Adults with ADHD

An Overview

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ABSTRACT: Attention-Deficit Hyperactivity Disorder (ADHD) is a common, genetically transmitted neurological disorder, with onset in childhood, probably mediated by decreased brain dopaminergic functioning. The first author was one of the earliest to describe the persistence of symptoms into adulthood. Prevalence and natural history data suggest that of the 3 to 10% of children diagnosed with ADHD, one- to two-thirds (somewhere between 1 and 6% of the general population) continue to manifest appreciable ADHD symptoms into adult life. This paper describes how ADHD in adults can be readily diagnosed and treated, despite resembling or coexisting with other psychiatric disorders. The Wender Utah diagnostic criteria address adult characteristics of the disorder. Informant and patient interviews and rating scales are used to determine the psychiatric status of the patient as a child, make a retroactive diagnosis of childhood ADHD, and establish the current diagnosis of the adult. Stringent diagnosis is key to determining effective treatment. Dopamine agonist stimulant medications appear to be the most effective in treating ADHD. About 60% of patients receiving stimulant medication showed moderate-to-marked improvement, as compared with 10% of those receiving placebo. The core symptoms of hyperactivity, inattention, mood lability, temper, disorganization, stress sensitivity, and impulsivity have been shown to respond to treatment with stimulant medications. Non-dopaminergic medications, such as the tricyclic antidepressants and SSRIs have generally not been useful in adults with ADHD in the absence of depression or dysthymia. Pemoline is no longer appoved for use in these patients, despite early favorable reports. Appropriate management of adult patients with ADHD is multimodal. Psychoeducation, counseling, supportive problem-directed therapy, behavioral intervention, coaching, cognitive remediation, and couples and family therapy are useful adjuncts to medication management. Concurrent supportive psychosocial treatment or polypharmacy may be useful in treating the adult with comorbid ADHD.

KEYWORDS: ADHD; Child psychiatry; Adult psychiatry; Psychiatric diagnosis; Stimulant medication; Dopamine.

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Attention-Deficit Hyperactivity Disorder (ADHD) is very common in children, making up 30 to 40% of referrals to child mental health clinics.[1] About 30 years ago, the senior author noted that the parents of ADHD children described similar problems in their own childhood and for many these problems had continued throughout life.[2] Around that same time Arnold and colleagues provided the first case report of an adult who was initially diagnosed with ADHD during adulthood.[3] Despite these early observations, until recently ADHD has usually remained an unrecognized psychiatric disorder in adults. With a focus on adults, this chapter outlines the history of the diagnostic concept, its prevalence, clinical symptoms, diagnosis and differential diagnosis, presumed etiology and (briefly) treatment. Much of this is based on 20 years of work conducted by Wender and colleagues. The interested reader is referred to his recent review article or book *Attention-Deficit Hyperactivity Disorder in Adults* for more detail.[4,5]

NOSOLOGICAL HISTORY OF ADHD

The names and criteria for the syndrome of ADHD have changed frequently. What is now referred to as ADHD has been variously designated as "minimal brain damage," "minimal brain dysfunction," "minimal cerebral dysfunction," "hyperkinesis," and the "hyperactive child syndrome." The main behavioral and/or cognitive abnormalities contained within the syndrome typically included overactivity, inattentiveness, impulsivity, affective lability and "immaturity." Associated abnormalities included, but were not limited to, poor peer relations, defiance, hostility, "acting out" behaviors and "learning problems." The earliest descriptions of a behavioral condition akin to ADHD were provided by George Still at the turn of the century.[6] He posited an overarching failure in moral control and proposed a biological substrate (either hereditary and/or the result of some acquired encephalopathy). His formulation of underlying CNS damage was reflected in the early diagnostic terms of minimal brain dysfunction or minimal brain damage (both MBD), which prevailed throughout the first half of the twentieth century.

