EXPERT REVIEWS

Addressing the lack of studies in attention-deficit/ hyperactivity disorder in adults

Josep Antoni Ramos-Quiroga*[1–3], Viviana Nasillo[1,2,4], Fernando Fernández-Arana[5–7] and Miguel Casas[1–3]

[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 and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[4]Department of Psychology, Universitat Autònoma de Barcelona, Barcelona, Spain
[5]Department of Psychiatry, University Hospital of Bellvitge-IDIBELL, Hospitalet del Llobregat, Barcelona, Spain
[6]CIBEROBN, Hospitalet del Llobregat, Barcelona, Spain
[7]Universitat de Barcelona, Barcelona, Spain
*Author for correspondence:
Tel.: +34 934 894 294
Fax: +34 934 894 587
jaramos@vhebron.net

Attention-deficit/hyperactivity disorder (ADHD) is commonly known to occur during childhood, characterized by excessive inattention and/or hyperactivity and impulsivity as well as lack of emotional self-control and motivation. The prevalence of adult ADHD in the general population is estimated to be between 2–5%. The aim of this review is to provide an overview regarding current controversies related to ADHD within the adult population. The concept of ADHD in adults has been questioned and criticized by professionals over the last years. Overall, adult ADHD is well evidenced based on epidemiological data, genetic data, neuroimaging, psychosocial impairment and treatment effectiveness. Although, research within this field has been significantly improved, suggestions for future research are provided, in order to be able to clarify the remaining questions regarding this disorder throughout adulthood. One of the most important changes to be made in the near future should be to increase educational training on ADHD in adults.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by neurodevelopmental damage, manifested in the form of excessive inattention and/or hyperactivity and impulsivity as well as lack of emotional self-control and motivation [1]. ADHD is a disorder that typically begins at childhood, with chronic evolution in main parts of the patient's body. A significant number of affected children continue manifesting symptoms throughout adulthood [2]. First clinical descriptions of attentional disorders were described by the German physician Melchior Adam Weikard in 1775 [3]. The persistence of ADHD symptoms into adulthood was first recognized in the 1970s and thereafter included as a diagnosis in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980 [4]. The number of studies focused on ADHD in adults made important advances from the 90s. Several studies have shown in large samples, the persistence of such symptoms during adulthood as well as functional neuroimaging studies, the specific symptomatology, negative impact and treatment in adulthood [5–11].

Overall, during the last 40 years, there has been an increasing level of evidence that ADHD affects adults [1,12]. Nevertheless, there are controversial opinions about the concept of ADHD, especially regarding its persistence into adulthood [13–15]. Much of the evidence to date suggests that among adolescents and adults, ADHD is underrecognized and undertreated [16–19]. However, some researchers have argued that ADHD may be overdiagnosed [15,20]. The aim of this review is to provide an overview of the controversies related to ADHD in adults. In addition, suggestions for future research that could perhaps clarify these remaining points are provided.

Epidemiological studies
General population
Research in adults with ADHD hold less epidemiological data compared with the large number of studies carried out within child population samples. However, from the results of the National Comorbidity Survey Replication (NCS-R), it has been estimated that

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4.4% of the general adult population met the DSM criteria for ADHD [16]. The NCS-R also had reported the prevalence of ADHD throughout lifespan, where 8.1% of adult subjects met the diagnostic criteria. The initial study sample included a total of 9282 US adults from general population, where those between 18 and 44 years were selected for a screening of ADHD (3199 subjects) using the adult self-report scale. A total of 154 individuals were randomized according to the result obtained at screening, where an estimate of the prevalence of ADHD in the total sample from the latter clinical evaluations was obtained. The results of the NCS-R are comparable with the 3.4% obtained in a study promoted by WHO [21]. The latter involved a total of 11,422 subjects from the general population from different countries including Germany, Belgium, Colombia, Spain, the USA, France, Italy, Lebanon and Mexico, aged between 18 and 44. The prevalence of this disorder ranges between 1.2 and 7.3%. However, it is interesting to note that the average prevalence within the most economically developed countries was 4.2%, a result very similar to the NCS-R. In another study with a sample of 7075 workers (employees or self-employed), the prevalence of ADHD was reported to be around 3.5% [22]. In this work, the frequency of the disorder was higher among men and employees than women and self-employed.

Prior to the publication of these three large epidemiological studies of ADHD in adulthood, there had been similar prevalence figures, close to those reported by the NCS-R or WHO studies. Even though different research designs were used, there were larger methodological limitations. The prevalence of ADHD in adults was estimated taking into account two sets of data, the occurrence of the disorder in childhood and the rate of progression to adulthood. Thus, it was considered that if 5–8% of school children had ADHD and that the disorder persisted in at least 66% of those subjects to adulthood, the prevalence at this stage of life could be around 3.3–5.3% [23]. But this strategy also led to erroneously consider that ADHD in adults was a rare disorder with a low frequency within general population [9]. This study reported that ADHD had a lower prevalence of 0.002% in adults older than 30 years. However, Hill and Schoener did not consider the evolving nature of the disorder and possible bias in the detection of symptoms depending on the source of information [9].

