NIMH Collaborative Multisite Multimodal Treatment Study of Children with ADHD: I. Background and Rationale

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ABSTRACT

Objective: The National Institute of Mental Health's recently initiated 5-year, multisite, multimodal treatment study of children with attention-deficit hyperactivity disorder (MTA) is the first major clinical trial in its history focused on a childhood mental disorder. This article reviews the major scientific and clinical bases for initiating the MTA. **Method:** A selective review of the literature is presented in the service of describing the estimated prevalence of ADHD among children and adolescents, its core clinical features, evidence concerning psychopharmacological and psychosocial treatment effects, and related research issues and trends leading to the development of the MTA. **Results:** Despite decades of treatment research and clinical practice, there is an insufficient basis for answering the following manifold question: *under what circumstances and with what child characteristics (comorbid conditions, gender, family history, home environment, age, nutritional/metabolic status, etc.) do which treatments or combinations of treatment (stimulants, behavior therapy, parent training, school-based intervention) have what impacts (improvement, stasis, deterioration) on what domains of child functioning (cognitive, academic, behavioral, neurophysiological, neuropsychological, peer relations, family relations), for how long (short versus long term), to what extent (effect sizes, normal versus pathological range), and why (processes underlying change)?* **Conclusions:** The important scientific, clinical, and public health issues nested within this manifold question provide both the impetus and scaffolding for the MTA. *J. Am. Acad. Child Adolesc. Psychiatry*, 1995, 34, 8:987–1000. **Key Words:** attention-deficit hyperactivity disorder, childhood disorders, multimodal treatment, psychopharmacological treatment, psychosocial treatment.

Attention-deficit hyperactivity disorder (ADHD) is arguably the most common of childhood mental disorders. It is also one of the most treatable; decades of treatment research and clinical practice have demonstrated the short-term strengths and limitations of various forms of psychopharmacological and psychosocial treatment strategies. Nonetheless, important questions remain unanswered concerning the conditions under which different subgroups of children with ADHD are likely to benefit differentially from particular treatments and/or treatment combinations. The need for a multisite treatment study of children with ADHD to address this important public health question was emphasized in the Institute of Medicine study, *Research on Children and Adolescents with Mental, Behavioral, and Developmental Disorders* (Institute of Medicine, 1989), and in the National Advisory Mental Health Council's *National Plan for Research on Child and Adolescent Mental Disorders* (National Advisory Mental Health Council, 1990). A multisite collaborative ADHD treatment study also was recommended by researchers at an earlier NIMH conference on hyperactivity convened in May 1990 and by an expert

Accepted December 28, 1994.

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The authors thank Drs. John Bartko, Robert Prien, Margot Richters, and Darrel Regier for their thoughtful comments on an earlier draft of this paper.

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panel at the NIMH summit meeting of leading child psychopathology researchers convened in the fall of 1990. After scientific peer review and approval of the concept paper proposing such a study in December 1991, the Request for Applications was published February 21, 1992 (DHHS, PHS, ADAMHA, NIMH, 1992). The 20 applications submitted in response were peer-reviewed in June 1992 by a second scientific review committee, and the 6 best-scored applications were selected in September 1992 for funding. The following year was spent developing a common protocol incorporating the best ideas from the funded proposals and additional ideas from consultants. This article reviews the background clinical, scientific, and public health considerations that gave rise to the initiation of this landmark study.

DEFINITION AND CLINICAL FEATURES OF ADHD

Prevalence estimates for ADHD vary widely as a function of the diagnostic criteria used (e.g., *DSM-III*, *DSM-III-R*, or *DSM-IV*), the populations sampled, and whether ADD without hyperactivity was included. Nationwide estimates of prevalence suggest that between 3% and 9% of children are afflicted (e.g., American Psychiatric Association, 1987, 1994). This disorder accounts for one third to one half of all referrals for child mental health services (Popper, 1988), and it comprises the lion's share of economic cost and human suffering caused by childhood mental disorders. The core clinical features of ADHD, many of which can be detected as early as 3 years of age (Campbell et al., 1986; Palfrey et al., 1985) and persist through the school years, include developmentally inappropriate activity levels, low frustration tolerance, impulsivity, poor organization of behavior, distractibility, and an inability to sustain attention and concentration (Pelham, 1982). As with other childhood disorders (cf. Richters and Cicchetti, 1993; Richters and Volkmar, 1994), there has been considerable debate over the years about the most appropriate definitional boundaries for hyperactivity and about the scientific legitimacy of its status as a distinct clinical syndrome (Hinshaw, 1994; Rutter, 1982a; Shaffer and Greenhill, 1979; Taylor, 1986). There has never been controversy, however, about whether a significant number of children suffer from the core clinical symptoms described above or about the social and academic impairments and comorbid psychiatric conditions described below (Hinshaw, 1994).