Subsequent conceptual shifts are embodied in the several versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) published by the American Psychiatric Association. A more descriptive view was taken in 1968 such that the second edition called the disorder Hyperkinetic Reaction of Childhood, and stressed abnormally high levels of motor activity as the primary deficit. Later research emphasized deficits in attention and impulse control, as well as hyperactivity.[7] Consequently in 1980 the third revision of the DSM (DSM III) re-titled it Attention Deficit Disorder (ADD), with two subtypes (with or without hyperactivity).[8] Debates continued as to the central importance of problems with hyperactivity, and in 1987 the disorder was renamed Attention Deficit/Hyperactivity Disorder (DSM-III-R). ADD without hyperactivity was named Undifferentiated Attention Deficit Disorder, and thought by many to embody a separate disorder of attention.[9–11] The most current DSM-IV (1994) melds the different emphases by titling the disorder ADHD/Primarily Inattentive Type, or ADHD/Primarily Hyperactive-Impulsive Type, or ADHD/Combined Type, depending on the mix of inattentive, impulsive or hyperactive symptoms.[12]

All of the above terminology reflects evolving theories of etiology or key symptoms. Notably, underlying CNS dysfunction as well as excessive motor activity and/or impulsivity have been the most consistently emphasized problem areas. Future advances in understanding the biology and pathophysiology of the disorder may yet lead us to further nosological shifts (see, for example, Mirsky and Duncan, this volume).[13]

PREVALENCE

There are no definitive epidemiological studies of the prevalence of ADHD in adults. We can, however, reach an order of magnitude calculation for its prevalence from studies estimating the prevalence of ADHD in children and the proportion of these cases that persist into adulthood. Depending on the methodology employed, and the cutoff scores chosen, the prevalence of ADHD in childhood ranges from 3 to 10%. In all studies the disorder is found to be at least two to three times as common in boys as in girls. Prevalence rate in different studies varies depending on the setting, the reporter (parent, teacher or self) and the requirements for diagnosis. For example, the prevalence rate is lower when the disorder is required to be pervasive (evident in more than one setting).[14,15] Unfortunately, the absence of a diagnostic gold standard limits the determination of the "true" prevalence of ADHD. That is, we lack the sort of microbiological, pathological, and physiological markers which are often associated with other illnesses, and which permit us to more definitively ascertain the reliability our diagnosis. It is difficult to meaningfully determine the sensitivity and specificity of our inclusion criteria for ADHD without a means by which to determine whether or not an individual patient "really" has the disorder. Absent such a standard we must make a decision to employ either looser or more stringent criteria. This decision is of course important in terms of determination of prevalence, as well as for determination of which patients we diagnose and subsequently treat. (This question will be further considered in the context of the "pay-off matrix" in our discussion of treatment.)

As a developmental disorder, the natural history of ADHD is best assessed by longitudinal studies of children followed into adult life. There are two relevant studies. Weiss and Hechtman provided adult follow-up at age 25, of 60% of the "hyperactive" children they had treated when they were 6 to 12 years old.[16] Two-thirds of their subjects complained of at least one symptom of restlessness, distractibility, or impulsivity, versus 7% in the controls. Approximately one-half of the patients continued to have moderate or severe problems, while approximately one-quarter had developed Antisocial Personality Disorder. Mannuzza and Klein[17–19] also followed a cohort of "hyperactive" children from childhood to ages 18 and 26, and were able to obtain follow-up data from nearly 100%. At age 18, 40% of the patients had ADHD (compared to 3% of the controls), 27% had Conduct Disorder or Antisocial Personality Disorder (versus 8% of the controls), and 16% had non-alcohol Substance Abuse Disorder (versus 3% in the controls).[20] By contrast, at age 26 only 11% continued to have full or partial ADHD symptoms, while 18% had Antisocial Personality Disorder, and the same number (16%) continued to have non-alcohol Substance Abuse Disorder.[21] The most striking feature of these studies is the relative

persistence of ADHD through adolescence and its apparent decrease in early adult life. This reported drop in the prevalence of ADHD between the ages of 18 and 26 may be interpreted in two different ways. One obvious answer is that the children simply outgrew the disorder. Alternatively this drop may reflect reporter differences, since the investigators depended solely on self-report (of their 25-year-old subjects) for the adult cohort, whereas for child cohorts both the subject and parents were used as informants. In this regard, the Utah studies have consistently found that many adults with persistent ADHD do not report their symptoms or fail to report their severity.[22] From a practical standpoint, patient's spouses or other informants are also often helpful for initial assessment and in determining treatment response. As the above adult outcome studies were based only on reports from the patients themselves, results likely may have underestimated the true persistence of ADHD in adulthood.

