Original article

Updated European Consensus Statement on diagnosis and treatment of adult ADHD

J.J.S. Kooij[a,b,*], D. Bijlenga[a], L. Salerno[9], R. Jaeschke[1], I. Bitter[J], J. Balázs[c],
J. Thome[S], G. Dom[X], S. Kasper[d], C. Nunes Filipe[7], S. Stes[e], P. Mohr[W], S. Leppämäki[f],
M. Casas[g], J. Bobes[O], J.M. Mccarthy[h], V. Richarte[i], A. Kjems Philipsen[j], A. Pehlivanidis[8],
A. Niemela[k], B. Styr[l], B. Semerci[10], B. Bolea-Alamanac[m], D. Edvinsson[n], D. Baeyens[o],
D. Wynchank[a], E. Sobanski[L], A. Philipsen[p], F. McNicholas[4], H. Caci[M], I. Mihailescu[q],
I. Manor[3], I. Dobrescu[r], T. Saito[H], J. Krause[5], J. Fayyad[s], J.A. Ramos-Quiroga[N], K. Foeken[t],
F. Rad[u], M. Adamou[v], M. Ohlmeier[6], M. Fitzgerald[w], M. Gill[Q], M. Lensing[U],
N. Motavalli Mukaddes[x], P. Brudkiewicz[y], P. Gustafsson[11], P. Tani[z], P. Oswald[12],
P.J. Carpentier[A], P. De Rossi[Y], R. Delorme[B], S. Markovska Simoska[C], S. Pallanti[D], S. Young[E],
S. Bejerot[V], T. Lehtonen[F], J. Kustow[G], U. Müller-Sedgwick[K], T. Hirvikoski[Z], V. Pironti[2],
Y. Ginsberg[T], Z. Félegyházy[I], M.P. Garcia-Portilla[R], P. Asherson[P]

[a] PsyQ Psycho-Medical Programs, Expertise Center Adult ADHD, Carel Reinierszkade 197, 2593 HR, The Hague, The Netherlands
[b] Amsterdam UMC, LocationVUMc, Dept. of Psychiatry, Amsterdam, the Netherlands
[c] Institute of Psychology, Eotvos Lorand University, Vadaskert Child Psychiatric Hospial and Outpatient Clinic, Budapest, Hungary
[d] Medical University Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria
[e] University Psychiatric Center, KU Leuven, Kortenberg, Belgium
[f] Helsinki University Central Hospital, Department of Psychiatry, HUS, Finland
[g] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain; Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain; Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain
[h] Visiting senior lecturer, King's College London, United Kingdom; Midland Regional Forensic Service, Hamilton, New Zealand
[i] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona; Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona; Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[j] DPC Naestved, Ladby, Naestved, Region Sjaelland, Denmark
[k] Wellmind Terveys Oy, Oulu, Finland
[l] Mccabi Health Services (H.M.O), Tel Aviv, Israel
[m] General Systems Division, Centre for Addiction and Mental Health/ Dept. Of Psychiatry, University of Toronto, Toronto, Canada
[n] Uppsala University, Uppsala University Hospital, Akademiska sjukhuset, Uppsala, Stockholm
[o] Parenting and Special Education, KU Leuven, Leuven, Belgium
[p] University of Bonn, Department of Psychiatry and Psychotherapy, Bonn, Germany
[q] Alexandru Obregia Clinical Hospital of Psychiatry, Bucharest , Romania
[r] University of Medicine and Pharmacy "Carol Davila". Child and adolescent Psychiatry Department, Prof. Dr. Alex Obregia"Psychiatry Hospital, Bucharest, Romania
[s] St George Hospital University Medical Center, Balamand University Faculty of Medicine, Institute for Development, Research, Advocacy and Applied Care, Department of Psychiatry and Clinical Psychology, St George Hospital, Achrafieh, Beirut, Lebanon
[t] Vieux Chemin de Cagnes à La Gaude, la Gaude, France
[u] University of Medicine and Pharmacy "Carol Davila"; Child and adolescent Psychiatry Department, Prof. Dr. Alex Obregia"Psychiatry Hospital, Bucharest, Romania
[v] University of Huddersfield and South West Yorkshire Partnership NHS, Manygates Clinic, Wakefield, England
[w] Trinity College, Blanchardstown Village, Dublin, Republic of Ireland
[x] Istanbul Institute of Child and Adolescent Psychiatry, Istanbul, Turkey
[y] Centrum Dobrej Terapii, Cracow, Poland
[z] Department of Psychiatry, Clinic for Neuropsychiatry, Helsinki University Central Hospital, HUS, Finland
[A] Reinier van Arkel Mental Health Institute,'s-Hertogenbosch, Netherlands
[B] Child and Adolescent Psychiatry Department, Robert Debré Hospital, Paris, France
[C] Macedonian Academy of Sciences and Arts, Skopje, Republic of Macedonia
[D] Stanford University Medical Center, University of Florence, INS Institute of Neuroscience, Florence, Italy
[E] Psychology Services Limited, Croydon, England
[F] Neuropsykologkonsult Taina Lehtonen, Hjärup, Sweden
[G] Barnet Adult ADHD Service, Barnet, Enfield and Haringey NHS Mental Health Trust, London; Barnet Adult ADHD Service, Springwell Centre, Barnet Hospital, Barnet, England
[H] Department of Child and adolescent Psychiatry, Graduate School of Medicine, Hokkaido University, North 15,West 7, Kita-ku, Sapporo, 060-8638 Japan

[I] ADHD Központ(center) Budapest, Budapest, Hungary
[J] Semmelweis University, Department of Psychiatry, Budapest, Hungary
[K] Adult ADHD Service, Barnet, Enfield & Haringey NHS Mental Health Trust, North London & Department of Psychiatry, University of Cambridge; Adult ADHD
Service, Springwell Centre / Barnet Hospital, Barnet, London, England
[L] Central Institute of Mental Health, Mannheim; University Medical Center Mainz, Mainz, Germany
[M] Hopitaux Pediatriques de Nice CHU Lenval, Nice, France
[N] Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; Psychiatric Genetics Unit, Vall d'Hebron Research Institute
(VHIR), Barcelona, Catalonia, Spain; Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain; Department of
Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain
[O] Department of Psychiatry, School of Medicine, University of Oviedo - Centro de Investigación Biomédica and Red de Salud Mental, CIBERSAM, Oviedo, Spain
[P] SGDP Building, Institute of Psychiatry Psychology and Neuroscience, Kings' College London, London, England
[Q] Department of Psychiatry, Trinity College Dublin, School of Medicine, Dublin, Republic of Ireland
[R] Dept. of Psychiatry, University of Oviedo, School of Medicine, Psychiatry, Oviedo, Spain
[S] Thome, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universitatsmedizin Rostock, Rostock, Germany
[T] Stockholm Center for Eating Disorder R&D Unit, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[U] Oslo University Hospital, Department of Rare Disorders, NevSom - Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias,
Oslo, Norway
[V] Örebro Univerity, School of Medical Sciences, Campus USÖ, Örebro, Sweden
[W] National Institute of Mental Health, Klecany, Czech Republic; Third Faculty of Medicine, Charles University Prague, Czech Republic
[X] Antwerp University (UA, CAPRI), Boechout, Belgium
[Y] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome; Department NSMOS, Faculty of Medicine and Psychology, University
"Sapienza"of Rome, Rome, Italy
[Z] Center for Neurodevelopmental Disorders at Karolinska Institutet (KIND), CAP Research Center, Stockholm, Sweden
[1] Jagiellonian University Medical College, Section of Affective Disorders, Department of Psychiatry, Krakow, Poland
[2] Cambridge Adult ADHD & ASD Clinic, Cambridge, England
[3] Geha MHC, Petach-Tikva, Israel
[4] University College Dublin, Dublin, Republic of Ireland
[5] Outpatient Clinic, Ottobrunn, Germany
[6] Klinikum Kassel, Department of Psychiatry and Psychotherapy, Kassel, Germany
[7] Nova Medical School. Universidade NOVA Lisboa, Lisboa, Portugal
[8] National and Kapodistrian University of Athens Medical School, Eginition Hospital, Department of Psychiatry, Athens, Greece
[9] INS, Institute of Neuroscience, Florence, Italy
[10] Hasan Kalyoncu University, Poyracık Sokak. Istanbul, Turkey
[11] Lund University, Clinical Sciences Lund, Child and Adolescent Psychiatry, Lund, Sweden
[12] High Security Hospital, CRP Les Marronniers, Tournai, Belgium

A B S T R A C T

Background Attention-deficit/hyperactivity disorder (ADHD) is among the most common psychiatric disorders of childhood that often persists into adulthood and old age. Yet ADHD is currently underdiagnosed and undertreated in many European countries, leading to chronicity of symptoms and impairment, due to lack of, or ineffective treatment, and higher costs of illness.

Methods The European Network Adult ADHD and the Section for Neurodevelopmental Disorders Across the Lifespan (NDAL) of the European Psychiatric Association (EPA), aim to increase awareness and knowledge of adult ADHD in and outside Europe. This Updated European Consensus Statement aims to support clinicians with research evidence and clinical experience from 63 experts of European and other countries in which ADHD in adults is recognized and treated.

Results Besides reviewing the latest research on prevalence, persistence, genetics and neurobiology of ADHD, three major questions are addressed: (1) What is the clinical picture of ADHD in adults? (2) How should ADHD be properly diagnosed in adults? (3) How should adult ADHDbe effectively treated?

Conclusions ADHD often presents as a lifelong impairing condition. The stigma surrounding ADHD, mainly due to lack of knowledge, increases the suffering of patients. Education on the lifespan perspective, diagnostic assessment, and treatment of ADHD must increase for students of general and mental health, and for psychiatry professionals. Instruments for screening and diagnosis of ADHD in adults are available, as are effective evidence-based treatments for ADHD and its negative outcomes. More research is needed on gender differences, and in older adults with ADHD.