The definitional boundaries and labels assigned to this syndrome have changed repeatedly over the years, creating numerous obstacles to comparisons across studies. Roughly synonymous but not congruent terms include hyperactivity and minimal brain dysfunction/damage (both pre-*DSM-II*), attention deficit disorder (ADD) and hyperkinetic reaction (*DSM-II*), attention-deficit hyperactivity disorder (ADHD; *DSM-III-R*), and attention deficit/hyperactivity disorder (ADHD; *DSM-IV*). ADD includes the concept of attention deficit disorder without hyperactivity which some experts estimate is about half as prevalent as strictly defined ADHD. The criteria for *DSM-IV* distinguish three subtypes: inattentive (roughly equivalent to *DSM-III*'s ADD without hyperactivity and *DSM-III-R*'s undifferentiated ADD), hyperactive-impulsive (hyperactivity without inattention), and combined (ADHD). In the discussions that follow we use the terms "ADHD" (noun) and "hyperactive" (adjective) where appropriate as generic references to this syndrome.

Associated Functional Deficits

Unfortunately, the core clinical symptoms of ADHD (inattention, impulsiveness, and hyperactivity) reflect impairments in precisely the domains of functioning that are central to mastery of the major developmental tasks of childhood. It is, therefore, not surprising that a majority of children with ADHD tend to perform poorly in school, often despite normal intelligence, and suffer significant social and emotional impairments in the formation and maintenance of relationships with classmates, peers, parents, and teachers (Abikoff et al., 1980; Goyette et al., 1978; Milich and Landau, 1982; Whalen et al., 1978).

Comorbidity

It has been known for some time that ADHD is characteristically comorbid with other childhood mental disorders, especially conduct and oppositional defiant disorders (Hinshaw, 1987; Klein and Mannuzza, 1990; Loney and Milich, 1982). More recently, some investigators have examined the comorbidity of ADHD with mood disorders, anxiety disorders, and learning problems. In a recent comprehensive review of the literature, Biederman et al. (1991) reported the rates of comorbidity for clinically referred children with ADHD to be 30% to 50% for conduct/oppositional

disorder, 15% to 75% for mood disorders, approximately 25% for anxiety disorder, and between 10% and 92% for learning disorders. More recent estimates of comorbid learning disorders range from 10% to 20% (Hinshaw, 1992; Semrud-Clikeman et al., 1992). Preliminary evidence from the *DSM-IV* field trials (Lahey, unpublished communication) suggests that 20% to 25% of children with ADHD also have comorbid learning disorders. The comorbid prevalence of learning disorders, like their general prevalence, varies with the stringency of definitional criteria used. One of the best studied comorbid conditions has been conduct disorder, for which Abikoff and Klein (1992) have pointed out an asymmetrical overlap, whereby children with a diagnosis of conduct disorder are more likely to have a diagnosis of ADHD than vice versa. Although the definitive epidemiological research on child and adolescent mental disorders has not yet been completed in the United States, a large community-based study in New Zealand reported that 47% of children with hyperactivity had a coexisting conduct or oppositional disorder, while 26% had a coexisting anxiety or phobic disorder, and 18% had two or more comorbid conditions (Anderson et al., 1987). Similar patterns of comorbidity with ADHD have been reported from epidemiological studies in both Puerto Rico (Bird et al., 1988) and Canada (Szatmari et al., 1989). As we outline in more detail below, these comorbid conditions and associated social and academic impairments (Anderson et al., 1989) provide evidence of the heterogenous nature of the disorder, add to its clinical complexity, and have significant implications for etiology, course, and treatment (Biederman et al., 1991).

Long-Term Prognosis

Although ADHD is classified as a childhood disorder and is typically identified in the early school years, it has been estimated that up to 70% of afflicted children continue to manifest a diagnosable syndrome in adolescence, albeit possibly with an altered set of symptoms (Gittelman et al., 1985; Klein and Mannuzza, 1991; Mannuzza et al., 1991). Children in whom hyperactivity was diagnosed in childhood often continue as adolescents to suffer ongoing problems of overactivity, poor school performance, and significant behavior problems at home and school such as temper tantrums, defiance, police contacts, and peer rejection (Barkley et al., 1990; Loney et al., 1981; Mendelson et al., 1971). Moreover, it has been estimated that as many as two thirds of hyperactive adolescents may suffer serious discipline problems at school, resulting in high rates of suspension and expulsion and chronically low levels of self-esteem (Mendelson et al., 1971; Weiss et al., 1971).

Although few long-term follow-up studies into adulthood have been reported, they converge on a portrait of continuing deficits in many domains of functioning among adults in whom ADHD was diagnosed in childhood (Klein and Mannuzza, 1991). Compared with matched normal controls, hyperactive young adults have been shown to suffer significantly higher levels of impulsiveness and restlessness, nonmedical drug use, court referrals, incarceration, and personality disorders (Hechtman et al., 1979, 1984; Loney et al., 1983). At the diagnostic level, follow-up studies of hyperactive children into young adulthood have shown that approximately 50% continue to have mental disorders, including ADD, antisocial disorder, and drug use disorder (Mannuzza et al., 1991). Consistent with these findings, it has also been shown that adult probands who had been seen for hyperactivity at a child guidance clinic 25 years earlier were between three and four times more likely than their brothers to report psychological problems of nervousness, restlessness, depression, lack of friends, and low frustration tolerance in adulthood (Borland and Heckman, 1976). These findings may actually represent an *under*estimate of adult problems associated with childhood hyperactivity because most subjects in these studies were assessed in early adulthood prior to the period of highest risk for developing many forms of adult psychopathology (Pelham, 1982).