Taken together, the existing prevalence and natural history data suggest that one- to two-thirds of the 3 to 10% of the childhood prevalence, or somewhere between 1 and 6% of the general population continue to manifest appreciable ADHD symptoms into adult life. It should also be pointed out that these longitudinal studies were begun at a time when the diagnostic criteria of "hyperactivity" were more narrowly defined. The male subjects so diagnosed might not be representative of more current clinical cohorts which include the "inattentive subtype," and which may also include more girls and women. No adequate prevalence data are available for these later subjects. Thus the generalizablity of the anterospective studies discussed above, regarding both adult prevalence and prognosis, may be more limited to only a subset of the ADHD population.

CORE SYMPTOMS

Although a former version of the DSM included the category of "ADHD-residual type," there are no specific criteria for ADHD in adults. The DSM-IV's symptomatic criteria where developed for children and, not surprisingly, many of them are age-limited. In this category are behaviors such as "often runs about or climbs excessively..." or "often has difficulty playing or engaging in leisure activities quietly." These criteria are not applicable to adulthood, which makes defining relevant and age-appropriate symptoms a critical issue. Accordingly, since 1976 the senior author has been developing tentative operational criteria for ADHD which better specify characteristics more directly relevant to adults.

Childhood Status

By definition ADHD begins in childhood. Thus the first task of the clinician is to determine the psychiatric status of the patient as a child and to make a retroactive diagnosis of childhood ADHD. Some patients may have been evaluated or treated as children. For others we inquire about the presence or absence of DSM-IV ADHD symptoms during childhood. However, many ADHD adults' memories of their childhood are cloudy and we lack a measure of reliability. As a screening procedure one can seek to obtain a history of the more macro (and presumably better recalled)

behavioral characterizations (see below). To further circumvent the memory problem we have also employed the three approaches outlined below.

Parental interview is the first and preferred method of obtaining childhood symptoms. If this is not possible, a useful second approach is for the patient's parents to rate their (now) adult offspring as he or she had been in childhood, using the "Parents' Rating Scale" (PRS). The PRS is an adaptation of the Conner's Rating Scale popularly used for childhood ADHD assessment, and yields an index of the magnitude of an adult's hyperactivity during childhood.[23] The third technique is to administer a self-report measure, the Wender Utah Rating Scale (WURS), in which the adult reports on his memories of 25 descriptors characteristic of ADHD in childhood.[24] This scale has been standardized in normal adults, adults with a major depressive disorder, and adults with ADHD.

Utah Criteria

The senior author and his collaborators have developed a set of characteristics to specify both necessary childhood criteria and current ADHD symptoms in the adult. These "Utah Criteria" are as follows:

I. CHILDHOOD CHARACTERISTICS

A childhood history consistent with ADHD is established through the methods discussed above. The following are considered the necessary standards for ADD in childhood.

A. Narrow Criteria (DSM-IV)
That the individual meet full DSM-IV criteria for ADHD in childhood.

B. Broad Criteria
Both characteristics 1 and 2, and at least one characteristic from 3 through 6 below:

1. Hyperactivity: More active than other children, unable to sit still, fidgetiness, restlessness, always on the go, talking excessively
2. Attention deficits: Sometimes described as a "short attention span," distractibility, unable to finish schoolwork
3. Behavior problems in school
4. Impulsivity
5. Overexcitability
6. Temper outbursts

C. Parents' Rating Scale (Conner's Abbreviated Rating Scale)
Although not essential for diagnosis, a score of 12 or higher places the patient in the 95th percentile of childhood "hyperactivity.")

II. ADULT CHARACTERISTICS

The Utah scheme requires that ADHD patients have both symptoms A and B below, plus two of the remaining symptoms (e.g., must be ADHD-Combined type). At the time of the development of these criteria, Inattentive and the Hyperactive-Impulsive subtypes were not well validated (see above and below). Even now, more work needs to be completed to validate the existence of exclusively Inattentive or Hyperactive-Impulsive subtypes in adults. The reader should also be aware that the Utah criteria

are not based exclusively on the behavioral criteria outlined in the DSM, but also include associated features and subjective symptoms (e.g., low frustration tolerance, temper outbursts, etc.) which the adult undergoing evaluation and his/her partner report.[25]

A. Motor hyperactivity

Manifested by restlessness, inability to relax; "nervousness" (meaning inability to settle down, not anticipatory anxiety); inability to persist in sedentary activities (e.g., watching movies or TV, reading the newspaper); always on the go, dysphoric when inactive.

