CLINICAL INVESTIGATION

EDITORIAL

Clin. Invest. (2013) 3(9), 803–805

Adult ADHD: an area lacking in clinical research?

Josep Antoni Ramos-Quiroga*[1,2,3] & Miren Ochoa Sagüés[4]

"...attention-deficit/hyperactivity disorder is one of the most common disorders in adults and is estimated to affect between 2–5% of the general adult population."

[1]Adult ADHD Program, Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[2]Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain
[3]Department of Psychiatry & Legal Medicine, Universitat Autònoma de Barcelona, Spain
[4]Departament de Farmacologia, de Terapèutica i de Toxicologia, Universitat Autònoma de Barcelona, Spain
*Author for correspondence:
Tel.: +34 93 489 42 94
Fax: +34 93 489 45 87
E-mail: jaramos@vhebron.net

Attention-deficit/hyperactivity disorder (ADHD) is characterized by damage of neurodevelopment, manifested in the form of excessive inattention and/or hyperactivity and impulsivity, as well as a lack of emotional self-control and motivation [1]. It is a chronic disorder of childhood onset and one of the most common psychiatric disorders worldwide within this stage of life (5–6%) [2].

During the last 40 years we have seen that a significant proportion of the affected children continue displaying symptoms throughout adulthood. Several international epidemiological studies, carried out in different cultures and socioeconomic environments, have shown that ADHD is one of the most common disorders in adults and is estimated to affect between 2–5% of the general adult population [1].

Studies on adults with ADHD have shown that its presence is associated with a significant impairment on academic achievement, work adjustment, interpersonal relationships, drug use, greater frequency of traffic accidents and crime problems [1,3]. Nowadays, evolutionary studies are available with over 30 years of monitoring [4,5]. Moreover, many genetic and neuroimaging studies have been performed that show differences between adults diagnosed with ADHD and those without. Regarding genetic research, differences have been found in the serotonergic and dopaminergic system, neurotrophic factors, the SNARE complex and the gene *latrophilin-3*, among others [6]. Similarly, neuroimaging studies have shown brain abnormalities at the structural, functional and connectivity level [7]. These findings have been mainly observed in the inferior frontal cortex and dorsolateral prefrontal, as well as striatal regions, anterior cingulate and cerebellar parietotemporales [7,8].

The diagnosis of ADHD in adults has been reflected in international diagnostic classifications since DSM-III, in 1980, which reported that the disorder can persist into adulthood for some of the affected children. The new version, DSM-V, makes even more explicit references to the progression of ADHD into adulthood, adapting the current criteria to the disorder's evolutionary reality [3]. At present, there are reliable psychometric instruments for diagnostic assessment of ADHD in adults, as in other psychiatric disorders for this population, such as bipolar disorder or schizophrenia [1,3].

Therefore, from the current research, ADHD in adults has good evidence based on epidemiological, genetic, neuroimaging, clinical characteristics, psychosocial impairments and diagnostic instruments. Despite the data presented above, ADHD remains an underdiagnosed disorder in adults worldwide [1,3,9,10]. This situation is common to other psychiatric disorders beginning in childhood, such as autism. As a result, there is an undertreatment of ADHD in adulthood, which has major societal and personal costs [11].

Keywords: ADHD • adults • amphetamine • atomoxetina • clinical trial • methylphenidate • multimodal treatment • time series

ISSN 2041-6792 10.4155/CLI.13.69

This situation is surprising given the positive outcomes obtained from clinical trials in adults with ADHD employing different therapeutic techniques. A multimodal treatment approach that addresses adult ADHD in the treatment plan and involves the patients' partners and family members is recommended [1,3]. The multimodal treatment approach should include psychoeducation, pharmacotherapy, and disorder-oriented psychotherapy for ADHD, including family or couple therapy if needed.

There have been many more clinical trials evaluating the efficacy and safety of the drugs used in ADHD treatment on children than adults. This situation is quite rare in terms of drug research overall, because there are more data available for adult populations. Nevertheless, there are now randomized, placebo-controlled clinical trials and meta-analysis showing the effectiveness and safety of stimulant drugs (methylphenidate and amphetamines) and nonstimulants (atomoxetine) for adults with ADHD [12–14]. Atomoxetine is currently the only nonstimulant medication for ADHD with regulatory approval in adult patients. There have been randomized clinical trials that evaluate the efficacy and safety of atomoxetine and methylphenidate up to 1 year and 6 months, respectively [15,16].

It is important to highlight the positive impact of ADHD treatment for adults regarding aspects of their daily functioning. Indeed, a recent investigation based on large population registries concluded that such medications reduce criminality [17]. Another recent revision shows that research using self-reported scales indicates that stimulant treatment leads to measurable improvement in daily functioning of adults with ADHD [18].

"There have been many more clinical trials evaluating the efficacy and safety of the drugs used in attention-deficit/hyperactivity disorder treatment on children than adults. This situation is quite rare in terms of drug research overall, because there are more data available for adult populations."

The cardiovascular safety of stimulant medications and atomoxetine has been the subject of debate over recent years. It is noteworthy that this controversy has occurred for drugs such as methylphenidate, which has been on the market for over 50 years. Recent cohort studies did not find an increase in serious cardiovascular events following ADHD medications in children and adults, although stimulants and atomoxetine are associated with slight increases in heart rate and blood pressure [19,20]. For that reason, it is important to monitor these heart parameters during treatment when using stimulants or atomoxetine.