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1. Introduction: the European Network Adult ADHD

The European Network Adult ADHD (ENAA) was founded in 2003 to help improve the diagnosis and treatment of ADHD in adults in Europe and beyond. ENAA represents mental health care professionals and researchers from 28 countries with expertise on ADHD in adults (www.eunetworkadultadhd.com). The Section Neurodevelopmental Disorders Across the Lifespan (NDAL) of the European Psychiatric Association (EPA) joined our effort to provide this update of our first Consensus Statement on adult ADHD published in 2010 [1].

1.1. Objectives of the updated consensus statement for clinicians

Despite strong evidence on the clinical presentation, genetics, neurobiology, the burden of the disorder, and on safe and effective treatment for ADHD in adults, many people are still under-diagnosed and undertreated. Specialized clinical services remain scarce in most parts of the world, including Europe [2,3]. Our aim is to provide an update of the literature on assessment and treatment of adult ADHD to [1] increase awareness on ADHD as an impairing life-long neurodevelopmental condition up to old age [2]; update

* Corresponding author at: European Network Adult ADHD, VUMc, Amsterdam, EPA, The Netherlands.
E-mail address: s.kooij@psyq.nl (J.J.S. Kooij).

the assessment procedure for diagnosing ADHD in adults; and [3] give updated recommendations for appropriate treatments.

1.2. Methodology

Creating a Consensus Statement does not follow the same procedure as required for the development of a guideline, such as systematic reviews using formal ratings of the evidence. Most of the authors participated in the development of a first Consensus Statement on adult ADHD in 2010, and were asked to provide an update of the previous text based on new findings in the literature since the time of publication. Subgroups dealing with different subjects were formed. The subgroups reached consensus on the text among themselves before sending it to the first author. The first author put all paragraphs together and edited the text with the help of a few other coauthors (DW, SY, PA, DB). This draft of the manuscript was send to all authors for their comments. The first author checked the comments and implemented adjustments into the text, and send the final version to all authors for agreement. All authors agreed with the final version.

2. Heritability and environment

Family, twin and adoption studies from the last 20 years show that ADHD is a familial disorder with high heritability, indicating that a significant genetic component influences risk for the disorder [4–12]. Environmental factors such as severe institutional deprivation are also likely to play a role, either as main causal factors in a few cases [13] or by interaction with genetic risks. Family studies indicate a risk to first-degree relatives of 4–5 fold the population rate or higher, with prevalence rates around 20% among first degree relatives [14]. Data on ADHD in children and adolescents find average heritability of around 76% [12]. Studies in adult twins using self-rated ADHD symptoms consistently report lower estimates of heritability, around 30–40% [15–17]. One reason for lower heritability of adult self-reported ADHD symptoms may be from the use of self-ratings. These lead to lower estimates of heritability compared to informant ratings regardless of age, perhaps due to variable levels of awareness among individuals rating their own ADHD symptoms [18,19]. Studies combining data across informants [20], or using clinical diagnostic information [21] find heritability estimates for adult ADHD in the same range (70–80%) as for children [22].

2.1. Candidate genes

Early molecular genetic studies of ADHD in children reported genetic associations with several candidate genes. Genetic variants within or near the D4 and D5 dopamine receptor genes provided the most consistent findings supported by meta-analysis [23]. Other specific candidate genes were implicated in the early studies [12,24,25], but none have provided consistent evidence or been replicated in more recent large-scale genome wide association studies. Taken together the traditional neurotransmitter system genes appear to explain only a small amount of the variance in ADHD [26]. There is also some converging evidence for the role of genes that fit into a neurodevelopmental network involved in directed neurite outgrowth [27].

2.2. Genome wide association studies (GWAS)

More recent findings have emerged from genome-wide association studies [28]. The most recent dataset reported included over 20,000 ADHD cases and 35,000 controls. These data were used to estimate that around 30% of the heritability of ADHD is explained by common genetic variation. In total, twelve loci achieved genome-wide significance, including FOXP2; notable because prior work had implicated it in adult ADHD [29]. These findings place ADHD firmly on the path to detecting very large numbers of associated common genetic variants as more samples are accrued.

LD regression analyses that estimate genetic correlations between disorders find strong genetic links between ADHD and a range of outcomes including educational performance, depression, obesity, smoking and lung cancer [28]. A further finding is the very strong genetic correlation between the diagnosis of ADHD, and trait scores in general population samples, demonstrating that ADHD represent the extreme of a continuously distributed trait in the general population [30]. These finding confirm the polygenic nature of genetic liability to ADHD.

Rare copy number variants (CNVs) occurring on less than 1% of chromosomes are also known to play a role in a subset of individuals with ADHD [31,32]. CNVs were found to be 2-fold more common in children with ADHD within the normal IQ range, and 6-fold higher in those with IQs below 70 [32]. Specific genes suggested as CNVs linked to ADHD include the nicotinic alpha-7 acetylcholine receptor gene (e.g., [33]), several glutamate receptor genes [34] and neuropeptide-Y [35], although these findings remain inconsistent and hard to verify due to low frequency in the population.

2.3. Molecular genetic studies of adult ADHD

Molecular genetic studies of adult ADHD are less advanced, but are expected to confirm some genetic associations identified in childhood and find other genetic associations related to persistence or remission of ADHD in adult life [20]. A preliminary report at the International Neuropsychology meeting (Washington, 2018) found the genetic correlation between child and adult ADHD to be greater than 80%. Most of the current research has been coordinated in Europe by Barbara Franke from the Netherlands for the International Multicentre Persistent ADHD Collaboration (IMPACT) group. This collaboration has successfully generated a multi-site sample of more than 3500 patients and continues to grow. To date several publications highlight potential associations with adult ADHD, some but not all of which are shared with genetic association findings in children [36–42].

2.4. Environmental factors

It has been known for a long time that environmental factors are associated with ADHD [43], particularly prenatal risk factors such as exposure to alcohol and drugs, valproic acid, high blood pressure, maternal stress during pregnancy, as well as preterm birth and low birth weight [44–46]. However sophisticated study designs are needed to clarify whether these association reflect direct effects of the environmental exposure or reflect genetically correlated risk measures. For example, although smoking during pregnancy is clearly associated with offspring ADHD, this association appears to be entirely accounted for by the genetic correlation between maternal smoking and offspring ADHD [47]. In contrast, evidence from Romanian adoptees suggests that severe early deprivation is causally related to ADHD in a dose dependent way [13]. Gene by environment interactions (G x E) have been proposed and may explain some of the missing heritability seen between heritability estimates derived from twin (0.76) and molecular genetic (0.22) data. However, to date no G x E effects have been clearly identified. The findings to date indicate that much more work is needed to understand the interplay between genetic and environmental risks.

3. Neurobiology of ADHD

3.1. Neuro-imaging: evidence for atypical gray and white matter areas

Structural brain scans of adults with ADHD showed grey matter abnormalities in several brain areas, including the right frontal and prefrontal areas [48,49], anterior cingulate [50–52], the basal ganglia and the cerebellum [53–56] with some preliminary research also showing abnormalities of the visual cortex [57]. Additionally, cortical thickness was found to be reduced in adult ADHD [56,58,59]. Some evidence suggests that grey matter abnormalities, in some subcortical regions, are more pronounced in children than adults. This might reflect the effects of age, medication, intrinsic heterogeneity of the ADHD syndrome, or a combination thereof [51,60–64].

Despite these reported findings the latest mega-analysis conducted by the Enigma consortium found no significant differences in brain structure between adult ADHD and controls; although, small but significant differences were found in children for subcortical regions including the accumbens, amygdala, caudate, hippocampus, putamen and intracranial volume with effects ranging from d = .10–.15 [65]. These findings indicate that while there are structural changes in subcortical brain regions in ADHD in children, these are relatively subtle effects that dissipate with increasing age.

Diffusion tensor imaging (DTI) highlighted that white matter tracts, including fronto-occipital, fronto-striatal, temporal and temporo-occipital fasciculi and part of the corpus callosum, bear microstructural abnormalities [66–71]. Additionally, some findings also linked microstructure variability to symptomatology such that greater inattention but not hyperactivity-impulsivity was associated with significantly lower fractional anisotropy (that is lower microstructural integrity) in the left uncinate and inferior fronto-occipital fasciculi compared to controls [70]. These results indicate that structural deficits in ADHD are not just confined to specific regions but involve interconnections among large scale brain networks [68,71–73].

3.2. Functional neuroimaging

Regarding functional MRI (fMRI) studies, task-based and resting-state findings converge. Meta-analyses show that ADHD is associated with dysfunctions in several domain-specific fronto-striatal and fronto-cerebellar neural networks. Thus a meta-analysis of 39 child and 16 adult ADHD fMRI studies concluded that in ADHD there are significant dysfunctions in multiple neuronal systems involved in higher-level cognitive functions [74]. These include hypoactivations in the frontoparietal executive control network, putamen, and ventral attention network, which is consistent with the classical model of ADHD as a disorder of deficient fronto-striatal activation.

Hyperactivations are also seen in regions of the default mode and visual networks, which support the contemporary view that ADHD is associated with faulty regulation of relationships between default mode and task positive networks. Similar findings come from meta-analyses, which show consistent underactivation in inferior fronto-striatal networks during cognitive tasks [75], in dorsolateral fronto-striato-parietal networks during attention tasks [75], and in fronto-cerebellar networks for timing functions [76]; in addition to abnormally enhanced activation in default mode regions [76].