B. Attention deficits

Manifested by an inability to keep one's mind on conversations; by distractibility (incapacity to filter extraneous stimuli); difficulty keeping one's mind on reading materials or tasks ("mind frequently somewhere else"); frequent "forgetfulness"; by often losing or misplacing things; forgetting appointments, plans, car keys, purse, etc.

C. Affective lability

Usually described as antedating adolescence and in some instances as far back as the patient can remember. Manifested by definite shifts from a normal mood to depression or mild euphoria or—more often—excitement; depression described as being "down," "bored," or "discontented"; anhedonia not present; mood shifts usually last hours to at most a few days and are present without significant physiological concomitants; mood shifts may occur spontaneously or be reactive.

D. Hot temper, explosive short-lived outbursts

A hot temper, "short fuse," "low boiling point"; outburst usually followed by quickly calming down. Subjects report they may have transient loss of control and be frightened by their own behavior; easily provoked or constant irritability; temper problems interfere with personal relationships.

E. Emotional over reactivity

Subjects cannot take ordinary stresses in stride and react excessively or inappropriately with depression, confusion, uncertainty, anxiety, or anger; emotional responses interfere with appropriate problem solving—they experience repeated crises in dealing with routine life stresses; describe themselves as easily "hassled" or "stressed out."

F. Disorganization, inability to complete tasks

A lack of organization in performing on the job, running a household, or performing school work; tasks are frequently not completed; the subject goes from one task to another in haphazard fashion; disorganization in activities, problem solving, organizing time; lack of "stick-to-it-iveness."

G. Impulsivity

Minor manifestations include talking before thinking things through; interrupting others' conversations; impatience (e.g., while driving); impulse buying. Major manifestations may be similar to those seen in mania and Antisocial Personality Disorder and include poor occupational performance; abrupt initiation or termination of relationships (e.g., multiple marriages, separations, divorces); excessive involvement in pleasurable activities without recognizing risks of painful consequences (e.g., buying sprees, foolish business investments, reckless driving); inability to delay acting without experiencing discomfort. Subjects make decisions

quickly and easily without reflection, often on the basis of insufficient information, to his/her own disadvantage.

H. Associated features

Marital instability; academic and vocational success less than expected on the basis of intelligence and education; alcohol or drug abuse; atypical responses to psychoactive medications; family histories of ADHD in childhood; Antisocial Personality Disorder and Briquet's syndrome.

The diagnosis of ADHD in an adult is only made when other psychological and psychiatric disorders, such as rapid cycling bipolar illness, schizophrenia, etc. have been eliminated. This stringency in terms of other psychiatric diagnoses is somewhat unique among diagnostic schemas.

Often considered the most stringent of diagnostic schema, the Utah Criteria make childhood hyperactivity continuing into adulthood a mandatory diagnostic symptom. This criterion obviously eliminates that subgroup of ADHD children and ADHD adults who were, and are, characterized by inattentiveness without hyperactivity and impulsivity. As these criteria were developed prior to the more recent onset of ADHD subtyping, the current Predominately Inattentive subtype might not fit as well into this framework. These more stringent requirements were employed in the senior author's research in order to limit investigations to the most clear-cut subgroup of adult patients with ADHD. What was useful, however, for research purposes need not be helpful clinically, because it is clearly the case that many children and adults with inattention alone respond to the same treatments. This also implies a common or related underlying pathophysiology.

The Utah diagnostic criteria are similarly stringent in excluding patients with comorbid psychiatric diagnoses such as major mood disorders, Schizophrenia, Antisocial Personality Disorder, and Schizotypal or Borderline Personality Disorders. Again, it was not the intention to thereby deny the frequent comorbidity between ADHD and those conditions (see Marks *et al*., this volume[26]). This rather represented the desire to investigate a more homogeneous sample. Individuals diagnosed with these excluded categories often also have prominent ADHD symptoms, and an important area for further investigation is the influence of drug treatment on the ADHD symptoms of adults with comorbid disorders.