TREATMENTS

Stimulant and Other Pharmacological Treatment

It has been estimated that between 2 and 2½% of all elementary school-age children in North America (approximately 600,000 students) receive some form of pharmacological intervention for hyperactivity (Bosco and Robin, 1980). Estimates have varied considerably, however, by region and year. For example, data from Baltimore County, Maryland, which regularly tallies the proportion of public elementary school students receiving medicine, showed a steady rise from 2.08% in 1975 to a 1987 peak of 5.96% (10% for boys), followed by a decline to 2.9% in 1991 (Price,

1991; Safer and Krager, 1988). Sherman and Hertzig (1991) suggested that the stimulants are rarely prescribed in a consistent fashion; they found that the majority of 1-month prescriptions for ADHD were not renewed during a 1-year period. Reported studies support the efficacy of a variety of medications for ADHD, including antidepressants (e.g., Biederman et al., 1991), clonidine (e.g., Steingard et al., 1993), and neuroleptics (e.g., Gittelman-Klein et al., 1976; Werry et al., 1975). By far the most widely prescribed and thoroughly studied, however, have been the psychostimulants, especially dextroamphetamine, methylphenidate, and pemoline (Conners and Werry, 1979; Greenhill, 1992; Jacobvitz et al., 1990), which are widely regarded in the psychiatric community as constituting the "first line" psychopharmacology for ADHD. Antidepressants are generally acknowledged as an established second-choice category, and they have even been advocated by a few practitioners and investigators as first-choice drugs, but fewer controlled studies of ADHD have been done with these drugs (Biederman et al., 1989).

The widespread clinical use of stimulant drugs stems from their demonstrated short-term efficacy, compared to placebo conditions, in dramatically reducing a range of core ADHD symptoms such as task-irrelevant activity (e.g., finger tapping, fidgetiness, fine motor movement, off-task during direct observation) and classroom disturbance (e.g., oversolicitation in class during direct observation), with associated increases in compliance and sustained attention (Abikoff and Gittelman, 1985b; Jacobvitz et al., 1990; Pelham, 1982). Positive effects of stimulants also have been shown on parent–child interactions (e.g., Barkley and Cunningham, 1979), on problem-solving activities with peers (Whalen et al., 1979), and in a variety of controlled laboratory tasks, including paired-associate learning (Conners et al., 1964; Gan and Cantwell, 1982; Swanson and Kinsbourne, 1976), experimenter-paced continuous performance task (Conners and Eisenberg, 1963; Conners et al., 1964; Halperin et al., 1992), cued and free recall, auditory and reading comprehension, spelling recall, and arithmetic computation (e.g., Pelham, 1982; Perel et al., 1991; Stevens et al., 1984). Some studies have shown that responses to a laboratory motor task correlate positively with stimulant plasma levels (Kupietz, 1991; Greenhill, 1992), but plasma levels generally have not predicted stimulant response. Likewise, stimulant benefits have been shown for both school-age and adolescent aggressive behavior, including that of hyperactive conduct-disordered adolescents in structured and unstructured school settings (Gadow et al., 1990; Hinshaw, 1991; Hinshaw et al., 1989; Kaplan et al., 1990; Whalen et al., 1979). Stimulants also have been shown to decrease covert antisocial behaviors such as stealing (Hinshaw et al., 1992) among hyperactive children. Such stimulant-induced behavioral changes appear to improve (but not normalize) hyperactive children's peer status as measured sociometrically (Whalen et al., 1989).

Unfortunately, these well-documented short-term benefits are clouded by quantitative, qualitative, and chronological shortfalls of generalization in two major categories. The first (but not necessarily more important) concerns the degree of normalization (quantitative) produced by stimulants and cross-domain extent (qualitative) of their effects. For example, the full effects seen in laboratory, school, and peer settings have not consistently been shown to generalize to home behavior as rated by parents (Gadow et al., 1990). This may result from methodological artifacts involving time-action effects; with twice-daily dosing (morning and noon), drug effects may wear off before parents can observe them in the evening.

Although stimulants have been shown to have a dramatic effect on the classroom behavior of hyperactive preadolescent children, with improvements in reading and arithmetic task performance (e.g., Douglas et al., 1986; Pelham and Hoza, 1987), group-level teacher-rated improvements often do not exceed one standard deviation, and some treated children do not move into the normal range of classroom functioning (Elia et al., 1991; Quinn and Rapoport, 1975) even after prolonged treatment with stimulants (Riddle and Rapoport, 1976). Similarly, although stimulants can normalize aggressive and other behaviors that often predict peer status, they do not by themselves tend to change behavior patterns sufficiently to move sociometric peer perceptions into the normal range (Whalen et al., 1989). Also disappointing is the fact that these dramatic stimulant-mediated improvements in classroom functioning have not always been shown to radiate reliably to equally powerful improvements in academic achievement scores (Barkley and Cunningham, 1978; Charles and Schain, 1981). However, more recent reports are more encouraging. For example, Abikoff et al. (1988)

found significant gains in academic achievement after 6 months of stimulant treatment. Richardson et al. (1988) and Aman and Rojahn (1990) also suggested some achievement benefit from stimulants. Similarly, Douglas et al. (1988) and Vyse and Rapport (1989) reported finding clear effects of stimulant medication on classroom academic performance and complex problem-solving. Nevertheless, the effects of stimulants on achievement seem less powerful and consistent than the effects demonstrated on impulsivity and inattention.

