REVIEW ARTICLE

Attention Deficit Hyperactivity Disorder and Methylphenidate: When Society Misunderstands Medicine

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a behavioral condition that typically manifests in young children. The cardinal symptoms of the disorder are inattention, impulsivity, and hyperactivity, traits that make learning and concentration difficult for children with ADHD. The disorder has been recognized as a serious medical and behavioral condition since George Still's series of lectures to the Royal College of Physicians in 1902 (1). ADHD is the most common neurobehavioral problem in school-age children, with current prevalence at 3-5%, and is 4-9 times more common in males than females (2). For diagnostic purposes, the disorder is separated into three classes depending on whether it mainly involves inattentiveness, hyperactivity/impulsivity, or both. Associated symptoms of ADHD include emotional lability and a resistance to conditioning whereby poor behavior is repeated despite punishment, making these children very difficult to discipline. The cardinal symptoms and the associated symptoms of ADHD lead to very poor peer relationships, poor school performance, and poor self-esteem. Oppositional Defiant Disorder (ODD), specific learning disabilities, and conduct disorder (CD) are common syndromes frequently comorbid with ADHD (3). It is unknown whether these are other primary syndromes or arise secondary to ADHD.

The most common treatment for children with ADHD is psychostimulant medication, primarily methylphenidate (MPH), marketed under the trade name Ritalin. The use of stimulant medication for children with behavior problems was first reported in 1937 when Charles Bradley used amphetamine (Benzedrine) on impatient children with symptoms of ADHD and noticed that conduct and school performance were substantially improved. Fueled by positive reports in the medical literature and the lack of information on deleterious long-term effects, use of MPH dramatically increased in the 1960s. By 1970, MPH was used by over 150 000 children for behavioral problems and by mid-1995, approximately 2.8 % (1.5 million) of US children between 5 and 18 were receiving MPH for ADHD (4). It has repeatedly been shown that MPH improves all symptoms of ADHD in 73-77 % of cases (1). Children on the drug demonstrate less erratic and more goal-directed behavior, have decreased restlessness, are more able to sustain attention to tasks and to concentrate, and are less impulsive. Aggression, noncompliance, and disruptiveness are also ameliorated by MPH. Social interactions of children with ADHD also appear to improve as a result of MPH therapy as these children comply more with parental authority and are more interactive, resulting in increased positive feelings from parents and teachers and hence increased self-esteem (1,3).

The sharp rise in the diagnosis of ADHD and the use of psychostimulant medication for the condition over the last 25 years has made both the disorder and its treatment one of the most controversial issues in the field of psychiatry. Many opponents of the disorder feel ADHD is a bogus diagnosis that the "affected" child will outgrow in adolescence and adulthood. There is

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ample criticism with regards to MPH therapy as well, with many feeling that it is vastly over prescribed and carries significant side effects that outweigh any beneficial effect that may occur. The majority of the scientific evidence has shown that these attitudes carry little merit and are detrimental to the care of children with ADHD. It is the opinion of the author that these misperceptions have arisen from a fundamental misunderstanding of both the nature of the disorder and its pharmacotherapy.

The purpose of this article is twofold. Firstly, a review of the current literature on the etiology and pathophysiology of ADHD, as well as the mechanism of action of MPH, will be presented. Secondly, evidence will be presented from basic science and clinical studies showing the marked inconsistencies between current knowledge about ADHD and MPH and the common misconceptions surrounding the use of MPH therapy.

ADHD ETIOLOGY AND PATHOPHYSIOLOGY

The etiology and pathophysiology of ADHD remain unknown and are presently areas of active research. It is believed that ADHD arises from a complex interaction of environmental and biological factors, with strong evidence for a genetic component. Several family studies have shown positive familial aggregation, and some have found patterns of inheritance suggesting autosomal dominant gene transmission (5). ADHD has been found to be more common in first degree biological relatives of children with the same disorder (2). Levy et al. (6) found that male monozygotic twins had a significantly higher rate of ADHD versus non-twin siblings, and Sherman et al. (7) found that concordance rate for ADHD was greater for monozygotic twins than for dizygotic twins.

