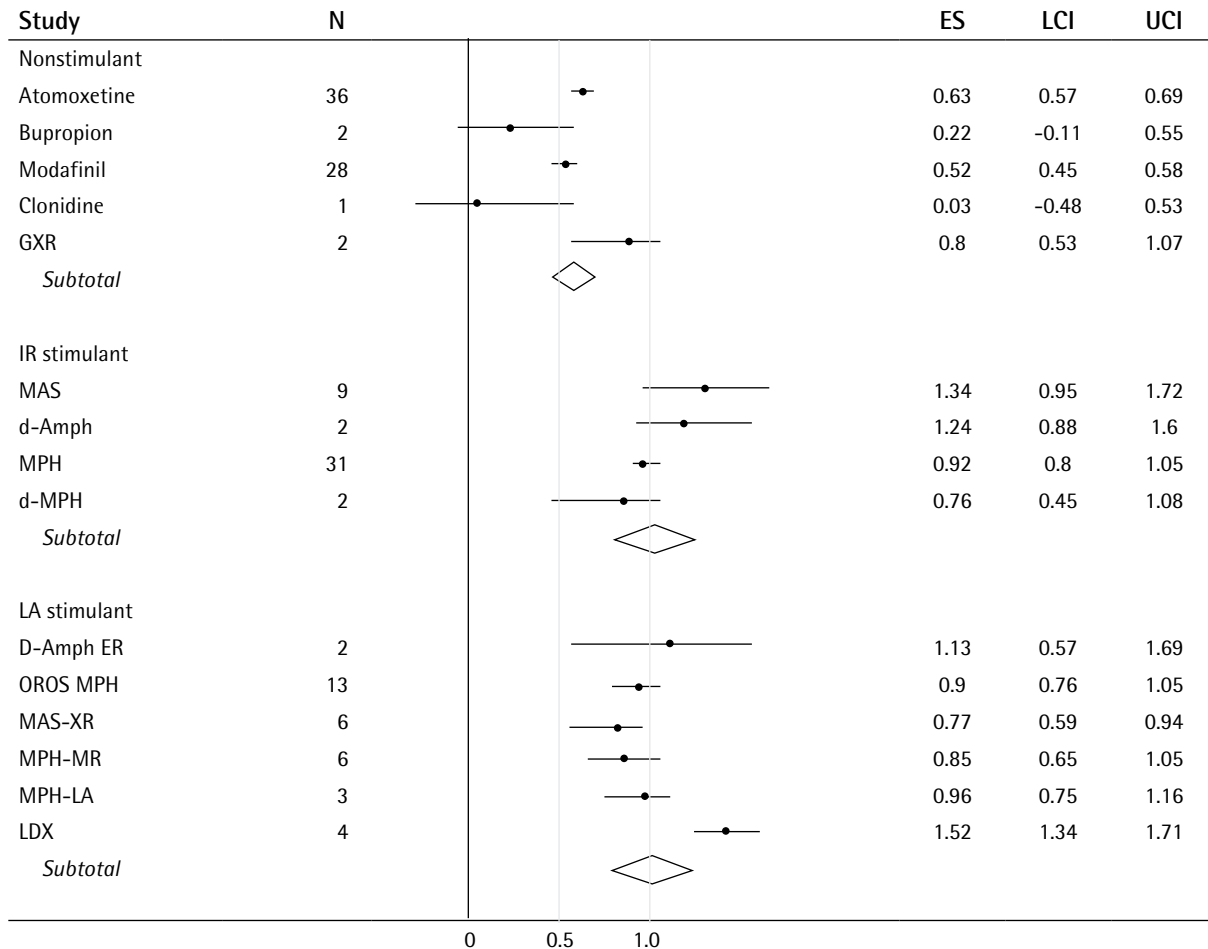
In clinical practice, atomoxetine is usually considered in those patients who do not respond adequately to MPH following dose adjustment, or in the presence of tolerance to this latter drug. However, the treatment guides of the AACAP (2007) and the Spanish Clinical Practice Guide (*Guía España de Práctica Clínica*) (2010) regard atomoxetine as first choice treatment. The choice of atomoxetine can be more clearly decided in the presence of certain comorbidities such as anxiety or tics[6].

Amphetamines are widely used outside Europe. In this regard, dextroamphetamine is regarded as first line treatment for ADHD in the United States and Canada[8].

PHARMACOLOGICAL TREATMENT OF ADHD

Differences in mechanism of action

Although the precise mechanism of action of the stimulating drugs has not been fully established, they are known to produce an increase in the presence of monoamines (noradrenalin and dopamine) in the synaptic gap of different brain areas. Methylphenidate produces this increase by inhibiting the reuptake particularly of dopamine on the part of the presynaptic neuron. In turn, dextroamphetamine moreover increases the release of both monoamines from the presynaptic neuron into the synaptic gap, and inhibits degradation of the neurotransmitter in the presynaptic vesicles.

