This article compares the two most common medications for Attention-Deficit/Hyperactivity Disorder (ADHD), using data from controlled studies. Medline and Psychinfo searches were done for 1984-1996 with the key words methylphenidate (MPH) and amphetamine (AMP); these were supplemented with known prior and recent literature. Of 92 animal studies found, 15 showed clear differences between the two drugs. Ten reports of controlled crossover ADHD clinical trials (three in the same sample) and a dozen other articles comparing the two drugs in humans were found. MPH is a pure re-uptake inhibitor of catecholamines, especially dopamine; AMP also releases catecholamines. Lab animals showed differential interactions with other drugs and with behavioral paradigms. Human response profiles are noncongruent. An ADHD patient who fails on one stimulant should try the other. Of 174 patients in the 6 clearest crossover studies, 48 responded better to AMP, 27 to MPH, and at least 72 to both, which is an 87+% overall response rate if both are tried. All crossovers, except the one with comorbid Tourette's, showed a nonsignificant tendency for AMP superiority in response rate. Summed data suggest suspected differences in side effects (AMP more sleep and appetite loss and exacerbation of tics in comorbid Tourette's, MPH possibly more depression/apathy and stomachaches) and effects on comorbid disorders (AMP better for conduct/oppositional symptoms, MPH for Tourette's and possibly learning disorder (LD). Most of the clinical differences are tendencies rather than statistically significant.

Methylphenidate (MPH, e.g., Ritalin®) and amphetamine (AMP), especially its dextro-isomer dextroamphetamine (e.g., Dexedrine®, Dextrostat®) and, more recently, a mixture of amphetamine salts marketed as Adderall®, have been respectively the most commonly used and second most commonly used drugs for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). Although they are more similar than different in their pharmacodynamics and clinical effects, there are subtle differences that can be important at the level of the individual patient, if not in group data. This article will review animal and human data to reach a better understanding of the differences and their potential clinical application. In addition to the author's knowledge of the literature, a computerized literature search through Medline and Psychinfo was done for the years 1984-1996.

Although the subjective effects of MPH and AMP are similar (Heishman & Henningfield, 1991), neurochemical effects of the two stimulants are distinct (Little, 1993), with different mechanisms of action (Glavin, 1985). Methylphenidate is a "pure uptake inhibitor" (Heron, Costentin, & Bonnet, 1994) without other presynaptic activity, while amphetamine has additional presynaptic activity (Hess, Collins, & Wilson, 1996), releasing dopamine (DA) and norepinephrine (NE) from the presynaptic neuron (e.g., During, Bean, & Roth, 1992). Also, AMP has a slightly longer plasma half-life: 4-6 hours compared to 2-3 hours for MPH (e.g., Barkley, DuPaul, & Costello, 1993). A significant proportion of AMP is directly excreted in the urine (especially acidic urine), while MPH is completely metabolized: 80% to inactive molecules (Barkley et al, 1993), though 20% is hepatically metabolized to parahydroxy-MPH, an active metabolite. AMP, but not MPH, lowers plasma and urinary 3-methoxy-4-hydroxyphenylglycol
(MHPG) and norepinephrine (NE) turnover, while MPH, but not AMP, increases plasma NE (Elia, Borcherding, Potter, Mefford, Rapoport, & Keysor, 1990). Presumably resulting from the subtle difference in mechanism of action, there are also behavioral and drug interaction differences in laboratory paradigms and individual patient variation in clinical response. These are reviewed and documented below.

**Animal Comparisons**

Table 1 (overleaf) summarizes the 15 reports found on animal research since 1984 that showed clear differences between MPH and AMP. Differences may have shown up in other laboratory studies, but were not reported clearly enough to suit the purposes of this review. Of the 92 articles reviewed, most did not report any differences in the effects of the two drugs. In fact, most laboratory studies that included both drugs were not focused on comparing them, but included them as probes to study some other issue; the differences found were, in many cases, unexpected. Many of the differences were significant at levels better than 0.05, making a Type I error unlikely despite the low proportion of studies finding differences — except for the case of an apparent contradiction. While Svensson, Hohansson, Magnusson, and Carlsson (1986) found that reserpine pretreatment prevented MPH-induced, but not AMP-induced, locomotor hyperactivity, Finn, Iuvone, and Holtzman (1990) found almost the reverse: reserpine pretreatment attenuated locomotor hyperactivity induced by AMP, but not that induced by MPH. The apparent contradiction is not explained by species difference because both investigators used rats. However, they could have been different strains (not specified). Another possible difference in technique was that Svensson et al. used habituated animals.

Reserpine, of course, has serotonin-blocking activity, supporting putative interaction between the serotonin and catecholamine (dopamine, norepinephrine) systems. If reserpine pretreatment does indeed differentially modify the effects of the two stimulants, this could have implications for polypharmacy with a stimulant and one of the newer, atypical neuroleptics with serotonin activity, and possibly even with a stimulant and a serotonin-reuptake inhibiting antidepressant. For example, if a given modern serotonin-active drug mimics the reserpine interaction found by Svensson et al. (1986), it might interfere with the therapeutic effect of MPH but not AMP; conversely, if it has the opposite effect of reserpine, it might potentiate MPH benefit but not AMP. On the other hand, if Finn et al. (1990) are correct, these theoretical considerations could be reversed. All this, of course, assumes extrapolation from rats to humans, not always a valid exercise.