Other Common Comorbidities

The Utah group has reported considerable comorbidity for ADHD and Conduct Disorder in their adult patients. While there are many ADHD children without Conduct Disorder, such findings should come as no surprise. ADHD children are often comorbid for Conduct Disorder and most Conduct Disordered children have ADHD as well. This observation is also an important prognostic sign as about one-half of children with Conduct Disorder go on to develop an Antisocial Personality Disorder. Little is known about the value of drug treatment of ADHD in the presence of Conduct or Antisocial Personality Disorder, despite reports of the high prevalence of ADHD in the criminal population.[17,27]

Lastly, the Utah studies encountered a high frequency of learning disorders in the adult ADHD patients. Similar to conduct problems, the continuation of these disorders could have been anticipated because ADHD children have an increased

incidence of learning disabilities in reading, spelling, and mathematics. These skills are rarely assessed in conventional psychiatric evaluations of adults. Yet it is often important to evaluate them in adults with ADHD, and to treat them appropriately, since learning disorders often still impact adult life (also see Wolf, this volume[28]).

DIFFERENTIAL DIAGNOSIS

One major diagnostic dilemma will be discussed here: the differentiation between ADHD and other psychiatric diagnoses with very similar symptoms. As indicated previously, differential diagnosis of this disorder is greatly aided by the presence of an "other" such as spouse, partner, adult children, or parents of the adult patients. Without their observations critical symptoms may be underestimated or simply not disclosed.

Adult ADHD individuals often exhibit depression, affective lability, and irritability. Consequently, ADHD may sometimes be confused with mood disorders such as Mania, Cyclothymic Disorder, and with Borderline Personality Disorder (BPD). However, the shifts of mood typically seen in Cyclothymic Disorder are of weeks or months duration, and differ from the hour-to-hour or day-to-day shifts seen in ADHD. Likewise, anhedonia and physiological concomitants of depression are absent in ADHD, as are the depressive personality traits which Akiskal describes as "subaffective dysthymia."[29] Patients with ADHD and BPD appear to share symptoms of impulsivity, affective instability, angry outbursts, and feelings of boredom. However, both quantitative and qualitative differences are seen between the two diagnostic groups. The impulsivity in ADHD is typically short-lived and thoughtless, rather than "driven." Similarly the ADHD patient's anger is short-lived and episodic, as opposed to the brooding anger typical of the BPD patient. The major differences between ADHD and BPD patients is that the former do not have the intense conflicted relationships, suicidal preoccupations, self-mutilation, identity disturbances, or feelings of abandonment seen in BPD. Nevertheless, these differences are not clear-cut in all instances, and medications useful in the treatment of ADHD might be of value in treating ADHD-like symptoms in some BPD patients.

PRESUMED ETIOLOGY

Genetics

In the early1970s the senior author advanced the hypothesis that the etiology of "minimal brain dysfunction" (as ADHD was then often still named) might be genetic in origin and produced by decreased functioning in the catecholaminergic system.[2,30] Conjectures about a genetic origin were based on an apparently increased frequency of MBD symptoms among the siblings of children with that disorder, as well as an increased frequency of other forms of psychopathology (including alcohol abuse and Antisocial Personality Disorder) among the parents of these patients. In addition, the absence of such psychopathology in the adoptive parents of MBD children suggested the transmission to be genetic in origin.

Since that time there have been many familial studies of ADHD, which allow one to come closer to the relative contributions of genetic versus environment and child-rearing factors. Investigators have looked at the familial association of ADHD; psychopathology in the first-degree relatives of ADHD children; concordance rates between monozygotic and dizygotic twins; and symptoms in foster or adopted children with ADHD. The initial family studies reported an increased frequency of alcohol abuse, Antisocial Personality Disorder and, possibly Briquet's syndrome in the biological parents of "hyperactive" children as compared to controls; as well as an increased frequency of "hyperactivity" in the siblings of hyperactive children.[26,31–36]

The clustering of ADHD, Antisocial Personality Disorder and alcohol abuse is of interest because family studies conducted by investigators at Washington University also found these three disorders to co-exist in families, suggesting that the cluster has a genetic basis.[37] Subsequent family studies of ADHD have reported psychopathology in the parents of ADHD children who are comorbid for Conduct Disorder, as well as in the parents of children with "pure" ADHD. Using other methods, a relationship between ADHD and alcohol abuse was reported by Tarter *et al*. and Wood and colleagues, both of whom found ADHD to be associated with early-onset alcoholism.[38,39] Furthermore, Goodwin and colleagues found that the adopted-away sons of alcoholics who were alcoholic were more likely than the non-alcoholics to have had symptoms of "hyperactivity" in childhood (also see Sullivan and Levin, this volume).[40,41]