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Study	N		ES	LCI	UCI
Nonstimulant					
Atomoxetine	36		0.63	0.57	0.69
Bupropion	2		0.22	-0.11	0.55
Modafinil	28		0.52	0.45	0.58
Clonidine	1		0.03	-0.48	0.53
GXR	2		0.8	0.53	1.07
Subtotal					
IR stimulant					
MAS	9		1.34	0.95	1.72
d-Amph	2		1.24	0.88	1.6
MPH	31		0.92	0.8	1.05
d-MPH	2		0.76	0.45	1.08
Subtotal					
LA stimulant					
D-Amph ER	2		1.13	0.57	1.69
OROS MPH	13		0.9	0.76	1.05
MAS-XR	6		0.77	0.59	0.94
MPH-MR	6		0.85	0.65	1.05
MPH-LA	3		0.96	0.75	1.16
LDX	4		1.52	1.34	1.71
Subtotal					

Standardized mean differences and 95% confidence intervals (CIs) stratified by type of drug. The point indicates the effect size for each study. The *horizontal line* through each box gives the 95%CI. The diamonds give CIs for each type of drug. d-Amph= dextroamphetamine; ER= extended release; ES= effect size; GXR= guanfacine extended-release; IR= immediate release; LA= long-acting; LCI= lower 95%CI; LDX= lisdexamfetamine dimesylate; MAS= mixed amphetamine salts; MPH= methylphenidate; MR= modified release; No.= number of observations; OROS= osmotic release oral system; UCI= upper 95%CI; XR= extended release. *Reproduced with permission from Faraone SV. Using Meta-analysis to Compare the Efficacy of Medications for Attention-Deficit/Hyperactivity Disorder in Youths. P T. 2009 Dec;34(12):678-94.*

Figure 1	Effect sizes of the different drug treatments for ADHD[9]

The mechanism of action of the non-stimulating drugs involves either selective inhibition of noradrenalin (NA) reuptake, as in the case of atomoxetine, or alpha-adrenergic receptor activation with the induction of an increased NA concentration in the synaptic gap, as in the case of guanfacine or clonidine.

Comparisons of drugs based on systematic reviews and metaanalyses

The assessment of effect size (ES) allows us to compare differences in efficacy among different drugs based on studies involving different methodologies and measurement approaches. Effect sizes are expressed as standardized mean differences and are calculated by dividing the difference of the mean effect of the active drug minus the mean effect of placebo by the standard deviations of the groups.

A review carried out by Faraone et al. in 2009 identified all the randomized, double-blind studies published since 1979 in which comparisons were made of the treatments for ADHD in children and adolescents. The authors identified 32 placebo-controlled studies evaluating 15 drugs, with 20 different measurements of the symptoms of ADHD. The

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effect sizes of the stimulating drugs were greater than those of the non-stimulating drugs (Figure 1)[9].

In a second metaanalysis of studies in adults, Faraone et al. observed a greater effect size for amphetamines *versus* MPH. This could explain the perceived greater clinical efficacy and suggest that the ultimate differences among stimulating agents are due to a more global and facilitating effect upon brain neurotransmission on the part of the amphetamines[10].

Furthermore, since the non-stimulating drugs have a smaller effect size, it has been suggested that a stimulating agent should be the first treatment option in the absence of clinical data suggesting otherwise[10].

The differences in effect size and once a day dosing may result in improved treatment adherence. This likewise supports greater effectiveness of the long-acting stimulating drugs *versus* immediate-release methylphenidate[11]. On the other hand, a lesser risk of recreational use has been observed with the intermediate- or long-acting drug formulations[12]. Considering all the above aspects, a decrease in cost might be anticipated when treating large numbers of patients[10].

Lastly, there is evidence that the variability in effect size between stimulating drugs, along with other aspects such as prolonged action, might be relevant for selecting the drug that best meets the needs of each patient.

Conclusions

There is great variability of the effect of the drugs used to treat ADHD. The efficacy profiles of the short- and long-acting stimulating drugs are not very different according to the clinical trials, though both types of drugs appear to be significantly more effective than the non-stimulating agents. The differences in effect size and other characteristics (fewer daily doses, longer action) result in cost differences when large numbers of patients are treated.

TREATMENT RESPONSE CRITERIA

In order to determine whether a drug is effective, we first must define the short- and long-term objectives for the patient, on an individualized basis.

Methylphenidate traditionally has been the most widely prescribed treatment for ADHD in Europe. Approximately 70% of all patients show a clinical response to MPH, though this includes a small percentage of individuals who are unable to continue the treatment because of adverse effects[13]. Although the MPH response rate is high, the "symptoms normalization" (or complete response) rates are quite low, reaching only 56%[14].

Of the 30% of patients who do not respond to MPH, 80% would respond to amphetamine derivatives, and vice versa, i.e., there is an individualized response profile for some patients. Overall, this means that 90-95% of the patients respond to at least one stimulating drug treatment[15].

