Medication Adherence in the MTA: Saliva Methylphenidate Samples Versus Parent Report and Mediating Effect of Concomitant Behavioral Treatment

ELIZABETH PAPPADOPULOS, PH.D., PETER S. JENSEN, M.D., ALANNA R. CHAIT, B.A., L. EUGENE ARNOLD, M.D., JAMES M. SWANSON, M.D., LAURENCE L. GREENHILL, M.D., LILY HECHTMAN, M.D., SHIRLEY CHUANG, M.S., KAREN C. WELLS, M.D., WILLIAM PELHAM, PH.D., THOMAS COOPER, M.S., GLENN ELLIOTT, M.D., PH.D., AND JEFFREY H. NEWCORN, M.D.

ABSTRACT

Objective: Although research supports the use of appropriately administered stimulant medication to treat children with ADHD, poor adherence and early termination undermine the efficacy of this treatment in real-world settings. Moreover, adherence measures often rely on parent report of medication use, and their validity and reliability are unknown. Method: Drawing on data from 254 participants in the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder, we examine the discrepancy between parents’ verbal reports of medication adherence and physiological adherence measures determined via methylphenidate saliva assays collected at four time points during the 14-month treatment period. In addition, we examine the impact of physiologically documented medication adherence on parent- and teacher-reported outcomes through 14 months. Results: Overall, nearly one fourth (24.5%) of the saliva samples indicated nonadherence. Among subjects, 63 (24.8%) of the 254 participants were nonadherent on 50% or more of their repeated saliva assays. Only 136 (53.5%) of the subjects were adherent at every time point at which saliva assays were taken, indicating that some degree of nonadherence characterized nearly half of all other NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder–treated children. Findings also indicated that nonadherence produced greater deleterious effects in children in the medication-only condition compared with those receiving both medication and behavioral treatment. Conclusions: Same-day saliva methylphenidate assays suggest that nearly half of the parents are inaccurate informants of their child’s ADHD medication adherence and that parents may overestimate actual (physiological) adherence. This finding suggests the need for interventions to improve accuracy of parental report. Clinicians need to focus on adherence enhancement strategies to improve outcomes of children being treated with medication, particularly when benefits are suboptimal. J. Am. Acad. Child Adolesc. Psychiatry, 2009;48(5):501–510.

Key Words: medication, pharmacotherapy, methylphenidate, saliva levels. Clinical trial registration information—The NIMH MTA Study. URL: http://www.clinicaltrials.gov. Unique identifier: NCT0000388.
Although numerous studies have shown that stimulant medication can significantly improve behavior, attention, concentration, visual short-term memory, and driving performance, poor treatment adherence and early termination can undermine the effectiveness of this treatment in real-world settings, producing suboptimal outcomes, a problem recognized even two decades ago. In a recent article, children with attention-deficit/hyperactivity disorder (ADHD) who participated in long-term stimulant treatment exhibited greater improvement in teacher-reported symptoms than those who discontinued stimulant medications. In the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA), medication use mediated the degree of baseline to 14-month, and 14- to 24-month changes in ADHD symptom ratings, buttressing the initial 14-month randomized clinical trial findings that the use of a carefully monitored t.i.d. schedule of stimulant medication (with or without behavioral therapy) produced significantly better outcomes than community care (CC) or behavioral therapy alone (Beh). Moreover, analysis of parent-reported actual (versus assigned) treatment with medication suggested that subgroups whose parents reported stopping medication after 14 months showed the largest deterioration from previously achieved levels of symptom improvement.

