Attention Deficit Hyperactivity Disorder: Current Progress and Controversies

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Objective: Attention deficit hyperactivity disorder (ADHD) is a common chronic and disabling condition in children. This paper reviews the taxonomic issues and the major comorbid conditions, neurobiological correlates, treatment and public health issues associated with ADHD.
Method: Pertinent recent papers are reviewed from the psychological and psychiatric literature.
Results: The two major taxonomies now define a similar group of children with ADHD of a combined type/hyperkinetic disorder. Advances in the understanding and treatment of ADHD demonstrate the complex multidimensional links between neurobiology, psychology and behaviour. Careful assessment of individual factors in treatment planning and ongoing monitoring of psychostimulant medication treatment in the longer term are recommended.
Conclusions: There is much still to learn about ADHD, and increased levels of clinical research and treatment resources are required.
Key words: ADHD, controversies, neurobiology, progress, review treatment.

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In Australia the recognition and treatment of attention deficit hyperactivity disorder (ADHD) has been debated for a number of years. This sustained interest is not surprising given its prevalence in primary school-aged children of approximately 3–5% [1]. Two important consensus statements have been recently drafted that highlight the importance of recognising ADHD and its adverse effects on the development of the child [2,3]. However, a general overview for psychiatrists in clinical practice of the current progress and controversies in this expanding field is timely. This paper will review this important field of psychiatry in relation to its taxonomy, comorbidity, neurobiology, treatment, and end with a discussion of pertinent public health issues (Table 1).

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Taxonomy

Attention deficit hyperactivity disorder, a pattern of childhood behaviour consisting of impulsiveness, inattention and overactivity, has been recognised and noted as impairing human development [4,5]. Yet, the International Classification of Diseases, revision 9 (ICD-9) and the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) had markedly different approaches to diagnosing ADHD, which resulted in a difference of as much as a factor of 20 [5]. The subsequent development of the ICD-10 'hyperkinetic disorder' and DSM-IV 'attention-deficit/hyperactivity disorder' diagnoses have brought the World Health Organization (WHO) and the American Psychiatric Association (APA) nosologies of childhood hyperactivity closer than they have been for almost three decades [6].

The major development is that both systems now agree that pervasiveness is a key diagnostic criterion, which means that the ADHD symptoms must occur in more than two settings. It is also clear that the absence of the symptoms, under clinical observation, does not necessarily exclude the diagnosis [7]. However, there are still major differences between the two systems. The DSM-IV recognises three subtypes of ADHD: (i) a predominantly inattentive type; (ii) a combined type; and (iii) a predominantly hyperactive-impulsive type, while ICD-10 requires both inattentive and hyperactive-impulsive behaviour to make the diagnosis. As a result, DSM-IV criteria identify a broader group of children than those identified by ICD-10 [6]. The predominantly inattentive group has been shown to be valid, and is associated with more anxiety and a lower level of intellectual functioning [8]. The combined type of ADHD is similar to the ICD-10 derived hyperkinetic disorder, and the validity of the predominantly hyperactive-impulsive group has not been established [9].

There are two further important aspects of the taxonomy of ADHD. The DSM-IV sets the upper limit of the age of onset at 7 years, whereas the ICD-10 sets this age at 6 years. While most people agree that ADHD usually has an onset in early childhood, the requirement to restrict the diagnosis to onset before the age of 6 or 7 is still being debated [10]. At present, it seems unwise to further broaden the diagnostic criteria in the absence of compelling data that support this change. Second, studies have shown that the concept of ADHD is applicable to preschoolers [11], adolescents [4] and adults [12]. However, the threshold and nature of the symptoms for the diagnosis of DSM-IV ADHD were developed for primary school-aged children [4]. Their validity for preschoolers, adolescents and adults will need to be examined and validated in the future.

The current diagnostic system for ADHD and hyperkinetic disorder will continue to evolve as our knowledge of specific aspects of the psychopathology improves. A major present issue is whether a dimensional approach is preferable. A recent classic study by Levy *et al*. [13], involving a genetic analysis of a large-scale twin study of ADHD, demonstrated that the ADHD symptoms are best understood as dimensional constructs, rather than as discrete categories. It follows that ADHD symptoms are the end result of the interaction of genetic factors with environmental factors, both of which can be of varying severity.