The recent focus on resting state fMRI (RS-fMRI) identified multiple intrinsic neural circuits, reflecting functional connectivity within and between regions which is continuously encoded in the spontaneous activity of the brain [77]. The intrinsic fronto-parietal, dorsal attentional, visual, motor and default mode networks all overlap with regions showing differential task activations during inhibition, attention, or working memory tasks in ADHD compared to controls [78]. Despite the wealth of established findings from fMRI and RS-fMRI studies of ADHD, cross-sectional neuroimaging data is correlational in nature and causal inferences cannot yet be made.

More recently outcome studies of children diagnosed with ADHD has been able to compare functional brain change in adults with persistent and remitted ADHD and compare these to age-matched controls. The largest such follow-up study to date, of 205 children with ADHD, found that persistence of ADHD was associated with loss of the balance of connections within the default mode network, and connections between the default mode and those supporting attention and cognitive control. In contrast there were no differences in these networks between those whose ADHD had remitted and non-ADHD controls [79].

Overall, despite the wealth of established findings from fMRI and RS-fMRI studies of ADHD, cross-sectional neuroimaging data is correlational in nature and causal inferences cannot yet be made. The finding that certain functional brain changes are seen to differ between persistent compared to remitted cases of childhood ADHD sheds some light on likely causal processes, but further longitudinal data is still required before firm conclusions can be drawn.

3.3. Neuropsychological and electrophysiological tests

As a group, individuals with ADHD are characterized by altered neuropsychological functioning across a variety of executive function (EF) measures. However, thus far there is neither a neurobiological nor a neuropsychological test (battery) for ADHD with sufficient positive predictive power to establish the diagnosis at the individual level [80]. In one study, the vast majority of neuropsychological instruments showed poor discriminative ability compared to clinical assessment measures such as the ASRS Screener v1.1 and the DIVA 2.0 Diagnostic Interview for ADHD in adults, with an overall classification accuracy ranging from 53% to 66% [81]. Nevertheless, when used in combination with the DIVA 2.0, objective cognitive performance tests measuring omission and commission errors, and physical activity, were found to increase the correct classification of adult ADHD [81]. There is currently insufficient evidence to warrant the use of neuropsychological testing to determine the diagnosis of ADHD [82] or to predict impairment in major life domains [83].

Moreover, clinicians should also be aware of the possibility that a few individuals may feign ADHD symptoms to gain external incentives, like stimulant medication or special academic accommodations. There is some evidence supporting the effectiveness of performance validity tests (PVTs) in differentiating between genuine and feigned ADHD compared to rating scales [84].

Electrophysiological studies suggest that brain dysfunctions are involved in the central components of ADHD in both children and adults [85–89], although the finding of increased DAT density remains controversial [90,91].

Data from Electro Encephalography (EEG) is relatively scarce in adult ADHD. Generally, EEG studies of ADHD find similar deficits in adults and children, while some findings change with age and might be sensitive to developmental changes [92]. Despite US Food and Drug Administration approval of an EEG device (2013) that assists in the diagnosis of ADHD subtypes [93–95], this remains controversial [96]. EEG tests are not sufficiently accurate but could be useful to increase diagnostic certainty.

4. ICD and DSM criteria for ADHD

There are two diagnostic manuals used to diagnose ADHD: The Diagnostic and Statistical Manual of Mental Disorders (DSM) and

the International Statistical Classification of Diseases and Related Health Problems (ICD). As ADHD has been recognized as a disorder affecting individuals across the lifespan, the diagnostic criteria for adolescents and adults have been adjusted in the DSM-5, published in May 2013:

1) ADHD is now in the chapter Neurodevelopmental Disorders, which includes conditions associated with factors affecting the brain development.
2) Diagnostic criteria have been adapted by adding some examples describing how ADHD symptoms are expressed across the lifespan.
3) The age of onset criteria has been changed requiring several symptoms to be present before age of 12 years, instead of some symptoms and impairment by age 7.
4) The term "subtype" has been replaced by "presentation", reflecting the variation of ADHD symptoms within the same individual during the lifespan.
5) The symptom threshold required has been reduced to 5 symptoms instead of six for older adolescents and adults (>17 years) in either the inattention or hyperactive/impulsive domain.
6) Criteria requiring significant impairment has been modified to "clear evidence that symptoms interfere with or reduce the quality of social, academic and occupational functioning", with specifiers regarding severity level.
7) The presence of Autism Spectrum Disorder (ASD) is no longer an exclusion criterion, consistent with evidence showing their frequent co-occurrence.
8) ADHD Not Otherwise Specified (NOS) has been changed into Other Specified ADHD and Unspecified ADHD.

The revision of ICD-10, ICD-11 has been published in June 2018. ICD-11, developed by the World Health Organization now refers to ADHD as Attention Deficit Hyperactivity Disorder, instead of previously Hyperkinetic Disorder (HKD) [97]. It now uses similar requirements as the DSM-5 regarding age of onset, and the same 3 presentation types. In Europe, ICD codes are often used for statistics on mortality, morbidity and by insurance agencies for health-related reimbursements [98], whereas DSM is primarily used in clinical practice by licensed mental health care professionals [99].

The diagnostic assessment starts by evaluation of self-reported symptomatology. The clinical interview is essential for diagnosing ADHD in adults, which investigates the characteristic symptoms and impairments of ADHD in both childhood and adulthood. In children and adolescents, informants' ratings are higher correlated with heritability and cognitive and EEG findings than self-ratings [19]. Also prevalence and persistence rates increase when parent reports are used [19]. In adults this may be slightly different, as some research shows that the adult patient is the best informant [100]. The presence of a family member however (a parent and/or the partner) during the assessment can still provide valuable additional information, e.g. on severity and its translation into daily activities.

There is compelling evidence that a cut-off of four current symptoms is the most appropriate for an adult diagnosis [101,102]. However, due to concern about the possibility of an artificial increase in the prevalence of the disorder, DSM-5 lowered the threshold for diagnosing ADHD from six to five symptoms for those older than 17 years of age. Several items have been expanded by some illustrative examples to facilitate the recognition of the disorder throughout development. Although not included in thecriteria as such, behaviors reflecting executive dysfunction usually appear clearly during the assessment, when patients describe problems with organization, facing daily responsibilities,

solving problems, managing time and self-regulating (inhibiting) behaviors.

DSM-5 also highlights the importance of mood lability and emotional dysregulation as "an associated feature that support the diagnosis". Although emotional dysregulation may dominate the clinical presentation [103–105], it is not a criterion for classifying individuals as it lacks specificity, occurring in many other mental health conditions.

DSM-IV required that symptoms and impairment were present before age 7, but as research demonstrated no differences between children with an age of onset before and after age 7 [106] this criterion was changed to several symptoms by age 12. Similar findings have also been reported regarding adults reporting later-onset of symptoms [107,108], and there is disagreement both within and across sources concerning recall of symptom onset [109]. The fact that adults with ADHD frequently fail to recall childhood behavior led to the suggestion that clinicians take note that the onset of the disorder was during the developmental period, or they should use age 16 years as the upper age limit. Using this criteria captured all cases of childhood ADHD and 99% of adults with the disorder [110]. The decision of DSM-5 to extend the age of onset to 12 instead of 16 may have a negative impact on adults with ADHD who have difficulties with retrospective recall of childhood behaviors, and may not receive the diagnosis for this reason. This may be particularly true for those who had some compensation due to high intelligence, or lived in a highly structured or supported environment, or presented predominantly with inattentive symptoms. In such cases, the presence of a collateral informant (generally a parent or spouse) is of great value. Many adults with ADHD that are used to their lifelong symptoms, have limited awareness of how ADHD symptoms adversely impact their interpersonal relationships and affect their life; some reporting higher symptoms but lower impairments or vice versa.

Such inconsistency has been attributed to a lack of introspection and an incoherent self-view [111,112], and supports the utility of a collateral informant. If a significant other is not available, school reports or social care reports may be helpful.

4.1. Clinical picture

4.1.1. Inattention and hyperfocus
Patients with mainly inattention problems are often slow to think and formulate due to distractions. They may formulate things in a long-winded and tangential way, losing themselves in irrelevant details and having difficulty making decisions. A difficulty for the clinician is that this may hinder the diagnostic assessment. Patients may also over-concentrate or 'hyperfocus'. This phenomenon most commonly occurs when engaged in activities that the patient finds very interesting and/or provide instant gratification, such as computer games or online chatting. For such activities, concentration may last for hours on end, in a very focused manner.

4.1.2. Hyperactivity
With respect to hyperactivity, adults do not present in the same way as children. Their hyperactivity usually manifests in a more subtle way. Clinicians need to assess their *feelings* of restlessness. A first impression of mobility is not definitive; sitting calmly during the diagnostic assessment does not exclude any ADHD. Hyperactivity in adults often manifests itself as feelings of continuous inner restlessness or agitation, talking too much, ceaseless mental activity, not being able to relax properly or needing alcohol or drugs to relax and/or sleep. Hyperactivity and/or restlessness may be temporarily relieved by the patient engaging in excessive sport activities, and in such cases the person may suffer physical

ailments as the body may have insufficient time to recover and/or due to sustained injuries.

4.1.3. Impulsivity

Impulsive behavior and associated interpersonal conflicts often have consequences for relationships with family, friends, colleagues and employers. It may also seriously impact on personal finance when impulsive spending causes debt. Impulsive binge behaviors may also be present (e.g. binge eating), often to combat restlessness or due to a need for immediate gratification. Closely related to impulsivity are 'sensation seeking' behaviors when patients may seek out excitement from novel and thrilling stimuli. These often involve risk taking behaviors such as playing with fire, reckless driving, sexual risks, and provocative behavior leading to fights.