As mentioned, the percentage of patients that respond to treatment varies according to the pre-established response criteria. Different authors have proposed the following definitions as ADHD treatment objectives:

- *Syndrome remission*: defined as the absence of diagnostic criteria of ADHD.
- *Symptoms remission*: defined as normalization of the scores of the scales used to measure the symptoms of ADHD, but with persistent executive functional defects.
- *Functional remission (recovery):* defined as normalization of the scores of the scales used to measure the symptoms of ADHD and of the scales used to measure executive function.

In general, ADHD remission can be considered in the presence of a reduction of ≤ 1 in the mean score of the standardized scales used to assess the symptoms of ADHD[16].

If we only consider a percentage decrease in symptoms *versus* baseline (i.e., what we would call response), we may risk classifying highly symptomatic individuals as "responders".

It is therefore difficult to establish what we mean by "response", since this varies according to what we mean by "remission"[17].

From a strictly practical perspective, there are circumstances in which a patient may be considered to show suboptimum response or fail to achieve clinical remission, e.g.:

- No improvement in all or certain functional areas.
- No total or partial clinical normalization.
- No 50% reduction in symptoms after four weeks of treatment with a correct drug dose.
- No clinical improvement evidenced by objective scales.

In addition, apart from the therapeutic outcome in terms of response or remission, there are situations in which a change in treatment must be considered, e.g.:

- When the patient is not satisfied with the treatment and wishes to consider an alternative.
- In the presence of comorbidities that might experience complications due to an ongoing treatment for ADHD that did not take such concomitant disorders into account.
- When treatment coverage is insufficient to ensure

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adequate patient function during certain daily time intervals.

- When failing to reach the pre-established individualized improvement objectives (including middle- to long-term functional deficiencies).

- Moderate side effects that cause patient discomfort and place adherence to therapy at risk.

Lack of adherence secondary to the control of symptoms which the patient or parents regard as a persistent character alteration. This is common in adolescents.

- Need for high medication doses or dose repetition to reach the desired therapeutic effect.

- Patients showing fast drug metabolization.

In view of the above, it would be very useful to estimate beforehand which patients are likely to respond better to a given treatment.

LIMITATIONS OF THE CURRENT DRUG TREATMENTS FOR ADHD AVAILABLE IN SPAIN

Inadequate response

Drug treatment with MPH is the most widely used first line management option for ADHD in Spain, though not all patients respond to or tolerate such treatment. It has been estimated that 30% of all patients do not respond to the first started drug treatment[7].

Psychoactive drugs for ADHD aim to be *effective*, this being understood as a decrease in symptoms and therefore as patient readjustment to daily life under usual conditions not necessarily analogous to those found in clinical trials. The drugs available in Spain for the treatment of ADHD have demonstrated clinical efficacy with an effect size of 1.2 for MPH and 0.8 for atomoxetine, though up to 56% of all treated patients are unable to function normally[14]. While these drug substances usually control the clinically most notorious symptoms, less apparent symptoms or manifestations which nevertheless may be functionally important are often seen to persist. In view of the above, a precise definition of "inadequate response" or "lack of improvement" is particularly important in order to improve the patient prognosis. Although the current ADHD management guides speak of concepts such as "optimum response", "remission" or "normalization of executive function", they do not offer criteria for defining treatment objectives. Furthermore, they do not delimit these concepts as being referred to the short or long term. Specifically, the existing drugs show limited evidence of improvement of executive functions that are very important for patient performance, or do so only in the context of open studies and for certain specific subdomains[18]. Considering the above,

the criteria used to define "improvement" will decide the extent to which a lack of response to the existing treatments may still be high and open to improvement.

Lack of specificity

Although MPH and atomoxetine are effective in application to ADHD, there are no specific indicators regarding the best choice according to a given ADHD phenotype, the severity of the disease, the age group involved, or the presence or absence of certain ADHD symptoms.

Limited methods of administration and interaction with food

An inconvenience of the existing drugs is their formulation limited to capsules and tablets, and their possible interaction with food. Although some formulations can be opened and powdered onto food, no soluble medications are available to facilitate administration in small children or patients with swallowing difficulties.

Lack of uniformity and within- and between-patient consistency

One same drug substance with different formulation characteristics in terms of release and action can result in different treatment responses and different adverse effects, depending on the patient involved.

Lack of adherence to therapy

Although the drugs used are generally safe, effective and well tolerated, certain moderate adverse effects can lead to lessened adherence, particularly among adolescents. Variability in the appearance of adverse effects, which may be conditioned by the different pharmacokinetic characteristics of the different drug formulations, can influence subjective patient or parent perception of the usefulness of the drug and thus affect adherence to therapy.

Limited treatment options

A number of MPH and atomoxetine presentations are currently available. The lack of alternative drug substances sometimes results in the use of drugs not indicated for the treatment of ADHD in the respective Summaries of Product Characteristics. The frequent presence of comorbidities makes it necessary to have new ADHD treatment options that do not have a negative impact upon such concomitant disorders.