Despite the risks associated with insufficient treatment adherence and persistence, estimated adherence rates in children with ADHD only range from 56% to 75%, and more than 50% of patients with ADHD discontinue treatment regardless of its efficacy or symptom severity. For example, one study of children (N = 1,635; aged 3–7 years) taking methylphenidate (MPH) immediate-release revealed that 54.0% of the subjects received only one prescription, and only 10.9% received five or more prescriptions during a 1-year period. Another study found that only 74% of children with ADHD initially assigned to stimulants took 50% or more of their pills for 12 months, and only 52% continued to use stimulant medication for 3 consecutive years. Unfortunately, it is often unclear from such reports how much of the 50% “adherence” rate resulted from planned drug holidays or deliberate medication only on school days. For example, with 180 to 185 school days in a year, one who takes medication only on school days with 100% fidelity could end up with 50% “adherence.” Nevertheless, it is unlikely that such planned nonmedication days would account for all reported nonadherence.

Nonadherence has been linked to a variety of factors, ranging from proximal and practical aspects of medication administration and/or immediately recognized side effects to more distal factors, including family socioeconomic status and ethnicity. Although precise estimates of actual adherence and persistence have remained unavailable, recent national data concerning ADHD treatment suggest that such problems may be increasing, perhaps in part because of many youths receiving insufficient medication treatment visits.

The validity and reliability of medication adherence measures, which often rely on parent report, vary or are unknown for stimulants and nonstimulants in youths. The current analysis represents the first attempt to investigate the discrepancy between parent report and physiological measures of medication compliance. Using data from the MTA Cooperative Group’s 14-month randomized controlled trial of ADHD treatments initiated in 1994, the present study evaluates the discrepancy between parent-reported and physiological measures of adherence by comparing saliva assay values of MPH adherence with parent verbal-report measures and also examines the extent to which physiological versus parent-reported adherence measures predict ADHD treatment outcomes through the 14-month treatment period of this clinical trial.

METHOD

Study Population

As described in the initial report of the MTA outcomes, children with ADHD combined type (aged 7–9.9 years) were randomly assigned to medication management consisting of titration with t.i.d. administration of 5 to 20 mg of immediate-release MPH followed by monthly visits (MedMgt); behavior treatment consisting of intensive parent, school, and child components, with therapist involvement gradually reduced over time (Beh); the two combined (Comb); or usual community care consisting of treatments by community providers (CC). The experimental interventions (MedMgt, Beh, and Comb) were delivered by MTA staff for 14 months and were carefully monitored for treatment fidelity. Multiple assessments from various sources and across domains were collected at baseline and at 3, 9, and 14 months (see MTA Cooperative Group for more details). The present study focuses on the 289 subjects in the medication-only and combined treatment groups, who were assigned to systematic, carefully titrated, monitored, and adjusted medication.
Study Design

As the original reports of the MTA outcomes indicate, subjects in the medication management and combination groups started with a 28-day, double-blind, daily-switch titration of MPH hydrochloride, using 5 randomly ordered repeats each of placebo, 5, 10, and 15 or 20 mg, with the higher dose, 15 mg versus 20 mg, being determined on the basis of the child’s weight (threshold ≥26 kg). Participants in the combined treatment group received medication (outlined above) and behavioral treatment; namely, parent group.

In the medication management and combination groups started medication phase of the study and subject-based physiological measures of adherence were available for comparative analyses. For the sake of clarity throughout this report, these two methods are termed verbal adherence and physiological adherence, respectively. Verbal adherence information (based on parental reports of their child’s medication status) was acquired from the MTA Medical Visit clinical report form. At each monthly medication visit, if the parent reported that their child was taking the study medication as prescribed, the child was then coded as being adherent for that visit (adherence defined as the parent’s report of overall adherence since the last visit and having taken medication as prescribed on the day of the visit). If the parent indicated that the child was not taking the study medication, then the child was coded as being nonadherent for that visit. However, because children were scheduled for monthly (up to 13) medication follow-up visits, all Comb and MedMgt subjects were reclassified as verbally adherent or verbally nonadherent, if parents reported that the children took medication on 80% or more of these monthly visits. Although our previous analyses revealed significant mediating effects of parent’s verbally reported medication adherence on ADHD treatment outcomes, our earlier analyses did not examine the extent to which parent reports correlated with physiological adherence (defined here as MPH saliva assays), nor whether physiological adherence was related to overall treatment outcomes.