The second and equally troublesome shortfall (chronological generalization) is that the long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning (e.g., Jacobvitz et al., 1990; Weiss and Hechtman, 1986). This shortfall may be explained partly by Sherman and Hertzig's (1991) finding that most 1-month prescriptions for stimulant medication are not renewed by the parents of children with ADHD.

Thus despite its dramatic short-term effects on the core clinical symptoms of ADHD/ADD for most patients, stimulant medication has been less reliable in bringing about lasting improvements, especially in social-emotional and academic problems such as poor peer and teacher relationships and school failure. A number of issues may complicate the assessment of stimulant efficacy, all of which have implications for the interpretation of treatment study outcomes:

First, many tests of the effects of stimulant medication have been short-term studies lasting only a few weeks or months. Many social and academic impairments associated with hyperactivity, however, may require significantly longer periods for altered trajectories to be engendered and recognized (Elia et al., 1991). The effects of stimulant medication on these domains of functioning may therefore have been underestimated in a number of studies. Schachar and Tannock (1993), reviewing stimulant studies of at least 3 months' duration, found that the randomized trials tend to report more stimulant benefit than the nonrandomized trials. According to the authors, the popular impression that stimulants do not improve long-term prognosis is an artifact of nonrandom trials in which more seriously impaired patients are more likely to be assigned to medication. Unfortunately, there is very little research evidence that the established short-term benefits of stimulant medication for ADHD improve the long-term prognosis of treated children (Jacobvitz et al., 1990). Thus, consistency and magnitude of long-term stimulant treatment effects remain open research questions that need to be addressed.

Second, some hyperactive children may not respond favorably to stimulants even in the short run. Earlier reports often estimated the prevalence of nonresponders among hyperactive children to range from 10% to 40% (e.g., Barkley, 1977; Swanson, 1989; Swanson and Kinsbourne, 1979), with estimates varying considerably as a function of populations studied, criteria used to assess clinical improvement, and whether more than one stimulant was tried (Pelham, 1987; Pelham and Hoza, 1987). More recently, however, Elia et al. (1991) concluded that many previous estimates of nonresponse may have been significantly inflated by (1) examining the effects of only one stimulant drug in a given study, and (2) not titrating stimulant doses on an individual basis. In a controlled treatment study that attended to these factors, the authors found that the vast majority (96%) of the 48 hyperactive children in their sample responded favorably to either methylphenidate or dextroamphetamine. They also concluded that the most common type of "nonresponse" was intolerable side effects. The fact that many earlier studies did not attend adequately to these factors suggests that they may have underestimated the true effects of stimulants. In addition, Pelham and Bender (1982) have noted that reliance on overall group differences may obscure substantial improvement in subgroups of children who respond particularly well to stimulant medication.

Third, some evidence suggests that dose-response relationships may vary considerably as a function of the domain of child functioning studied. For example, Sprague and Sleator (1977) reported that the higher dosages necessary for maximal effects on teacher-rated classroom comportment may actually impair learning abilities in certain hyperactive children, whereas lower stimulant doses seem to improve learning. However, more recent studies by other investigators have challenged these findings (e.g., Charles et al., 1981; Gan and Cantwell, 1982; Pelham et al., 1985). Although the specific question of differing dose-response thresholds for learning and behavior remains controversial, it is nonetheless true that unexamined dose-response relationships may obscure important individual differences across children that have implications for assessing stimulant treatment effectiveness (Pelham, 1982). As

we point out in more detail below, information about dose-response relationships also may be critical in decisions about whether, when, and how to combine psychosocial treatments with stimulants.

Fourth, the possibility of state-dependent learning remains a nagging question. Swanson and Kinsbourne (1976) suggested that some children's performance gains resulting from stimulant medication fail to carry over effectively to the unmedicated state. Despite replication of this effect in the laboratory, the preponderance of data suggest that this is not a problem for low doses of stimulants between the medicated and unmedicated states (Gan and Cantwell, 1982; Steinhausen and Kreuzer, 1981; Stevens et al., 1984). However, one of the studies that found no evidence of state-dependent learning between stimulant and placebo conditions *did* find on one test some evidence of state-dependent learning between methylphenidate and pemoline (Stevens et al., 1984). This complex question is undoubtedly related to the dose-response issue raised above (Stevens et al., 1984).