Environmental factors, although not as well studied, also appear to play a role in ADHD development. Biedermann et al. (8) found a positive association between six previously identified risk factors within the family environment that correlated significantly with childhood mental disturbances and risk for ADHD: severe marital discord, low social class, large family size, paternal criminality, maternal mental disorder, and foster placement. It must be kept in mind that the presence of familial clusters of ADHD does not necessarily imply a biological predisposition, as this could result from environmental interaction.

The majority of evidence for ADHD pathophysiology points to dysfunctions of two interconnected brain areas: the prefrontal cortex and the striatum (caudate and putamen). The prefrontal cortex is believed to play a key role in the weighing of consequences and subsequent actions based on these consequences, and is involved in goal determination and the cognitive steps that go toward achieving these goals, such as directing attention, prioritizing actions, and creating and executing plans (9-11). Another important function of this brain area appears to be response inhibition. Studies with experimental animals have shown that lesions of the inferior prefrontal convexity result in decreased ability to delay response and poorer performance on tasks that require certain motor responses to be suppressed at given times (9). Thus, derangement of the prefrontal cortex would appear to produce symptoms quite similar to those in children with ADHD.

Structural and functional imaging studies have provided evidence for right-sided frontal-striatal dysfunction. This general finding is particularly significant since the right hemisphere appears to play a primary role in the general maintenance of attention and arousal (12). An early magnetic resonance imaging (MRI) study by Hynd et al. (13) on 10 children with ADHD showed that the ADHD group had bilaterally smaller frontal cortices, especially on the right, and a loss of the normal R > L asymmetry of the frontal lobes compared to controls.

Subsequent structural imaging studies focused on the corpus callosum and the caudate nucleus. Since the corpus callosum mediates hemispheric communication of attention as well as relative arousal levels, and fibers from the somatosensory regions travel through the corpus callosum in a somatotopic pattern, researchers reasoned that dysfunction of a certain part of this brain structure may indicate pathology in those areas of the brain which originally gave rise to these fibers. The premotor, orbitofrontal, and prefrontal cortices are all connected by nerve fibers contained within the anterior corpus callosum. As a result, researchers hypothesized that the anterior aspect of the corpus callosum would be smaller in children with ADHD (5). The most recent studies have provided evidence both for and against this hypothesis. Giedd et. al (14) used MRI to measure the cross-sectional area of the corpus callosum of children with ADHD and normal controls and found that two anterior regions (rostrum and rostral body) were significantly smaller in the children with ADHD. In addition, these children demonstrated increased hyperactivity and impulsivity as rated by parents and teachers. Semrud-Clikeman et al. (15), however, did the same on a sample of 15 children with ADHD and 15 well-matched controls and found that the ADHD group had significantly smaller splenial areas in the posterior corpus callosum, with no significant difference in the anterior region. Clearly, more studies are needed to elucidate the role of the corpus callosum in ADHD.

A recent MRI study by Castellanos et al. (16, 17) has shown that the mean right caudate volume was significantly smaller in children with ADHD versus

controls, while no significant difference was found for the left caudate, resulting in the loss of the normal R > L asymmetry of the caudate in these children. Thus, despite equivocal corpus callosum studies, the latest structural imaging studies provide evidence for frontal-striatal dysfunction in ADHD.

Functional imaging studies have also yielded much information on the pathophysiology of ADHD. Lou et al. (18,19) studied cerebral blood flow and, by extension, metabolic and functional activity, in children with ADHD using xenon-133 inhalation and positron emission tomography (PET). In the first study (18), it was found that the frontal lobes and the caudate nuclei were less well perfused in all eleven and seven of the eleven children studied, respectively. They also scanned six children before and after a treatment dose of MPH and found increased perfusion of these regions after the treatment. In the second study (19), which unlike the first divided "pure" ADHD children from those with ADHD and other neuropsychiatric symptoms, the researchers found decreased perfusion of the right striatal area and increased perfusion to the striatal and periventricular (including frontal) areas with MPH, replicating the results from the previous study. The increased striatal flow was to the left striatal region, which the researchers speculated was due to more irreversible damage to the right striatum.

In a recent series of studies, Zametkin et al. (20,21) used PET and [^{18}F] fluorodeoxyglucose to study glucose metabolic rates. In the first study (20), they found that global glucose metabolism was significantly lower in adults with ADHD versus normals. They also found that, when normalized (regional metabolism/global metabolism), the regionalized metabolic rates of four regions including the left premotor area were significantly decreased. In a subsequent study with adolescents (21), however, no significant differences were found in global or absolute glucose metabolism between ADHD and control groups. However, when normalized, metabolism was significantly reduced in six of sixty regions of interest, including a part of the left anterior frontal lobe. Lower metabolism in this area was associated with more severe ADHD symptoms.