Physiological Adherence

The protocol specified that four saliva assays would be conducted on each MTA medication-treated child during the course of the 14-month treatment period (at follow-up visits 2, 6, 9, and 14), with no pretreatment given to families of whether saliva assays would be drawn during that particular visit. Saliva swabs were gathered from the child only after the parent had verbally reported about the child’s medication adherence. For each saliva record, detectable MPH was used to indicate the presence of MPH taken that day (limit of detection for the assay used was >3ng/mL). All assays were refrigerated upon receipt at Nathan Kline Institute and promptly analyzed on the next available workday. Assays were coded to be physiologically adherent if MPH was detectable upon chromatographic analysis and nonadherent if MPH was not detectable. Across all 289 subjects in the MTA Comb and MedMgt groups, 31 children did not have any saliva swabs collected and, as a result, were excluded from the analyses: 20 children who terminated early from the maintenance phase before their first scheduled medication visit when saliva samples would have been collected and 11 children who continued in the study but for whom no saliva measures were taken because of scheduling problems or inadvertent omission by study staff. Of the remaining 258 children (123 MedMgt and 135 Comb subjects), 254 had one or more readable saliva assays (32 saliva vials were broken in transit or otherwise not readable). No significant differences were found between the two medication groups in medication participation, swab frequency, or study retention. The available 254 subjects (87.9%) provided a total of 780 assays (3.1 assays/participant; range 1–4 assays, with 748 (2.9/ participant) usable assays.

Subject-based physiological adherence during the maintenance phase was computed by dividing the number of adherent assays for each child by the total number of assays collected during the medication maintenance phase for the same child. Because of the variable number of assays per subject, subjects were recoded as adherent if greater than 50% of the given subject’s assays had detectable MPH levels.

Data Analyses

As a first step, adherent versus nonadherent subjects were compared on baseline demographic characteristics. In addition, the degree of concordance between parent-reported verbal adherence and physiological adherence was examined, first by cross-tabulating all 748 instances of MPH assays with the parents’ verbal reports during the same visits and again, at the subject level, by reclassifying the 254 available subjects for whom data were available into verbally adherent/nonadherent and physiological adherent/nonadherent binary variables.

Given the advantages of random-effects regression (RR) techniques over traditional analyses of variance for longitudinal clinical trials data, we used RR for subsequent analyses examining the potential mediating impact of our subject-based binary physiological adherence/nonadherence variable on ADHD symptom outcomes, with tests for two between-subject factors (site and adherence) and one within-subject factor (time), plus the interaction of these factors, time × treatment (any differences over time between MedMgt and Comb), adherence × time (any differences over time between adherent and nonadherent subgroups), and adherence × time × treatment (differential effects of medication adherence over time between the two treatment groups) within the RR analyses.

Following previous reports, ADHD symptom ratings were used as the primary outcome measures. These ratings were derived from the SNAP-IV (an acronym for the scale developers, Swanson, Nolan, and Pelham) rating scale completed by parents and teachers of the child. The SNAP summary scores were computed by the weighted averages of the nine inattention and nine hyperactivity-impulsivity items in the SNAP-IV questionnaire, separately for parents and teachers. Following previously established procedures, we examined the separate parent and teacher informants’ scores in a combined analysis of parent and teacher ADHD symptom ratings using a mixed-effects regression model with two factors: a fixed-effect informant (parent or teacher) factor nested within a factor defined by subject (random effect). This approach allows the power and reliability of both informants to be considered in the test, with all subjects included even if some observations are missing, while also testing for informant differences by the interaction of informant with treatment group. According to conventions for factorial analyses in which main effects and interaction effects are orthogonal, significance levels were set at p < .05, to determine whether adherence × time
or adherence \times \text{time} \times \text{treatment effects} \text{ could be identified. In effect, these analyses addressed the question whether any differences might be found because of differential medication taking based on the physiological MPH assays.}