4.1.4. Emotional dysregulation

Emotional dysregulation is listed by DSM-5 as a characteristic feature of ADHD, supporting the diagnosis [113]. The type of emotional dysregulation seen in ADHD has been characterized as deficient self-regulation of emotional symptoms such as irritability, frustration and anger [114], and low frustration tolerance, temper outbursts, emotional impulsivity, and mood lability [115]. Emotional dysregulation in ADHD is different from episodic symptoms such as marked sustained irritability occurring within the context of altered mood states, such as an episode of depression or mania. In ADHD, emotional symptoms tend to reflect short lived exaggerated changes, often in response to daily events, with rapid return to baseline within a few hours [114]. Whether the type of emotional instability seen in ADHD is qualitatively different to that seen in other chronic conditions such as borderline personality disorder or post-traumatic stress remains unclear.

4.1.5. Excessive mind wandering

Another common feature of adult ADHD is excessive mind wandering, also referred to as mental restlessness [116–118]. In DSM-5 mind wandering is briefly mentioned as the occurrence of *unrelated thoughts.* Although mind wandering is a universal experience, some forms of mind wandering are detrimental because they interfere with task performance. Adults with ADHD frequently report a distractible mental state with multiple unrelated thoughts that are constantly on the go and jump from one topic to another [119,120]. Mind wandering is also a feature of other mental health disorders such as depressive or obsessive disorders. However, in ADHD mind wandering is characterized by unfocused, short lived distractible thoughts with no pattern of repeated thoughts or abnormality of content. Research found that excessive mind wandering was strongly correlated with ADHD symptoms, was a strong predictor of the diagnosis (sensitivity and specificity around 90% for case-control differences), co-varied with ADHD symptoms over a 6-month period, and was a better predictor of ADHD-related impairments than the inattentive and hyperactive-impulsive symptoms of ADHD [120]. In ADHD it can be measured using the Mind Excessively Wandering Scale [116,118,120] (Table 1).

4.1.6. Behavioral self-regulation (executive function deficits)

ADHD has been described as a disorder of executive functions such as inhibition and working memory. These include problems organizing, prioritizing and initiating work; focusing, sustaining and shifting attention to tasks; regulating alertness, sustaining effort and processing speed; managing frustration and regulating emotions; utilizing working memory and accessing recall; and monitoring and self-regulation of behavior [121,122]. Although clinically these are good descriptions of the types of difficulties experienced by adults with ADHD, behavioral measures do not

Table 1
Examples of ADHD-related symptoms.

Inattention	• Forgetfulness
	• Distractibility
	• Chaotic presentation
	• Difficulty organizing & planning
	• Difficulty listening
	• Difficulty with punctuality (arriving either too late or too early)
	• Temporary hyperfocus for highly salient tasks, but no control of attention when required or for many essential activities of daily life
	• Getting lost in details
	• Doubtfulness – unable to make decisions or solve problems
	• Needing too much time to complete tasks
	• Difficulty starting and finishing tasks
	• Mind Wandering:
	○ Mental restlessness
	○ Unrelated spontaneous thoughts, constantly on the go, jumping and flitting, multiple thoughts at the same time
	○ Associative thinking
Hyperactivity	• (Inner) Restlessness
	• Difficulty relaxing
	• Pacing up and down
	• Talking too much and too loud
	• Fidgeting, rocking or tapping
	• Not being able to bear an office job because of restlessness
	• Knocking things over because of excessive mobility
	• Being able to sit still but this comes with muscle strain
	• Restless sleep
Impulsivity	• Acting without thinking
	• Difficulty waiting turn – linked to feelings of irritability
	• Blurting things out that cause distress to others
	• Interrupting others
	• Impatience and difficulty waiting turn
	• Spending too much
	• Walking out of jobs
	• Starting relationships quickly
	• Not being able to postpone gratification
	• Sensation seeking and risk taking behaviors
	• Binge eating
Emotional dysregulation	• Mood lability
	• Low frustration tolerance
	• Emotional impulsivity
	• Irritability
	• Anger outbursts
	• Premenstrual increase of symptoms

correlate well with cognitive or neuropsychological tests of executive control [121–123]. A distinction needs to be made between rating scale measures of behaviours reflecting self-regulation of behavior referred to as EF (behavioral) deficits, and the results of neurocognitive tests of EFs such as working memory and inhibition. Neuropsychological test scores reflecting executive functioning lack ecological validity in that they have no significant relationship to behavioural rating scale measures of EF [124]. The EF test scores also are very poor at predicting impairment in a variety of domains of major life activities, compared to EF behavioural rating scales [125].

4.1.7. Burden of ADHD

The impairments associated with ADHD across the lifespan are impressive. ADHD is associated with learning difficulties, school dropout, underachievement at work [126], frequent job changes [127], chronic fatigue [128], financial problems, gambling and

internet use [129,130], home and traffic accidents leading to increased mortality rates [131–133], relationship difficulties and intimate partner violence [134,135], early onset of addiction [136], teenage pregnancies and sexual transmitted diseases [137,138], a two-fold increased smoking rate [139], an increased number of suicide attempts and self-harm in adolescents [140,141], and increased criminality [142,143]. Moreover, physical disorders and ailments may become chronic due to forgetfulness, health problems induced by a negative lifestyle, poor eating and sleeping habits, and lack of health care follow-up [144–147]. ADHD has further been associated with auto-immune diseases [148], obesity [149], and physical multi-morbidity. In one large study, individuals with more than 4 diseases had over more than 3-fold higher odds of possible ADHD [146]. The risk of diabetes, hypertension, cardiovascular disease and cancer, that are related to obesity, may be increased as well. An additional burden on family life may be the presence of one or more children with ADHD, which happens frequently due to the high familial risks of the disorder.

Clinicians should also be aware that high functioning adults with ADHD may not present with a typical pattern of functional impairments in their daily life. Adaptive or compensatory skills can develop that mask the more overt behavioral problems related to ADHD [150]. Some may find work that is well suited to their symptom profile. Furthermore, in ADHD neurocognitive performance and inattentive symptoms are sensitive to the salience of task activities [151,152]. Such people with ADHD may excel in certain aspects of their lives, but still be impaired in others, such as more routine and mundane tasks such as paying bills, looking after the house, or developing stable social relationships. Problems can include subjective distress from symptoms such as mental and physical restlessness, sleep problems, and emotional instability; and the use of drugs such as cannabis or alcohol to reduce these symptoms.

5. Prevalence of ADHD across the lifespan

In childhood, ADHD is among the most common psychiatric disorders with a prevalence rate of 3–5 % [153]. For this age group, well established diagnostic and treatment services are available throughout most of Europe. In the last four decades, a large body of evidence has accumulated, showing how in the majority of cases ADHD is a lifespan disorder, persisting as either the full blown disorder, or in 'partial remission' with persistence of some symptoms and continued clinical and psychosocial impairments [154–161]. The prevalence of ADHD in adults across twenty countries was recently estimated at 2.8%, with a range between 1.4 - 3.6% [3]. ADHD was also found in a Dutch population study to persist into old age (> 60 years) with a prevalence of 2.8–4.2% depending on cut-off (6 or 4 current symptoms respectively), and associated with impairment [162–166]. ADHD in older adults is accompanied by increased rates of mood and anxiety symptoms, general health problems, conflicts, divorce, loneliness, and a lower income, showing a similar pattern of problems as in younger age groups. Research exploring the needs for treatment of older adults with ADHD has commenced, and the first treatment protocol of older adults with ADHD has been published [167].

5.1. Sex issues

Sex differences in ADHD diagnosis are well documented, with girls being less likely to be diagnosed, and sex ratios ranging between 1:5 to 1:9 [168]. Such discrepancy is less evident in epidemiological research in children where the sex ratio is 1:3, suggesting under recognition of ADHD in girls in the clinic. In both epidemiological and clinical studies of adult ADHD the sex ratio is closer to 1:1 [169]. Several factors may explain the sex disparity during the lifespan. Girls with ADHD may

have less hyperactive/impulsive symptoms than boys; because of higher disruptiveness, boys are more likely to be referred by parents and teachers, whereas girls remain undiagnosed [170]. Missed diagnosis may be due to a lack of knowledge and recognition of ADHD in girls by health care professionals, and to the presence of other conditions: low self-esteem, anxiety as well affective disorders occur frequently in females with ADHD, and it is possible that ADHD symptoms may be mistakenly attributed to such comorbidities [171,172]. Females with ADHD appear to develop better coping strategies than males, and are better able to mask symptoms of ADHD throughout childhood. However, this may no longer work well when they face salient life challenges, such as leaving school, attending college or university, commencing employment, managing intimate relationships, and taking responsibility for their own life decisions [173]. Different genetic liability between the sexes [174], as well neuroendocrine factors affecting the dopaminergic system, such as thyroid and estrogen hormones [172,175], have all been also suggested to play a role in the masking of ADHD in girls and women. In addition, girls and women with ADHD are less well studied than males.

Women with ADHD are particularly vulnerable to early adversities, health and mental health problems compared to controls [176]. A higher prevalence of insomnia, chronic pain, suicidal ideation, generalized anxiety disorder, depressive disorders, a greater vulnerability to nicotine dependence [176,177] and an increased likelihood of risky sexual behaviors [138] has been reported in women with ADHD in comparison with controls.