In the late 90s, different epidemiological studies on adults from the general population were published, but unfortunately much smaller in sample size in comparison to the two aforementioned studies. A study recruited a total of 720 adults (aged between 18 and 84) who came to renew their driving license. Their results surprisingly showed a prevalence of ADHD of 4.7% according to DSM-IV [24]. Studies with samples of college students showed similar figures, where 2.5 and 4% presented ADHD, depending on the methodology used [25–27]. The first European study was conducted in the Netherlands, where a sample of 1813 adults within the general population was assessed for the presence of ADHD [28]. Two cutoffs points were considered in order to estimate the actual prevalence of this disorder. The first was the presence of six or more symptoms of inattention or hyperactivity-impulsivity and the second, the presence of four or more symptoms, reporting prevalence between 1.0 and 2.5%, respectively for each cutoff point. Both breakpoints were also associated with a greater psychosocial dysfunction. De Zwaan et al. found a prevalence of 4.7% in a large representative sample of the German population aged 18–64 (1655) [29]. Moreover, a meta-analysis of studies has been published regarding prevalence of ADHD in adults, yielding an average of 2.5% within the general population [30]. Simon et al. concluded that this prevalence may be too restrictive given that generally speaking the DSM-IV criteria have a tendency toward underestimating ADHD diagnosis in adults. One limitation of the epidemiological studies in adults with ADHD is that a great number of the studies are based on young or middle-aged adults, whereas little is known about ADHD in older age population. Three studies in the general population included participants older than 60 and one study assessed the prevalence of ADHD in older adults up to 94 years [28,31,32]. Michielsen et al. [31] found an ADHD prevalence of 2.8% in older adults [31]. Table 1 shows the results of the main epidemiological studies for non-clinical population.

In terms of gender, prevalence of adult ADHD has been reported to be more common in men than women, but this difference seems to be much smaller than those reported during childhood. In adults, it has been observed that the male-female ratio is 1:6 [16,21,22], whereas in children it varies between 3:1 and 9:1 [1]. In infant non-clinical population samples, it has been estimated with the use of meta-analysis that the prevalence is 2.45-times higher in boys than girls [33]. The disparity in gender differences in children versus adults could be explained by the fact that a few females, not correctly diagnosed during childhood, received their first diagnosis of ADHD when they had become adults. On the other hand, the literature did not find a stronger remission of ADHD in males with regards to females [34,35]. Nevertheless, symptoms of hyperactivity/impulsivity remained relatively stable from adolescence through young adulthood for both girls and boys, describing a higher declination of these symptoms in adulthood. Some authors have hypothesized that the reasons for these differences between the sexes could be explained by the fact that ADHD symptoms in boys may be more sensitive to developmental changes [9,34]. More studies are needed with the aim to further evaluate this issue.

The influence of ethnic and socioeconomic status regarding prevalence of adult ADHD has been much less studied [33]. The NCS-R has reported that the frequency of the disorder is higher in white participants and Hispanics than non-Hispanic or African Americans. However, it is known that ADHD is associated with less academic achievement compared with subjects without ADHD within the WHO study [4,16,21,36,37].

Table 1. Main prevalence studies of attention-deficit/hyperactivity disorder in non-clinical populations.

Author	Sample size	Population	Prevalence (%)	ADHD criteria	Ref.
Weyandt et al. (1995)	770	Students	2.5	DSM-IIIR	[27]
Murphy and Barkley (1996)	720	Drivers	4.7	DSM-IV	[24]
Heiligenstein et al. (1998)	448	Students	4.0	DSM-IV	[26]
DuPaul et al. (2001)	1209	Students	2.9–3.9[†]	DSM-IV	[25]
Kessler et al. (2006)	3.199	General population	4.4	DSM-IV	[12]
Kooij et al. (2005)	1.813	General population	1.0–2.5	DSM-IV	[28]
Fayyad et al. (2007)	11.422[‡]	General population	3.4	DSM-IV	[21]
De Graaf et al. (2008)	7.075	Employed	3.5	DSM-IV	[22]
Michielsen et al. (2012)[§]	1.494	General population	2.8	DSM-IV	[31]

[†]2.9% males and 3.9% females.
[‡]This study includes participants from Kessler et al., 2005 research.
[§]General population with age between 60 and 94 years.
ADHD: Attention-deficit/hyperactivity disorder; DSM: Diagnostic and statistical manual of mental disorders.

Clinical population

The prevalence of ADHD in adults is significantly higher within clinical samples compared with the results obtained from studies within the general population. In patients attending an outpatient basis for psychiatric disorders other than ADHD, excluding patients with psychotic psychopathology, a frequency of 16.8% for ADHD has been observed [38]. Other authors have reported that 12% of adult patients who suffer from major depressive disorder also presented comorbidity with ADHD [39]. Studies in adults with substance use disorders (SUDs) have also shown a higher prevalence of adult ADHD compared with the overall population [40]. In a more recent meta-analysis by Van Emmerik-van Oortmerssen et al. based on 12 studies of adult patients seeking SUDs treatment, the pooled ADHD prevalence rate was 23.3%, ranging from 10 to 54.1% for single studies [41]. In the first multinational study on the prevalence of ADHD in treatment-seeking SUD adult patients, based on the DSM-IV criteria, adult ADHD varied between countries, from 5.4% (95% CI: 2.4–8.3) in Hungary to 31.3% (95% CI: 25.2–37.5) in Norway [42].