Although the investigation of adult ADHD has experienced a significant improvement since the 1970s, there are a several areas where more research is required. One of them is the performance of clinical trials comparing different treatments (pharmacological or psychological) face-to-face. At the same time, it is necessary to improve the external validity of these studies. Most of the clinical trials are pivotal studies to reach the drugs indication on adults. These used a very restrictive inclusion and exclusion criteria with a low external validity. It is necessary to increase the number of longitudinal naturalistic studies with the same profile of patients that are in habitual clinical settings. The presence of other psychiatric disorders, together with ADHD is a common occurance in adult ADHD, but there are few clinical trials that systematically assess the efficacy and safety of the treatments with comorbid disorders. The exception is the comorbidity with substance use disorders, since the number of clinical trials examining this scenario has increased during the last years [1]. Regarding the principal variables used in clinical trials, it could be useful to introduce strong variables such as academic work, driving performance or criminality more often, rather than the final result of scales *per se*. Recent studies incorporating these variables have obtained interesting results [17]. On the other hand, as has already been stated, ADHD is a chronic disorder and patients are required to take ADHD medication for years. Nonetheless, only atomoxetine has a controlled study in adult patients up to 1-year of follow up [16]. More independent, long-term studies are required. The prediction of treatment–response or the presence of secondary effects with pharmacogenetic studies can be of utility in daily clinical practice. However, the number of these studies is scarce on adults with ADHD. Finally, it is known that around 30% of ADHD patients do not respond to the actual treatments [3]. It is essential to investigate new pharmacological targets beyond the dopaminergic and noradrenergic systems.

Financial & competing interests disclosure

JA Ramos-Quiroga has served on the speakers' bureau and/or served as consultant for Eli Lilly and Co., Janssen-Cilag, Novartis, Almirall, Shire and Rubio'. JA Ramos-Quiroga has received travel awards for taking part in psychiatric meetings from Janssen-Cilag, Shire, Rubio', and Eli Lilly and Co. The attention-deficit/hyperactivity disorder program, chaired by JA Ramos-Quiroga has received unrestricted educational and research support from Eli Lilly and Co., Janssen-Cilag, Shire and Rubio'. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Kooij SJ, Bejerot S, Blackwell A *et al.* European consensus statement on diagnosis and treatment of adult ADHD: the European Network Adult ADHD. *BMC Psychiatry* 10, 67 (2010).

2 Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am. J. Psychiatry* 164(6), 942–948 (2007).

3 Ramos-Quiroga JA, Montoya A, Kutzelnigg A, Deberdt W, Sobanski E. Attention deficit hyperactivity disorder in the European adult population: prevalence, disease awareness, and treatment guidelines. *Curr. Med. Res. Opin.* doi:10.1185/03007995.2013.812961 (2013) (Epub ahead of print).

4 Klein RG, Mannuzza S, Olazagasti MA *et al.* Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Arch. Gen. Psychiatry* 69(12), 1295–1303 (2012).

5 Biederman J, Petty CR, Monuteaux MC *et al.* Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. *Am. J. Psychiatry* 167(4), 409–417 (2010).

6 Franke B, Faraone SV, Asherson P *et al.* The genetics of attention deficit/hyperactivity disorder in adults, a review. *Mol. Psychiatry* 17(10), 960–987 (2012).

7 Ramos-Quiroga JA, Picado M, Mallorqui-Bague N *et al.* The neuroanatomy of attention deficit hyperactivity disorder in adults: structural and functional neuroimaging findings. *Rev. Neurol.* 56(Suppl. 1), S93–S106 (2013).

8 Proal E, Reiss PT, Klein RG *et al.* Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Arch. Gen. Psychiatry* 68(11), 1122–1134 (2011).

9 Aragones E, Lluis Pinol J, Ramos-Quiroga JA, Lopez-Cortacans G, Caballero A, Bosch R. Prevalence in adults of attention deficit hyperactivity disorder using the medical records of primary care. *Rev. Esp. Salud Publica* 84(4), 417–422 (2010).

10 Kessler RC, Adler L, Barkley R *et al.* The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am. J. Psychiatry* 163(4), 716–723 (2006).

11 Kessler RC, Lane M, Stang PE, Van Brunt DL. The prevalence and workplace costs of adult attention deficit hyperactivity disorder in a large manufacturing firm. *Psychol. Med.* 39(1), 137–147 (2009).

12 Castells X, Ramos-Quiroga JA, Rigau D *et al.* Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. *CNS Drugs* 25(2), 157–169 (2011).

13 Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. *Cochrane Database Syst. Rev.* 6, CD007813 (2011).

14 Michelson D, Adler L, Spencer T *et al.* Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol. Psychiatry* 53(2), 112–120 (2003).

15 Rosler M, Fischer R, Ammer R, Ose C, Retz W. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 259(2), 120–129 (2009).

16 Upadhyaya H, Adler LA. Maintenance of response after open-label treatment with atomoxetine hydrochloride in international European and non-European adult outpatients with attention-deficit/hyperactivity disorder: a placebo-controlled, randomised withdrawal study. *Eur. J. Psychiat.* (2013) (In Press).

17 Lichtenstein P, Halldner L, Zetterqvist J *et al.* Medication for attention deficit-hyperactivity disorder and criminality. *N. Engl. J. Med.* 367(21), 2006–2014 (2012).

18 Surman CB, Hammerness PG, Pion K, Faraone SV. Do stimulants improve functioning in adults with ADHD? A review of the literature. *Eur. Neuropsychopharmacol.* 23(6), 528–533 (2013).

19 Cooper WO, Habel LA, Sox CM *et al.* ADHD drugs and serious cardiovascular events in children and young adults. *N. Engl. J. Med.* 365(20), 1896–1904 (2011).

20 Habel LA, Cooper WO, Sox CM *et al.* ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 306(24), 2673–2683 (2011).