Fifth, there is evidence that the magnitude of stimulant benefit is probably not consistent across age groups or mental age/IQ groups (e.g., Aman et al., 1991; Handen et al., 1991; Klorman et al., 1990).

Sixth, the high levels of comorbidity characteristically associated with ADHD may have important implications for the differential effectiveness of stimulant medication in subgroups of hyperactive children. In fact, Pliszka (1989), studying methylphenidate in anxious and nonanxious ADHD children, found a significant interaction with comorbid anxiety, with an effect size of about .8 on the Iowa Conners Teacher Inattention-Overactivity scale. Whereas the nonanxious subjects showed the expected significant improvement from placebo scores (and little placebo response), the anxious subjects manifested a nonsignificant placebo-drug difference (less than half the magnitude of the nonanxious subjects), partly because of an equally large (although also nonsignificant) placebo response. There may also be a tendency for anxiety-comorbid children to have more side effects, detracting from effectiveness. On the other hand, there is little support in the literature for suspecting a differential methylphenidate effect as a function of whether the comorbid condition is conduct disorder or aggression; Abikoff et al. (1987), in fact, reported an absence of such an interaction. Comorbid conditions such as conduct, anxiety, and affective disorders all have been shown to be associated with a wide range of perturbations in normal development. Although Rutter (1982b) has suggested that the criteria for successful treatment of childhood disorders should include the fostering of normal development, most stimulant treatment studies have focused more narrowly on reducing symptoms of hyperactivity.

Seventh, a related issue is the possibility of a differential effect as a function of comorbidity and/or domain of function between the two major stimulants. If there is little overlap in the nonresponse rate, as suggested by some reports (Arnold et al., 1978a; Elia et al., 1991), then we might suspect that different patient characteristics determine nonresponse for methylphenidate than for *d*-amphetamine. There is reason to suspect that one such characteristic is comorbidity. The literature does not currently offer evidence of this for methylphenidate versus *d*-amphetamine, but there is some presumptive evidence from a comparison of amphetamine's two optical isomers (Arnold et al., 1976, 1978b). A related issue is the fact that the differential general/global efficacy (regardless of comorbidity) of the two major stimulants also remains in question. The unsubstantiated characterization of methylphenidate as the "drug of choice" persists in clinical circles, perhaps supported by the notion of less impact on growth velocity or less addictive potential (in adults) than amphetamines, despite the fact that all five published studies that could be found directly comparing it to dextroamphetamine in the same subjects failed to show an advantage for methylphenidate (Arnold et al., 1978a; Elia et al., 1991; Pelham et al., 1990; Vyborova et al., 1984; Winsberg et al., 1974). In fact, all five of these studies showed a slight advantage for *d*-amphetamine that was nonsignificant at the sample size used. Of the 141 total subjects in the five studies, 50 responded globally better to *d*-amphetamine and 37 responded better to methylphenidate (with most of the other subjects responding to both). The stimulants also differ subtly in their side effects; for example, the temporary mild retardation of growth in some children seems to be dose-dependent for methylphenidate yet possible even at low doses for *d*-amphetamine. Although one study (Greenhill et al., 1981) has suggested that *d*-amphetamine may slow height velocity more than methylphenidate, this growth slowing is minor and is not explained by changes in the pituitary hormones

controlling long-bone growth (Greenhill, 1981; Greenhill et al., 1981, 1984).

Eighth, for some children stimulant benefit may be offset by maladaptive psychological attributions of failure and success. Pelham et al. (1992) found that most preadolescent medicated hyperactive children attribute success to their own efforts or ability and failure to others or to the pill, a relatively normal and arguably adaptive self-enhancing attributional style; but a subgroup attributed success to the pill and failure to lack of ability, leading to a cessation of effort/motivation. This apparently maladaptive style is similar to that of depressed children (Alloy and Abramson, 1988; Kaslow et al., 1988; Mannuzza et al., 1991), again raising the possibility of comorbidity interacting with stimulant response.

Ninth, the possible linkage of drug response with such biological patient characteristics as minor physical anomalies (e.g., Deutsch et al., 1990; Fogel et al., 1985) or neurophysiological, metabolic, or nutritional attributes (e.g., Arnold et al., 1990; Bhatara et al., 1978) has not been adequately explored.

Finally, many studies of medication effects have not adequately considered the issue of prior medication. At any given age a history of earlier medication suggests more serious symptomatology, earlier manifestation, and/or socioeconomic/familial variables such as parental concern/attitudes and access to health care. Therefore, merely excluding subjects with a prior medication history would tend to bias a sample toward less serious and later-recognized cases, among other biases. On the other hand, including such subjects raises important questions about appropriate withdrawal from prestudy medication. The time needed for medication washout depends on the nature of dependent variables being studied: Although many behaviors and cognitions usually revert to baseline within days after stimulant withdrawal, Zametkin and his colleagues (Zametkin et al., 1985; Zametkin and Rapoport, 1986) have suggested that some stimulant-induced biochemical changes do not wash out for more than 2 weeks.