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Conclusions

In conclusion, the experts agree that the current limitations for optimum ADHD management include the following:

- Limited treatment options (MPH and atomoxetine)
- Limited specificity for the different ADHD phenotypes
- Functional normalization only in a limited number of ADHD patients
- Partial or no effectiveness in a certain number of patients
- Psychoactive drugs more targeted to ADHD without comorbidities
- Limited evidence (based only on open studies) of effectiveness in application to the cognitive disorders associated to ADHD (executive function) comparable to that demonstrated in nuclear domains by means of psychoactive drugs[19]
- Administration problems in small children
- Treatment adherence problems in adolescents.

REQUIREMENTS FOR OPTIMUM TREATMENT

In sum, the characteristics defining a treatment as optimum for the management of ADHD would be the following:

- Pharmacological efficacy with a tolerability profile acceptable for the patient
- Treatment allowing therapeutic individualization according to the needs of the patient, with efficacy in key moments and for the required period of time
- Uniform action throughout the day
- Easy dosing and administration in order to ensure adequate adherence to therapy
- Little within- and between-patient variability
- Acceptable tolerability with a low potential for abuse
- Acceptable cost.

LISDEXAMFETAMINE DIMESYLATE (LDX)

Current situation and indication

Lisdexamfetamine dimesylate (SPD489/LDX) is a dextroamphetamine prodrug developed for the treatment of ADHD in the form of a single daily dose.

LDX was authorized in the United States in February 2007 for the treatment of ADHD in patients between 6-18 years of age. Posteriorly, the drug was also approved in the United States for the treatment of ADHD in patients between
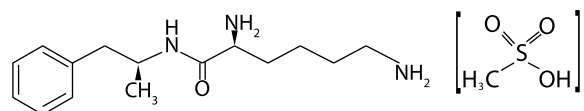
| Figure 2 | Chemical structure of LDX |

18-55 years of age. In February 2009 and July 2010 it was authorized in Canada and Brazil, respectively.

At present, LDX is therefore authorized in children, adolescents and adults in the United States and Canada, and in children in Brazil.

In December 2012, LDX received approval from the European Medicines Agency (EMA) through a decentralized procedure for marketing in the United Kingdom (reference country), Spain, Germany, Sweden, Denmark, Norway, Finland and Ireland, under the brand name ELVANSE®. In May 2014 the product was marketed in the United Kingdom, Denmark, Germany, Ireland, Sweden and Spain.

Information on the drug substance

The active pharmaceutical component of LDX is (2S)-2,6-diamine-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate (Figure 2).

Amphetamines are non-catecholaminergic sympathomimetic amines that exert stimulating action upon the central nervous system (CNS).

Mechanism of action

The activity of the drug is attributable to its capacity to block noradrenalin (NA) and dopamine (DA) reuptake by the presynaptic neuron. Furthermore, and in contrast to MPH, it increases the release of these monoamines into the synaptic gap.

Prodrug technology

A prodrug is a therapeutically inactive molecule that transforms into the active drug through natural processes in the body.

LDX is a pharmacologically inactive prodrug. It consists of dextroamphetamine bound to a lysine amino acid group. Binding to lysine is what causes the molecule to be pharmacologically inactive. Following oral administration, LDX

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Tabla 3	Low within- and between-patient variability of LDX					
	Within-patient		Between-patient		Total	
Parameter	Estimate	95% IC	Estimate	95% IC	Estimate	95% IC
Log $AUC_{0-\infty}$	0.195	(0.164. 0.240)	0.204	(0.139. 0.316)	0.282	(0.238. 0.374)
Log $C_{máx}$	0.215	(0.181. 0.264)	0.163	(0.096. 0.264)	0.269	(0.232. 0.346)

is quickly absorbed in the gastrointestinal tract, and is hydrolyzed in the red blood cells, releasing dextroamphetamine from the lysine group. This form of dextroamphetamine – separated from lysine – is the active form of the drug. The availability of the active form is conditioned by red cell hydrolase saturation capacity.

Homogeneity of action

This mechanism of action prevents the formation of an immediate dextroamphetamine bolus, as occurs upon administering immediate-release formulations or other formulations of dextroamphetamine, or mixed salts of long-acting amphetamines. Long-term release (the duration of action / clinical efficacy being 13 hours after dosing in children and 14 hours in adults) is not achieved by means of any specific drug release technology. This results in very homogeneous action, with a similar effect from the first 90 minutes to 14 hours after administration[20].

Scant between- and within-patient variability

In the pharmacokinetic studies, LDX showed little between- and within-patient variability at the different administered doses. On evaluating different doses (50-250 mg) in different patients, as well as the mentioned dose range in one same patient, variability estimated according to the area under the curve (AUC) and C_{max} was very low in both instances (between 10-20%) (Table 3)[21].

Pharmacokinetics

Following oral administration, LDX is quickly absorbed in the gastrointestinal tract thanks to the transport capacity of protein PEPT1.

The conversion of LDX to dextroamphetamine has no negative effect upon the time to onset of drug action, which is estimated to occur 1.5 hours after administration of the dose.

The presence of food does not appear to exert a substantial effect upon the AUC or C_{max} of dextroamphetamine

following a dose of LDH, though T_{max} is prolonged approximately one hour. After an 8-hour fasting period, the AUCs of dextroamphetamine following the administration of LDX in solution or hard capsule form were found to be equivalent.