Other possible differential drug interactions are suggested by the animal literature. One arises from the fact that haloperidol blocked place preferences that were induced by AMP, but not those induced by MPH (Mithani, Martin-Iverson, Phillips, & Fibiger, 1986). (The combination of haloperidol and a stimulant is sometimes used in treatment of comorbid Tourette's and ADHD or comorbid bipolar disorder and ADHD.) To my knowledge, there are no controlled studies comparing the clinical effects of the two stimulants in the presence of haloperidol or other neuroleptics.

It is not clear what we should make of the finding of Hess et al. (1996) in naturally hyperactive Coloboma mice, where AMP reduced, but MPH increased, activity. Since MPH decreases activity in most naturally hyperactive humans, the mice must be hyperactive through a different mechanism than most humans. Study of that difference might illuminate not only mechanisms of stimulant action but also pathogenetic mechanisms and subtypes of ADHD. It is conceivable, of course, that the hyperactive Coloboma mice suffer the same pathogenetic mechanism as the minority of hyperactive humans who respond to AMP but not MPH.
**Human Comparisons Other Than ADHD Clinical Trials**

Table 2 (overleaf) summarizes the 6 reports found comparing MPH and AMP in human studies other than ADHD clinical trials. Interestingly, Little (1993) reported the same situation in treating depression, as we will see below with treatment of ADHD: 2/3 efficacy for either drug, with only partial overlap of efficacy and no way of predicting which will be better for a given patient.

**Parallel and Uncontrolled Comparisons in Treatment of ADHD**

Before examining the controlled crossover comparisons of MPH and AMP for treatment of ADHD, it is worth noting seven other relevant reports ranging from placebo-controlled parallel-group comparisons to naturalistic chart reviews:
### Table 1. Effects of Drugs on AMP and MPH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Isomer(^1)</th>
<th>Effects Studied</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mithani et al. (1986)</td>
<td>dl</td>
<td>behavioral</td>
<td>Haloperidol pre-treatment blocked place preferences induced by AMP, but not those induced by MPH.</td>
</tr>
<tr>
<td>Rosen et al. (1986)</td>
<td>dl</td>
<td>behavioral</td>
<td>Under high-AMP-dose discriminative stimulus training, MPH, but not AMP, generalization gradient was different for lead-exposed and control rats.</td>
</tr>
<tr>
<td>Svensson et al. (1986)</td>
<td>dextro</td>
<td>behavioral</td>
<td>Reserpine pre-treatment completely prevented MPH-induced, but not AMP-induced, locomotor hyperactivity.</td>
</tr>
<tr>
<td>Holtzman (1986)</td>
<td>dextro</td>
<td>behavioral</td>
<td>In rat discrimination experiments, MPH generalized completely, but AMP only partially, with caffeine.</td>
</tr>
<tr>
<td>Sershen, Berger, Jacobson, et al. (1988)</td>
<td>dl</td>
<td>behavioral</td>
<td>Metaphit, a phencyclidine analog, antagonized the locomotor stimulation induced by MPH, but not that induced by AMP.</td>
</tr>
<tr>
<td>Zetterstrom, Sharp, &amp; Collin (1988)</td>
<td>dl</td>
<td>biochemical</td>
<td>AMP, but not MPH, decreases striatal extracellular 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of DA(^2).</td>
</tr>
<tr>
<td>Logan, Seale, Cao, &amp; Carney (1988)</td>
<td>dextro</td>
<td>behavioral</td>
<td>In BALB/cByJ mice, AMP up to 10 mg/kg acutely had no effect or inhibited locomotor activity (LA); MPH 10-32 mg/kg acutely stimulated LA. After 21 days AMP 10 mg/kg, 3.2 mg/kg stimulated LA (no longer inhibited), and MPH no effect in doses that had acutely stimulated.</td>
</tr>
<tr>
<td>Zaczek et al. (1989)</td>
<td>citation of dl</td>
<td>biochemical</td>
<td>MPH (and pemoline) did not induce the decrease in brain monoamine markers found with methamphetamine and previously with AMP.</td>
</tr>
<tr>
<td>Finn, luvone, &amp; Holtzman (1990)</td>
<td>dextro</td>
<td>behavioral</td>
<td>Pretreatment with reserpine or alpha-methyl-para-tyrosine attenuated the increase of locomotion induced by AMP or caffeine, but not that by MPH.</td>
</tr>
<tr>
<td>Nomikos, Damsma, &amp; Wenkstern (1990)</td>
<td>dextro</td>
<td>biochemical</td>
<td>Tetrodotoxin, which blocks voltage-dependent Na(^+) channels, prevented MPH-induced, but not AMP-induced, increase in extracellular DA.</td>
</tr>
<tr>
<td>During, Bean, &amp; Roth (1992)</td>
<td>dl</td>
<td>biochemical</td>
<td>MPH released DA and neurotensin co-synchronously from rat prefrontal cortex; but with AMP, neurotensin release lagged behind DA release.</td>
</tr>
</tbody>
</table>
Chronic administration of AMP sensitizes; chronic MPH develops tolerance. 
(Repeated doses of AMP over 7-day period augment the usual response of increased activity; repeated MPH decreases the subsequent responses.)