Since the familial clustering of psychiatric disorders may be due either to genetic or to environmental influences, other methods are necessary to differentiate between these two modes of transmission. The study of concordance rates for ADHD among monozygotic and dizygotic twins is an effective tool for such investigation. Presumably, since both types of twins share the same familial psychological environment, an increased concordance in the monozygotic pairs (who share a greater degree of genetic material than dizygotic pairs) is due to genetic factors. In a large sample of twins Goodman and Stevenson found an increased concordance of ADHD among monozygotic as compared to dizygotic twins, with an estimate of heritability expressed by genetic linkage to be 64%.[42,43] More recently, heritability estimates of 75–91% for ADHD, and 60–80% for attention problems on the Child Behavior Checklist have been reported, along with monozygotic concordance rates of 58 to 83% (versus dizygotic rates of 31% and 47%).[14,44,45] These data support transmission of ADHD to be strongly genetic in nature. Monozygotic twins, however, may in fact experience a different psychological environment from that of dizygotic twins, and the twin methodology cannot completely control for this effect. An appropriate strategy to resolve this question is to study foster and adopted children.

Safer investigated the status of full and half-siblings of ADHD children who had been placed in foster care.[46] He found an increase of ADHD-like psychopathology among the siblings which was twice as great among the full as opposed to the half-siblings (as would be expected on genetic grounds). Two other older adoption studies investigated the psychiatric status of the biological parents of children with ADHD, the adoptive parents of children with ADHD, and the biological parents of children without psychiatric disorder.[47,48] They again found an increased frequency of ADHD-like psychopathology only among the biological parents of ADHD children.

Taken together these studies demonstrate the clear presence of genetic factors in the transmission of ADHD and suggest that children with ADHD may be at an increased risk for Antisocial Personality Disorder and alcohol abuse (for more detail, see Wender[5]). It should also be noted that ADHD type symptoms can sometimes be caused by other acquired medical conditions, which are reviewed elsewhere in this volume (see Pearl *et al*.[49]).

Catecholamine Hypothesis

Conjectures about the neurophysiological nature of ADHD, or the "catecholaminergic hypothesis," were based on several observations: the first being reports of the behavioral problems among children who had contracted von Economo's encephalitis during the epidemic of the late teens and early 1920s. Many children who recovered from the acute illness developed a Post-Encephalitic Behavior Disorder with symptoms very similar to those of mixed ADHD and Conduct Disorder. Moreover, adults who recovered from the acute encephalitis frequently displayed symptoms of Parkinson's Disorder. Post-mortem examination of both adults and children who had died from the disorder revealed lesions in the basal ganglia and substantia nigra. These same subcortical brain regions were later linked to idiopathic Parkinson's Disorder, which is associated with decreased dopaminergic functioning due to degeneration of dopaminergic neurons.

A second rationales for a dopaminergic hypothesis was the observation that many of the drugs that are most effective in reducing or dramatically eliminating the symptoms of ADHD, the amphetamines and methylphenidate, are indirect dopamine agonists. As described below, the Utah studies of ADHD adults permitted the investigation of these factors without the risk of exposing children to invasive procedures. One of the first of these studies examined the level of homovanillic acid (HVA), the principal metabolite of dopamine, in the cerebral spinal fluid of adults with ADHD and in controls.[50] As was also the case for people with Parkinson's Disorder, decreased levels of HVA were found ADHD adults who had responded to treatment with methylphenidate. By contrast, increased levels of HVA were found in the nonresponding ADHD patients. This replicated the results of two earlier smaller studies in "hyperactive" children and in children with minimal brain dysfunction.[51,52]