LDX is converted to dextroamphetamine and l-lysine in blood as a result of the hydrolytic action of the red cells. Erythrocytes have a great capacity to metabolize dextroamphetamine, as has been demonstrated by *in vitro* studies, even in the presence of very low hematocrit values. LDX is not metabolized by the P450 cytochrome enzyme system.

Special populations

The pharmacokinetic parameters of dextroamphetamine in children (6-12 years) and adolescents (13-17 years) with ADHD are very similar to those observed in healthy adult volunteers.

The systemic exposure to dextroamphetamine is similar in males and females at the same doses (mg/kg).

Clinical development

LDX has been studied in healthy volunteers and in children, adolescents and adults with ADHD. Its efficacy and safety as treatment for ADHD therefore have been well established.

Among the key short- and long-term studies made to demonstrate the efficacy of the drug, mention should be made of the following:

- A European registry in children and adolescents, with follow-up of the remission figures after completing 6 months[22,23].
- Six American registries in children, adolescents and adults[24-26], with the respective follow-up studies[20,27,28].

In addition, other studies have included the determination of effect in a simulated school environment, while others have conducted phase IV post-marketing surveys in

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adults, children and adolescents. Some of these studies are in course.

At present there are 10 clinical trials in course or with a completed recruitment phase, including studies in patients with ADHD and altered executive function, resistant major depression, or eating problems such as binge eating disorder.

Efficacy studies

The efficacy of LDX in the treatment of ADHD has been demonstrated in three controlled trials among children between 6-12 years of age, one study in adolescents between 13-17 years of age, one methylphenidate-controlled study in children and adolescents (6-17 years of age), and four clinical trials in adults meeting the DSM-IV-TR criteria for the diagnosis of ADHD.

In all the clinical trials in children and adults, the effects of SPD489/LDX persisted up to 13 hours after administration in the morning in children, and up to 14 hours in adults.

Analysis of LDX versus placebo and post hoc analysis versus MPH OROS

The European registry was conducted in children and adolescents[22]. The primary objective was to assess efficacy in reducing the symptoms of ADHD *versus* placebo. The primary endpoint (efficacy variable) was the change in score of the ADHD-RS-IV scale. The study involved a randomized and placebo-controlled design with MPH OROS as comparator treatment arm.

- The mean decrease in ADHD-RS score from the start of the study was -5.7 in the placebo group, -24.3 in the LDX group, and -18.7 in the OROS MPH group.
- The decrease in score *versus* placebo was statistically significant for both LDX and OROS MPH (p <0.001).

Low variability in the course of the day

The mean percentage change in the Conners scale for parents from the start of the study to the first evaluation timepoint (10 in the morning) was -50.2% in the LDX group *versus* -10.3% in the placebo group. At 2 in the afternoon the mean percentage change was -50.6% in the LDX group *versus* -11.6% in the placebo group, and at 6 in the afternoon the change was -46% in the LDX group *versus* -7.9% in the placebo group (Figure 3). All of these differences were statistically significant[29].

The effect size was 1.804 for the LDX group and 1.263 for the MPH OROS group.

Improvement of executive function, overall functioning and quality of life

The effect of treatment with LDX upon patient functioning has been estimated based on improvement of clinical global impression (CGI). Statistically significant differences have been observed in different studies, with a large percentage of patients who improved or improved greatly *versus* placebo according to these scales. Specifically, in the European registry, the percentage of patients that "improved" according to the CGI scale was 78% *versus* 61% in the MPH OROS group, and 14% in the placebo series. The differences between the two active treatment groups and placebo were significant[22].

The European registry also recorded statistically significant differences in the WFIRS-P scale referred to the domains affecting family, learning and school, social activities and risk activities between the active treatment groups and placebo[30].

The instrument used to measure quality of life was the CHIP-CE:PRF scale[20]. LDX resulted in improvements in all domains of the scale *versus* placebo[31].
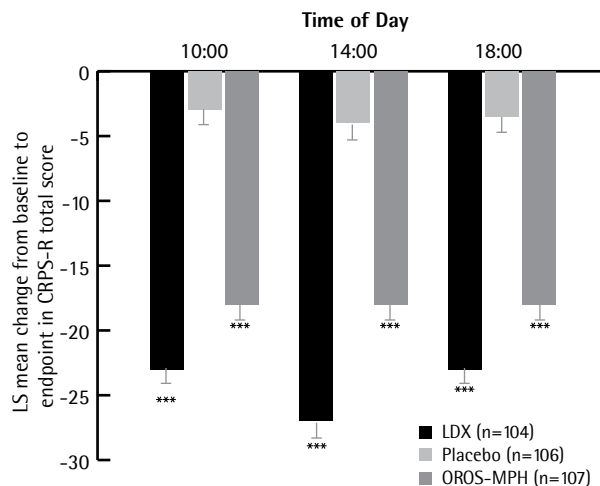
*** $p<0.001$ versus placebo, based on the difference in LS mean change (active treatment-placebo) from baseline to endpoint. A decrease in CPRS-R total score indicates an improvement.

| Figure 3 | Mean least squares adjusted change from baseline to the endpoint in the total CPRS-R score according to the time of day |

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Maintenance of efficacy

A study was carried out for a minimum of 6 months in children and adolescents treated with LDX[31]. A lesser treatment failure rate was recorded for LDX (13.5%) *versus* placebo (65.8%). A two-year safety study is currently being carried out that includes quality of life scales.