Naloxone attenuated gross (though not fine) HA\(^1\) induced by both amphetamine isomers, but not HA induced by MPH.

MPH binds slowly to DA neuronal carrier; AMP interacts rapidly with DA neuronal carrier.

AMP caused efflux of DA & NE\(^4\) across respective transporters in cell culture; MPH did not. Both inhibited influx.

AMP reduced activity in naturally HA Coloboma mice, increased in controls; MPH increased activity in both.

1Isomer = the form of amphetamine (AMP) that was compared to methylphenidate (MPH); dextro = d-amphetamine; levo = l-amphetamine; dl = racemic amphetamine

2DA = dopamine \(^3\)HA = hyperactivity \(^4\)NE = norepinephrine

**Table 1** Some animal research comparing methylphenidate (MPH) and amphetamine (AMP)

<table>
<thead>
<tr>
<th>Reference</th>
<th>AMP Isomer(^1)</th>
<th>Type of Study, N</th>
<th>Dose</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman, Kane, &amp; Alvir (1987)</td>
<td>dl, dextro?</td>
<td>Clinical; review of 36 studies</td>
<td>variable</td>
<td>In challenges with schizophrenic patients, MPH appears to have greater psychotogenic potency than AMP.</td>
</tr>
<tr>
<td>Little (1988) (Review article)(^2)</td>
<td>dl, dextro</td>
<td>Clinical; review of 5 studies; adults</td>
<td>variable</td>
<td>In depression, 85% of AMP responders but only 43% of AMP nonresponders improve with antidepressant Tx; MPH resprs &amp; nonresprs improve equally.</td>
</tr>
<tr>
<td>Elia et al. (1990)</td>
<td>dextro</td>
<td>Biochemical; blind crossover; 31 children</td>
<td>AMP 1.5 mg/kg/d; MPH 3.0 mg/kg/d</td>
<td>AMP but not MPH lowered plasma/urinary MHPG, NE turnover; MPH but not AMP raised plasma NE.</td>
</tr>
<tr>
<td>Little (1993)</td>
<td>dextro</td>
<td>Clinical; blind crossover; 12 M, 8 F; 24-45 yr</td>
<td>MPH 40 mg; AMP 20 mg; test doses</td>
<td>17/18 depressed inpatients improved acutely after AMP or MPH, but only 5/18 showed equal improvement to both. 7 responded only to AMP, 5 only to MPH. Which was better was unpredictable, with no drug-specific target Sx.</td>
</tr>
</tbody>
</table>
Little et al. (1993) dl Biochemical postmortem in vitro homogenized membrane MPH binds more strongly, but AMP more weakly, than cocaine or bupropion to binding sites of [125I]RTI-55, a cocaine congener.

Matochik et al. (1994) dextro Biochemical; PET scans before and after 6 wk MPH (n=19) or AMP (n =18); adults MPH 5-25 mg b.i.d.; AMP 5-15 mg b.i.d. MPH changed metabolism in 2 of 60 brain regions sampled by PET; AMP did not change metabolism in any region (adult Ss with ADHD). With randomly assigned noncrossover Tx, CGI= 2.1 for MPH, 1.9 for AMP (lower score better but not significantly different); Conners change scores = 11.6 and 9.1 for MPH, 10.6 and 7.3 for AMP (n.s.). On 2 other scales, MPH significantly improved 11/60 feelings/symptoms, AMP 19/60, only 7 in common. Ratings nonblind.

All drug administration was by mouth except the in vitro study (Little et al., 1993).

1Isomer = the form of amphetamine (AMP) that was compared to methylphenidate (MPH); dextro = d-amphetamine; levo = l-amphetamine; dl = racemic amphetamine.

2The 1988 Little review was challenged by Gwirtsman and Guze (1989), who argued that MPH response predicted antidepressant response to an adrenergic TCA, while MPH nonresponse predicted response to a serotonergic TCA.

**Table 2** Some human comparisons of methylphenidate and amphetamine other than ADHD clinical trials
1. Millichap and Fowler (1967) reviewed the available literature, consisting of one-drug studies in different samples, some not well controlled. After averaging the response rate across studies for each drug (with response defined differently from study to study, even using different instruments), they found a higher mean response rate for MPH and concluded that it is "the drug of choice." Arnold and Knopp (1973) pointed out that this conclusion was not based on any controlled direct comparison of MPH and AMP in the same sample, but it persists to the present as clinical belief in some circles despite the fact that the only one of the subsequent controlled crossover comparisons in Table 3 (overleaf) that supports it is the one in comorbid Tourette's (Castellanos et al., 1997).

2. Weiss, Minde, and Douglas (1971) compared the results of chlorpromazine, MPH, and d-AMP from three different samples studied in three different years. They believed that MPH was slightly more efficacious with about the same side effects.