5.2. Transition of adolescents to adult mental health services

As two-thirds or more of children with ADHD continue to have impairment into adulthood [178], many require the transition from child to adult mental health services. However, transition between services is generally difficult, placing youths with ADHD in an even more vulnerable position [179]. Research shows that disruption of care during transition adversely affects clinical outcome [180,181]. Clear recommendations have been formulated, mostly based on clinical experience, to facilitate successful transition of patients with ADHD from child to adult mental health services [1,182–185]. These are a) transition should ideally be completed by the age of 18 years, b) transition should be planned in advance by both child and adult mental health services, c) young people with ADHD and their parents should have sufficient information regarding the transition process (e.g. psychoeducational material including available services), d) both continued parental care and child's growing autonomy should be considered, e) if necessary a formal meeting involving child and adult mental health services (with specific knowledge on this age group) and patients and parents should be considered. All these can help to prevent the drop-out of young people with ADHD from services. However, the reality is quite different, as indicated by two reviews [186,187]. Compared to other diagnostic groups, youth with ADHD were significantly less likely to be referred, they were more likely to refuse referral, and a significant number remained in child services well beyond their 18th year. Studies also have found transition policy deficits [186,188], suboptimal experience of transition when it does occur [186,189], a dearth of adult ADHD services [190], and a lack of expertise on ADHD amongst adult clinicians [3,191]. This suggests there is an urgent need for a multifaceted approach combining transition specific clinical guidelines, and funding for the training the training of clinicians, to ensure that those in need of ongoing intervention may successfully transition to adult services.

5.3. Late-onset ADHD?

Recent longitudinal studies have indicated that besides typical childhood onset ADHD, with the full diagnostic criteria being met

before the age of 12 years, there may be later-onset cases with onset of the full diagnostic criteria beyond this age [104,189,190]. These findings have proven controversial due to severe methodological limitations [192,193], however the large majority of later onset cases appear to meet the DSM-5 age of onset criteria of several symptoms by the age of 12 [113]. Late onset of symptoms was evaluated in the control arm of the long-term follow-up of the Multimodal Treatment study of ADHD (MTA). In most cases, other factors were present that could discount the late onset of ADHD symptoms and exclude the diagnosis of ADHD [194], such as symptoms representing non-impairing cognitive fluctuations, a comorbid disorder, or the cognitive effects of substance use [192]. However, there remained a very small sample of adolescent onset cases. Another population cohort study found that the majority of those with apparent late-onset ADHD had high ADHD scores at least one point in childhood, suggesting that they may have been misclassified on the basis of their score at age 12 years [195]. These cases with high score before the age of 12 years might not have met full criteria before the age of 12 years, but would meet the current DSM-5 criteria for several symptoms in childhood. One conclusion is that clinicians should be aware that subthreshold cases of ADHD during childhood might go on to meet the full diagnostic criteria as older adolescents. Clinicians should take care to fully assess impairment, psychiatric history, and substance use when diagnosing and treating cases with apparent later-onset ADHD [192].

6. Screening and diagnostic assessment

6.1. Screening

Several screening tools are available for ADHD in adults. The validated tool recognized by the World Health Organization (WHO) and updated for DSM-5 criteria is the Adult ADHD Self report Rating Scale (ASRS). This revised ASRS was studied in managed care, the general population and in a clinical group. The sensitivity was 91.4%; specificity 96.0%; AUC, 0.94; PPV, 67.3% [196]. The previous version of the ASRS has been translated into many languages (see http://www.hcp.med.harvard.edu/ncs/asrs.php). The Wender Utah Rating Scale assesses besides ADHD a broader spectrum of symptoms that often accompany ADHD or are comorbid. Several other scales that ask about the 18 items as defined in the DSM-5 to classify ADHD are available, see Table 2.

A key question is who should be screened for ADHD. In general, since the hallmark of adult ADHD is a chronic trait-like condition that emerges out of childhood or early adolescence, anyone presenting with such a clinical picture should be screened [2]. This should include those with chronic histories of inattentive, restless or impulsive behaviors, as well as those with emotional instability. Targeted groups where rates of ADHD are significantly increased and should therefore be screened include family members of people with ADHD, and those with a history of behavioral problems, any chronic mental health disorder including anxiety,

depression, cyclothymia, personality disorder, bipolar disorder, substance use disorders, those with multiple physical diseases [146], and those within the criminal justice system [197].

6.2. Diagnostic assessment

For diagnostic assessment, the use of a semi-structured diagnostic interview is advised, such as the Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0) [198], based on the DSM-IV-TR criteria. DIVA 2.0 is available online without charge, currently in 19 languages (www.divacenter.eu). The Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID) has been validated in English and Spanish [199]. DIVA 2.0 has been validated in two European populations [81,199], and is increasingly used in international research. A DIVA 2.0 app is available in the App and Google Play stores. The update of DIVA 2.0 for DSM-5 criteria into 'DIVA-5' in all languages is ongoing. DIVA-5-ID, for people with Intellectual Disability (ID) and Young DIVA, for children and adolescents, are new versions of DIVA-5. An alternative is ACE+ (http://www.psychology-services.uk.com/resources.htm), a semi-structured diagnostic interview to assess ADHD in adults (>16 years). ACE + assesses the core symptoms of ADHD in both adulthood and childhood, the extent to which they impair functioning, and the presence of co-existing conditions. ACE + is currently online available in 7 languages, with more translations underway. For these and other diagnostic tools, see Table 2.

6.3. The assessment process of ADHD and comorbidity

Diagnosis of ADHD is based on a careful and systematic assessment of a lifetime history of symptoms and impairment. Central to this process is the assessment of childhood-onset and current symptoms of ADHD, and the presence of symptoms and impairment in at least two domains (school, work, home, interpersonal contacts). For this lifetime assessment, collateral information from family members and spouse are useful. It is important to take a full medical history of psychiatric and somatic conditions, as well as a family history of psychiatric and neurological problems. High intelligence should be taken into account as a potential moderator in the diagnostic assessment, as ADHD is underdiagnosed in patients with high intelligence because they use more compensatory strategies [200]. Clinicians should also be aware that high functioning adults with ADHD may not present with a typical pattern of functional impairments in their daily life. Adaptive or compensatory skills can develop that mask the more overt behavioral problems related to ADHD [150]. Some may find work that is well suited to their symptom profile. Furthermore, in ADHD neurocognitive performance and inattentive symptoms are sensitive to the salience of task activities [151,152]. Such people with ADHD may excel in certain aspects of their lives, but still be impaired in others, such as more routine and mundane tasks such as paying bills, looking after the house, or developing stable social relationships. Problems can include

Table 2
Open access Scales and Interviews for Diagnostic Assessment of ADHD in adulthood.

Scales[a]	
Adult ADHD Self-Report Scale	Developed by WHO; 6-item version, based on DSM-5 (ASRS), in many languages https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5470397/
Wender Utah Rating Scale	https://www.thecalculator.co/health/Wender-Utah-ADHD-Rating-Scale-Calculator-858.html
Diagnostic Interviews[b]	
DIVA-5	Structured Diagnostic Interview for ADHD in adults; according to DSM-5; in 19 languages www.divacenter.eu
ACE+	Semi-structured Interview for ADHD in adults https://www.psychology-services.uk.com/adhd.htm

[a] Other scales without open access are: Conners Adult ADHD Rating Scale (CAARS), and the Adult ADHD Investigator Rating Scale (AISRS).
[b] Other interviews without open access are: Conners Adult ADHD Diagnostic Interview (CAADID), Adult ADHD Clinical Diagnostic Scale (ACDS).

subjective distress from symptoms such as mental and physical restlessness, sleep problems, and emotional instability; and the use of drugs such as cannabis or alcohol to reduce these symptoms.

Adult diagnoses may be missed in clinical practice due to lack of knowledge about ADHD in adulthood among practitioners and due to the high frequency of comorbid psychiatric conditions [201]. The lifetime co-morbidity rate is 60–80%. Having three or more disorders was associated with a ten-fold increase of the chance of having ADHD in a population study in 20 countries [3]. Before treatment start, all comorbidities must be established so that the best order of treatment can be determined together with the patient. In the study by Fayyad et al, data on ADHD and comorbidities was collected on 26,744 respondents [202]. In adults with ADHD having one comorbidity was found in 23% of cases, two in 14% of cases and three in 14% of cases. Rates were particulary high for any mood disorder (22%), any anxiety disorder (34%), substance use disorders (11%) and any behavioural disorder (15%).

Psychiatric comorbidity is thus a clinically important dimension of ADHD heterogeneity and a factor that contributes to the persistence of ADHD in adulthood [203,204]. It is important for the diagnosis of ADHD, as well as the correct targeting of treatments, to identify mood, anxiety, eating, sleep, somatic and substance use disorders, in addition to personality, tic and autistic spectrum disorders [205]. Because adults with ADHD often exhibit low self-esteem, low mood, mood lability and irritability, these symptoms may sometimes be confused with dysthymia, cyclothymia, bipolar disorder or borderline personality disorder. Furthermore, daily mood changes in ADHD are very common, and represent a poorly regulated but essentially normal range of moods, rather than the more severe extremes of depression and elation as seen in bipolar disorder. It has been argued that chronic mood instability should be considered part of the core syndrome of ADHD [206,207]. ADHD and borderline personality disorder share symptoms of impulsivity, mood instability, anger outbursts and feelings of boredom [158,208,209]. In the ADHD patient, impulsivity and anger are usually short-lived and thoughtless rather than driven. Conflicts in relationships, suicidal preoccupation, self-mutilation, identity disturbances and feelings of abandonment are usually less intense than in borderline personality disorder. However, the differences may not be clear-cut because these symptoms are chronic and trait-like in both conditions [210].

ADHD in children is also associated with increased rates of neurodevelopmental disorders like autism spectrum disorder, dyslexia and impaired motor coordination which are thought to arise from overlapping genetic influences [211]. Such neuro-developmental comorbidities are less well studied in adults, but they are commonly observed in clinical practice and may lead to continued impairments. As the order of treatment will depend on the presence and severity of comorbidities, evaluation of comorbid disorders is a key component of the ADHD assessment process, using appropriate clinical diagnostic approaches.