Cross-cultural studies have shown that cultural factors can facilitate or suppress ADHD symptom dimensions [14]. Thus, when assessing children from different cultures, the clinical threshold for diagnosing ADHD may need to be adjusted. Cross-cultural studies have also suggested that the prevalence of ADHD may be different across cultures [15]. This is an important area for future research in terms of further examining these aetiological factors of ADHD.

In summary, both DSM-IV and ICD-10 nosologies now recognise a pervasive pattern of overactivity, inattention and impulsiveness with onset in early childhood. These problems are chronic and likely to significantly impair the development of the affected child. Clinicians should clarify the presence or absence of this behavioural pattern when they are assessing children. Recognition in preschool years is possible [11].

Comorbidity

There have been significant advances in the definition and understanding of comorbid conditions associated with ADHD in primary school-aged children over the last 20 years [16–18]. In this section four current major comorbidities with ADHD will be noted, their characteristics reported and future directions discussed.

Attention deficit hyperactivity disorder and oppositional defiant disorder/conduct disorder

Oppositional defiant disorder

There is a robust association between ADHD and oppositional defiant disorder (ODD) [18,19]. Approximately 30–50% of primary school-aged children with ADHD have comorbid ODD [1]. Children with ADHD and ODD have worse verbal and visuospatial skills that are associated with a lower full-scale and verbal IQ, higher performance than verbal IQ, decreased verbal fluency and a poorer academic level of achievement [17,20]. Studies of families have shown that this group of children has significantly more first-degree relatives with ODD symptoms, antisocial behaviours and alcohol abuse or dependence disorders [1,17]. Symptom levels of inattention and impulsiveness have been reported as increased in children with ADHD and ODD [1,17]. Longer-term outcomes are also worse in this group of children with rates of committed offences, rates of drug and alcohol abuse or dependence disorders, levels of antisocial personality disorder and unemployment being increased [1,17].

Conduct disorder

Attention deficit hyperactivity disorder and conduct disorder (CD) have similar correlates to the above, although of increased frequency and severity [17,19]. All cases of ADHD and CD have a prior history of ODD [21], but recent 2-year follow-up data suggest that approximately 50–60% of comorbid ODD remains, 40–50% resolves and only 2–3% becomes CD [22]. Comorbid CD can be associated with relatively increased aggression, anxiety, maternal anxiety and depressive symptoms, and decreased self-esteem, while comorbid ODD is associated with increased social withdrawal [23]. First-degree family members tend to have increased rates of CD symptoms and comorbid CD is associated with greater shared environmental effects [24].

Interestingly, short-term and longer-term response rates to psychostimulant medication are no different between children with ADHD alone and ADHD and ODD/CD [17,19]. Taken together, these findings suggest that there are important clinical implications in recognising and treating this comorbidity of ADHD. Future directions include the determination of specific medication combined with psychological treatments for this group of children, along with monitoring for effectiveness in both the short and the longer term [19].

Attention deficit hyperactivity disorder and learning disorders

Methodological issues associated with the definition of learning disorders, the samples studied and the psychometric properties of the instruments used have led to a prevalence range of 10–92% [1]. However, approximately 20–30% of primary school-aged children with ADHD will have an associated learning disorder of reading, spelling, writing and/or arithmetic [1,17]. Family studies suggest that the trans-generational association of learning disorders and ADHD are robust, but independent of each other [25]. Similarly, the cognitive dimensions of inattention and impulsiveness do not account for a worse performance on standardised tests of reading, writing, spelling and arithmetic [17]. Importantly, ADHD with comorbid CD is associated with increased rates of language-based learning disorders [20]. Given the clinical and educational importance of ADHD and comorbid learning disorders, longitudinal study designs with homogeneous subtypes of ADHD and carefully defined learning disorders are needed, along with evaluation of multimodal psychopharmacological and psychological interventions for this group.