In summary, there is a substantial body of evidence demonstrating the short-term effectiveness of stimulant medication in normalizing many of the core clinical symptoms of ADHD (Jacobvitz et al., 1990; Satterfield et al., 1974). Stimulants appear less reliable in producing long-term benefit, although this has not been adequately studied (Schachar and Tannock, 1993). Also, stimulants seem to have weak and/or unreliable therapeutic effects on many secondary or comorbid emotional and academic deficits of children with ADHD. For these reasons, there is an emerging consensus in the field concerning an important yet limited role for judicious use of stimulant medication in the treatment of ADHD. Although stimulant medication may be the necessary and sufficient treatment for a subset of hyperactive children, especially among those not referred to a mental health setting, for others (e.g., those who have severe side effects) it may be contraindicated. And for still others, stimulant medication alone should not be expected to yield gains beyond its immediate effects on impulsivity, attention, and activity levels. Stimulants may be most effective in normalizing and stabilizing the primary functioning characteristics of some hyperactive children, whose behavior and learning problems must then be addressed directly and strategically through a range of psychosocial treatments (Pelham and Bender, 1982; Sprague and Sleator, 1977).

Psychosocial Treatments

Early treatment studies of hyperactivity focused primarily on the effects of stimulant medication on the disorder's core symptoms of inattention and impulsivity. Hollon and Beck (1978) reported that only 1 out of more than 2,000 hyperactivity treatment studies had been adequately designed to examine the differential effectiveness of stimulant medication and psychosocial treatments. Many of the research results and considerations raised above, however, have since given rise to investigations focused on the use of psychosocial treatment modalities alone and in combination with stimulants (Pelham and Murphy, 1986).

Psychosocial interventions that have been systematically explored include classroom-based behavior modification, social skills and cognitive training, parent training/home-based interventions, and intensive summer treatment programs. Controlled studies of stimulant medication, psychosocial treatments, and their combination have often revealed that combined approaches, under the right circumstances, may yield more favorable results than single treatment modalities alone (Hollon and Beck, 1978; Pelham and Murphy, 1986). On the other hand, several studies, especially among the early ones, suggested that stimulants were more effective than various behavioral treatments and

almost as good as the combination (e.g., Gittelman et al., 1980; Hinshaw et al., 1984a). Such findings may have been a result of too low an intensity of behavioral treatment, whereas more recent work emphasizes more intense behavioral interventions.

Abikoff and Gittelman (1984) have demonstrated that token reinforcement systems may "normalize" aggressive and other off-task behaviors in the classroom. Cognitive-behavioral intervention has been shown in some reports to produce both increased self-control and the use of specific coping strategies by hyperactive children—effects that in one study were neither enhanced by the addition of nor produced independently by stimulant medication (Hinshaw et al., 1984b).

Other child-focused interventions, such as self-control procedures, have produced desired treatment effects in experimental classrooms (Barkley et al., 1980), but a critical problem in this and other studies has been the lack of evidence that such interventions generalize to other settings (e.g., regular school classrooms) or across children's behavioral domains. For example, interpersonal problem-solving skills therapy has failed to facilitate interpersonal competence in either medicated or unmedicated children (Abikoff, 1987). In general, cognitive training and social skills training have produced only weak and variable effects, with little evidence to date that they have a significant impact on the academic performance or social behavior of hyperactive children (Abikoff, 1987; Abikoff and Gittelman, 1985a).

Home-based treatments with parental involvement, coordinated with school interventions, are thought by many workers in this field to be an essential component of treatment effectiveness and may increase the salience of school interventions for many children and facilitate the generalization of treatment effects across settings and behavioral domains (Barkley, 1990). Parent training in child behavior modification has been shown to improve both the school and home behavior of hyperactive children; however, only with medication were there also reductions of impulsivity and inattention (Firestone et al., 1981; Horn et al., 1983). Horn and colleagues (1991) reported data suggesting that a combination of parent training, child self-control training, and school consultation allowed a reduction in the dose of methylphenidate normally required for optimal benefit.

In summary, there is promising evidence for the clinical utility of a variety of psychosocial interventions in the treatment of hyperactive children, and some winnowing has been accomplished. Many specific treatments have been formalized in manuals and validated, at least for short-term results. Paralleling the limitations of stimulant treatment studies, however, most psychosocial treatment studies have not attended to important issues of generalization and individual differences in comorbid conditions and functional impairments, and long-term efficacy has not been adequately documented.

Other Treatments

Numerous other treatments have been tried or advocated but are not included in the multisite treatment study because they either have insufficient controlled research evidence of efficacy or else seem to benefit only a small proportion of ADHD children. They range from speculative or discredited treatments, to anecdotally supported, to the promising but unproven, and the effective but narrowly restricted. Notable among these have been elimination diets (NIH, 1982), manipulation of carbohydrate intake or carbohydrate-protein ratio (Chiel and Wurtman, 1981; Conners et al., 1987; Rapoport, 1982), vitamin supplementation beyond the recommended daily allowance (Arnold, 1984; Coleman et al., 1979), amino acid supplementation (Nemzer et al., 1986; Reimherr et al., 1987), essential fatty acid supplementation (Arnold et al., 1989), iron and other mineral supplementation (Arnold et al., 1990; Pollit et al., 1982, 1986), deleading with chelating agents, channel-specific perceptual training as prevention (Arnold et al., 1977), vestibular stimulation (Arnold et al., 1985; Bhatara et al., 1981), and sensorimotor integration (Ayres, 1973; Bauer, 1977). But the efficacy of many of these has not been sufficiently documented in preliminary studies to sustain continued research interest and/or does not appear applicable and generalizable to the majority of children with ADHD.