Post hoc comparative analysis of LDX versus MPH OROS

Although not the primary objective of the study, a comparative analysis has been made of the efficacy of LDX *versus* MPH OROS in different subpopulations[32].

Efficacy as measured by the ADHD-RS scale shows statistically significant differences on comparing both groups: The decrease in the LDX group was -24.3 *versus* -18.7 in the MPH OROS group, with a difference in effect size of 0.541.

Differences by age groups

This study, which included children (6-12 years of age) and adolescents (13-17 years of age), recorded a greater decrease in the ADHD-RS score in both age groups among those patients treated with LDX. The decrease in score was almost twice as great in the adolescents treated with LDX (-27.5) than in those treated with MPH OROS (-14.3) (*p*<0.001) (Figure 4).[32]

This in turn was accompanied by a marked difference in effect size in both age groups (2.264 in adolescents, *versus* 1.694 in children).

Differences in the severity of ADHD and other markers

A comparison of efficacy was also made according to the severity of the symptoms as assessed by the initial ADHD-RS score, stratifying the patients between lesser severity (baseline score < 42) and greater severity (baseline score 42-54). Efficacy was seen to be significantly greater with LDX than with MPH OROS in both subgroups. The effect size was greater (+0.564) in the LDX group in both the less severe cases (*p*=0.005) and in the more severe cases (+0.586) (*p*=0.007)[33].

Conclusion

In the mentioned study, the improvement among the patients treated with LDX *versus* MPH OROS was not only confirmed by the ADHD-RS scale but also by the CGI-I, the
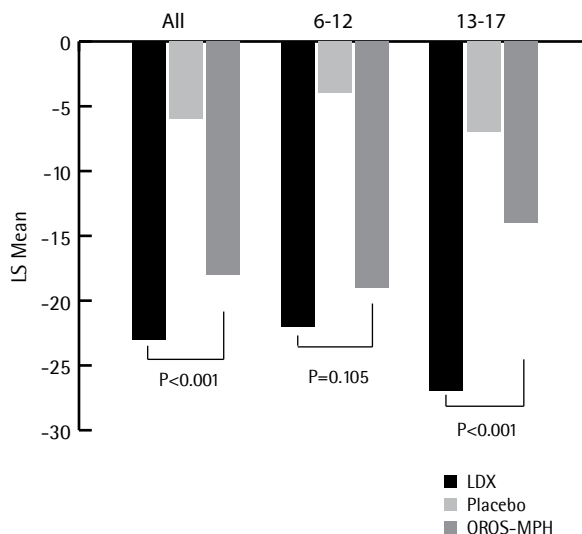
| Figure 4 | Mean least squares adjusted change from baseline in the total ADHD-RS-IV score by age groups |

WFIRS scale (especially in the domains referred to family, learning, social function and risks), and the CHIP-CE scale (achievement, risks, resistance and global).

Efficacy in patients who do not respond adequately to prolonged-release methylphenidate

A *post hoc* analysis of 26 patients who continued to present significant ADHD symptoms despite long-acting methylphenidate found that when treatment with LDX was provided, the clinical response rate was 79.3%[34].

Analysis of LDX versus atomoxetine[35]

This comparative study of LDX *versus* atomoxetine (ATX) was a randomized, controlled, double-blind, parallel groups phase IIIb trial comparing the time to response of LDX *versus* ATX in children and adolescents between 6-17 years of age with ADHD, and who presented an inadequate response to methylphenidate. In assessing inadequate response to methylphenidate, the authors took into account the presence of residual symptoms, inadequate duration of action, variability of the symptoms and the existence of a better treatment alternative according to investigator criterion.

The time to response was significantly shorter among the patients treated with LDX (12 days) than in those
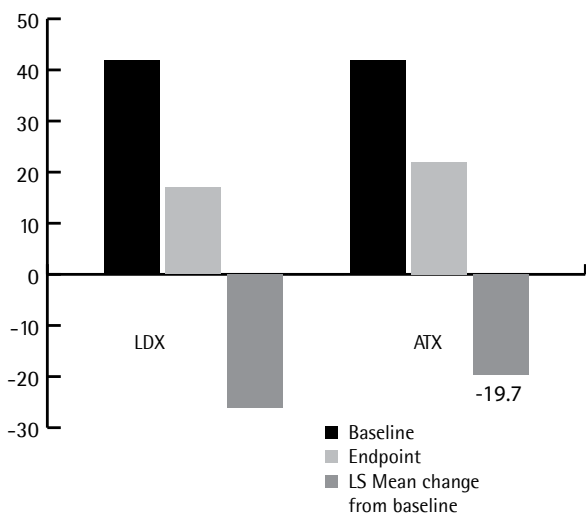
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| Figure 5 | Baseline and endpoint mean scores and mean change after 9 weeks in the LDX (lisdexamfetamine) and ATX (atomoxetine) treatment groups |

administered ATX (21 days) ($p<0.001$).