Attention deficit hyperactivity disorder and anxiety

The co-occurrence of ADHD and anxiety has been repeatedly shown to be greater than chance [17,18]. Epidemiological and clinical studies support a prevalence of 20–30% [1,17]. The subtyping of ADHD is important to consider because the inattentive type of ADHD has been associated with higher rates of anxiety than a combined type of ADHD [16,17]. However, recent work suggests that ADHD of a combined type is also significantly associated with anxiety [16,26]. The parent and the child reports are both important in determining ADHD and anxiety, for significant clinical correlates, such as levels of self confidence and impairments in activities of daily living, may be associated with the child report alone [27]. In addition, only approximately 50% of children with self-reported anxiety have been noted to also be reported with anxiety by their parents [26]. A ‘less-robust’ response to short-term psychostimulant medication has been a replicated finding in the literature [17,27], while longer-term psychostimulant medication treatment maybe also be associated with ADHD and anxiety [28–30]. Family studies suggest that first-degree relatives of primary school-aged children with ADHD and anxiety have increased rates of both ADHD and anxiety disorders, and that parents with anxiety disorders are more likely to have children with ADHD and with anxiety disorders [1,17]. In summary, important clinical correlates have been noted in primary school-aged children with ADHD and anxiety. Future clinical research will focus on differentiating ADHD of inattentive and combined types and their respective associations with anxiety, specific medication and psychological treatment responses, longer-term outcomes, and the clinical correlates of the parent and the child reports of anxiety [19,30,31].

Attention deficit hyperactivity disorder and bipolar disorder

Werry *et al*. [32] note that the association of bipolar disorder (BPD) with ADHD, as a comorbid condition, a misdiagnosis, or a precursor, is not new. However, the diagnosis of BPD and its frequency in primary school-aged children with ADHD are

contentious issues, with debate focused in the USA [33,34]. The reported primary clinical features include marked irritability of mood, rather than elevated expansive mood, prolonged aggressive temper outbursts (affective storms), marked disinhibition, hypersexuality, evidenced by masturbation (for example), increased depressive symptoms 'mixed with' manic symptoms, and grandiose delusions [33]. The course of the disorder is chronic, without discrete periods of manic symptoms, as the manic symptoms do not fully remit, and without distinct periods of good intermorbid function [33]. Importantly, children with ADHD and BPD have been described as having a poor response to psychostimulant medication, in both the short term and longer term, and a positive response to mood stabilisers, such as lithium carbonate [33]. Prevalence rates of 11–22% of BPD in children and adolescents with ADHD and 57–98% of ADHD in BPD have been noted [33]. In contrast, protagonists in the child and adolescent BPD debate have argued that no criteria exist for stable, continuous mania [34]. The existing criterion of a distinct period of manic symptoms must be met. Prevalence rates of five per 100 000 are noted, using strict DSM-IV criteria, which stand in stark contrast to the prevalence rates noted above [34]. In summary, a subgroup of children with ADHD, who have a poor response to psychostimulant medication in the short term and longer term, and chronic irritability and prolonged aggressive outbursts exist [33,34]. There are no accepted criteria to support a putative comorbid bipolar disorder [34]. Existing classification systems support a severe form of ADHD alone [34]. Careful longitudinal studies with large epidemiological samples in different cultures are required to resolve this debate.

Neurobiological correlates

Four primary areas of progress in neurobiological research are reviewed below. The authors recognise that there are a large number of further areas of study undertaken that are beyond the scope of this paper.

Behavioural and molecular genetic studies

The last decade has produced a number of advances in the behavioural and molecular genetic understandings of ADHD [35]. Both a broad dimensional definition of ADHD symptoms and a focused definition of 'extreme' scores on these core ADHD symptom dimensions in epidemiological populations, suggest that these ADHD symptom dimensions are highly heritable [35]. Twin studies of mono- and dizygotic subjects, family studies of first-degree relatives and adoption studies have consistently reported significant transgenerational transmission of core symptom dimensions of ADHD, although specific gene–environment interactions at critical periods of development remain unclear [36]. Gender differences are evident, which support a model of multiple genes with multiple thresholds being involved in the determination of the core features of ADHD [37]. The covariation of ADHD symptoms and ODD/CD symptoms in males and females, from middle childhood through to middle adolescence, has been noted to be primarily due to genetic factors [24]. This has considerable implications for the understanding of this important comorbidity as a risk factor for conduct disturbance [38]. Future directions include the investigation of a range of clinically significant phenotypes of ADHD and putative subtypes, commencing with whether the core symptom domains of ADHD are associated with the same set of multiple genes.

