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EDITORIAL

What value do norepinephrine/dopamine dual reuptake inhibitors have to the current treatment of adult attention deficit hyperactivity disorder (ADHD) treatment armamentarium?

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1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is defined as a persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development. ADHD is the most common neurodevelopmental disorder diagnosed in childhood and persists into adolescence and adulthood in 40%-70% of cases [1].

In adults, hyperactivity usually improves, while executive dysfunctions (such as inattention, disorganization, and impaired working memory), behavioral and emotional impulsivity, and emotional dysregulation (ED) persist or even worsen, resulting in reduced quality of life and impaired interpersonal, occupational, and social functioning.

Additionally, most adults with ADHD have numerous psychiatric comorbidities and complications, such as alcohol/substance use, mood, anxiety, eating, impulse control, and personality disorders [2], which are often the reason why patients seek psychiatric care. In many cases, ADHD symptoms are not even recognized because psychiatric comorbidities complicate the clinical picture, making the diagnostic process more difficult. Finally, in a substantial proportion of cases, psychiatric comorbidity (e.g. a severe psychotic mood episode, severe addictive disorders, etc.) constitutes a therapeutic priority. However, the coexisting symptoms of ADHD can strongly influence the clinical picture and drug response and should always be considered during treatment management.

Although multiple neurotransmitters seem to be involved in the development of ADHD (serotonin, acetylcholine, glutamate, opioids), dopaminergic and noradrenergic pathways are the most investigated. In individuals with ADHD, a general reduction in brain size is observed, particularly in the prefrontal cortex, corpus callosum, cerebellar vermis, caudate nucleus, and globus pallidus, and several symptoms can be traced to deficient dopaminergic and noradrenergic transmission in different brain circuits [3]. In addition, polymorphisms in genes encoding for dopamine D4 and D5 receptors and the dopamine transporter (DAT), causing deficits in dopaminergic transmission, have been associated with ADHD [4], although subsequent large GWAS studies have not confirmed this finding [5].

In youths and adults with ADHD, currently approved pharmacological agents act by increasing catecholaminergic transmission and include stimulant and non-stimulant medications [6]. Psychostimulant agents (i.e. methylphenidate and amphetamines) are the mainstay of ADHD treatment both in pediatric and adult populations, and act as norepinephrine/dopamine dual reuptake inhibitors. On the other hand, most non-stimulant compounds (i.e. atomoxetine, viloxazine) target mostly the noradrenergic system. Nonetheless, atomoxetine also seems to indirectly increase dopaminergic tone in the prefrontal cortex in animal models [7], while viloxazine, which has recently been approved for the treatment of ADHD in children and adolescents, acts as a serotonin and norepinephrine modulating medication [8]. Third-line drugs include alpha 2A-adrenergic receptor agonists (guanfacine, clonidine), bupropion, modafinil, and tricyclic antidepressant (e.g. desipramine, nortriptyline).

2. Summary of the available evidence

Overall, all pharmacological compounds approved for short-term treatment of ADHD in children and adolescents can also improve clinical symptoms and executive functions in adult subjects. However, they appear to be less effective than in pediatric populations [9], particularly with regard to some drugs; this may also reflect the inadequate dosing used in some adult studies. For example, lisdexamfetamine has shown particular efficacy in clinical trials in adult populations.

All guidelines agree that stimulants, i.e. amphetamines and methylphenidate, especially in ER formulations, are first-choice treatments [6,9]. However, psychostimulants are either ineffective or poorly tolerated in 30–50% of adults with ADHD [10]. Given their addictive properties, stimulants are associated with a significant risk of long-term misuse, especially in individuals with a history of stimulant/cocaine abuse.

For ADHD in adults, bupropion is considered a third-line agent. Given its low abuse potential, bupropion may have

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a role in treating ADHD individuals with comorbid substance use disorders (SUD); it also seems to be useful for the treatment of comorbid depressive episodes [10].

2.1. Methylphenidate and dexmethylphenidate

The main mechanism of action of methylphenidate is the inhibition of DAT and norepinephrine transporters (NET), as well as acting as a 5HT1A receptor agonist, remodulating the distribution of VMAT-2, and probably interacting directly as a catecholaminergic agonist, generating an increase in catecholaminergic availability in the synaptic terminal [11].

Methylphenidate is considered a first-choice treatment for ADHD in both children and adults [9,12]. It is currently available in immediate-release (IR) and extended-release (ER) formulations. Most newer ER formulations include varying proportions (22–50%) of IR component to ensure both rapid onset of action and symptoms control for at least 8 hours, allowing for a single daily administration in the morning [13].

Clinical trials have shown greater efficacy of methylphenidate than placebo for the treatment of ADHD in adults [9]. However, despite its wide use in clinical practice, the evidence in adults is very low for the ER formulation and uncertain for the IR formulation, especially in the long-term [14]. Presumably, these unsatisfactory results are due to the paucity of clinical trials, limited samples, short-term follow-up and inadequate dosing of stimulants in adults. In addition, no studies compared the efficacy between IR and ER formulations, nor between the different ER agents. Treatment adherence is generally greater with ER formulations and could represent a positive factor in the ADHD long-term treatment.