Among other aspects, the secondary objectives evaluated the number of responders (based on the CGI-I scale) and the number of patients showing improvement according to the ADHD-RS scale.

A statistically significant decrease ($p<0.0001$) was observed in the ADHD-RS scores in the LDX group (-26.1) *versus* the ATX group (-19.7) (Figure 5).[35]

Likewise, the study evaluated the proportion of responders to treatment based on the CGI and ADHD-RS scales. Both scales showed the percentage of responders to be significantly greater in the LDX treatment group.

Experience with LDX according to routine clinical practice

Improved adherence and persistence

LDX thus could be associated to improved adherence to therapy when compared with MPH OROS and atomoxetine. Setyawan et al. compared adherence to therapy in patients with ADHD who had been treated in the United States[36]. A Thomson Reuters® Market Analysis was used to identify the patients with ADHD who had started treatment after the year 2007, which is when LDX was marketed. The study included both naïve and previously treated children, adolescents and adults, and it was seen that with the

exception of the naïve children and adolescents, all the other groups showed significantly better adherence with LDX than with MPH or atomoxetine after 12 months of follow-up.

Likewise, the dropout rate with LDX was lower than with either MPH or atomoxetine[37].

Safety

Safety of LDX in children (6-12 years of age)

The short-term adverse effects, reported in the aforementioned LDX-325 study[22], are no different from those already known for the stimulating drugs. Previous studies with LDX describe the most common side effects (with an incidence of > 1%)[24]: loss of appetite, insomnia, headache and abdominal pain, together with the reasons leading to withdrawal from the study. In another study, the adverse reactions with a frequency of >5% were likewise loss of appetite, headache, insomnia and abdominal pain[38].

At long term, the findings referred to the QTc interval of the ECG tracing and pulse showed no alterations according to the administered dose or in comparison with other amphetamines[39]. In the comparative study of LDX *versus* MPH OROS[22], the types of effects with a frequency of >5% were similar in both groups, but more frequent among the patients treated with LDX. This may be due to the mechanism of action of the drug, its kinetics, the effect size or the bioequivalences used.

There are cases reported by toxicology centers[40], and other exceptional effects such as alopecia[41] and eosinophilic hepatitis[42].

Conclusions

The "characteristic" adverse effects of psychostimulant drugs are loss of appetite, headache, insomnia and abdominal pain, and tend to improve with continuation of the treatment after the first few weeks and in the course of the subsequent months. Very few adverse effects require treatment suspension. The cardiological effects profile shows LDX to be safe, with no risk of arrhythmias or other cardiac events.

Safety of LDX in adolescents (13-17 years of age)

In comparative studies of LDX *versus* placebo[43], the only significant effects were insomnia, dry mucosal membranes, tension / nervousness and headache, in that order. The cardiovascular effects are those expected of this group of drugs, with a slight increase in heart rate and blood pressure.

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Likewise, no differences in adverse effects are observed in this population group *versus* placebo according to the administered LDX dose[43].

The side effects profile of LDX has been evaluated in relation to the different age groups (children, adolescents and adults)[44], with the already cited results, but with some particularities. As an example, insomnia and abdominal pain are less frequent in adolescents, while adults frequently experience dry mouth and headache. Loss of appetite is similar in all three age groups.

Conclusions

The safety profile of LDX is similar to that of other stimulating treatments for ADHD. As a result:

- It is important to know how to deal with and monitor possible adverse effects such as weight loss, possible slowed growth and loss of appetite.
- Blood pressure and pulse are to be monitored on a regular basis.
- It is important to evaluate patient sleep and to always adopt sleep hygiene measures or the use of melatonin, depending on the clinical characteristics of insomnia.

Potential for stimulants abuse

General considerations

The potential for abuse, misuse and recreational use of stimulating treatments has been extensively studied for MPH and dexamphetamine.

It should be mentioned that the previous studies make no distinction between MPH and the rest of stimulants. In this regard, all stimulants increase the dopamine levels in different areas of the brain, and also in the areas involved in the brain reward circuitry. The reinforcement effect is less pronounced when administration is via the oral route and using sustained-release formulations[12].

The studies of the effect of psychostimulant therapy upon the risk of developing substance use disorders are almost all divided between those studies that observe no relationship and those which report even protective effects[45], particularly during adolescence.

In this sense, prospective studies in patients with ADHD have shown that the use of psychostimulants at an early age does not increase the risk of substance abuse in adult life. Moreover, it is known that the risk of addictive substance abuse in future is greater in patients in which treatment for ADHD is delayed until after 8 years of age versus those who receive treatment at an earlier age.

Only one study has reported an increased risk of developing nicotine dependency in patients treated with psychostimulants *versus* those who do not receive such treatment. Behavioral disorders were more prevalent in the treated patient group. This in itself implies an increased risk, independently of the treatment received or of the presence of ADHD, and might constitute a confounding factor.