The dopamine transporter gene and the dopamine D_4 receptor gene (DRD-4) have begun to be systematically investigated. The dopamine transporter locus (DAT1) is considered important because psychostimulant medication and bupropion inhibit the dopamine transporter mechanism [35,39]. A replicated finding is the increased frequency of the 480-base pair allele of the DAT1 in patients with DSM-III-R diagnosed ADHD [35,39]. A similar positive association of the seven-repeat allele of the DRD-4 has been reported in a number of cross-sectional studies [35,40], although other studies have failed to replicate this finding [35,41]. Further investigations are required to identify quantitative trait loci associated with the core symptom dimensions of ADHD [36,38]. The formation of very large samples, from different international epidemiological and clinical populations, will also be needed to enable particular genes and environmental factors associated with small effect sizes to be identified, and relatively homogenous phenotypic groups to be defined [35,36].

Neuropsychological studies

There has been an increasing focus on deficits of the executive functions of cognition in primary school-aged children, adolescents and adults with ADHD [42,43]. This exploration has been driven, in part, by the lack of convincing evidence for deficits

in components of attentional constructs [43,44]. In contrast, deficits in response inhibition [42,44], verbal working memory [42,45], and, more recently, non-verbal working memory [45,46] have been studied. Barkley [45] has developed an elaborate, general working model of behavioural and cognitive dysfunction, associated with ADHD, that emphasises response inhibition as the primary deficit. Models of dysfunction in effort and/or activation components of energetic and state mechanisms, that are posited to subserve discrete short-term elementary responses of information processing, have been developed [44,47]. In addition, theories of a specific aversion to delay that is associated with situation-specific increased impulsiveness [48], a decreased response to conditioned stimuli that is associated with an underactive behavioural inhibition system [49], and an excessively slow process of inhibition that is associated with a deficit in inhibition of prepotent responses [50] have been propounded.

In summary, response inhibition and verbal and non-verbal working memory constructs have begun to be systematically investigated. However, methodological limitations need to be addressed in ways that include (i) studying homogenous groups of ADHD subtypes, rather than a broader phenotype of the disorder; (ii) validating the executive function tests used (for example, the Wisconsin Card Sort Test) in children, because of their complex and multifactorial nature [46], and their prior limited validation in adult humans with focal brain lesions; (iii) investigating more than one aspect of a given executive function, such as verbal working memory, that is multifaceted, as few studies have done this; (iv) rigorously investigating and defining the construct validity of neuropsychological measures, for example, attention and verbal working memory [42]; and (v) investigating the relationship between performance on executive function tests and normal maturation of the central nervous system, as this is not well understood [42]. Therefore longitudinal prospective study designs, rather than cross-sectional study designs, are required to inform interpretations of changed performance over time.

Neuroimaging studies

Structural imaging studies of ADHD subjects, to date, suggest localised anomalies in several brain regions; most notably, decreased size of the right prefrontal cortex [51,52], loss of a normal, age-related decrease in caudate volume in boys with ADHD [53,54], and loss or reversal of normal asymmetry of caudate volumes [54,55]. Functional imaging studies have suggested deficits in the same broad brain regions as structural imaging studies. Lou *et al*. [56–58], using a xenon-133 single photon emission computerised tomography (SPECT) method, have demonstrated hypoperfusion in the striatal region in children with ADHD that is corrected by short-term psychostimulant medication. Increased ^{18}F-DOPA, a marker of dopa decarboxylase activity determined by positron emission tomography (PET), has been reported in the right midbrain region of 10 children with ADHD compared with matched controls, which suggests abnormal presynaptic dopaminergic functional activity in the substantai nigra and ventral tegmentum areas [59]. Reduced cerebral glucose metabolism has been demonstrated in frontal cortical and subcortical areas, using PET, in adults and adolescents with ADHD [60,61]. Also, functional magnetic resonance imaging (fMRI) studies have reported a decreased pattern of activation of neurones in fronto-striatal cortical and subcortical areas when the subject was performing various neuropsychological tasks that involve response inhibition [62,63]. However, given the diverse age range, gender range, diagnostic procedures and predominant cross-sectional study designs, along with the technological limitations of the imaging procedures, and neuropsychological test paradigms themselves [42], the results cannot be directly compared. Future studies will need to address these limitations, with a particular focus on age-and gender-dependent alterations in cerebral metabolism that form a developmental context that needs to be controlled for [64].