In adult patients with bipolar disorder, it has been observed that the prevalence of adult ADHD reaches 16.3% [43]. Moreover, when examining comorbidity within Axis II disorders, women with borderline personality disorder were found to present a prevalence of ADHD combined subtype between 16.1% (when excluding inattentive and hyperactive-impulsive subtypes) and 38.1% (when including males and females) [44,45]. Greater clinical severity was presented in those patients with comorbidity of personality disorder and ADHD, replicating the same prognosis for patients with eating disorders, like bulimia nervosa [44–46].

Over the last decades, several studies have explored the prevalence of ADHD among adult prisoners [47,48]. After using specific screening instruments for the assessment of ADHD, these studies reported consistently that childhood ADHD among adult inmates ranges between 24 and 67%, and adult inmates with current ADHD ranges between 13 and 45%; being even a higher prevalence among the youth offender population [47,48].

Genetics & neuroimaging data

The genomic revolution developed over the recent years has provided a wealth of genetic information, expanding knowledge regarding complex disorders such as ADHD. Although there have been multiple studies on the genetics of this disorder, currently the exact causes are unknown and it has been accepted that ADHD is a complex disorder where both environmental factors explain 20–30% of the observed phenotypic variability involved, and genetic risk factors could explain 70–80% of the rest of the variability [49]. Family, twin studies and adoption studies have estimated an average heritability of ADHD of 76% [50]. Although there have been numerous molecular studies that focused on adult ADHD, results were similar to those obtained in genetic studies with children and adolescent samples. In others, the findings were not in concordance [49]. There can be a possibility that symptoms in adult ADHD are persistent throughout life, while in studies with children there are greater heterogeneity among the samples, including children with ADHD who will continue to have the disorder throughout adulthood compared with those who will not. Therefore, it is probable that the biological basis may be different between that ADHD persists and enclosing disorder. In this aspect, there is a lack of prospective study assessing the genetic factors in subjects with remittent ADHD and persistent ADHD in adulthood. Thus, our research group has found common genetic susceptibilities between adults and children with ADHD to the dopaminergic system, serotonergic and neurotrophic factors as well as specific variants for persistent ADHD [51,52]. An example of common genetic susceptibility to ADHD in both children and adults is the gene coding for the latrophilin-3 receptor (LPHN3) [53,54].

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The function of this gene is still not well understood, but recent studies indicate that LPHN3 and its ligand fibronectin leucine-rich repeat transmembrane-3 play an important role in glutamatergic synapse development, a role in development and/or regulation of monoamine signaling and the LPHN3 gene impacts behavioral and neurophysiological measures of cognitive response control [55,56]. Animal model studies have provided more knowledge regarding the role of LPHN3. A study with Zebrafish showed that LPHN3 controls locomotor activity and impulsivity [57] and mice mutant for the *Lphn3* gene had a hyperactive phenotype in the open field test and were more sensitive to the locomotor stimulant effects of cocaine [58]. On the other hand, LPHN3 is expressed in brain regions related to attention and activity. LPHN3 has been related with frequent ADHD comorbidities, such as dyslexia and SUDs [58,59]. Most importantly, the same variant associated with ADHD susceptibility was also associated with the response to stimulant medication [53]. The studies that focus on LPHN3 and ADHD across lifespan susceptibility are a good example of translational research and the efforts that independent research make to obtain a clearer understanding of ADHD. Nevertheless, more research is needed in the genetics field of adults with ADHD. In order to have enough statistic power, it is necessary to perform genome-wide association study that includes samples with around 30,000 adult subjects, like other psychiatric disorders. More studies are needed to focus on the interaction of genetic and environmental factors in adults with ADHD.

Neuroimaging studies conducted in adults with ADHD have shown alterations in the brain at the structural and functional levels, and also in terms of connectivity [4,60]. These findings have been observed mainly in the inferior frontal and dorsolateral prefrontal cortex, as well as in striatal, anterior cingulate, parietotemporal and cerebellar regions [60]. A meta-analysis of task-based functional MRI studies, which included 16 studies with adults, found that ADHD-related hypoactivation was predominant in the frontoparietal system, while ADHD-related hyperactivation was present in the visual, dorsal attention and default networks [61]. A recent study with diffusion tensor imaging at 33-year follow-up of a sample of boys with ADHD showed that decreased fractional anisotropy, a diffusion tensor imaging index related to white matter structural properties, in adults with childhood ADHD regardless of current ADHD might be an enduring trait of ADHD [62]. These results are in line with previous studies carried forward by the same group, reporting anatomic gray matter reductions in adults with childhood ADHD (33-year follow-up), regardless of the diagnosis at the time of evaluation [63]. The most affected regions in this study are involved in the control of attention and regulation of emotion and motivation. Interestingly, the authors suggested that diagnostic remission may result from compensatory maturation of prefrontal, cerebellar and thalamic circuitry [63]. Shaw *et al.* demonstrated in a longitudinal study with repeated neuroanatomic magnetic resonance imaging that adult ADHD status is linked with the developmental trajectories of cortical components of networks supporting attention, cognitive control and the default mode network [64]. Despite these evidences, certain inconsistencies have also been found in the neuroimaging studies in adults with ADHD, which may be related to the presence of comorbidity, a history of medication, gender-related differences and the small size of the sample used in some studies [60]. Differences have also been noted in relation to studies carried out on children with ADHD. Thus, future studies should pay more attention to avoid bias and potential confounders for misdiagnosing adult ADHD, and, of being able to determine whether the anatomical and functional deficits continue through adulthood.