6.4. ADHD and criminality

The prevalence of ADHD is increased in forensic populations compared to the general population [212], and the risk of criminality is increased in individuals with ADHD, especially in those with comorbid oppositional defiant disorder, conduct disorder, substance misuse and antisocial personality disorder [213]. A meta-analysis comprising 42 studies from 15 countries reported a 5-fold increased prevalence of ADHD in youth prison populations (30%) and a 10-fold increased prevalence in adult prison populations (26%) as compared to the general population [214]. When using diagnostic clinical interviews, the estimated ADHD prevalence in prisoners was 25.5%, without significant

differences for gender and age [214]. Further, inmates with ADHD compared to those without are reported to have higher rates of psychiatric morbidity including substance misuse, an earlier onset of offending, more violent offences, criminal recidivism and more frequent and severe institutional aggression [215,216].

7. Treatment

7.1. Effective treatments

The treatment of adults with ADHD should follow a multimodal and multidisciplinary approach, which includes psychoeducation, pharmacotherapy, cognitive behavior therapy (CBT) and coaching for ADHD, which are all discussed in this article.

Ideally, the treatment plan also involves the adult's partner, family or close relationships, and in some cases systemic (family) therapy may be required when gross disruption to family relationships and functioning is present.

7.2. Treatment focus in comorbid ADHD

In the most recent report of 20 nationally or regionally representative World Mental Health surveys, data on ADHD and comorbidities was collected on 26,744 respondents [202]. In adults with ADHD having one comorbidity was found in 23% of cases, two in 14% of case and three in 14% of cases. Rates were particulary high for any mood disorder (22%), any anxiety disorder (34%), substance use disorders (11%) and any behavioural disorder (15%). Treatment of ADHD is therefore most often in the context of co-occuring disorders.

Before treatment starts, all comorbidities must be established so that the best order of treatment can be determined together with the patient. In general, the most severe disorder is prioritized. For instance, psychosis, bipolar disorder, substance abuse, severe depression and severe anxiety are usually treated first. Milder mood or anxiety disorders, and emotional instability, may respond to treatment of ADHD and can be treated at the same time as ADHD. Drug and alcohol abuse should be stabilized but can be treated at the same time as ADHD.

7.3. Psychoeducation on ADHD

According to consensus based on good clinical practice and the need to work on an informed consent basis within a multimodal treatment approach, psychoeducation should be the first step as a standard of care [217]. First evidence from an open trial and a randomized clinical trial shows, that patients and significant others who attend a structured psychoeducation program increase their knowledge about ADHD, and improve the quality of their relationships and psychological well-being [218,219].

7.4. Pharmacotherapy for ADHD

7.4.1. Introduction on pharmacotherapy

In the first European Consensus Statement [1] psychostimulants (methylphenidate and dexamphetamine) were recommended as the first-line pharmacotherapy for adult ADHD [1,184,220], as they exert moderate-to-high clinical effects, with average effects higher than atomoxetine (ATX) and other non-stimulant medications [2]. There were, however, no head-to-head studies providing robust comparative analysis of efficacy differences [221]. Across most of Europe, lisdexamfetamine (LDX) has been introduced as a slow release formulation of dexamphetamine. The recent systematic review and network meta-analysis on the comparative efficacy and tolerability of medications for ADHD in children, adolescents and adults by Sam Cortese et al.

showed, that the first pharmacological choice for ADHD in children and adolescents is methylphenidate, and amphetamines in adults [222]. In fact in adults, amphetamines were not only the most efficacious compounds, as rated by clinicians and by self-report, but also as well tolerated as methylphenidate and the only compounds with better acceptability than placebo.

7.4.2. Licensing

Licensing of ADHD medications for adults is more diverse than in 2009 [1], reflecting greater understanding of ADHD, and efforts to market ADHD medications in Europe. In Denmark, Ireland, Norway, Sweden, Switzerland, the Netherlands and the United Kingdom, most ADHD medications can be prescribed, either with a full license (e.g. Medikinet®, Strattera®, Elvanse®) or transitional licenses (e.g. Concerta XL®) and off-label prescribing is endorsed by national guidelines and formularies. Dexmethylphenidate (Focalin XR®) is licensed in Switzerland only. In other countries, only a limited selection of medications is available for funding by the state sector, but off label prescribing is possible. In another group of countries (e.g. Greece, Slovenia, Poland), only very few ADHD medications are available, with off-label prescribing mostly in the private sector. The European Network on Adult ADHD (ENAA) and the Neurodevelopmental Disorders Across the Lifespan (NDAL) section at EPA strongly recommend that evidence-based treatments for adult ADHD are made more available and licensed across European countries.

7.4.3. Efficacy and adverse effects of stimulants

Meta-analyses of randomized controlled trials (RCTs) demonstrate the efficacy of stimulants and ATX in the reduction of ADHD symptoms in adults [223–227]. Standardized mean differences (SMDs) range from 0.4 to 0.7, with stimulants showing greater efficacy than ATX [224]. The longest RCT in adults still found significant effects of MPH after one year [228]. National registry data also suggest long term benefits. Although these studies are not definitive due to lack of randomization and controls, they demonstrate 'real-world' societal benefits associated with the use of ADHD medications. These studies show that during periods of receiving medications for ADHD there are marked reductions in transport accidents and mortality rates [132,229], criminal convictions [230], suicidal behavior [231], violent reoffending [230], depression [232] and substance misuse [233]. Similar analyses with antidepressants find no effects, suggesting the effects are specific to ADHD medications.

A 2011 meta-analysis [225] revealed that MPH (mean dose 41.2–82 mg/day) exerted a moderate effect on ADHD symptoms, with large effects observed at doses of >77.4 mg/day. Immediate release (IR) MPH has a short duration of action of maximum 4 h. Due to difficulties with compliance when needing to take medication up to several times a day, long-acting MPH preparations have been developed, with durations of action ranging between 6–12 h.

The recommended dose range of Immediate Release dexamphetamine (IR) is 5–60 mg/day [220]. Lisdexamfetamine (LDX) has a slow release profile giving the drug a relatively low abuse profile [234]. LDX is taken once daily with a mode of action of up to 14 h [235]. Three RCTs in adults indicate moderate to large effects on ADHD symptoms [236–238] (SMD = 0.97) [239], comparable to MPH. The safety and tolerability profile is similar to other stimulants [240,241].

The main adverse effects of stimulants are increased heart rate and blood pressure, and reduced appetite and sleep [242–245]. Heart rate, blood pressure, sleep problems and weight are therefore assessed before, and monitored at least twice a year during treatment. Serious cardiac complications are rare [243,246,247] with reported risks for myocardial infarction,

sudden cardiac death, ventricular arrhythmias or stroke no more than 0.2-0.4% higher in one study [248]. MPH might trigger arrhythmias in patients with congenital heart diseases [249]. The consensus is caution in patients with known cardiac defects, but risks are small.

7.4.4. Atomoxetine

ATX yields moderate efficacy in reducing ADHD symptoms (SMD: −0.33 to −0.40) [227]. Onset of action is 1–2 weeks, and full effects may take up to 6 months to develop [250]. If rapid onset of effect is not essential, ATX may be a good choice for high risk patients who need stable control of ADHD symptoms [251].

The use of ATX as first line in drug abusers continues to be debated with other experts preferring stimulants due to rapid onset and potentially greater effects [252]. Although in the past there were concerns that stimulants may increase the risk of substance use disorders (SUD), there is now a wealth of data demonstrating reductions in SUD during periods of treatment of ADHD with stimulants [233,253].

ATX may be a good choice with co-occurring anxiety that might be exacerbated by stimulants, as a RCT of adults with comorbid ADHD and social anxiety disorder found improvements in both ADHD and social anxiety [254]. ATX does not appear to be effective in the treatment of comorbid depression in adolescents [255].

7.4.5. Guanfacine and clonidine

In Europe, guanfacine extended-release (GXR), an alfa-2 adrenergic agonist, is licensed for the treatment of children and adolescents with ADHD for whom stimulants are not suitable, not tolerated or where shown to be ineffective [256,257]. Notably, there are currently no RCTs in adult patients to support the use of GXR in this age group, only a study using GXR or placebo as an adjunct to stimulant treatment that had insufficient effect. Both treatments did not differ in efficacy [258].

Extended-release (ER) clonidine is approved in the US for treatment of ADHD in 6–17- year olds as monotherapy or an adjunct to stimulants. There are RCTs on both ER clonidine [259,260] and IR clonidine [261,262] in children and adolescents with ADHD, but no equivalent studies in adults.

7.4.6. Bupropion

There are conflicting findings for bupropion from a small number of adult studies. Positive results were reported with higher doses (400–450 mg per day) [263,264]. Due to a limited evidence base, bupropion use should be restricted to cases who do not tolerate other ADHD medications.

7.4.7. Other medications

Selective noradrenaline reuptake inhibitors such as reboxetine may be an alternative to ATX [265,266]. There is limited evidence for tricyclic antidepressants [267,268]. Selective serotonin reuptake inhibitors (SSRIs) are not effective for the treatment of ADHD [229,230,269]. Modafinil, a wakefulness-promoting agent used in the treatment of narcolepsy, has not been demonstrated as an effective treatment for adult ADHD in a phase 3 trial that had high rates of side effects (86%) and drop-out (47%) possibly resulting from excessive doses (210–510 mg/day) [270].

7.4.8. Long-term safety concerns

Currently there is no evidence of significant long-term risks using stimulants. Tomography scans find higher striatal dopamine transporter availability in ADHD patients treated with stimulants [271]. The clinical implications of this up-regulation are not clear. Potential toxicity on heart valves of medications with an agonist

effect on 5-HT$_{2B}$ receptors have been discussed [272], including MPH and guanfacine. Some argue that echocardiography should be routinely performed prior to treatment with potential valvulo-pathic drugs [273]. This risk is not however established, and we and others do not recommend routine echocardiograms [184,252,274], except in older adults (> age 50) [167].