Physiologic studies have also provided evidence for frontal-striatal dysfunction in ADHD. Ross et al. (23) used an oculomotor delayed response task to measure the functioning of the frontal cortex in children with ADHD and found that these children show deficient inhibition of response compared to normal controls, a function attributed to the frontal cortex and hypothesized to be the primary deficit in ADHD.

Research in experimental animals has supported the hypothesis that ADHD results from an imbalance between norepinephrine (NE) and dopamine (DA). Namely, there may be an excess of NE in the locus ceruleus and a deficiency of DA in the frontal-mesolimbic system (12). The areas believed to be primarily dysfunctional in ADHD, the frontal cortex and the striatum, are intricately connected to the catecholaminergic system. Dopaminergic innervation is particularly prominent in the frontal area of primates and other animals. Pathways from the frontal cortex to the striatum which are thought to modulate dopaminergic release are hypothesized to be dysfunctional in children with ADHD (12).

The endocrine system is also putatively involved with ADHD. Several studies (24-28) have showed an association between thyroid gland dysfunction and ADHD. This association was first reported by Hauser et al. (24) who found ADHD was strongly associated with a rare disorder caused by mutations in the thyroid receptor-B gene, called generalized resistance to thyroid hormone (RTH). RTH is characterized by abnormally increased concentrations of T_4 and T_3, TSH levels inappropriately normal or high, and decreased responsiveness of the pituitary gland and peripheral tissues to the metabolic actions of thyroid hormone. In subsequent studies on children with congenital hypothyroidism, which causes levels of thyroid hormone and TSH to vary, Rovet and Alvarez (25, 26) found an association between high T_4/high TSH and poor attention. Higher T_4 levels were most closely associated with poorer attention, with hyperactivity level decreasing with higher TSH levels (26). Since these authors found that the children who demonstrated this association did not do so at an older age (25), they hypothesized that thyroid hormone, and not the receptor, was primarily responsible for regulating attention.

In another study, Alvarez et al. (27) showed that children with hyperthyroidism demonstrate poorer visuospatial cognitive processing and attention. These children showed decreased ability to disengage and shift their attention while thyrotoxic, but improved once they became euthyroid. Since recent neuropsychological studies had shown that the frontal cortex is responsible for these functions of attention, the researchers hypothesized that the prefrontal cortex may be particularly sensitive to elevations in circulating thyroid hormone. Matochik et al. (28) found that performance on a continuous auditory discrimination task was significantly poorer in adult RTH subjects versus controls, and used PET to find that cerebral glucose metabolism was higher in both the right parietal cortex and anterior cingulate gyrus. Although the majority of patients with ADHD do not have thyroid abnormalities, these studies perhaps offer a glimpse into

the biological basis for ADHD. Along with the parietal cortex, other areas putatively implicated in attention, activation, and arousal include parts of the reticular formation, which includes the thalamus and mesencephalon (10). More studies are needed to further elucidate their roles in ADHD pathophysiology.

METHYLPHENIDATE: MECHANISM OF ACTION

The mechanism by which MPH exerts its effects remains elusive, despite being the subject of much research. MPH is an indirectly acting sympathomimetic (or psychostimulant), a drug class which includes dextroamphetamine and pemoline. MPH is the most widely used clinically of the three. In 1971 MPH became the drug of choice to treat ADHD, following a study by Weiss et al. (29) comparing its therapeutic effects to that of chlorpromazine and dextro-amphetamine. MPH is well absorbed from gastrointestinal tract and reaches peak plasma levels in 1-2 hours. It has a short half-life of 2-3 hours and thus requires multiple daily dosing. It is completely metabolized by the liver (30).

MPH is thought to affect catecholamines, the neurotransmitter system believed to be involved with ADHD pathophysiology. As previously discussed, ADHD pathophysiology is thought to involve a pattern of decreased dopamine and increased norepinephrine neurotransmission. MPH administered to animals has been shown to block norepinephrine and dopamine uptake in the striatum, hypothalamus, and cortex while expediting the release of DA, but not NE, from the striatum (12). Thus, it appears that MPH might act by "correcting" the catecholaminergic imbalance thought to be central to ADHD. The dopaminergic component of MPH's actions appears to be particularly crucial for its clinical effects. Levy and Hobbes (31) found that MPH improved attention in hyperactive children during vigilance tasks, but that this effect was no longer observed when a dose of haloperidol, a dopamine antagonist, was given prior to MPH administration.