Clinical implications

Over the years, the concept of ADHD has changed from a relatively simplistic statement to one that includes diagnoses, chronic alterations in critical functions for the activation, integration and organization of mental activity, which are determinants for effective adaptation to the demands of school, work and social relations [65]. 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, higher frequency of traffic accidents and legal problems [65].

Many disorders, including ADHD are not well known or are highly questionable not only during childhood, but also during adulthood. Unfortunately, the impact of this disorder still remains minimized since there are numerous false arguments relating to its overdiagnosis or its pharmacological treatment, even considering the most current scientific evidence. Additionally, the presence of some disorders, especially in the case of ADHD, directly mediates the early onset of cannabis use during adolescence, a factor that greatly exacerbates the difficulties of young students and academic problems suffered from childhood onward [66].

Several studies have found an association between ADHD and negative school performance. Specifically, children with ADHD have shown worse performance, presenting lower academic scores in subjects like mathematics and reading, repeated courses and resulted in lower graduation rates during secondary school and college [67]. There are other risk factors associated with ADHD that contribute to academic problems. Conduct disorder, characterized by a persistent pattern of violence and violation of rules has been frequently found to be comorbid with ADHD and as a result associated with poor academic performance, especially during adolescence [67]. However, this risk factor is presented in the literature as controversial, given that some studies have shown that once ADHD is taken into account and treated, the association between behavioral disorders and poor academic performance tends to diminish. This result could suggest that the observed association with academic problems may be affected by the individual's attentional difficulties [67].

Several hypotheses have been raised about the causal link between ADHD and academic failure. It has been proposed

that ADHD could be associated with poor school performance due to a dual mechanism, involving both self-regulation of behavior and cognitive mechanisms [68]. The behavioral symptoms of the disorder could lead to presence of learning difficulties as a result of the difficulty to cater instructions, inability to remember what they have learned, frequent anxiety, excessive motor activity and verbal activity and inability to inhibit impulsive responses.

Furthermore, later on in life, there have been numerous studies linking adult ADHD with high-risk behaviors, such as, reckless driving, repetitive fines and serious road accidents. It is well studied that adolescents and adults with ADHD show a marked increase in dangerous driving behaviors, receiving more traffic fines, losing their driving license for longer period and experiencing more road accidents than the general population [4,36,69,70]. This risk is increased for ADHD drivers who regularly use their vehicle or have professions that require driving long distances (delivery, taxi drivers, bus drivers, etc.). It has been reported that these patients have a clear tendency to present a premature decline in their attentional capacity required for proper driving, particularly when exposed to external stimuli, as it tends to happen when driving on motorways or with no companion, that is, announcement boards, people on the road, etc. [71]. Finally, a recent meta-analysis has been conducted based on 16 studies comprising 32 results [72]. The present study provides support for the hypothesis that the relative accident risk of ADHD drivers with comorbid oppositional defiant disorder, conduct disorder and/or other conduct problems is higher than that of ADHD drivers without these comorbidities. The estimated relative risks were 1.86 (1.27; 2.75) in a sample of ADHD drivers, in which a majority had comorbid oppositional defiant disorder and/or conduct disorder compared with 1.31 (0.96; 1.81) in a sample of ADHD drivers with no comorbidity. From the findings obtained, the authors give support to the hypothesis that ADHD drivers speed more frequently than controls because it stimulates attention and reaction time.

In Spain, the distraction factor, something generally linked to ADHD, has been recently identified as the leading cause of accidents in this country, even more than speeding, fatigue and inadequate sleep. In 2012, out of the 1010 fatal accidents that occurred on the road, 517 had concurrent distraction as a risk factor, according to the 'First Distractions Barometer in Spain' by the Royal Automobile Club of Spain. Comorbidity with ADHD within this group includes personality disorders, impulse control disorders and drug use as main contributing factors to increase very significantly the already existent serious problem of undiagnosed ADHD and driving [73].

Moreover, other domains being affected as a result of ADHD symptomatology include interpersonal difficulties as well as legal problems like delinquent behavior leading to imprisonment. In the last decade, several studies have explored the prevalence of ADHD among adult prisoners [48,74,75]. These studies with the use of screening instruments for the assessment

of ADHD, reported consistently that childhood ADHD among (adult) prisoners ranged between 24 and 67%, and adult inmates with ADHD ranged between 13 and 45%; being even a higher prevalence among the youth offender population [48]. Therefore, the presence of ADHD is much more common among prisoners than within the general population. Finally, a study conducted in Sweden [76] reported lower crime rates (32% in men and 41% in women) among ADHD inmates during periods when they were receiving pharmacological treatment for ADHD. These results raise the possibility that early detection and the use of an effective treatment reduces the risk of crime among ADHD patients.

Recent studies are beginning to report positive results regarding the early detection of current problems when driving for people suffering from ADHD, especially when establishing specific pharmacological treatments (methylphenidate [MPH], atomoxetine, etc.) as well as cognitive-behavioral therapy [4,71]. However, more research is needed in order to run proper therapeutic interventions for each type of patient, according to their own risk factors.