Neurophysiological studies

Quantitative electroencephalography (qEEG) has the advantages of relatively minute time resolution (ms intervals) and decreased cost, and the problems of poor spatial resolution and a signal affected by considerable electrical artefacts [42]. Studies in children with ADHD suggest that there is a subgroup with increased slow wave activity in the frontal region [65], although the significance of this finding with respect to brain maturational delay or deficit remains unclear [42]. However, differences in the sample selected, age and gender of the subjects, EEG methods and analysis prevent direct comparison of the results [42]. Event-related potentials (ERP) studies suggest disordered central arousal patterns and decreased stimulation in evoked response patterns

that may reflect disordered subcortical activation [66]. Brain electrical activity mapping (BEAM) studies have reported decreased activity (increased latencies) in frontal regions in children with ADHD [67,68]. In particular, Silberstein *et al*. [68] studied 17 boys aged 7–14 with ADHD according to DSM-III-R criteria, and demonstrated no change or an increased amplitude and latency of steady state visually evoked potential at right prefrontal sites during the continuous performance task, while matched control subjects had a transient decreased amplitude and latency. Again, poor spatial resolution and electrical signal artefacts make the interpretation of these findings difficult, at present. Future studies will be required to better account for the dynamic nature and multidimensional changes that occur throughout central nervous system development.

Treatment

There continues to be immense research effort investigating a range of psychological and psychopharmacological treatments for children with ADHD. The two primary areas of current research are outlined below.

Behavioural therapeutic interventions

The published literature investigating the short- and longer-term effectiveness of a variety of behavioural therapeutic interventions is relatively small compared to the corresponding literature studying psychostimulant medication [69,70]. Yet the chronic nature of the disorder and its associated comorbid conditions have led to a range of behavioural interventions being applied in parallel or series to psychostimulant medication in clinical practice [70,71]. Short-term improvements in the core symptoms of ADHD, academic performance, measures of social skills, aggression and oppositional defiant behaviour have been noted with teacher and parent training programs that involve reinforcement of positive behaviour and response–cost procedures for undesired behaviour [72–74]. Cognitive behavioural strategies of self-instruction and social skills training to enhance the effectiveness of behavioural strategies in the home and school environments remain unproven in their effectiveness [70,75]. Similarly, the longer-term effectiveness of behavioural therapeutic interventions remains unclear [70]. Given that the primary limitation of behavioural interventions is their lack of generalisability across home and school situations, the potential synergistic effect of behavioural interventions with psychostimulant medication has been reported in the short term [72,76]. However, the recently reported findings from the National Institute of Mental Health (NIMH) Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA study) suggest that psychostimulant medication alone is as effective as the combination of psychostimulant medication and behaviour therapy over 14 months [77]. Interestingly, lower doses of psychostimulant medication were required in the combined psychostimulant medication and behaviour therapy group compared with the psychostimulant medication alone group [77]. However, pertinent issues not addressed in this study include the assessment of cognitive and behavioural outcome, home and school environment-based behavioural therapeutic interventions, the possible differential effects of behavioural and psychostimulant medication interventions on defined aspects of cognitive and behavioural functioning in both the short and longer terms, and the specific effects of different comorbidities such as learning disorders, conduct disorder and anxiety. Future research will need to account for these issues in order to aid the clinician to specifically tailor empirically validated treatments to the nature and severity of an individual child's defined impairments and disabilities [71].

Psychostimulant medication

Psychostimulant medication continues to be a primary treatment modality for children with ADHD [2]. The mechanism of action involves presynaptic inhibition of re-uptake through the stimulation of inhibitory autoreceptors and alteration in the functional activity levels of catecholamines [78]. Initially, dopaminergic and noradrenergic neurotransmitter systems involved in prefrontal-striatal circuits were implicated [78,79]. But recent animal models suggest that changes in functional serotonergic activity may be also involved, leading to a current model that the differential balance between dopaminergic, serotonergic and noradrenergic neurotransmitter systems, in particular, prefrontal-striatal circuits may be the mechanism through which psychostimulant medication exerts an effect [79].

In the short term (up to 4–6 weeks), the core behavioural features of ADHD and cognitive features, such as response inhibition and verbal and non-verbal working memory performance, improve in approximately 80% of children with ADHD [45,80].