Multimodal Treatment

Both the well-developed literature on stimulant medication and the emerging literature on psychosocial treatments for children with ADHD suggest that no single treatment alone is likely to yield clinically significant long-term, cross-domain therapeutic gains in an

unselected, heterogeneous group of hyperactive children. Subgroupings of children are likely to have significantly different patterns of comorbidity (Anderson et al., 1987; Bird et al., 1988), family backgrounds, and functional deficits (Satterfield et al., 1979), all of which are likely to have important implications for treatment needs. On the basis of existing research findings, there is little reason to expect isolated treatments of any type (psychopharmacological or psychosocial) to produce lasting, clinically significant, broad-spectrum therapeutic effects when administered without regard for these important individual differences.

These considerations have given rise in recent years to an interest in multimodal treatment strategies that combine multiple forms of intervention (e.g., Abikoff, 1991; Hechtman, 1993; Horn et al., 1991; Pelham and Murphy, 1986; Satterfield et al., 1987). One such multimodal treatment study, closely approximating the ideal of sound clinical practice, includes tailoring stimulant medication and/or psychosocial interventions to the particular needs of individual ADHD children and their families (Satterfield et al., 1987). The rationale underlying this tailoring strategy is both simple and powerful: Some hyperactive children who are failing academically or socially may suffer primarily from skill deficits; for these children, academic and/or social skills training may suffice to bring about desired therapeutic change. For others with these skill deficits, it may be necessary to stabilize their impulsivity and/or inattention before embarking on skills training. Others suffering academically and/or socially may possess the requisite skills but experience difficulties in exercising those skills due solely to the core symptoms of inattention, distractibility, and/or impulsivity. A subset of these children may benefit solely from the therapeutic effects of stimulant medication; others may require additional interventions involving family members and/or peers to help ameliorate strained relationships engendered by the core impairments that preceded treatment. Yet other children may respond most favorably to skills training, behavior modification, and/or family therapy, even in the absence of stimulant medication.

Although this tailored multimodal approach has long been considered the ideal of sound clinical practice, it has received relatively little attention in the empirical literature. The most detailed reports of the effects of multimodal treatment have been published by Satterfield and his colleagues, based on their multidimensional treatment study of 117 hyperactive boys and their families (Satterfield et al., 1979, 1981, 1987). Following recruitment into the study, boys and their families underwent extensive assessments to determine treatment needs, including multiple dimensions of each child's psychosocial adjustment, academic performance, intellectual functioning, neurological status, antisocial behavior, parental psychopathology, and family problems. On the basis of these assessments, treatment plans were developed and implemented by a coordinated team. Treatment modalities, matched to the needs of particular children and their families, included individually titrated doses of methylphenidate, individual and conjoint therapy for the parents and children, family therapy, parent training, individual and group educational therapy, as well as group therapy for the parents. One-year follow-up data indicated that the combination of clinically useful medication with appropriate psychosocial treatments directed to specific child and family functioning deficits yielded unexpectedly positive outcomes. According to independent reports from the children, their parents, their teachers, and psychiatrists, treated children manifested significant reductions in antisocial behavior and psychological symptoms, and significant improvements in academic performance, self-esteem, and global functioning. Moreover, a 3-year follow-up study indicated sustained improvements in this sample among those children (approximately 50%) who were still receiving treatment (Satterfield et al., 1981). More specifically, these children were found to be farther ahead educationally, to demonstrate significantly less antisocial behavior, to be more attentive in class, and to be better adjusted at home and at school than those who discontinued treatment. The beneficial effects of multimodal treatment were supported also by a subsequent report showing that the drug-only group experienced significantly more arrests and institutionalization than those who received multimodal treatment (Satterfield et al., 1987).

Although these impressive results have generated enthusiasm in the field, the enthusiasm has been tempered by concerns over severe limitations on both the internal and external validity of the research design,

including possible recruitment bias, the absence of a no-treatment control group, the failure to use blinded assessment procedures, and the uncontrolled assignment of subjects to treatment conditions. Moreover, limitations of sample size precluded meaningful comparisons of treatment combinations, and design limitations precluded tests for interactions between treatment combinations and comorbidity patterns or child/family characteristics.

THE NEED FOR A COLLABORATIVE, MULTISITE STUDY

Considerable research into treatment strategies will be needed to establish some answers to the manifold question posed earlier: Under what circumstances (comorbid conditions, age, gender, family background) do which treatment combinations (medication, behavior therapy, parent training, school-based intervention) have what impacts (improvement, stasis, deterioration) on what domains of child functioning (cognitive, academic, behavioral, physical, peer relations, family relations), for how long (short- versus long-term), to what extent (effect sizes, normal versus pathological range), and why (processes underlying change)? The very nature of multimodal treatment is such that answers to these questions will require substantial sample sizes, with adequate numbers of ADHD children with similar comorbid profiles, functional deficits, and family characteristics.