Diagnosis of ADHD in adults

The diagnosis of ADHD in adults is reflected in international diagnostic classifications since DSM-III, in 1980, which reported how this disorder can persist into adulthood in some of the affected children. The new version, DSM-5, makes more explicit references to the progression of ADHD into adulthood, adapting the current criteria to the disorder's evolutionary reality [4]. The publication of the ADHD DSM-5 criteria has generated new criticism [15]. However, the changes introduced in the DSM-5 for the diagnosis of ADHD in adults, although founded in empirical research, are still restrictive. The previous DSM-IV required the presence of symptoms of the disorder at an onset age prior to 7 years of the ADHD diagnosis, but according to their own research studies (DSM-IV), there is no empirical evidence that the age itself (7 years) has a diagnostic utility [77]. Besides, it was the only disorder beginning in childhood for which an explicit onset age of symptoms was required. Similarly, diagnostic validity of ADHD with onset after 7 years has also been proven in various studies [1,78]. Therefore, the change introduced in the DSM-5 regarding the age of onset has been fully justified. The important issue is that the disorder begins before age 12, that is, during childhood. The biggest change affecting ADHD diagnosis in adulthood has to do with the existence of fewer symptoms for criteria A required during adulthood. In the DSM-IV, at least six of the nine symptoms of inattention and/or hyperactivity-impulsivity was required, while at the DSM-5, five of the nine symptoms are needed to be present. This change has been introduced given that the initial defining symptoms of the disorder are based on the clinical evidence during childhood, thus ignoring the developmental changes that take place afterward. For instance, during adulthood, one doesn't generally witness a person climbing on chairs, tables or

having boundless energy, running around in a place where one should remain still. Hyperactivity at this age (adulthood) is more internal, as patients report feeling a subjective inner restlessness, an internal motor that never stops, making it hard for the individual to relax [1]. Studies have shown that the presence of four out of the six symptoms in adulthood, having had six of the nine in childhood correlates with a significant impairment later on in life [1,28]. The DSM-5 makes a special effort to address the need and symptoms of adults affected by ADHD in order to ensure they get the right care when needed. Indeed, the first international multicenter epidemiological study that evaluates the effect of the change in adults from DSM-IV to DSM-5 demonstrates that the new criteria do not dramatically increase the prevalence of adult ADHD in SUD patients [42]. Different researchers have drawn attention to the presence of emotional symptoms in adults with ADHD and have pointed out at the importance of emotional self-regulation as a core symptom of ADHD [79,80]. Moreover, there are psychometric instruments for the assessment of emotional self-regulation in adults with ADHD, like the Emotional Dysregulation Scale and the subscale of Emotional Liability of the Conners Adult Attention Deficit Scale [81]. Unfortunately, DSM-5 does not include emotional lability as a diagnostic criterion for ADHD.

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 [1,4]. Nevertheless, it is important to stress that ADHD is a clinical diagnosis, which can be made with good reliability and validity in adults according to the DSM criteria [82].

Despite the high prevalence of this disorder, there are only two semi-structured interviews currently available for the accurate diagnosis of ADHD within the adult population. Standardized instruments are important tools for diagnosing ADHD in adults because it makes it possible to assess the ADHD symptoms in depth during both childhood and adulthood. In addition, it adapts the definition of childhood hyperactivity symptoms to adulthood. It also provides a series of examples that help better assess the presence of each of the symptoms of the disorder, with the examples being adapted for childhood and adulthood. Having semi-structured interviews to assess the symptoms of ADHD in adults in depth can allow us to improve ADHD detection in clinical contexts. In addition, it can make research in adult domains easier, given that administering the interviews lets us define groups that are more homogeneous and better limited clinically.

The Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) provides clinicians and researchers a categorical diagnosis of this disorder via an interview including information about patient's personal history, developmental course of ADHD symptoms and level of impairment caused by it [1]. The Spanish version of this instrument was demonstrated to be a reliable tool for the diagnosis of ADHD within clinical and research settings [83]. However, an important limitation of the CAADID that needs to be highlighted is the financial cost of its administration.

On the other hand, the diagnostic interview for ADHD in adults (DIVA) is a semi-structured instrument based on the same principles as the CAADID. However, it is free of charge and available on the website currently maintained by the DIVA Foundation and via a small one-off charge as a downloadable app [4]. This structured interview allows a thorough evaluation of the diagnostic criteria (DSM-IV-TR) for ADHD in adulthood, as well as in childhood. It is divided into three parts, each applicable from childhood to adulthood: criteria for attention deficit-hyperactivity, criteria for impulsivity and starting period as well as the dysfunction caused by ADHD symptoms. The validation of DIVA interview, made by our group in the context of the European Network Adult ADHD, showed a diagnostic accuracy of 100% when compared with those diagnoses obtained via the CAADID interview (data under publication).

However, it is important to remember that both diagnostic tools explore only the core symptoms required, according to the DSM-IV, to diagnose ADHD, and not any symptoms, syndromes of other psychiatric disorders. Therefore, it is important to complete the psychiatric evaluation with questions regarding the presence of other possible symptoms or comorbid psychiatric disorders. In order to assess the comorbidity of ADHD in adults, there are useful interviews, including the psychiatric research interview for substance and mental disorders IV (PRISM-IV) and the Mini International Neuropsychiatric Interview-Plus (MINI-Plus) [4]. PRISM-IV is a structured interview based on DSM-IV-TR diagnostic criteria and specifically designed to study comorbidity in subjects with substance use disorders. Kappa index showed a concordance between PRISM adult ADHD module and CAADID of 0.78 (95% CI: 0.64–0.91), the sensitivity of PRISM adult ADHD module was 90% (95% CI: 76.9–96.0) and the specificity was 87.5% (95% CI: 73.9–94.5) [84]. The MINI is one of the most widely used psychiatric structured diagnostic interview instrument in the world, employed by mental health professionals and health organizations in more than 100 countries. MINI-Plus allows for the coding of more than 60 variables, including DSM-IV disorders and suicide risk at the time of the interview or at some time in the past. A module of adult ADHD is included in this interview. MINI-Plus was used in epidemiological studies to assess adult ADHD with good psychometric properties [41]. A limitation of the current interviews for adults with ADHD is that to date no validated instruments on the basis of DSM-5 are currently available.