Regarding the apparent protective effect of psychostimulant treatment against the development of substance abuse in adolescence, recent studies have reported a decrease in the number of such problems in the four years following the start of treatment. Furthermore, the longer the duration of treatment for ADHD, the lower the percentage of substance use[45]. However, a metaanalysis published in 2013 found the effect to disappear in adult life, with no observed protective or favoring effects[46].

It is considered that although an element of drug misuse exists, it does not constitute an absolute contraindication to starting psychostimulant therapy. It has been found that treatment in patients with ADHD and drug misuse improves the symptoms of ADHD and does not worsen misuse.

Likewise, alcohol and cannabis consumption does not contraindicate psychostimulant prescription. Consensus is lacking in the case of cocaine, since the existence of synergic effects might cause the combination to be hazardous according to documents such as the clinical practice guides[47], although different clinical trials have not found relevant side effects.

Regarding the risk of abuse or misuse, important differences are observed depending on the pharmaceutical form involved, with a strong risk predilection for immediate-release formulations. Most studies show that individuals who misuse psychostimulants are also consumers of other drugs – both legal and illegal – and tend to present concomitant behavioral disorders as well as alterations inherent to substance use. ADHD patients without behavioral disorders or problems associated to substance use usually follow treatment correctly and do not present problems in the form of psychostimulant misuse.

Sustained-release formulations of mixed amphetamine salts have a low addictive risk, though the tablet can be manipulated and powdered for dissolution in drinks or administration via the intranasal route, a situation that strongly increases the reward effect by quickly reaching the brain and sharply increasing the dopamine levels in the reward circuitry[48]. Unmodified dextroamphetamine (DEX), i.e., the d-isomer of the amphetamine, is more potent than the l-isomer in terms of dopaminergic activity. Its intranasal administration triggers dopaminergic activation and a reward effect similar to that of methamphetamine. Oral administration preferentially in sustained-release formulations considerably reduces the reinforcement effect, though some potential effect still exists.

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This does not happen with LDX, which experiences saturation of red cell hydrolysis - thereby ensuring sustained release and a limitation of the effects in overdose. Administration via the oral route is essential for activation of the drug. The dissociation of lysine is not possible through other administration routes that might favor misuse and increase the risk of addiction.

Studies on the potential for abuse with LDX

LDX has been shown to be chemically stable in aqueous solutions and at room temperature. The use of acids, bases or buffers to simulate different pH conditions has found LDX to be stable and very resistant to buffering under mild, moderate and even extreme hydrolytic conditions. Altering the LDX molecule to obtain as best result a poor-quality dextroamphetamine molecule is extremely laborious and costly.

Different preclinical studies in rodents indicate that the stimulating potential of LDX is less than that of dextroamphetamine or methylphenidate. In self-administration rodent models, LDX showed weak reward effects.

Studies have been made to evaluate the potential for abuse of LDX in adults with a history of stimulants abuse. In this respect, the potential for abuse has been observed at supratherapeutic doses[12].

Furthermore, studies have been made to assess the potential for abuse of LDX administered via the intravenous route in adults with a history of stimulants abuse. The authors concluded that the intravenous administration of LDX does not exhibit a potential for abuse as measured by affinity for the drug or its euphorizing effects – in contrast to dextroamphetamine at an equivalent dose (40 mg).

The authors underscored the fact that because of the difficulty of extracting dextroamphetamine from the LDX molecule, this new drug formulation has a lesser potential for abuse via the intravenous route than the other currently available stimulant formulations.

Comparison has been made of the pharmacokinetic profiles after the oral and intranasal administration of LDX in healthy adults. The authors concluded that the oral and intranasal administration of LDX results in systemic exposures to similar dextroamphetamine concentrations[49].

Surveys in the United States through the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System have found the potential for abuse of LDX to be very low, with no observed increments over the years between 2007 and the date of analysis (2011)[50,51].

PERSONALIZATION OF TREATMENT WITH LDX IN ADHD. USE IN CLINICAL PRACTICE

As has been underscored, the personalization of ADHD therapy requires an individualized evaluation of the patient needs. Among other aspects, these needs depend on the objectives defined by both the patient and his or her family. Symptoms improvement may eliminate the need to seek additional benefits that could be obtained with more ambitious treatment goals.

Because of its pharmacokinetic and clinical characteristics, LDX is indicated in patients that show an inadequate response to therapy. As examples, the drug could be useful in:

- Patients that may reach more ambitious goals with a change in treatment.
- The different clinical situations in which the patient fails to respond to MPH or atomoxetine.
- Patients that can benefit from longer drug action (13-14 hours).
- Patients that may benefit from more uniform drug action.
- Patients with a greater intensity of symptoms.
- Patients requiring high doses of the previous treatment, adjusted to body weight and height.
- Patients requiring repeated medication doses.
- Patients who do not tolerate MPH or atomoxetine due to adverse events.

CONFLICT OF INTEREST

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