3. Conners (1972) came closer to a valid comparison, studying both stimulants in the same sample, but unfortunately with a parallel pretest-posttest design so that individual subject variables were not well controlled. He randomly assigned 70 boys and 5 girls age 6-12 to 6 weeks of placebo (n =22), MPH (n =29), or d-AMP (n =24). Doses were individually titrated weekly to a cap of 30 mg MPH or 15 mg d-AMP daily in divided doses (morning and noon). Titration started at 1/3 the cap dose.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Ss</th>
<th>Age</th>
<th>MPH Dose</th>
<th>AMP Dose</th>
<th>Better Response</th>
<th>Other Findings</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winsberg et al.</td>
<td>15M,</td>
<td>8.5</td>
<td>≤30</td>
<td>≤20</td>
<td>0 MPH</td>
<td>AMP&gt;MPH by E.5.2 = 0.45 on aggressivity, 0.14 on inattentiveness, 0.41 on hyperactivity (all n.s.).</td>
<td>Same frequency, 6 Ss. Insomnia only AMP, CI only MPH, apathy more MPH.</td>
</tr>
<tr>
<td>(1974)</td>
<td>3F</td>
<td>5-10</td>
<td>bid</td>
<td>bid</td>
<td>3 AMP, 11 both</td>
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<td></td>
<td>4 neither</td>
<td></td>
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</tr>
<tr>
<td>Arnold et al.</td>
<td>22M,</td>
<td>8</td>
<td>38 mg</td>
<td>19 mg</td>
<td>10 MPH</td>
<td>Good or excellent response on 9-point blind rating in 18 Ss with MPH, 17 with AMP. MPH&gt;AMP on DTS short attn item with E.S. 0.32. AMP&gt;MPH with E.S.: CTRS=0.16; CTRS HA=0.13; CTRS aggr=0.25; CTRS LOH=0.21; DT2=0.11; DT inatt=0.14; DT irrat=0.19; DT expl=0.15; DT var =0.28; PRC2=0.15; PRC aggr=0.16; PBC inatt=0.15; PBC HA=0.13; PBC soclo=0.18; PBC dep =0.13; Target Sx=3.18 (n.s.).</td>
<td>MPH more tummyaches (E.S.=0.17) and diastolic BP rise (0.10). AMP more appetite (E.S.=0.10) and sleep (0.11) disturbance, wt loss (all n.s.). AMP significantly less stomachaches than placebo.</td>
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<tr>
<td>(1978)</td>
<td>7F</td>
<td>5-12</td>
<td>10-60/d</td>
<td>5-30/d</td>
<td>12 AMP</td>
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<td></td>
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<td>1 caffeine</td>
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<td>2 MPH-A31 AMP tie</td>
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<td>1 AMP, caffeine tie</td>
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<td></td>
<td></td>
<td></td>
<td>3 none</td>
<td></td>
<td></td>
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<tr>
<td>Vjorova et al.</td>
<td>25M,</td>
<td>6-14</td>
<td>38 mg/</td>
<td>38 mg/</td>
<td>MPH better on mean global score. MPH preferentially helped children with visuo-motor disorders, AMP those without.</td>
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</tr>
<tr>
<td>(1984)</td>
<td>3F</td>
<td></td>
<td>day</td>
<td>day</td>
<td>9 better</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>with AMP5</td>
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<tr>
<td>Perlman et al.</td>
<td>22M</td>
<td>8-13</td>
<td>20 mg/</td>
<td>10SR</td>
<td>MPH&gt;MPH with E.S.: following rules 0.25, non-compliance 0.35, neg-verbalization 0.24, CTRS3 0.33 counselor rating 0.12, %DRCB 0.14 (all n.s.); AMP less within-S variability (more consistent response).</td>
<td>MPH more crabby, teary, muscle aches, dry mouth, twitches. AMP more whiny, drowsy, sad, withdrawn, jittery, stomachaches, NV, headaches, insomnia, anorexia. (all n.s.).</td>
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<tr>
<td>(1990)</td>
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<td>day7</td>
<td>1a.m.</td>
<td>5 MPH</td>
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<td></td>
<td>6 AMP</td>
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<td>4 Fem7</td>
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<td></td>
<td>7 none</td>
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<tr>
<td>Berchending et al.</td>
<td>45M</td>
<td>6-12</td>
<td>12.5-</td>
<td>5-</td>
<td>Abnormal movements (tics) and perseverative-compulsive behaviors (OC on only 1 drug per patient (usually).</td>
<td>AMP more OC; MPH more co-occurrence of abnormal movement &amp; OC.</td>
<td></td>
</tr>
<tr>
<td>(1990)</td>
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<td></td>
<td>45 mg</td>
<td>22.5</td>
<td>See below</td>
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<td>(Ela sample)</td>
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<td></td>
<td>bid</td>
<td>bid</td>
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<tr>
<td>Elia et al.</td>
<td>48M</td>
<td>8.6</td>
<td>12.5-</td>
<td>5-</td>
<td>On C-GAS, 9 MPH &amp; 3 AMP worse or same.</td>
<td>5 Ss had SE with MPH, 3 with AMP, 32 with both. AMP more meticulousness, anorexia; MPH more nervous habits, unhappy.</td>
<td></td>
</tr>
<tr>
<td>(1991)</td>
<td></td>
<td></td>
<td>45 mg</td>
<td>22.5</td>
<td>4 MPH</td>
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<td></td>
<td></td>
<td>bid</td>
<td>bid</td>
<td>6 AMP</td>
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<td></td>
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<td>34 both</td>
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<td></td>
<td>2 neither</td>
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<tr>
<td>Castellanos et al.</td>
<td>72 incl.</td>
<td>6-12</td>
<td>12.5-</td>
<td>5-</td>
<td>11 of 13 Ss with IQ&gt;110, but only 24/59 with low IQ; responded better to AMP. Correlation IQ with improvement 0.39 for AMP; 0.06 for MPH.</td>
<td>Not reported.</td>
<td></td>
</tr>
<tr>
<td>(1992) (Expanded</td>
<td>45 mg</td>
<td></td>
<td>45 mg</td>
<td>22.5</td>
<td>35/72</td>
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<td></td>
</tr>
<tr>
<td>Elia sample)</td>
<td></td>
<td></td>
<td>bid</td>
<td>bid</td>
<td>11 better</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with AMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castellanos et al.</td>
<td>20M</td>
<td>9.4</td>
<td>12.5-</td>
<td>5-</td>
<td>All comorbid with Tourette's: At highest dose only, AMP but not MPH increased tic severity by 25% cf placebo.</td>
<td>OC Sx: 5 MPH, 1 AMP; Apaxitet: 3 MPH, 4 AMP; Insomnia: 2 MPH, 10 AMP.</td>
<td></td>
</tr>
<tr>
<td>(1997)</td>
<td></td>
<td></td>
<td>45 mg</td>
<td>22.5</td>
<td>11 MPH</td>
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<td></td>
<td></td>
<td></td>
<td>bid</td>
<td>bid</td>
<td>6 AMP</td>
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<td></td>
<td>3 neither</td>
<td></td>
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</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study / Design</th>
<th>N</th>
<th>MPH Dose</th>
<th>AMP Dose</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp et al. (1999)</td>
<td>32F</td>
<td>8.9±2</td>
<td>5-35</td>
<td>2.5-4 MPH</td>
<td>Benefits &quot;nearly identical&quot; but both drugs significantly better than placebo at $p&lt;0.0001$ on teacher ratings. Side effects &quot;nearly identical&quot; except more weight loss with AMP: 1.1+ 1.0 kg vs. 0.4+1.1 kg over 3 weeks.</td>
</tr>
<tr>
<td>Pelham et al. (1999)</td>
<td>21M/4F</td>
<td>9.6</td>
<td>10-7.5</td>
<td>4 MPH</td>
<td>12.5 mg AMP more SE than 7.5 mg or other dose MPH. AMP more anorexia, insomnia, listlessness (esp. high dose).</td>
</tr>
<tr>
<td>Totals without '92 Castellanos or '90 Borchering</td>
<td>222</td>
<td>38 MPH</td>
<td>63 AMP</td>
<td></td>
<td></td>
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<tr>
<td>Vyborova or Castellanos '92, '97</td>
<td>174</td>
<td>27 MPH</td>
<td>RESPONSE RATES&lt;sup&gt;10&lt;/sup&gt; (see text):</td>
<td></td>
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</tbody>
</table>