Treatment of ADHD in adults

The drugs indicated for the treatment of ADHD in adults are the same to those recommended for children and adolescents. There have been many more clinical trials evaluating the efficacy and safety of the drugs used in ADHD treatment on

Table 2. Meta-analysis performed to evaluate the efficacy of drugs for the treatment of attention-deficit/hyperactivity disorder in adults.

Study (year)	Drug studied	Number of studies	Patients (n)	Mean effect size	Results	Ref.
Faraone et al. (2004)	MPH	6	253	0.9	MPH is efficacious for treating adult ADHD	[85]
Peterson et al. (2008)	Shorter-acting stimulants (MPH and amphetamines) Longer-acting stimulants (MPH and amphetamines) Bupropion	22	2203	4.32[†] 1.35[†] 1.87[†]	Immediate release methylphenidate as first-line treatment for most adults with ADHD	[86]
Koesters et al. (2009)	MPH	16	747	0.42	The overall effect size was significantly different from zero, but was only half the size expected on the basis of a previous meta-analysis	[87]
Mészáros et al. (2009)	Stimulants (MPH, amphetamines) Non-stimulants (ATX, desimipramine, bupropion)	11	1991	Stimulants = 0.67 Non-stimulants = 0.59 All treatments = 0.65	Stimulants and non-stimulants demonstrated statistically significant and clinically robust improvement in symptom severity compared with placebo treatment	[88]
Faraone and Glatt (2010)	Shorter-acting stimulants (MPH and amphetamines) Longer-acting stimulants (MPH and amphetamines) Non-stimulants (ATX, bupropion, paroxetine, modafinil, ABT-418)	19	2108	0.86 0.73 0.39	Both stimulant and non-stimulant medications are effective for treating ADHD in adults. Stimulant medications show greater efficacy for the short durations of treatment characteristic of placebo-controlled studies	[89]
Castells et al. (2011)	MPH	18	2045	0.57–0.58	This study shows that methylphenidate improves ADHD symptoms in adults in a dose-dependent fashion	[90]
Castells et al. (2011)	Amphetamines	7	1091	0.72	Amphetamines improved short-term ADHD symptom severity	[91]
Maneeton et al. (2011)	Bupropion	5	349	1.67[†]	The findings suggest that bupropion is effective and safe for adults with ADHD	[92]
Cunill et al. (2013)	ATX	12	3375	0.38–0.40	Atomoxetine showed 77 modest efficacy in reducing ADHD symptoms	[93]

[†]This value is the relative risk.
ADHD: Attention-deficit/hyperactivity disorder.

children than adults. This situation is quite rare in terms of drug research overall, because there are more data available for adult populations.

Pharmacotherapy for adults with ADHD has been shown to be effective. The NICE guidelines recommended pharmacotherapy as first-line treatment for adult ADHD [17]. The NICE guidelines consider stimulants (MPH and dexamphetamine) as the first choice for treatment of adult ADHD, and the non-stimulant atomoxetine as a second-line treatment option, followed by other non-stimulant medications such as bupropion and tricyclic

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antidepressants. This recommendation is in the same line that describes the European Consensus made by European Network of Adult ADHD [1].

Actually, there are now randomized, placebo-controlled clinical trials and meta-analysis showing the effectiveness and safety of MPH and amphetamines and atomoxetine for adults with ADHD (Table 2) [85–93]. MPH and/or amphetamines have the indication of adult ADHD treatment from regulatory agencies in diverse countries, such as the USA, Canada, Germany and so on. Atomoxetine is currently the only non-stimulant medication for ADHD with regulatory approval in adult patients and the only drug approved for *de novo* adult ADHD use in the EU [4]. There are randomized clinical trials that have evaluated the efficacy and safety of atomoxetine and MPH for up to 1 year and 6 months, respectively [94,95].

It is important to highlight the positive impact of ADHD treatment for adults in terms of improving aspects of their daily functioning. Indeed, a recent investigation based on large population registries concluded that such medications reduce criminality [76] or improve driving performance in real traffic with atomoxetine in adults with ADHD [96]. A systematic review of 351 studies in childhood and adulthood evaluating the long-term outcomes (defined as 2 years or more) of ADHD across lifespan with the goal of identifying long-term outcomes and the impact that any treatment (pharmacological, non-pharmacological or multimodal) has on ADHD long-term outcomes has been carried out [97]. The authors investigated nine areas of outcome: academic, antisocial behavior, driving, non-medicinal drug use/ addictive behavior, obesity, occupation, service use, self-esteem and social function outcomes. This study found that the long-term outcomes for participants with ADHD when left untreated were poor compared with non-ADHD controls, and that treatment of ADHD improved long-term outcomes, but usually not to the point of normalization. Driving and obesity outcomes were most often reported to be responsive to treatment. 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 [98].