7.4.9. Combined psychopharmacology

The high rate of psychiatric comorbidity in adult ADHD frequently necessitates combined psychopharmacology [275]. Accordingly, the risk of possible drug-drug interactions when treating adults with ADHD must be considered. These include the following:

– Monoamine oxidase inhibitors are generally contraindicated due to the risk of hypertensive crisis.
– Although MPH is mainly metabolized in the liver, drug interactions via CYP enzymes are uncommon. Amphetamines, however, are metabolized primarily via the CYP 2D6 enzyme system making drug interactions possible (with inhibitors or inducers of this enzyme system, e.g. fluoxetine and paroxetine) [276].
– Treatment with medications that act on the noradrenaline system, including certain antidepressants (e.g. duloxetine, venlafaxine), will have an additive effect and may increase the risk of hypertension and other adverse cardiovascular events.
– Due to its metabolism by the CYP 2D6 enzyme system, ATX levels can increase in combination with enzyme-inhibiting SSRIs (e.g. fluoxetine and paroxetine) [277].

7.5. Considerations when treating special groups with pharmacotherapy

7.5.1. ADHD with comorbid bipolar disorder

A pharmaco-epidemiological study found that MPH mono-therapy in patients with bipolar disorder increased the risk of switch to a manic episode (hazard ratio 6.7). However, when combined with a mood stabilizer, MPH reduced the risk of mania (hazard ratio 0.6) [278]. This supports the current recommendation to treat ADHD in bipolar disorder patients with stimulants, so long as they are also taking mood stabilizers.

7.5.2. ADHD with comorbid substance use

Meta-analysis of RCTs in adults found that most ADHD medications reduce the core symptom severity of ADHD, but have limited effect on comorbid substance use [279]. However, a large Danish Registry study showed a decrease of substance use in ADHD patients when using MPH [280]. Recent RCTs using higher doses of ER Mixed Amphetamine Salts (Adderall XR®) or OROS MPH (Concerta®), combined with CBT found better effects on both ADHD and substance use, compared to studies using lower dosages [281,282]. The relevance of higher doses is supported by a pharmaco-epidemiological study from Sweden showing that higher MPH dose was associated with long-term treatment adherence in patients with ADHD and substance use disorders (SUD) [283]. Immediate-release stimulants should be avoided in patients with ADHD and SUD, whereas OROS-MPH and LDX have lower abuse potential [284]. Further recommendations for treating comorbid substance use disorders can be found in Bolea-Alamanac et al. [184], and in the recently published international Consensus Statement on diagnosis and treatment of substance use disorders with comorbid ADHD [285]. This Consensus Statement mentions that the use of stimulant treatment for ADHD does not precipitate the onset of SUD in adults without previous SUD [286]; also that in SUD patients, treatment of ADHD can be useful to reduce ADHD symptoms without worsening the SUD, and should not be avoided [287].

7.5.3. Cognitive enhancement in students

Another group where screening for ADHD is appropriate is the student population. This is because we know that ADHD specially interferes with educational attainment. Further, this has been highlighted be the finding that genetic risks for ADHD overlap with those for educational outcomes [28]. Student groups with particularly high rates of ADHD include those presenting with specific learning difficulties [288] and mental health problems [202]. Related to this, there are concerns, particularly in countries with a higher rate of stimulant prescriptions, that students may seek the diagnosis of ADHD to receive stimulants for cognitive enhancement. Some studies show that although most students use their ADHD medication as prescribed, misuse and diversion is not uncommon [289]. Care must therefore be taken to ensure that students are diagnosed and treated for ADHD when appropriate, while minimising risks of diversion.

7.5.4. Pregnancy and breastfeeding

There is only limited information on the effects of ADHD medication on the fetus and new-born [290]. As suggested by population-based studies, MPH or amphetamine exposure during pregnancy is not related to higher rates of any congenital malformations [291–293]. For cardiac malformations, MPH use was associated with a small increased risk (RR 1.28 (95% CI, 0.94–1.74), where amphetamines were not. There is some evidence suggesting that treatment with MPH or ATX might increase the risk of miscarriage [294,295], although there were several confounding factors such as younger age and social disadvantage, that could explain the association [296]. Another study found that the use of stimulant medication during pregnancy is associated with miscarriage to the same degree as having ADHD itself [295], these findings need further investigation. Potential adverse effects on the fetus from intra placental exposure to medication in pregnancy should be considered against the possible adverse effects of interrupting treatment abruptly in women with ADHD [184,297,298]. Each case should be assessed individually taking into account possible risks of both treating and interrupting treatment.

Amphetamines may be given preference over other medications. Some authors do not consider Atomoxetine because of lack of safety data [299,300]. MPH seems to be safe during breastfeeding. The amounts of medication excreted in breast milk, and consumed by the infant, are very small (with the Relative Infant Dose (RID) (< 1%) [290,299], and no drug-related side effects have been were reported. The impact of ATX, guanfacine, and clonidine on breastfeeding-related outcomes is largely unknown [301–303], and they are not recommended [299].

Until now no adverse reactions were reported among infants of mothers receiving LDX or dexamphetamine (RID: 4–10.6%). There are some preliminary reports suggesting that dexamphetamine treatment may lead to a suppression of prolactin secretion in postpartum women, though with unclear clinical implications [304]. Bupropion was found to produce low levels in milk, suggesting relative safety. Of note, there are two known cases of seizures developed by children breastfed by women receiving bupropion [305].

7.5.5. ADHD and sleep problems

In the majority of cases, ADHD in children and adults is associated with a circadian rhythm disorder with delayed sleep onset [306–308]. Meta-analysis of nine studies investigating the effects of stimulant medication on sleep in children and adolescents found that stimulants can lead to longer sleep latency,

worse sleep efficiency, and shorter sleep duration [309]. Similar findings have been reported in adults [310]. Careful titration of stimulants and psychoeducation around sleep optimization can improve the quality of sleep, possibly due to improved daytime structure, the maintenance of regular physical activity and improved mood [198,309,311]. In children with ADHD and chronic insomnia, melatonin has been shown to advance the sleep onset, and increase sleep duration [312]. A trial targeting insomnia in adults with ADHD is ongoing, and clinical experience points in the same direction of possible efficacy of treatment with melatonin at night, and also of light therapy in the morning [308]. Treatment of insomnia should always start with sleep hygiene education and optimizing the stimulant or non-stimulant treatment of ADHD [311]. A low dose of IR MPH (usually 5 mg) taken at night time can reduce ceaseless mental activity to a degree that allows sleep in some cases.

7.6. Cognitive behavior therapy (CBT) and coaching for ADHD

Although pharmacological treatment of ADHD is very effective, many patients continue to experience significant symptoms and functional impairment in daily living. Empirical evidence from numerous uncontrolled studies, more than ten randomized controlled trials (RCTs) and a meta-analysis has shown that in group or individual settings, cognitive behavioral therapy (CBT) reduces ADHD-core symptoms, associated symptoms such as emotion dysregulation, anxiety and depression, and functional impairments across different areas of daily living in adults [228,313–315]. CBT is best used within a multi-modal treatment approach and as an adjunct to medication as current research does not fully support the efficacy of CBT as a sole treatment for adult ADHD [274,316–318]. Most controlled studies have been conducted in patients taking ADHD medication and demonstrate an additional significant treatment effect [313,318–322]. The largest controlled multi-center CBT-study to date has demonstrated that psychological interventions result in better outcomes when combined with MPH as compared to psychological interventions in unmedicated patients [228]. In a systematic review of 51 pharmacological and non-pharmacological interventions [316], the highest proportion of improved outcomes (83%) was for patients receiving combination treatment. However, not all adults with ADHD desire or tolerate pharmacological treatment. In these cases CBT may be the best option.

Across all studies there are some consistent characteristics of CBT treatment, both in form and content. All approaches are highly structured. Most are manualized, and establish psychoeducation as the first step. Most programs are skills-based and focus on organizational and time management skills, emotional regulation/control, problem solving skills, prosocial competence and strategies to improve attention and impulsivity management. In addition to behavioral interventions that require patients to try out and rehearse in daily life techniques suggested in the therapy session, programs include cognitive strategies, such as the identification of negative automatic thoughts, methods to address 'thinking errors' and the introduction of cognitive restructuring techniques [323]. There is emerging evidence that cognitive distortions and dysfunctional cognitive schemes related to a biographic accumulation of negative experiences associated with ADHD-symptoms contribute to negative functional outcomes and lead to avoidance behavior, failure-orientation, reduced self-efficacy, procrastination, depressive symptoms and anxiety [324–326]. Furthermore, most programs highlight the importance of including significant others in the treatment process to reduce dysfunctional interactions and stigmatization associated with ADHD symptoms.

Coaching or mentoring is a derivative of the cognitive behavioral paradigm involving the development of a collaborative mentoring partnership. Coaching aims to provide structure, support and feedback for building life skills and changing negative outcomes related to ADHD in daily living [217,327,328]. However, there is no standard methodology and the coaching process varies considerably, including face-to-face contact, telephone calls and/or email contact. To date, there are no controlled studies assessing the efficacy of coaching as a therapeutic means in the treatment of adults with ADHD. Nevertheless there is some preliminary support for positive outcomes from uncontrolled studies [327,328]. Similarly there is some support for the effectiveness of mindfulness based cognitive therapy (MBCT) for adults with ADHD [329–331].

8. Cost and cost effectiveness

Because of the broad impact of ADHD on general functioning, the disorder is likely to have serious economic implications for children, families, and society. The studies which calculate costs however are so far limited as they typically examine only one aspect of the costs, for example "from the perspective of a major German health insurance fund" [332]. Particularly for adults with ADHD, estimates should include not only direct costs (the costs of labor, supplies, and equipment to provide direct patient care services) but also indirect costs (mainly related to the loss of productivity) such as costs to family, costs due to impairment in employment, costs due to accidents [333], smoking and substance misuse, and costs due to involvement with the criminal justice system.