Methylphenidate is a racemic mixture; only the enantiomer d-methylphenidate (dexmethylphenidate) possesses intrinsic activity and has been marketed in modified-release tablets [15]. Unfortunately, in Europe, it is available only in Switzerland. Its efficacy in reducing ADHD symptoms in adults was confirmed in a single 5-week randomized clinical trial, in which dexmethylphenidate also showed good tolerability. However, the study excluded subjects who had a previous poor response to stimulants. Dexmethylphenidate has not been compared with methylphenidate in adults; in children and adolescents, the two drugs showed equivalent efficacy.

2.2. Amphetamines

Amphetamines primarily act by inhibiting the reuptake of dopamine and norepinephrine through inhibition of DAT and NET. They also increase dopaminergic and noradrenergic transmission through inhibition of the vesicular monoamine transporter (VMAT-2), inhibition of catechol-methyltransferase (COMT), reduction in cytosolic monoamine oxidase (MAO) catabolism, and stimulation of the trace amine-associated receptor 1 (TAAR1) [11,16,17]. In addition, amphetamine-induced NET blockade in the prefrontal cortex, resulting in increased noradrenaline levels and alpha-1 receptor activation, appears to change the firing pattern of dopaminergic neurons in the ventral tegmental area that project to the nucleus accumbens [18]. Finally, amphetamines also appear to affect the glutamatergic, opioid and cholinergic systems [11].

Considering both efficacy and safety, evidence from clinical trials and a recent meta-analysis suggests the use of amphetamines, including lisdexamfetamine, as first-choice drugs for short-term treatment of ADHD in adults [9,19–21]. Indeed, in the U.S.A., amphetamines are more widely used than methylphenidate in adult ADHD [16]. However, clinical trials include only short-term follow-up investigations, not allowing the evaluation of the amphetamine efficacy and tolerability in the medium- and long-term treatment.

2.3. Bupropion

Bupropion is an antidepressant structurally similar to amphetamines; it acts primarily through inhibition of dopamine and norepinephrine reuptake, while also impacting the cholinergic system through a noncompetitive antagonistic action on nicotinic receptors [22].

The efficacy of ER bupropion in improving ADHD symptoms in adults was found to be superior to placebo, but inferior to stimulants [10]. This could be due to the lower DAT receptor occupancy of bupropion compared to methylphenidate (20% and more than 50%, respectively) [10]. Some evidence suggests an increased efficacy for dosages above 300 mg/day [14]. The tolerability profile of bupropion is well documented, although the risk of drug-induced seizures should be carefully evaluated.

3. Expert opinion

Medications increasing dopaminergic and noradrenergic transmission are widely used to treat ADHD in youths, but their efficacy and safety in adults are still uncertain. In particular, none of these drugs have been tested in long-term clinical trials, not allowing their long-term effectiveness to be clarified. In addition, individuals with ADHD whom psychiatrists deal with in routine clinical practice, who often have several psychiatric comorbidities and reduced adherence to treatment, are usually excluded from clinical trials.

Most adult individuals with ADHD present with severe ED and multiple comorbid psychiatric disorders that complicate the clinical picture and treatment management [2]. Moreover, comorbidity with SUD is very common and often interferes with the use and efficacy of stimulant drugs.

Several studies and meta-analyses have suggested that methylphenidate is effective in controlling ED [23]. Unfortunately, data are difficult to interpret in adult populations due to the lack of homogeneity in ED assessment and the frequent presence of affective comorbidities. Amphetamines have been less studied than methylphenidate for the treatment of ED in adults with ADHD [23]. Therefore, methylphenidate should be preferred in patients with clinically relevant ED. Regarding the possible use of mood stabilizers, lithium seems to have a similar effect as methylphenidate in reducing mood reactivity and instability, irritability, and hyper-arousal in adults with ADHD [24]. Therefore, in cases of severe ED or comorbidity with bipolar disorder, lithium-methylphenidate combination should be considered. Methylphenidate and bupropion do not appear to cause (hypo)manic switch or mood destabilization in ADHD patients with bipolar comorbidity [25].

Both stimulants and bupropion can increase anxiety and psychosis [10,11,26]. In ADHD subjects with comorbid anxiety disorders, valproate should be preferred over lithium. In addition, stimulants can be combined with selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), although in ADHD subjects, these medications have been poorly investigated. When an exacerbation of psychotic features occurs, stimulants should be discontinued and possibly reintroduced after an adequate period (months) of remission. The combination of antipsychotics and stimulants should be limited to patients with severe agitation and aggression. Indeed, a stimulant-antipsychotic syndrome has been described as a long-term consequence of this drug combination [26].

Finally, the use of stimulants in comorbid ADHD and SUD has always been challenging because of the presumed risk of misuse, especially in adults [27]. The latter is less common with methylphenidate than with amphetamines. Several studies have shown greater efficacy of long-acting methylphenidate at high doses in controlling ADHD symptomatology in these subjects, although other studies have pointed to a therapeutic benefit of mixed amphetamines combined with cognitive behavioral therapy in reducing ADHD symptoms and cocaine use [27]. Certainly, early recognition of ADHD in children/adolescents, associated with timely psychopharmacological treatment, reduces the incidence and consequences of SUD.

Larger randomized clinical trials and naturalistic studies with longer follow-ups are needed to better define the long-term efficacy and safety of norepinephrine/dopamine dual reuptake inhibitors, especially in subjects with comorbid SUD.

Declaration of interest

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