At present, only two small randomized controlled direct comparison studies have been performed, but none showed evidence for different efficacy between MPH and atomoxetine [99,100]. However, in one study greater improvement in atomoxetine was found than in immediate-release MPH in spatial planning [100].

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 MPH, 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 [101]. For that reason, it is important to monitor these heart parameters during treatment when using stimulants or atomoxetine.

A multimodal treatment approach that addresses adult ADHD in the treatment plan and involves the patients' partners and family members is recommended [1,17]. The multimodal treatment approach should include psycho-education, pharmacotherapy and disorder-oriented psychotherapy for ADHD, including family or couple therapy, if needed.

Behavioral therapy has proven to be the most effective psychological approach for treating symptoms of adult ADHD and comorbid symptoms of anxiety, depression and emotional instability; to overcome those symptoms that have an important impact on the day-to-day functioning in patient's life [102–111]. Currently, there are controlled studies of cognitive behavioral therapy for the treatment of ADHD within the category of empirical evidence made by Brithish Association for Psychopharmacology (Table 3). These investigations have common elements such as psycho-education treatment, problem-solving approach, strategies for improving care, management of impulsivity and cognitive restructuring.

A growing amount of evidence shows that in pharmacologically treated ADHD patients with residual symptoms, psychological treatment has an additive effect above medication treatment alone. Most guidelines and expert reviews recommend adding a course of either group or individual disorder-oriented psychotherapy, in patients receiving pharmacotherapy who continue to experience significant symptoms and impairment [1,4,17]. However, no controlled studies of dialectical behavior therapy have been applied to ADHD or have been compared using traditional cognitive behavioral therapy and dialectical behavior therapy in order to discern which aspects of ADHD improve every type of psychological treatment or what treatment is most effective for different subtypes of ADHD. According to studies, the meta-cognitive therapy is more effective in improving inattention, but there are no data that allow us to state an improvement in symptoms of hyperactivity or comorbid symptoms. Similarly, cognitive rehabilitation has not been shown to improve symptoms of comorbid anxiety and depression [106,112].

Expert commentary & five-year view

From the current research, ADHD in adults has good evidence based on epidemiological data, genetic data, neuroimaging, clinical characteristics, psychosocial impairments, diagnostic instruments and treatment. Misdiagnosis will always be an issue within clinical practice, nonetheless this issue is one part of the problem, as there are also individuals who warrant an early diagnosis from childhood preferably and still go unidentified. For example, research refers to the current problem in identifying girls who suffer from attentional deficit disorder (without hyperactivity) as the disruptive component, that is, misconduct, and dysfunctional behavioral in the classroom, is less obvious [113]. Despite the

Table 3. Controlled studies of psychological treatment of attention-deficit/hyperactivity disorder in adults.

Study (year)	Treatment	Patients (n)	Intervention format	Results	Ref.
Safren et al. (2005)	CBT + medication versus medication alone[†]	31	Individual	CBT for adults with ADHD with residual symptoms was a feasible, acceptable, and potentially efficacious next-step treatment approach	[103]
Safren et al. (2010)	CBT versus relaxation with educational support[†]	86	Individual	CBT compared with relaxation with educational support resulted in improved ADHD symptoms, which were maintained at 12 months	[104]
Virta et al. (2010)	Short-term CBT versus cognitive training versus control	29	Individual	The group of CBT showed greater improvement in ADHD measures than other groups	[105]
Stevenson et al. (2002)	CRP versus control	43	Group	CRP provides a practical way of enhancing daily functioning for adults with ADHD	[106]
Stevenson et al. (2003)	CRP with minimal therapist contact (self-directed) versus control	35	Group	Improvements in ADHD symptoms were obtained in organizational strategies, self-esteem and anger management to maintain this improvement at 2 months of treatment	[112]
Solanto et al. (2010)	Meta-cognitive therapy versus supportive psychotherapy	88	Group	Decrease in symptoms was observed both at the self, and the clinical observer. But no significant differences between the two groups regarding organizational skills and planning or comorbid symptoms of depression were observed	[107]
Weiss et al. (2012)	CBT + dextroamphetamine versus CBT + placebo	48	Group	Both groups showed robust improvement in both symptoms and functioning, but the use of medication did not significantly improve outcome over and above use of CBT and placebo	[108]
Emilsson et al. (2011)	CBT + drug treatment versus drug treatment	54	Group	The findings give support for the effectiveness of CBT in reducing ADHD symptoms and comorbid problems, and improving functions associated with impairment	[109]
Hirvikoski et al. (2011)	Dialectical behavioral therapy versus loosely structured discussion group	51	Group	The treatment was feasible in an outpatient psychiatric context and significantly reduced ADHD symptoms in on-treatment individuals who remained stable regarding medication status	[110]
Estrada et al. (2013)	Psychoeducation versus CBT	32	Group	Psychoeducation demonstrated to be an effective treatment in reducing ADHD core symptoms	[111]

[†]In patients stabilized on medications but still show clinically significant symptoms.
ADHD: Attention-deficit/hyperactivity disorder; CBT: Cognitive behavioral therapy; CRP: Cognitive remediation program; MPH: Methylphenidate.