Associated comorbid symptoms, such as oppositional defiant behaviour and a worse academic performance, have also been reported as improved in the short term [80]. The most frequent short-term side-effects of psychostimulant medication are associated with the physiological effects of the activation of the noradrenergic neurotransmitter system, among other neurotransmitter systems. These physiological effects include initial and middle insomnia, loss of appetite, stomach-aches, headaches, dizziness and daytime drowsiness [81]. An affective group of symptoms are also short-term side-effects of psychostimulant medication. These symptoms include mood lability, dysphoria, sudden severe sadness, sudden crying, social withdrawal and aggressive outbursts. The latter may intensify the impulsiveness of ADHD [30]. Motor symptoms, such as tics, are a further group of short-term side-effects of psychostimulant medication.

In the longer-term (greater than 3 months), the essential symptom domains of ADHD maybe significantly improved [28,77,82], although there is also some evidence that the short-term improvements of psychostimulant medication may be attenuated [28,29,83]. Concern about growth problems and the development of drug tolerance and psychological and physiological dependence may be unfounded as these have not been demonstrated as longer-term side-effects of psychostimulant medication treatment [2], although Schachar *et al*. [29] note that there has not been systematic empirical study of this area. In particular, there has not been systematic study of cognitive and behavioural measures of response in the longer term [29,46]. Future research is required into the following areas: specific subtypes of ADHD (for example, ADHD of a combined type and an inattentive type, and ADHD and anxiety), their longer-term cognitive and behavioural responses to psychostimulant medication, their longer-term dose–response relationships for cognitive and behavioural measures, and their side-effect profiles, particularly with respect to delayed-onset versus immediate-onset side-effects that may intensify the core features of ADHD in particular subgroups of children [30].

Public health issues

There has been a concurrently rapid increase in the prescribing rate of psychostimulant medication throughout Australia, as ADHD becomes more recognised [84]. Concern has been expressed about this rapid rise in prescription rate [85], and critics have suggested that much of the ADHD diagnosis is a myth and that these children are being given medication inappropriately [86,87].

The same concern has been expressed in the USA [85]. A recent consensus statement from the National Institute of Health has recognised that ADHD represents a costly major public health problem. It also raises a number of issues: the use of psychostimulants for longer-term treatment; the dimensional aspects versus the categorical aspects of ADHD; the need for long-term studies with medications, behavioural modalities and their combination; and the threshold for the clinical use of psychostimulant medication [88]. In the UK, psychostimulant medication was seldom used during the 1980s, although there is now a renewed interest in its use. An evidence-based briefing for psychostimulant medication use has been recently published [89].

The controversy about the rapid increase in the use of psychostimulant medication will only be resolved by a careful epidemiological study examining the prevalence of ADHD, the prevalence of children given psychostimulant medication, the relation between the two groups of children, and their long-term outcome. A study of this nature has been reported recently [90]. The authors reported that 5.1% of children met DSM-III-R ADHD criteria, but only 12.5% of these children had been treated with psychostimulant medication during the previous 12 months. Of the children who were prescribed psychostimulant medication, 50% did not meet full ADHD diagnostic criteria. Hence, underprescribing/overprescribing of psychostimulant medication occurred [85,90]. A similar study examining current clinical practice in Australia is urgently needed.

Conclusion

The advance of knowledge in the field of ADHD demonstrates the complex multidimensional links between neurobiology, psychology and observed and reported behaviour. Attention deficit hyperactivity disorder exemplifies the importance of assessing the individual factors within the child when clinicians are faced with children presenting with behavioural problems. Attention deficit hyperactivity disorder has subtypes and is associated with several important comorbid psychiatric conditions. Future studies will need to define these subgroups clearly. There is much to learn about the treatment of ADHD, especially the longer-term use of psychostimulant medication.

Table 1. A summary of major current issues, progress and future directions in the field of attention deficit hyperactivity disorder