Since MPH appears to affect the dopaminergic system primarily, and the brain regions thought to be primarily involved in ADHD pathophysiology are rich in dopaminergic innervation, it follows that there should be an increase in metabolic activity in these regions following MPH administration. As previously discussed, Lou et al. (18,19) found increased blood flow to the frontal and caudate regions when MPH was administered to a sample of children with ADHD. Researchers using PET and [^{18}F]flourodeoxyglucose have tried to find similar phenomena. For the most part, these studies have yielded negative results. Matochik et al. studied the effects of both acute (32) and chronic (33) stimulant medication on cerebral glucose metabolism in adults with ADHD. They found that neither the acute nor chronic oral administration of MPH or dextroamphetamine affected global metabolism. With the data normalized (regional/global), the metabolic rate of the right caudate increased only with acute dextroamphetamine administration. Chronic MPH administration changed metabolic rate in two regions including the right posterior frontal region, but this difference proved not to be significant. A subsequent study by Ernst et al. (34) also found equivocal results using intravenous dextroamphetamine. It is clear that more research is needed to further elucidate the actions of MPH on the brain.

THE CONTROVERSY OVER ADHD AND METHYLPHENIDATE

ADHD and MPH therapy have come under considerable attack in the last decade. This has, for the most part, been fueled by largely erroneous and irresponsible media reports that have grossly misrepresented the scientific literature (35-37). There was a well-publicized "media blitz" against MPH between 1987-1989, in which nationally broadcast television talk shows such as *Oprah Winfrey*, *Phil Donahue*, and *Geraldo Rivera,* played a large role in permitting unsubstantiated allegations about widespread irresponsible MPH use and dangerous side effects, which resulted in several civil suits being threatened or actually begun (37). Two other particularly well-known examples include the *New York Times* op-ed piece by John Merrow (October 21, 1995) and the *20/20* segment by Tom Jarrell (October 20, 1995) in which a number of other false allegations were made regarding ADHD and MPH. ADHD has been labeled a "bogus diagnosis" by these media reports, and these reports have also included unfounded allegations concerning the widespread abuse of MPH by teenagers, MPH acting as a "gateway" drug leading to other kinds of substance abuse, and the possible "national problem" of over prescription of stimulants like MPH. These reports have continued to attack MPH as having "dangerous" side effects (e.g., permanent brain damage, severe emotional stress, severe depression, psychosis, Tourette's syndrome) that far outweigh any beneficial effects the drug may have. There have also been many anecdotal reports on the internet vilifying MPH for its deleterious side effects. Protests against MPH have also come up on such national news shows as *AM America*, *CBS News*, and *Night Line*. Psychiatric meetings in which ADHD is a topic of discussion are routinely picketed. *The Church of Scientology* has formed a group called the *Citizens Commission for Human Rights* which has filed suit against several physicians who have

prescribed MPH (35, 36). There is evidence to suggest that these attacks against MPH have negatively impacted the care of children with ADHD. Safer and Krager (37) found a 39% decline in the rate of MPH therapy in the Baltimore area in 1989 and 1991 surveys, from its peak in 1987, following the 1987-1989 media blitz and threatened lawsuit by an attorney supported by the *Church of Scientology* against a local public school system that was dismissed one month later as without basis. They found that the decline was due not only to parental apprehension towards MPH usage because of the dangerous side effects irresponsibly reported in the media blitz, but also reluctance on the part of school staff to bring children showing the symptoms of ADHD to the attention of physicians (37).

It is important to mention that misunderstanding of MPH is not limited to lay society. Kwasman et al (38) found much variation in pediatricians' knowledge and perspectives regarding the mechanism of action and clinical effects of MPH. It is apparent that the understanding of MPH therapy among some physicians is still poor. Improved understanding among physicians is vital to bridging the gap between society and medicine.