**RESULTS**

**Physiological Adherence**

Overall, nearly one fourth (176 of 748 [23.5%]) of the saliva samples were physiologically nonadherent, below the detectable 3 ng/mL (indicating no MPH ingestion within 8 hours). To characterize the findings by child rather than by assay, for each child, we calculated the proportion of positive assays versus total number of assays drawn. Because these proportions were constructed based on anywhere from 1 to 4 saliva samples, depending on the number of swabs from each subject, proportions varied from 0, 0.25, 0.33, 0.50, 0.67, 0.75, and 1. When findings were grouped by children (rather than by records), 24.8% (n = 63) of 254 children’s medication regimens were classified physiologically nonadherent (i.e., ≤50% of their saliva samples below detectable 3 ng/mL). Moreover, across all children, 31 subjects (12.2%) were nonadherent on all collected saliva samples, and just more than half of the subjects (n = 136 [53.5%]) were physiologically adherent on all of their available samples. See Table 1 for details. The MedMgt and Comb groups did not differ significantly in rates of physiological adherence.

Table 2 presents data on the demographic characteristics of physiologically adherent versus nonadherent subjects. As seen here, two factors were differentially related to greater physiological medication adherence, ethnicity (more adherence in whites), and having a mother who was working outside of the home.

**Verbal (Parent-Reported) Medication Adherence**

Most parents reported that their child took the medication during that day. A total of 228 (89.8%) of 254 parents reported their children as taking the study medication on all occasions, 4 children (1.2%) were reported as taking their medications three fourths of the time, 14 children (5.6%) took their medication two thirds of the time, 5 children (2.0%) took their medications half of the time, 1 child (0.4%) took medication one third of the time, and 2 children (0.8%) none of the time by parent report. Thus, applying the same definition for nonadherence to parental reports (≤50%) as for physiological adherence, only 8 (3.1%) of the parents reported nonadherence.

**Concordance Between Verbal and Physiological Adherence**

Table 3 presents concordance information of verbal and physiological adherence for the 641 of 748 saliva assays for which parental reports of compliance were also obtained. As seen in the table, concordance of parental reports of adherence with physiological measures was substantially better than chance, but actual agreement was only “slight” (i.e., k’s < 0.20), using the rating system of Landis and Koch, suggesting parental overreporting of actual medication taking as measured by saliva MPH. From the perspective of the sensitivity

**TABLE 1**

<table>
<thead>
<tr>
<th>Proportion of Positive Assays vs. Total Assays Drawn, by Subject</th>
<th>No. and Percentage of Subjects for Each Proportion of Positive vs. Total Assays Drawn (N = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects’ Physiological Adherence Classification*</td>
<td>Proportion of Positive Assays</td>
</tr>
<tr>
<td>Nonadherent total (n = 63)</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Adherent total (n = 191)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
</tr>
</tbody>
</table>

Note: Each subject was classified as physiologically adherent or nonadherent, based on his/her ratio of positive saliva assays to the total number of saliva assays drawn. By protocol, each subject should have had four assays, but actual range was one to four assays (average 2.9 assays/subject). Subjects with assay positive proportions of 0.50 or lesser were classified as “physiologically nonadherent,” whereas those with proportions of greater than 0.50 were classified as “physiologically adherent.”
and specificity of a test against a gold standard, if we use parent verbal reports as a "test" to detect nonadherence against the physiological assay, the test has poor sensitivity, with only 14 of 136 physiological nonadherence cases (10.3%) identified by parental report. Negative test results (i.e., the parent reports adherence) has a specificity of 80.3% (496/618), indicating that reliance on reports of adherence within a single visit will be correct only 80% of the time, misclassifying 1 in 5 visits as adherence that is not. From a clinical perspective, therefore, a positive parental report of nonadherence merits clinical attention, whereas a negative report of nonadherence (i.e., report of adherence) merits clinical suspicion if clinical results are not satisfactory.