Differences generally not statistically significant. MPH was racemic threeo-methylphenidate; AMP isomer was dextroamphetamine except Vyborova et al. (amphetaminil) and Pelham et al. (1999) (Adderall®).

**SE** = side effects; **CPT** = continuous performance test

<sup>1</sup>Some studies were done prior to DSMIII-R introduction of the term ADHD, and used designations such as hyperkinetic/hyperkinesis or minimal brain dysfunction/damage (MBD).

<sup>2</sup>E:S. = Effect Size = Cohen’s d = difference of means/mean standard deviation. Only effect sizes of 0.10 or more are tabulated. For comparison, the effect size of the stimulant-placebo difference usually runs 1.0+ in ADHD studies. AMP>MPH means AMP better than MPH on the dependent variables listed.

<sup>3</sup>DP = Davids’ Hyperkinetic Rating Scale by parent; **DT** = Davids Hyperkinetic Scale by teacher. Davids items: hyperactivity, short attention span (short attn), variability (varib), impulsiveness (imp), irritability (irrit), explosiveness (expl), poor schoolwork.

<sup>4</sup>CTRS = Conners Teacher Rating Scale. Factors: aggressive misconduct (aggr), daydreaming and inattention (inattn), hyperactivity (HA), lack of health (LOH).

<sup>5</sup>PBC = Parent Behavior Checklist by parent (similar to Conners' parent rating scale). Factors: unsocialized aggression (aggr), inattentive unproductiveness (inattn), sociopathy (sociop), withdrawal-depression (dep), somatic complaints.

<sup>6</sup>Vyborova et al. did not give # of MPH and AMP responders or scale data, merely stating that the number of responders to amphetaminil was higher than the number of responders to MPH by 1/3 of the sample, but that the AMP mean improvement in global score was lower by nearly half.

<sup>7</sup>Pelham et al., 1990, compared MPH 10 bid, MPH 20SR/day, d-amphetamine Spanzule (SR) 10/day, and pemoline (Pern) 56.25/day. For purpose of this comparison table, the results of the two MPH dosage forms are averaged.

<sup>8</sup>DRC = % positive days on daily report card.

<sup>9</sup>The AMP used by Pelham et al., 1999 was Adderall®, a proprietary mix of 3/4 dextro- and 1/4 levo-amphetamine.