data presented in this article, adult ADHD remains an underdiagnosed disorder in the adult population worldwide [4,17,19,114]. This situation is common in other psychiatric disorders beginning in childhood, such as autism. As a result, there is undertreatment of ADHD in adulthood, which has major societal and personal costs. In the future, it will be necessary to increase the number of professionals with experience in the diagnosis and management of ADHD in adults because one of the most important problems regarding the management of ADHD in adults is the scarce number of professionals with experience in adults with this disorder. Furthermore, it is absolutely essential to include education of ADHD in adults in the pre-degree programs in Universities because of the high prevalence of the disorder and the severe consequences of underdiagnosis. There is a common demand among patients and Family

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Caretakers Associations to have experts who can continue helping their children with ADHD when becoming adults [115]. The clinicians deal on a daily basis with the problems that adults with ADHD suffer from; it is very common to hear patients say "my life has changed positively after the diagnosis and the treatment of ADHD". Frequently, the criticism toward the diagnosis of adult ADHD arrives from professionals without clinical experience.

Although the investigation of adult ADHD has shown a significant improvement since the 1970s, there are several areas where more research is needed. Genetics studies have provided a better understanding of the risk factors involved in the development of ADHD, but they do not involve large sample groups. For the genome-wide association study in complex disorders, like psychiatric disorders, no fewer than 30,000 subjects are required. ADHD Genetics Consortium has reached this level of sample power and in the coming years positive results are expected. The diagnostic area has gone through a great increase in the number of studies in recent years, but it is necessary to test the validity of the new instruments in patients with comorbidities, because the original studies are performed in patients who seek treatment for ADHD. The new DSM-5 criteria represents a clear advance in the recognition of ADHD in adults, but, in our opinion, it is still very restrictive because there are researchers who found specific symptoms of ADHD in adulthood that can reduce its detection and therefore cause underdiagnosis [116]. More research is needed on biomarkers that can increase the friability of the diagnosis. In this sense, the new techniques on neuroimaging could be very positive. Another area is the performance of clinical trials, which compare 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 who are in habitual clinical settings. The presence of other psychiatric disorders together with ADHD is common rule 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 SUDs, since the number of clinical trials examining this scenario has increased during the last years [1]. The principal variables used in clinical trials could be useful to introduce strong variables, like academic, work or driving performance, criminality, etc. rather than the final result of scales *per se*. Recent studies have incorporated these variables obtaining interesting results [76,117]. Furthermore, recently treatment studies also incorporated functional measures [118–121]. On the other hand, as already mentioned, ADHD is a chronic disorder and patients are required to take ADHD medication for years. Nonetheless, a double-blind Phase III study recruited 2017 patients who underwent 12-weeks open-label treatment with atomoxetine, which was then continued for 12 weeks of double-blind treatment [95]. From 12 to 24 weeks, 524 patients continually achieved response criteria and were then randomized equally to double-blind placebo or continuation of atomoxetine. The primary outcome was the proportion of patients in the intention-to-treat population who maintained this response throughout the 6-month post-randomization treatment phase. This was significantly greater in the atomoxetine group compared with the placebo group: 64 versus 50%, difference 14% (95% CI: 5.9–22.7) [95]. More independent long-term studies are necessary to access the effectiveness. The prediction of treatment response or the presence of secondary effects with pharmacogenetic studies can be of utility in daily clinical practice, but 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 [4,17,65]. It is essential to investigate new pharmacological targets beyond the dopaminergic and noradrenergic systems. New findings on genetic studies, like LPHN3 could open the door to new drugs regulating the glutamatergic system.

Key issues

- Attention-deficit/hyperactivity disorder (ADHD) is a disorder that typically begins at childhood, with a chronic evolution in main parts of the patient's body. For that, a significant part of the affected children continue manifesting symptoms throughout adulthood.

- Much of the evidence to date suggests that among adolescents and adults, ADHD is underrecognized and undertreated. Epidemiological studies showed a prevalence of ADHD in adults up to 4.4% in general population.

- Although numerous molecular studies focused on adult ADHD, where results were similar to those obtained in genetic studies with children and adolescent samples; in others, the findings were not in concordance.

- Neuroimaging studies conducted in adults with ADHD have shown alterations in the brain at the structural and functional levels, and also in terms of connectivity. These findings have been observed mainly in the inferior frontal and dorsolateral prefrontal cortex, as well as in striatal, anterior cingulate, parietotemporal and cerebellar regions.

- 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.

- The publication of the ADHD diagnostic and statistical manual of mental disorder-5 criteria has generated new criticism. However, the changes introduced in the diagnostic and statistical manual of mental disorder-5 for the diagnosis of ADHD in adults, although founded in empirical research, are still restrictive.

- There are reliable psychometric instruments for diagnostic assessment of ADHD in adults, as diagnostic interview for ADHD in adults, Conners adult ADHD diagnostic interview for DSM-IV, MINI-Plus or psychiatric research interview for substance and mental disorders.

- Pharmacotherapy for adults with ADHD has been shown to be effective. There are now randomized, placebo-controlled clinical trials and meta-analysis showing the effectiveness and safety of methylphenidate and amphetamines and atomoxetine for adults with ADHD.

- Cognitive behavioral therapy has proven to be the most effective psychological approach for treating the symptoms of adult ADHD and comorbid symptoms of anxiety, depression and emotional instability approach.

- It is absolutely essential to include education of ADHD in adults in the pre-degree programs in Universities because of the high prevalence of the disorder and the severe consequences of misdiagnosis.

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