Random Regression Analyses of Adherence as a Mediator of Outcomes

For our analyses using mixed effects regression, we examined ADHD outcome as a function of the composited parent-teacher SNAP reports, examining site, time, physiological adherence (adherent versus nonadherent), treatment (Comb versus MedMgt), site × treatment, time × treatment, treatment × adherence, time × adherence, and time × treatment × adherence. Effects were as follows: site ($F_{5,468} = 0.92$, ns), time ($F_{1,248} = 754.8, p < .0001$), treatment ($F_{1,468} = 3.52, p = .06$), adherence ($F_{1,468} = 0.23$, ns), site × treatment ($F_{5,468} = .35$, ns), time × treatment ($F_{1,468} = 0.46$, ns) treatment × adherence ($F_{1,468} = 5.73, p = .017$), time × adherence ($F_{1,468} = 12.2, p < .0005$), and time ×

**TABLE 2**

Demographic Characteristics of Physiological Adherence Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonadherent ($n = 63$)</th>
<th>Adherent ($n = 191$)</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>7.89 (0.81)</td>
<td>7.79 (0.79)</td>
<td>$t_{52} = 0.85$</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>51 (80.95)</td>
<td>150 (78.53)</td>
<td>$\chi^2 = 0.17$</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>$\chi^2 = 12.6$</td>
</tr>
<tr>
<td>White</td>
<td>33 (52.38)</td>
<td>124 (64.92)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15 (23.81)</td>
<td>27 (14.14)</td>
<td></td>
</tr>
<tr>
<td>Nonblack Hispanic</td>
<td>8 (12.70)</td>
<td>12 (6.28)</td>
<td></td>
</tr>
<tr>
<td>Black Hispanic</td>
<td>2 (3.17)</td>
<td>3 (1.57)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.59)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (4.76)</td>
<td>23 (12.04)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.59)</td>
<td>2 (1.05)</td>
<td></td>
</tr>
<tr>
<td>Grade, n (%)</td>
<td></td>
<td></td>
<td>$\chi^2 = 5.88$</td>
</tr>
<tr>
<td>1</td>
<td>3 (4.76)</td>
<td>32 (16.75)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26 (41.27)</td>
<td>72 (37.70)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25 (39.69)</td>
<td>66 (34.55)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 (14.29)</td>
<td>21 (10.99)</td>
<td></td>
</tr>
<tr>
<td>Previous stimulant medication, n (%)</td>
<td>22 (34.92)</td>
<td>60 (31.41)</td>
<td>$\chi^2 = 0.27$</td>
</tr>
<tr>
<td>Welfare, n (%)</td>
<td>11 (17.46)</td>
<td>35 (18.32)</td>
<td>$\chi^2 = 0.01$</td>
</tr>
<tr>
<td>High school graduate, n (%)</td>
<td></td>
<td></td>
<td>$\chi^2 = 0.92$</td>
</tr>
<tr>
<td>Mother</td>
<td>59 (93.65)</td>
<td>177 (93.16)</td>
<td>$\chi^2 = 0.02$</td>
</tr>
<tr>
<td>Father</td>
<td>45 (88.46)</td>
<td>140 (90.91)</td>
<td>$\chi^2 = 0.03$</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td></td>
<td></td>
<td>$\chi^2 = 0.16$</td>
</tr>
<tr>
<td>Mother</td>
<td>21 (33.87)</td>
<td>103 (53.93)</td>
<td>$\chi^2 = 7.54$</td>
</tr>
<tr>
<td>Father</td>
<td>45 (86.54)</td>
<td>129 (83.77)</td>
<td>$\chi^2 = 0.23$</td>
</tr>
<tr>
<td>Income, $$, n (%)</td>
<td></td>
<td></td>
<td>$\chi^2 = 0.03$</td>
</tr>
<tr>
<td>0–20,000</td>
<td>11 (18.03)</td>
<td>37 (19.68)</td>
<td></td>
</tr>
<tr>
<td>20,000–50,000</td>
<td>26 (42.62)</td>
<td>75 (38.89)</td>
<td></td>
</tr>
<tr>
<td>&gt;50,000</td>
<td>24 (39.34)</td>
<td>76 (40.43)</td>
<td></td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>43 (68.25)</td>
<td>132 (69.47)</td>
<td></td>
</tr>
</tbody>
</table>