<sup>10</sup>The lower number of the ranges of percent response includes the two Pelham et al. studies, which were done in a full-time behavioral summer program that removed much of the variance needed to show
a drug effect, thus artificially depressing the response rates. The upper number of the ranges is calculated by excluding those two studies. These ranges are lower-bound estimates (see text).

**Table 3** Controlled crossover comparisons of methylphenidate (MPH) and amphetamine (AMP) in ADHD and its historical precursors¹
Both drugs were better than placebo on multiple measures. MPH showed an advantage over d-AMP on the arithmetic and similarities subtests of the Wechsler Intelligence Scale for Children, but not on other subtests, tests, or scales in a reasonably comprehensive assessment battery. Both drugs showed more insomnia and anorexia than placebo; in fact, d-AMP showed more than MPH, but few of the side effects were moderate or severe.

4. Swanson et al. (1998) reported a comparison of MPH and Adderall®; a mix of amphetamine salts containing 3/4 d-amphetamine and 1/4 l-amphetamine. Though it was a double-blind placebo-controlled crossover study with random assignment to order, it is not listed in Table 3 because the design and dosing did not lend themselves to the efficacy and side effects comparisons made in the table. Thirty-three MPH responders with DSM-IV ADHD were assigned in random order to a week each of their established effective MPH dose (5-20 mg), placebo, and 5, 10, 15, and 20 mg Adderall® (6 conditions total), all given once each morning of the respective week, including at a Saturday analogue school. The focus of the study was duration of effect. Both drugs significantly benefited behavioral symptoms and academic productivity compared to placebo. MPH reached peak effect earlier and wore off earlier than all but the smallest Adderall® dose. Duration of MPH effect averaged about 4 hours, with duration of Adderall® effect up to 6.4 hours at the 20-mg dose.

5. Manos, Short, and Findling (1999), in a nonrandomized but otherwise well-done parallel placebo-controlled design, compared 42 subjects age 5-17 taking Adderall® to 42 matched subjects taking MPH (selected out of 117 subjects in the MPH protocol). The choice of active drug was by the patient's physician, but titration was double-blind placebo-controlled. Fifteen of the Adderall® patients had previously failed a MPH trial. In this trial, no significant differences between the two active drugs were found, with both significantly improving parent and teacher ratings of behavior. The "best dose" blindly identified ranged from 5-15 mg, q a.m. for Adderall® and b.i.d. for MPH. A single morning dose of Adderall® seemed as effective as b.i.d. MPH.

6. In a retrospective chart review of prospectively collected data on 200 private patients, Grcevich, Rowane, Marcellino, and Sullivan-Hurst (1999) found that 75% of MPH patients were dosed t.i.d. or more often, while 89% of Adderall® patients were dosed b.i.d. or less. A survival curve showed an impressive difference in length of time on the first drug tried, with 25% switching from MPH to another drug after 2 months but only about 10% switching from Adderall® after 5 months.

7. In a double-blind design, Pliszka, Browne, Wynne, and Olvera (1999) randomly assigned 58 children to placebo, a MPH dosing algorithm, or an Adderall® dosing algorithm. Both algorithms started with a morning dose of 10 mg, then (if indicated) increased this and/or added a noon and/or afternoon dose as indicated by feedback about behavior and performance at various times of day. Both active drugs were significantly better than placebo, but the slight Adderall® advantage over MPH was not statistically significant. Of note, 70% of Adderall® patients, but only 15% of MPH patients, could be satisfactorily maintained on once-a-day dosing.

Controlled Crossover Comparisons in Treatment of ADHD

Table 3 summarizes the 10 reports of controlled crossover comparisons found. These actually represent only 8 independent samples because the large samples of Borcherding, Keysor, Rapoport, Elia, and Amass (1990), Elia, Borcherding, Rapoport, and Keysor (1991), and Castellanos, Gullota, and Rapoport (1992) overlapped. Uncontrolled or noncrossover comparisons of MPH and AMP are not tabulated here (see preceding section).

In examining Table 3, we need to remember that most group mean differences between the
two stimulants are not significant because of the small samples, so that we are essentially studying
nonsignificant subtle trends. Within this constraint, it seems appropriate to note some themes. The
most obvious is that no study shows congruence in response at the individual subject level. That is,
every study has some subjects who responded to one drug but not the other. In most studies, this is
a two-way street: some respond better to MPH, others better to AMP.

Another noteworthy theme is that every crossover study except the one in comorbid
Tourette's (Castellanos et al., 1997) shows a slight (nonsignificant) advantage for AMP in the
number of individuals judged responsive or in the number judged to have a better response than to
the other active condition(s). The references do not use strictly comparable reporting methods: for
example, Winsberg, Press, Bialer, and Kupietz (1974) and Elia et al. (1991) report response or
nonresponse in a binary fashion, while Arnold, Christopher, Huestis, and Smeltzer (1978) and
Pelham et al. (1990, 1999) report which is better or clinically preferable for maintenance, even
where both are efficacious. Castellanos et al. (1992) reported only those better with AMP and not
those better with MPH, presumably 35 or less, since there were at least 2 nonresponders in that
sample (reported by Elia et al., 1991 in the first 48 Ss). Nevertheless, since both drugs are reported
the same way within a given study for each of the other 8 studies, it seems permissible to sum them
for comparison.