The difficulties inherent in implementing a viable multimodal treatment study at a single site are illustrated in a dual-site multimodal ADHD treatment study recently funded by NIMH (Abikoff, 1991; Hechtman, 1993). Two sites were necessary because accomplishing this study at one research center—even one with a substantial patient flow and treatment infrastructure—would require between 7 and 8 years to complete. Furthermore, although this study was designed to address critical questions about the additive benefit of psychosocial treatment in methylphenidate responders, the combined sample nonetheless lacks sufficient heterogeneity and statistical power to address most aspects of the manifold treatment question raised earlier. For example, even though subjects in this study are diagnosed according to *DSM-III-R* criteria, the design specifically excludes children with comorbid conduct disorder and/or severe learning disorders. Thus, the resulting data will not support much-needed subgroup analyses of ADHD children with different comorbid conditions. This was not a design oversight, but rather a necessary sacrifice imposed by sample size restrictions, which in turn were necessitated by the resource constraints of any single- or dual-site study. Nonetheless such necessary compromises will severely constrain the generalizability of study findings, given that as many as two thirds of ADHD children seen in routine clinical settings may suffer from a range of comorbid conditions (Biederman et al., 1991; Conners and Wells, 1986; Trites and Laprade, 1983), and it is precisely these comorbid conditions that may be related to long-term outcomes (Klein and Mannuzza, 1991).

It is clear that the strategy of crossing of comorbid patterns, child functioning deficits, and family functioning characteristics with different treatment strategies will require a sample size that outstrips the professional resources (staff and facilities) and patient flows of even the largest research/treatment centers in the country. For this reason, and to enhance the representativeness of the sample and generalizability of the findings, NIMH made a decision to mount a multisite study.

The cooperative agreement mechanism used for this study has several advantages: Not only does it provide the needed large sample, but by implementing a common protocol derived from cooperative planning, it involves a high degree of quality control and integration of multiple profiles of expertise. Statistically, it provides multiple replicates of the same design, thus addressing the heterogeneity of ADHD and ecological site differences in a manner not possible by the same number of single-site studies.

PLANNING ISSUES

The goal of the NIMH Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) is to implement a 5-year study of treatment of ADHD and its associated comorbid conditions and social-emotional and academic impairments. Following from the issues addressed earlier, the primary questions to be explored will concern the long-term effects of both pharmacological and psychosocial treatments, synergistic or additive effects of stimulant and psychosocial treatments, and interactions of treatment types with comorbidity pattern and socioeconomic status. No

single study, however ambitious, can adequately address all of the important issues.

The first year of the collaborative effort is devoted mainly to developing a common protocol from the selected proposals, developing the necessary training and implementation procedures, finalizing manuals to ensure cross-site consistency in study execution, and hiring and training assistants/therapists. The common protocol must be designed to maximize the potential of the cross-site data set to address manifold treatment questions and to support major studies focusing on related issues of the assessment, comorbidity, etiology, validity, and natural history of ADHD with its comorbid conditions. Domains of assessment are expected to include formal psychiatric assessments of probands and parents, as well as assessments of all probands in the domains of neurological, intellectual, cognitive, academic, and behavioral/psychosocial functioning. Project years 2 through 4 are devoted to the implementation of the protocol developed during the first project year. Entry of subjects is staged over not more than 2 years at each site to allow at least 2 years of treatment and follow-up. Year 5 of the project will be used mainly to analyze the results, prepare scientific reports for publication, prepare data tapes for the public domain, and develop a competing renewal application for study extension, as warranted by study findings and scientific merits of examining long-term outcomes.

SUMMARY AND CONCLUSIONS

The field of ADHD treatment research has progressed in cumulative fashion over the past half century from a narrow focus on stimulant medications to a consideration of isolated psychosocial interventions—both alone and in combination with stimulants—to a recognition of the need to test multimodal treatment strategies. Although the field is now poised to engage this challenge, it is clear that individual investigators and research centers lack the necessary resources and sample sizes to implement the needed research design. These are precisely the conditions that warrant a multisite collaborative treatment study.

The MTA will address crucial treatment issues concerning an extremely important public health problem among young children, as judged by the number of lives disrupted and the amount of health care resources consumed. The disorder perturbs not only afflicted children but their families and classmates as well. Furthermore, in many child psychiatric patients with other primary complaints, ADHD is often diagnosed as a complicating condition. Therefore, any improvement in efficacy and efficiency of treating this disorder may have a tremendous public health ripple effect.

The scientific impact of this study will be equally valuable. Children's mental health research has lagged behind other areas of adult mental health research, which has in turn lagged behind general medical research. The NIMH recognizes the need to move the children's mental health research agenda forward. As the first major cooperative mental health treatment study of children in the United States, this effort will be critical in advancing that agenda.

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