ADHD: NOT JUST "BOYS BEING BOYS"

ADHD has been widely criticized for being a bogus label applied by adults to children who are more difficult to discipline and control than others. To these critics, ADHD is a nondisorder, specific to childhood, that these improperly labeled children will grow out of during adolescence and will not be a factor in their adult lives. It is felt that ADHD is simply "boys being boys" and a diagnosis made for the benefit of parents and teachers who now have an excuse for not being able to handle these children.

The majority of evidence suggests that ADHD is by no means simply a childhood phenomenon, but often extends in some form into adolescence and even into adulthood, and thus can be a debilitating lifelong condition. There is a high rate of continued behavioral and academic dysfunction in early adolescence (39). Most patients with ADHD undergo only a partial remission in late adolescence, with hyperactivity usually the first symptom to remit and distractibility, if ever, the last. Children whose ADHD persists into adolescence are at high risk for developing conduct disorder, and 50% of those with conduct disorder will develop antisocial personality disorder as adults. These children are also vulnerable to continued learning problems. About 15-20% of the cases have been shown to persist into adulthood, with continued impulsivity and propensity for accidents (30).

Barkley et al. (40) followed a large sample of hyperactive children over an eight-year period into adolescence. They found that 80% of the sample continued to qualify for an ADHD diagnosis, and 60% for a diagnosis of CD or ODD. The rates of antisocial acts, cigarette and marijuana use, and negative academic outcomes (e.g., failed grades, suspension, expulsion, drop-outs) were considerably higher in hyperactive children. CD was found to mediate most of these effects along with ADHD. However, CD alone was responsible for the development of substance use and school expulsion in hyperactive adolescents, while grade failure was for the most part mediated by ADHD and not by CD. Family stability (e.g., marriage, occupation, and residence of the families of ADHD children) was decreased in the children with ADHD (40). Mannuzza et al. (41) studied a cohort of ADHD children through adolescence and adulthood and found that childhood ADHD predicted adult antisocial personality and (nonalcohol) drug abuse disorders. These disorders were dependent upon the continuation of ADHD symptoms in adolescence, but not in adulthood where they appeared independent of continuing ADHD. Formerly, hyperactive children also completed less formal schooling, underachieved and dropped out more, and attained lower occupational rankings than normals. No significant relationship was found between childhood ADHD and adult mood or anxiety disorders (41).

In summary, the evidence suggests that for children with ADHD, there is a high rate of continued negative psychiatric, social, legal, academic, and family functioning in adolescence. Children with ADHD continue to have ADHD symptoms, antisocial personality, and nonalcoholic substance use disorders as adults and are relatively compromised vocationally.

METHYLPHENIDATE: A TOOL TO TREAT A DISORDER, NOT A PANACEA

The evidence does not support the argument that MPH is over prescribed. As mentioned earlier, the prevalence of ADHD among school-aged children is estimated to be between 3-5% (2). As Barkley (35) points out, surveys conducted in several U.S. states reveal that among all school-aged children, only about 1-1.5% currently take stimulants for behavioral problems. Thus, even taking into account the problems of comparing two different epidemiological studies, it appears that MPH is not over prescribed.

A great number of well-controlled studies have documented the positive short-term effects of MPH on the cardinal symptoms of ADHD: increased attention span, increased concentrating ability, decreased activity, increased cognitive performance, and decreased oppositional behaviors (1). Safer and Allen

found (42), contrary to earlier beliefs held by psychiatrists, that MPH therapy in teens with ADHD resulted in clinical benefit of the same quantity and quality as younger children with ADHD. Importantly, they also found no evidence for stimulant drug abuse or sale by these teens, clearly not supporting MPH's critics. They found that teens were more resistant to taking stimulant medication, and reasoned that it would therefore be less likely that teens would abuse MPH. It is likely that children with ADHD experiment with other drugs more often than children without the disorder, but this has generally been attributed to the impulsivity and school failure that comes from having ADHD and not to MPH therapy. No study has been conducted that shows MPH therapy predisposes those receiving it to abuse other drugs as teenagers, and most researchers consider the potential of abuse of other drugs very small (1). Although sparse, the evidence suggests that the self-esteem of children with ADHD who are effectively treated with stimulants and other modalities is increased, therefore making abuse of drugs less likely (36).