Direct costs have been examined [334–336], but are heavily depending on the healthcare system from which they are derived and the type of pathway/care package provided. These estimates therefore, although potentially useful for comparisons between disorders within the same healthcare system, should not be generalized to different contexts. The most comprehensive approach to calculate the total costs of ADHD in the Danish Psychiatric Central Register, showed that there is an economic burden of ADHD which is considerable and falls both on the individual and the state [337].

Apart from the costs (either direct or indirect) of ADHD, there is also the question of cost benefit for treating ADHD. This first asks whether a treatment of a disorder is worthwhile when compared against alternatives in terms of allocation of healthcare funds, and second which ADHD intervention brings the most benefit at the lowest cost. For the former, an argument can be made that adult ADHD is a condition which is cost effective to treat from the societal perspective because of the efficacy and relatively low cost of the medicines used for its treatment [224,338]. For the latter, among children and adolescents with ADHD, there is consistent evidence [339–343] that pharmacotherapies are cost effective compared with no treatment or behavioral therapy [344]. Unfortunately there is insufficient research to conclude the same for adults with ADHD (Table 3).

9. Stigma surrounding ADHD

Substantial stigmatization and myths continue to surround ADHD [345]. A recent study on negative coverage of ADHD and autism in Flemish newspapers found a 2-fold more negative than neutral or positive coverage of ADHD than of autism [346]. Stigma arises from lack of awareness, of prejudice about symptom etiology (e.g. poor parenting, lack of moral), incompetence (e.g. laziness) and perceived dangerousness (e.g. unpredictable and potentially violent behavior) [347]. Other variables contributing to stigma are doubts about the validity and reliability of an ADHD diagnosis, along with age, gender, ethnicity and the public's skepticism toward ADHD medication. Also, the restricted regulatory status for

Table 3
Summary of key points.

Neurobiological and environmental background	High heritability (60-80%), environmental risk factors and their interaction, are involved in the majority of ADHD cases.
	Abnormalities in grey matter, cortical thickness and white matter microstructure have been shown in ADHD compared to controls, indicating that structural deficits in ADHD involve interconnections among large scale brain networks.
	Functional neuroimaging shows dysfunctions in several domain-specific fronto-striatal and fronto-cerebellar neural networks, as well as an enhanced activation of default mode regions.
	These findings, as well as the effectiveness of pharmacological treatments with dopamine agonists, support the neurobiological underpinnings of ADHD.
Diagnosis	The clinical diagnosis of ADHD depends on self-report during a structured diagnostic interview, whenever possible with collateral information about lifetime symptoms and impairment. It cannot be established using solely neuropsychological tests.
	Recent research shows that besides inattention, hyperactivity and impulsivity, emotional dysregulation and excessive mind wandering are common symptoms associated with ADHD in adults.
	The underdiagnosis of girls and women with ADHD may be due to a different expression of symptoms and comorbidities, to referral bias, and to interaction of hormones with the dopaminergic system. Further research is needed.
	The concept of late-onset ADHD refers to an age of onset after 12 years, and needs further study concerning the overlap and differences with childhood onset ADHD.
	High rates of psychiatric comorbidity, physical multi-morbidity, increased mortality and suicide rates, and criminality may 'mask' the underlying ADHD condition.
	Stigma leads to misconceptions about ADHD and underdiagnosis.
DSM-5 criteria	Main changes in the DSM-5 criteria for ADHD are:
	ADHD is placed in the chapter of Neurodevelopmental Disorders
	The age of onset of symptoms is before age 12, instead of age 7
	The cut off for current symptoms in adults is 5/9 instead of 6/9
	A diagnosis of ADHD can now be combined with Autism Spectrum Disorder (ASD)
Prevalence	The mean prevalence of ADHD in adults across 20 countries is estimated at 2.8%. In people above age 60, a similar prevalence rate has been found.
	The prevalence of ADHD in prisons is 25%, a 10-fold increase compared to the general population.
Transition	Two-thirds of children with ADHD continue to have ADHD symptoms associated with impairments in adulthood, therefore adjustments in the health care system to support the transition from child to adult services are needed.
Treatment	Psychoeducation for adults with ADHD and their significant others is recommended as a first treatment step.
	Stimulants are the treatment of choice for adults with ADHD. Long-lasting, extended release formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing.
	Licensing of stimulants for adult ADHD is urgently needed in European countries and beyond.
	The non-stimulant atomoxetine is recommended as a second line treatment. There is limited evidence in adults for guanfacine, bupropion, tricyclic antidepressants and reboxetine in controlled studies.
	Cognitive Behavior Therapy reduces ADHD-core symptoms, associated symptoms such as emotion dysregulation, anxiety and depression, and functional impairments across different areas of daily living in adults. CBT is best used within a multi-modal treatment approach and as an adjunct to medication, as research does not fully support the efficacy of CBT as a sole treatment for adult ADHD.
Pharmacological treatment of special groups	In patients with ADHD and substance use disorder, to be effective, treatment with stimulants may use higher dosages than normal.
	In patients with ADHD and bipolar disorder, the combined approach of a mood stabilizer with a stimulant has been shown to treat both disorders effectively without inducing (hypo)manic states.
	During pregnancy stimulants are not advised, though large cohort data showed no increased risk for congenital malformations using stimulants during the first trimester. The risk for cardiac malformations using MPH however was slightly increased, while this was not the case for amphetamines.
	Research on the wishes of older people with ADHD regarding treatment, and trials on the safety and efficacy of medicines are needed.
	Based on data from large cohort studies, following treatment, the negative outcomes associated with ADHD significantly diminish, i.e. traffic accidents, mortality, criminality, depression and suicide, and substance abuse.
Costs	The economic burden of ADHD is considerable and falls both on the individual and the state. Pharmacotherapy in children is cost effective compared to no treatment and behavioral therapy, but data in adults are still lacking.

ADHD medications in many countries adds to the stigma within the mental health profession and the media. Public stigmatization of ADHD, and the following self-stigma and courtesy stigma are underestimated risk factors for treatment adherence, treatment efficacy, symptom aggravation, life satisfaction, and mental well-being of individuals affected by ADHD [348].

Self-stigma has been studied in children and adolescents and is characterized by a sense of feeling different from peers, and negative self-evaluation as a consequence of that perception. However, some young people were prepared to challenge the stigma by self-disclosure and openness about their condition [349]. Lower stigma in teachers towards adult ADHD seems to relate to greater knowledge about the condition [350]. Among general practitioners (GPs) from the UK, Europe and Australia, there is mixed and often unhelpful attitudes regarding the validity of ADHD as a construct, the role of medication and how parenting contributes to the presentation [351]. A paucity of training was identified, alongside a reluctance of GPs to become involved in shared care practice. If access to services is to be improved for people with ADHD, there needs to be a focused and collaborative approach to training [351].

9.1. Combatting stigma

Disclosure of mental health problems can be a challenge [352], but an increasing number of celebrities have cast aside stigma by revealing they had ADHD and, in some cases, have been pharmacologically treated for many years (https://www.additu-demag.com/successful-people-with-adhd-learning-disabilities/). This is of course supportive for patients but it is strongly recommended that psychoeducation about ADHD should be included in anti-stigma programs [347]. Of note, adult ADHD is rarely included in college programs for medical and psychology students, or in the training of professionals working in adult

mental health services. This contributes to misconceptions, underdiagnosis and undertreatment among professionals [2,3]. Psychoeducation programs therefore need to target all clinical disciplines at all stages of professional development (e.g. from students through to primary and secondary care physicians, psychologists and nurses) to ensure that appropriate early recognition, diagnosis and treatment is provided.

Internationally recognized guidelines are available on the assessment, treatment and management of adults with ADHD, as well as the development and provision of clinical services [182,184,274,353]. The current lack of licensed indications for the use of stimulants in adults in most European countries (but not in the US or Canada) is not supported by available data, but rather results from the outdated focus that ADHD is a 'child disorder', caution from regulators regarding potential cardiovascular side effects, and commercial manipulation by the pharmaceutical industry. In Europe, this situation may change in the coming years as formulations of methylphenidate and dexamphetamine are being put forward for registration.

Stigma prevents patients to ask for help and increases their suffering and impairment. Hence the successful management of ADHD by prescribers will include an awareness of the potential stigma that may be perceived by the patient and its consequences on treatment initiation and maintenance. The only way to reduce stigma surrounding ADHD is community, health and education systems in Europe and beyond working together by education of professionals and the public, and by a unified licensing of medications for ADHD in adults.

10. Conclusions

This consensus statement reflects agreement on the state of ADHD, but by definition it is provisional. It does not negate the ongoing scientific debate in the field and the different opinions and hypotheses about adult ADHD among experts. Yet none of that undercuts the legitimacy or validity of the construct, or of the conclusions one can make about the current status of the consistency of the evidence. ADHD is a neurodevelopmental and heritable disorder with a lifespan perspective: starting in childhood, persisting in adulthood until old age, with significant psychosocial impairment, a high comorbidity rate and multi-morbidity. It is associated with high levels of personal distress, and a substantial economic burden for society if left unidentified and untreated. DSM-5 has changed some of the criteria that facilitate the diagnosis in adolescents and adults. Assessment should include a detailed account of the developmental history, of both current and retrospective ADHD symptoms and impairment, and associated comorbidities. To prevent under-reporting of symptoms, external validation is desirable by collateral information. Multimodal treatment is required, comprising of psychoeducation, pharmacotherapy, and cognitive behavior therapy and/or coaching. Psychoeducational European programs to combat stigma and to inform the public and (mental) health professionals about new knowledge on the lifespan perspective of ADHD are needed to improve and increase diagnostic and treatment services for adult ADHD. Research on the different presentation of ADHD in women, and on treatment of ADHD in old age should be further developed in order to improve their treatment options.

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