Current issues	Current progress	Future directions
Comorbidity		
ADHD/ODD	30–50% comorbidity [1], decreased language-based skills [20], transgenerational transmission [18], poor long-term prognosis [19], similar response rates to short- and longer-term psychostimulant medication [17]	Monitoring of effectiveness and specific psychological (individual and group) and medication treatments to be clarified [19]
ADHD/CD	Increased frequency and severity of above correlates [19], increased shared environmental effects [24], all cases have a prior history of ODD [21]	Monitoring of effectiveness and specific psychological (individual and group) and medication treatments to be clarified [19]
ADHD/LD	20–30% comorbidity: spelling, reading, writing and/or arithmetic [1], independent transgenerational transmission [25], comorbid CD associated with increased rates of LD [20]	Longitudinal studies of ADHD subtypes and defined LD, evaluation of multimodal psychological and medication treatments [19]
ADHD/anxiety	20–30% comorbidity [1], ADHD combined type and inattentive associated with elevated levels of anxiety [16], child and parent report important in determining anxiety [27], associated with a 'less robust' response to psychostimulant medication in the short and longer terms [29], transgenerational transmission [1]	Longitudinal studies of ADHD inattentive and combined subtypes and parent and child defined anxiety, evaluation of multimodal psychological and medication treatments [30]
ADHD/BPD	Chronic irritability and prolonged aggressive outbursts associated with a poor response to psychostimulant medication have been suggested as criteria for comorbid BPD [33], although there are no accepted criteria to support this definition [34]	Longitudinal epidemiological studies in different cultures of children with ADHD and these additional difficulties are required
Taxonomy	WHO and APA nosologies more aligned [6], pervasiveness a key criterion [5]	Subtypes [1], upper limit of age of onset [2], validity of diagnostic construct in preschoolers, adolescents and adults [9], and cross-cultural factors [14] to be clarified
Neurobiological correlates		
Behavioural genetics/ molecular genetics	ADHD as a category and as symptom dimensions is highly heritable [35], multiple genes with multiple thresholds for expression are involved [37], covariation of ADHD and ODD/CD symptoms primarily genetic [38]	Specific gene–environment interactions at critical developmental periods, and involving specific subtypes of ADHD to be clarified from large, international epidemiological samples [36,39]
	Particular alleles of dopamine D_4 receptor gene and dopamine transporter locus have begun to be investigated [40,41]	

Table 1. Continued

Current issues	Current progress	Future directions
Neuropsychological studies	EF abnormalities, particularly response inhibition, verbal and non-verbal working memory deficits are the primary focus of current research [46,47] as deficits of attentional constructs have not been reliably found [44]	Longitudinal studies of homogeneous ADHD subtypes with specific EF tasks to clarify deficits, covarying for developmental processes [47]
Neuroimaging studies	Loss of normal asymmetry of caudate regional volumes [54], hypoperfusion of this region [58], decreased size of the right prefrontal cortex volume [55], and decreased activation of fronto-striatal regions with tasks of response inhibition [64] have been reported but not replicated	Longitudinal studies of homogeneous ADHD subtypes, with more specific and reliable imaging techniques and specific EF tasks to determine disorder- and development-specific abnormalities [43]
Neurophysiological studies	Quantitive EEG and brain electrical activity mapping have suggested frontal and prefrontal regional differences [66,69]	Limitations of poor spatial resolution and considerable electrical artefacts limiting the usefulness of these techniques to be addressed [43]
Treatment		
Behavioural treatment	Short-term studies of behavioural treatments implemented by parents and teachers alone or in combination with psychostimulant medication are effective, while longer-term interventions are unclear [71,73]	The MTA Cooperative Group study and future longitudinal studies with more specific behavioural treatments and cognitive and behavioural outcome measures will clarify effectiveness issues [72]
Psychostimulant medication (PSM)	Changes of functional activity in dopaminergic, noradrenergic and serotonergic neurotransmitter systems are associated with PSM ingestion [80], short-term benefits on core ADHD symptoms are clear while longer-term benefits are less clear [28]	The MTA Cooperative Group study and future longitudinal studies with more specific cognitive and behavioural outcome measures and dosage type, levels and timing will clarify effectiveness and dose-response relationship issues [72]
Public Health Issues	Rapid increase in prescription rates of PSM over the last 10 years identified [85], overprescribing and underdiagnosing of ADHD were reported in a recent epidemiological survey in USA [91]	An Australian epidemiological survey identifying the prevalence of ADHD, PSM usage, relationship between these two groups and their longer-term outcome is required

ADHD, attention deficit hyperactivity disorder; APA, American Psychiatric Association; BPD, borderline personality disorder; CD, conduct disorder; EEG, electroencephalography; EF, executive functioning; LD, learning disorder; MTA, Multisite Multimodal Treatment Study of Children with ADHD; ODD, oppositional defiant disorder; WHO, World Health Organization.

Careful monitoring of medication treatment is essential. There is a group of children with ADHD who do not respond well to treatment. More resources should be made available to help them, through clinical research and clinician-based treatment.

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