Summary of Responders

Of the 222 subjects in the 8 nonduplicative studies in Table 3 (Arnold et al., 1978;
Castellanos et al., 1997; Elia et al, 1991; Pelham et al, 1990, 1999; Sharp et al, 1999; Winsberg et
al, 1974; Vyborova, Nahunek, Drtilkova, Balastikova, & Misurec, 1984), 63 responded better to
AMP and 38 better to MPH. If we eliminate the study of Vyborova et al. because of the
noncomparable dosing and the contradiction between response rate and mean global score, and
eliminate the study of Castellanos et al. (1997) because of the focus on relatively rare comorbidity
(Tourette's), the totals are 48 AMP and 27 MPH in the remaining 6 studies. If we add the 72 known
double responders (there may have been more undetected by the reporting methods) to each total,
there were 120 (or more) AMP responders vs. 99 (or more) MPH responders in these 6 studies,
with 174 subjects and 22 nonresponders. This translates to a 69+% response rate for AMP and
57+% for MPH, with an 87+% stimulant response rate if both are tried.

This overall response rate of 87% should be considered a lower bound estimate because it
was skewed by the high "nonresponse" rate in the two studies of Pelham et al, in which the subjects
were children in an intense full-time summer behavioral treatment program, which normalized
behavior on placebo, eliminating the variance needed to detect drug effect. Excluding the two
studies of Pelham et al. yields a response rate of 92% for trying both drugs (68% for MPH, 77% for
AMP). The response rates by individual drug (69-77% AMP, 57-68% MPH) should be considered
lower bound estimates because the reporting method for some studies left some double responders
undetected.

Relative Strengths

Beyond the global response, finer-grained scrutiny of effects on specific symptoms
suggests some subtle differences. Some of these relate to comorbidity. Castellanos et al. (1997), of
course, found MPH better in the presence of comorbid Tourette's. In several of the studies, AMP
seemed to have a greater effect on such oppositional-defiant and conduct-disorder (ODD/CD)
symptoms as aggression (with effect size [E.S.], Cohen's d, of 0.16, 0.25, and 0.45), irritability
(E.S.=0.19), explosiveness (E.S.=0.15), noncompliance (E.S.=0.35), negative verbalization
(E.S.=0.24), rule-breaking (E.S. =0.25), and Iowa Conners O/D rating (E.S.=0.3, p <0.01 by
Most of these were nonsignificant, of course, at the sample sizes studied. In no study did MPH show a tendency of superiority on such symptoms. On the other hand, AMP did not show an impressive advantage on inattention symptoms, even though Pelham et al. (1999) found the AMP advantage significant on counselor (p < 0.001) and parent (p < 0.05) ratings of inattention/overactivity. The study (Winsberg et al., 1974) that found an E.S. of 0.45 for AMP superiority on aggression found an E.S. of only 0.14 for AMP superiority on inattention. The study (Arnold et al., 1978) that found an E.S. of 0.25 for teacher rating of aggression found only E.S. = 0.02 and 0.14 for teacher ratings of inattention on 2 different scales. The advantage of MPH on the Conners Continuous Performance Test (CPT) reported by Elia et al. (1991) may be related to the report of Vyborova et al. that MPH preferentially helped patients with visuo-motor disorders. If the suggestive trends noted here were upheld by further study, it could lead to a preference for MPH in ADHD comorbid with Tourette's or learning disorder (LD) and for AMP in ADHD comorbid with ODD/CD.

One of the few statistically significant differences reported was that AMP showed a more consistent response day-to-day, with less within-subject variability (Pelham, 1991). The significant association of AMP superiority with high IQ (Castellanos et al., 1992) was one of the more exciting differences found. It offered hope of a simple clinical predictor of which stimulant should be tried first in a given case. It also articulated neatly with the report of Vyborova et al. that MPH was better for children with visuo-motor disorder and AMP better for those without; both findings could be accommodated by a hypothesis that AMP worked better for those without cognitive handicap and MPH better for those with handicap or low functional level. Unfortunately, this finding (association with IQ) was not replicated in a prospective study (F.X. Castellanos, personal communication).

Side Effects

Side effects were, in general, similar with both drugs. For example, Winsberg et al. (1974) reported 6 (of 18 Ss) had side effects with each drug, while Elia et al. (1991) reported that 37 (of 48 Ss) had side effects with MPH and 35 with AMP. Within this context of similarity, there were some subtle trends and tendencies (mostly nonsignificant). Five studies, with 156 Ss, found more anorexia with AMP compared to no study finding more anorexia with MPH. Five studies, with 114 Ss, found more sleep delay with AMP compared to none finding more with MPH. Three studies, with 88 Ss, found more apathy/tear-fulness/unhappiness with MPH compared to two studies, with 47 Ss, finding more sadness/withdrawal/listlessness with AMP. Castellanos et al. (1997) found more exacerbation of tics with AMP than with MPH in patients comorbid for Tourette's disorder.