Another technique was to administer pharmacological doses of the precursor amines of dopamine, namely phenylalanine, tyrosine, and L-dopa.[39,53,54] The principal finding of this group of studies was a moderate-to-marked improvement of ADHD symptoms in approximately half the patients receiving tyrosine, while phenylalanine and L-dopa did not have such an effect. These findings can be interpreted *post facto*. Increasing phenylalanine or tyrosine should not increase dopamine. The primary metabolic chain is phenylalanine→tyrosine→L-dopa→dopamine; and the conversion of tyrosine to L-dopa (which is catalyzed by the enzyme tyrosine hydroxylase) is the rate-limiting step in the formation of dopamine. On the basis of the enzyme kinetics, the observed clinical effectiveness of tyrosine could be explained by its increasing tyramine, which would increase dopamine by an alternative metabolic pathway. Notably, the response to L-dopa was increased fatigue and a decreased ability to concentrate. This can be attributed to its acting as a false neurotransmitter (i.e., it could have been taken up by nondopaminergic neurons and might have displaced their transmitters and inactivated them).

The third approach was to administer drugs with a comparatively specific action in patients with ADHD. The hypothesized relevant neurotransmitter dopamine is metabolized in the brain by monoamine oxidase B (MAO-A predominantly metabolizes serotonin and norepinephrine). In low doses, two MAO inhibitors—pargyline (no longer marketed) and 1-deprenyl (selegeline)—are specific MAO-B inhibitors. Correspondingly, it was found that in low doses both drugs produced moderate-to-marked improvement in about 60% of ADHD adults.[39,55] Since at low levels these drugs presumably increase the availability of dopamine and do not increase levels of serotonin and norepinephrine, the results also support the dopaminergic hypothesis. Further trials of selegeline (now available as an orphan drug) are warranted.

TREATMENT

Medication

The Utah group has conducted placebo-controlled and open label drug trials in over 300 patients, including a total of 224 ADHD patients treated with stimulants. These include four double-blind placebo-controlled trials: three of methylphenidate with varying subject numbers and one of 48 patients with pemoline.[5,22,56,57] In addition, the Utah group treated 79 patients in open label trials: pargyline, 1-deprenyl (selegiline), bupropion, levodopa, DL-phenylalanine, and 1-tyrosine.[39,53–55,58,59]

In crossover and parallel design studies about 60% of patients receiving stimulant medication showed moderate-to-marked improvement, as compared with 10% of those receiving placebo. These degrees of responsivity were reflected in Global Assessment of Functioning (GAF) scores in patients with moderate-to-marked improvement. The average pre-treatment GAF scores in the studies are about 55 (moderate symptoms) and post-treatment scores were about 75 (slight symptoms present only in reaction to stress). As mentioned, open studies of pargyline and selegeline in 27 patients found, again, that about 60% exhibited moderate-to-marked improvement to treatment with an MAO inhibitor. Lastly, a therapeutic trial of bupropion in 19 patients, who had previously responded to stimulants or MAO inhibitors, found that approximately half responded to bupropion and decided to remain on that drug.

Turning to less dopaminergic drugs, the tricyclic antidepressants have generally not been useful in adults (or children). Patients displayed an immediate response, but after six to eight weeks became tolerant to the drug despite increased dose. They also seemed less tolerant of the side effects of these drugs than are depressed patients; complaining of the anticholinergic effects, weight gain, and impaired sexual functioning. SSRIs appear to be of no value in ADHD patients who are not depressed or dysthymic, but may be of considerable benefit for those with comorbid depression or dysthymia.

There have been two attempts to replicate the Utah treatment studies. Mattes *et al*. conducted a placebo-controlled trial of methylphenidate in 66 patients, but did not demonstrate a favorable response to the drug.[60] There are several reasons why this may have occurred. Sampling variables may be a factor: 60% of the sample did not meet the criteria of childhood "hyperactivity" employed in the Utah studies. Moreover, many of the patients were comorbid for substance abuse and BPD,

patients who would have been excluded in the Utah studies. More recently, Spencer and colleagues were able to replicate the Utah findings with methylphenidate in a placebo-controlled trial of 23 subjects.[61]

Taken together, these studies clearly demonstrate the efficacy of methylphenidate, pemoline (however, see caution below), bupropion and MAO-B inhibitors in the treatment of adults with ADHD.