Despite these facts, MPH has clear limitations. Between 23-27% of children with ADHD do not respond or show adverse effects that preclude their ability to continue with the medication. MPH has been shown to have questionable effects on academic efficiency. DuPaul and Rapport (43) showed that MPH treatment at a group level resulted in improved classroom conduct and improvement of childrens' on-task attention and academic efficiency but failed to show normalization at an individual level in 25% of children, thus necessitating the need for supplemental interventions (e.g., behavioral therapies) in a large proportion of children with ADHD. Rapport et al. (44) found that a large percentage of MPH-treated children with ADHD showed significantly improved or normalized attention (76%) and classroom behavior (94%) but that only 53% were found to have significantly improved academic efficiency; 91% of children who demonstrated a decrease in academic efficiency under at least one dose of MPH did not show significant improvement under any dose. Again, the researchers concluded that additional interventions were necessary for the large subset of children with ADHD whose academic functioning did not improve on MPH. Thus, while MPH does have a positive effect on academic performance in some cases, this does not extend to a significant proportion of children with ADHD.

Results on the long-term outcome of MPH therapy have yielded disappointing results. Weiss et al. (45) studied the long-term clinical effects of MPH therapy and found that children with ADHD who had been taking the drug for five years did not show significantly improved outcomes versus controls (unmedicated or chlorpromazine treated) in many important outcome parameters (e.g., cognitive testing, psychiatric variables such as emotional adjustment, delinquency, mother-child relationship, mother's impression of change, academic performance), forcing the authors to conclude that MPH, while improving behavior in hyperactive children at home and at school, did not significantly improve their long-term outcome. Hechtman et al. (46) found mixed results for young adult outcome after at least 3 years of MPH therapy. In some areas (e.g., automobile accidents, more positive view of childhood, later delinquency, improved social skills and self-esteem) MPH-treated children with ADHD had better outcomes than untreated children with the disorder. However, in many other areas (e.g., school, work, personality disorders), the treated group performed no better than their untreated counterparts and significantly poorer than normal controls. Long-term MPH treatment does not appear to be able to eliminate educational, occupational, or life difficulties. Research on long-term outcome of MPH therapy is extremely sparse and more is clearly needed.

The side effects of MPH have come under considerable public scrutiny. While MPH clearly has side effects, no study has ever shown these to outweigh its beneficial effects. The most commonly encountered short-term side effects are insomnia (90% of studies) and reduced appetite (79% of studies), followed by irritability and weight loss (fewer than half of the studies) and headaches and abdominal pain (slightly less often than irritability and weight loss). All other side effects were infrequent in comparison (1). MPH has been reported to possibly increase the frequency of nervous tics and, quite controversially, to perhaps result in development of secondary Tourette's syndrome on occasion. As a result, MPH is relatively contraindicated in children with a personal or family history of tic disorder, but the literature has not fully supported this view: Gadow et al. (47) found evidence for a weak MPH effect on increasing the frequency of motor and decreasing the frequency of vocal tics but found no evidence that MPH made tic disorder more severe. A very recent study by Ahmann et al. (48) showed that only insomnia, decreased appetite, stomachache, headache, and dizziness were increased by MPH while euphoria, sadness, crying, talking less, disinterest, drowsiness, nightmares, and motor and vocal tics were unaffected. In contrast to media reports, side effects are usually quite mild in their severity (1). Gross-Tzur et al. (49) found that MPH may increase seizures in epileptic children who had been having seizures but found no evidence that it induced attacks in those children with epilepsy who were not having seizures at

Table 1. Comparative efficacy and side effects of alternative medications for ADHD

Medication	Efficacy vs. MPH	Common Side Effects
Tricyclic Antidepressants	Decreased effect on behavioral and especially cognitive functioning; more effective than MPH on affective symptoms (61).	Increased blood pressure (58, 60, 66) and heart rate (61); anorexia (59).
Monoamine oxidase inhibitors	Equal or decreased (no proven effects on academic performance and cognitive functioning) (1, 62).	Drowsiness, requires restrictive diet; concern of possible drug interaction with stimulants (62, 66).
Clonidine	Equal or decreased (no proven effects on academic performance and cognitive functioning) (1, 63); may be particularly effective with comorbid tic disorder (30).	Sleepiness, mild decreases in blood pressure (63).
Bupropion	Equal or decreased (positive effect on cognitive functioning (65) but unproven effect on academic functioning).	Drowsiness, fatigue, nausea, anorexia, dizzyness (65).

the time of the study.