Clinical Implications and Discussion

Table 4 summarizes the relative advantages of MPH and AMP for treatment of ADHD, as suggested by the foregoing review and supplementary clinical experience. Many of the differences listed do not reach statistical significance. Although very similar in many ways, the two stimulants are in some ways complementary in patient responsiveness. The clearest lesson gleaned from the controlled studies is that the individual patient response profiles are noncongruent, and that nonresponse or intolerable side effects with one stimulant does not preclude a good response to the other. Interestingly, Little (1993) could have been talking about ADHD when he said this about MPH and AMP for depression: "Relatively few responded with equal improvement to both ... symptomatic improvement is unpredictable and can only be determined by an empirical trial on an individual basis." Therefore, each should be tried before giving up on stimulant treatment, and patients and parents should be forewarned of this.
While this review found no evidence to make MPH the drug of choice for ADHD in comparison to other stimulants, this does not detract from the fact that stimulants as a class constitute the drugs of choice. One can fill in where another fails, so that together they can help the vast majority of patients with ADHD. Possibly the response rate with trials of both MPH and AMP could be increased even further with a third stimulant: Pelham et al. (1990) reported that four of their 22 patients did best with pemoline. The advantage of trying both MPH and AMP has public policy implications: the bureaucratic Medicaid obstacles to AMP prescriptions in some states may be depriving some Medicaid ADHD children of their best treatment.

Beyond the basic principle of systematically trying a second stimulant if the first fails, there are some hints in Table 4 that might guide the choice of which stimulant to try first. For example, a child who already has a poor appetite might do better with MPH, while one prone to stomachaches might do better with AMP. If the child has a history of seizures and is not currently taking an anticonvulsant, AMP may be slightly safer. The type of comorbidity may be a consideration: a child with either Tourette's disorder or LD and with no conduct or oppositional-defiant (CD/ODD) symptoms might try MPH first, while one with CD/ODD and no LD or Tourette's might try AMP first. This is not to say that either stimulant would not help the other comorbidity or that either is guaranteed to help its favored comorbidity, but in the absence of any more compelling reason for choosing the first trial drug, why not follow the hint suggested by the literature review?

**Chiral Pharmacology**

This review has not addressed the issue of stereo-isomers, which may also have subtle differential effects in individual patients. Five decades ago Bradley (1950) noted that some hyperkinetic children responded better to racemic amphetamine, while others responded better to the dextro isomer. MPH has four stereo-isomers: the erythro- and threo- forms each have a dextro- and levo-isomer. The commercially available MPH (Ritalin®) is a racemic (dl) mixture of the threo-enantiomer (however, dextro-threo-MPH is currently being developed for market). The most popular form of amphetamine has long been the dextro-isomer (Dexedrine® or Dextrostat®), which was used in most of the clinical studies in Table 3 and constitutes most of the basis for the comparison with MPH in Table 4. Arnold et al. (1973, 1976) found that levo-amphetamine has clinical benefits in ADHD comparable on group data to the dextro-isomer, and reported that a few patients responded to one isomer but not the other. They also suspected some subtle tendencies for different side effects and even different clinical benefit by comorbidity. Further, the effect of the two isomers on visual-motor function was significantly different (Arnold, Huestis, Wemmer, & Smeltzer, 1978). Adderall® is 3/4 dextroamphetamine and 1/4 levoamphetamine, with anecdotal claims that a few children with ADHD respond better to this mix than to straight dextroamphetamine. It

<table>
<thead>
<tr>
<th>Advantages of MPH</th>
<th>Advantages of AMP</th>
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<tr>
<td>Better CPT response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>More consistent response day-to-day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Better with comorbid Tourette's&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Higher proportion of patients with good/excellent response&lt;sup&gt;*3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Better with visuo-motor disorder&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Better with comorbid CD/ODD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Possibly better with comorbid LD&lt;sup&gt;c&lt;/sup&gt;</td>
<td>May be better with high IQ&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>Less anorexia, less weight loss&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Less depression/apathy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Less sleep delay&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fewer stomachaches&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Less temporary growth suppression in low doses\(^c\) Safer when history of seizures\(^c\); slightly anticonvulsant in low doses\(^b\)
Lower street value and abuse potential Usually cheaper legally (generic)
Variety of regular tablet strengths: 5,10,20 mg* Variety of SR Spansule strengths (5,10,15 mg); SR seems more
More readily available to Medicaid patients consistently efficacious than SR MPH

<table>
<thead>
<tr>
<th>Few of these reach statistical significance; most are tendencies noted in more than one report in literature review.</th>
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<tbody>
<tr>
<td>(^a)Statistically significant in a controlled study</td>
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<tr>
<td>(^b)Probable</td>
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<tr>
<td>(^c)Possible, suggested</td>
</tr>
<tr>
<td>(^d)Significant in post hoc analysis of controlled study but not replicated in prospective study</td>
</tr>
<tr>
<td>(*)Dextro-threo-methylphenidate, when available, may be marketed in 2.5 mg as well as 5 and 10 mg</td>
</tr>
</tbody>
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**Table 4** Relative advantages of methylphenidate (MPH) and amphetamine (AMP) for treatment of ADHD
was the form of AMP used by Pelham et al. in their 1999 study (Table 3), which showed statistical superiority of MPH by counselor ratings. On the assumption that stimulants as a class will continue to be the drugs of choice for treatment of ADHD, clinical science could benefit from more systematically controlled comparisons of the various isomers, and combinations thereof, of both these drugs. Such studies would require rather large samples in order to analyze for all the patient characteristics that might influence the choice of stimulant (e.g., age, sex, comorbidity, physical habitus).

**Acknowledgment**

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