After evaluation and a discussion of the patient's level of symptoms, the senior author presents the patient with the therapeutic pay-off matrix alluded to previously, i.e., the benefits and liabilities of a therapeutic trial of medication when he does or does not have the disorder. A consideration of the four possibilities reveals that the risks of treating a patient who does not have ADHD are minimal, while there are considerable disadvantages to not offering a trial of treatment to someone with the disorder. The above holds with the proviso that the use of stimulant drugs does not lead to abuse of those medications. We do not know whether individuals with ADHD will experience "highs" if they take large or intravenous doses of methylphenidate or amphetamines. A few clinical cases suggest that they can produce euphoric "highs." For this reason, stimulants should be used cautiously or not at all in persons with a history of drug abuse. In general, however, it is emphasized that therapeutic trials are warranted whenever the diagnosis seems probable because the benefits can be assessed rapidly.

The Utah group has used a structured rating scale to assess adult ADHD symptoms and their changes in our treatment studies.[5] Symptom changes seen with effective treatment include the following:

1. Hyperactivity—Fidgeting and restlessness decrease; patients are able to relax; then are able to stay at their desks or at the dinner table or at a movie or in church.
2. Inattention—Concentration is greatly improved. It is not only those patients can concentrate better; they can concentrate when they want to. Distractibility diminishes or disappears. Attention to spousal conversation improves and frequently is quickly manifested in better marital relations.
3. Mood lability—Both highs and lows decrease, as do feelings of boredom; mood is described as "level" or "stable."
4. Temper—The threshold for outbursts is raised. Patients are less irascible and their angry outbursts are less frequent, less extreme, and frequently disappear altogether.
5. Disorganization—Organizational activities improve. This is evident at school, in running a household, in vocational function. Patients may spontaneously establish orderly strategies.
6. Stress sensitivity—Patients' self-descriptions include having their thin skin thickened, able to take life problems in their stride, feeling less "hassled" about daily existence.
7. Impulsivity—Patients report that they do not interrupt others while listening to them (another feature that improves conversations and relationships), that they think before they speak, that they have become tolerant drivers and that they stop impulse buying.

Practically speaking, ADHD is a life-long disorder and the duration of drug treatment may also be life-long.[62] Amphetamines have been used since 1937 with no long-term toxicities reported. However, both methylphenidate and D-amphetamine increase heart rate and blood pressure, which must be carefully monitored in adult patients. Their use may require adjuvant therapy to control heart rate and blood pressure. Whether such drugs interfere with the therapeutic action of the stimulants remains to be demonstrated.

Lastly, although earlier studies did suggest pemoline to be effective in reducing symptoms of ADHD, recent reports of liver toxicity—including 11 cases of liver failure and death before 1996 and withdrawal from the market in Canada—have resulted in its withdrawal from approval for treatment of this disorder.[63,64]

Psychosocial Interventions

Appropriate management of adult patients with ADHD involves more than adequate drug therapy alone. Similar to the case for children, the best treatment is multimodal, involving education about the disorder and psychotherapy addressing concomitant problems. Once the diagnosis has been made, we help patients recognize how ADHD is manifested in their current behavior. As the therapeutic relationship develops, discussion may broaden to include the role played by ADHD characteristics in the patient's life history, including academic and vocational choices, friendships, sexual relationships, and functioning as a spouse and as a parent. ADHD symptomatology may be intimately woven into all these aspects of life, and it takes patients much time—during continuing treatment—to identify and understand its contributions to their life story.

In educating patients we also help them understand that the chronic nature of the disorder has likely resulted in their developing compensatory techniques which are no longer adaptive. These maladaptive techniques may resolve spontaneously with pharmacotherapy, or they may require psychotherapeutic intervention. Supportive problem-directed therapy, behavioral intervention, coaching, or cognitive remediation can help with these problems (see Lynn and Wasserstein, this volume).[65] Couple therapy and/or family therapy may be useful. Finally, ADHD does not prevent one from having other psychological problems and these may be more apparent, or therapeutically accessible, after the symptoms of ADHD have remitted with medication. In short, concurrent supportive psychosocial treatment can be key.

CONCLUSION

The take-away message from this overview is that ADHD in adults is a common genetically transmitted neurological disorder, which is probably mediated by decreased brain dopaminergic functioning. It is usually undiagnosed, but it can be diagnosed fairly easily and can resemble or coexist with other psychiatric disorders. At least 60% of patients experience a substantial, and in many instances a dramatic, response to drug treatment, and such drug treatment can make ADHD patients more amenable to a number of psychotherapeutic approaches. The benefits of combined treatment may be of life-changing proportions.

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