MPH has also been attacked for its supposed psychosocial side effects. It has often been reported anecdotally that children on MPH are less creative and spontaneous. This has prompted researchers to study this formally. The results have generally not shown that MPH causes these kinds of cognitive deficits. Frank et al. (50) found that ADHD boys were no more creative in their thinking than their peers without ADHD and that MPH did not negatively affect creativity. Solanto (51) showed that MPH did not decrease performance on tests that required cognitive flexibility or "divergent thinking", but that its absence did result in decreased productivity on these tests.

It is important to note that the majority of the short-term side effects of MPH are dose-related, subject to differences among individual patients, and that many diminish within 1-2 weeks of the onset of medication (1). A small decrease in MPH dose can eliminate many problems, although reportedly 1-3% of children are intolerant to all doses.

Although the long-term side effects of MPH have not been well-studied, a suppression of height and weight gain on MPH has been noted by several studies (1). This effect can be seen after two years of treatment and is dose-related, seen only with doses of more than 20 mg per day (52). Importantly, this effect has been shown to be of a transient nature, with adolescent reversal of growth velocity inhibition and normal final adult height (53). Furthermore, drug holidays at various points in the year have been shown to result in growth rebound (1).

In part due to MPH's limitations and side effects, much research has focused on determining factors that will predict a response to MPH and on alternative drug treatments. DuPaul et al. (54) have shown that children with ADHD and comorbid internalizing symptoms (e.g., depression, anxiety) were less likely to show a benefit in their academic functioning as a result of MPH therapy. Buitelaar et al. (55) found that increased IQ, more inattentiveness, younger age, decreased severity of ADHD, and decreased anxiety were predictors of strong response to MPH. They also found that a positive response to a single MPH dose contributed to prediction of response. On the experimental front, both Frank (56) and Young et al. (57) have found that certain differences in EEG event related potentials differentiates groups of children with ADHD and may be predictive of MPH response in children with these differences.

To date, no other medication has supplanted MPH as the therapy of choice for ADHD. Table 1 provides a summary of these treatment modalities, their efficacy versus MPH, and their side effects. The tricyclic antidepressants (58-61), monoamine oxidase inhibitors (MAOIs, e.g., clorgyline and tranylcypromine) (62), clonidine (63), and bupropion (64,65) have been the most widely studied (66). The MAOIs, clonidine, and bupropion are particularly in need of further studies comparing their efficacy to MPH in large groups of ADHD subjects.

Psychosocial treatments for ADHD have also been studied. For the most part, the evidence has shown that behavior therapy on its own is not as effective as MPH, yet the combined effect of the two treatments is superior to either alone (1). Some research has disagreed with this assertion: Pelham et al. (67) found that combined treatment was superior to behavior modification, but not to medication alone. However, the researchers themselves pointed out several methodological problems that may have contributed to their results (e.g., they only studied acute classroom intervention effects, and behavioral modification at home may be needed in addition to MPH). Ajibola and Clement (68) found that the combination of low-dose stimulant with self-reinforcement was superior than either intervention

alone. Although this finding is hindered by the very small sample size of six, it perhaps represents an encouraging new direction.

CONCLUSIONS

ADHD and MPH therapy continue to be very controversial issues. The majority of the research on ADHD and MPH has not supported the positions espoused by critics. ADHD has been shown to be a very real disorder with biological underpinnings, that often continues into adolescence and adulthood in some form and thus can be a devastating lifelong problem. MPH has clearly been shown to have beneficial short-term effects on the cardinal symptoms of ADHD. However, like any drug, it has its limitations (e.g., 23-27% nonresponders, questionable academic efficacy, questionable long-term effects) and side effects. Contrary to media reports, side effects to MPH therapy are generally mild and usually do not outweigh the benefits of drug therapy. However, every child taking the medication responds differently and thus side effects can become important during treatment. To date, no drug has been shown to be more effective than MPH for treating ADHD. It appears that critics have unfairly expected MPH to be a panacea when, given the fact that the symptoms of ADHD cover so many domains of functioning (e.g., behavioral, cognitive, academic, psychosocial), it is unlikely that one drug could ever function as such. It is hoped that once ADHD and MPH are understood in their proper context, the gap between society and medicine will be lessened, and societal focus will return to the children suffering from a potentially devastating illness instead of fixating on erroneous allegations.

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