*Each subject was classified as physiologically adherent or nonadherent, based on his or her ratio of positive saliva assays to the total number of saliva assays drawn. By protocol, each subject could have up to four assays, but actual range was one to four assays (average 2.9 assays/subject). Subjects with assay positive proportions of 0.50 or lesser were classified as "physiologically nonadherent," whereas those with proportions greater than 0.50 were classified as "physiologically adherent."
treatment/C2adherence (\(F_{1,468} = 0.50, \text{ ns}\)). Actual means of parent-teacher composited SNAP scores by physiological adherence status are shown in Table 4 and plotted in Figure 1.

These findings demonstrated that ADHD symptoms decreased significantly over time and was mediated by physiological adherence (adherent subjects showed greater improvement over time). The significant effect of treatment/C2adherence suggests that the main effect of adherence on ADHD ratings was different in the Comb versus MedMgt groups, as seen in Figure 1, but the lack of a triple interaction (time/C2adherence) indicates that the MedMgt and Comb groups did not show a significant differential effect of adherence on the rates of improvement over time.

**DISCUSSION**

This article uniquely examines prospective medication adherence in the MTA study by contrasting parental reports of adherence with MPH saliva content values collected at the same visit. Before considering the implications of our findings, several caveats are in order. First, findings must be seen in light of the possibility that MPH saliva assays may not have yielded detectable levels (i.e., \(>3\) ng/mL) if the child had last taken MPH 8 or more hours earlier. So if the parent reported at a late-day assessment that the child had taken medication as directed that day but was unaware that the noon-day dose had been missed at school, a discrepancy between the late-day saliva assay (negative) and the parent’s report would have resulted inadvertently. In addition, our conclusions should be tempered by the uncertainty about how long saliva values are detectable (\(\geq 3\) ng/mL) on chromatographic analysis and whether that constitutes an appropriate threshold for adherence.

Caution is also warranted, to the extent that our results apply only to the MTA sample (combined type ADHD, age 7–10 years) and medication regimen, principally based on immediate-release MPH t.i.d. Short-acting formulations have been mostly replaced by newer longer-acting profiles, so the adherence/compliance rates for newer formulations may differ from those reported here.

From an optimistic perspective, one might view our medication nonadherence based on saliva samples as relatively low, with only one fourth (176 records [23.5%]) of all the saliva samples indicating nonadherence. Pessimistically, however, 24.8% of the subjects...
were nonadherent in 50% or more of their collected samples, although almost 90% of the parents reported that their child was adherent at every visit. Only 3.1% of the parent reports indicated adherence at or below the 50% threshold versus 23.5% of the physiological samples below the adherence threshold.

Interestingly, our results of verbal adherence (89.8% across all visits) are higher than generally seen in longitudinal studies, likely because of the intensive follow-up procedures put in place to facilitate adherence during 14 months. Despite our high reported adherence rates, our physiological adherence findings are consistent with studies that have linked poor adherence to adverse outcomes. However, unlike some previous studies, we found no associations between adherence and demographic factors such as age, sex, family income, and single-parent status. In contrast, we did find somewhat greater physiological nonadherence as a function of minority ethnic status, as well as among children whose mothers were not employed. The meaning of this finding is unclear and may result from the different types of subjects who participate in long-term treatment studies versus those drawn from more naturalistic service use databases and short-term studies.

The current literature on ethnic disparities in adherence is somewhat inconsistent: some studies indicate that minority youths are at increased risk for premature treatment discontinuation and lower use of psychiatric services and medication, but other studies suggest no ethnic disparities in mental health prescription rates, referrals, and counseling once a diagnosis is made. Moreover, although some research suggests that minority parents, compared with their white counterparts, harbor more negative attitudes about ADHD medication treatment, a recent examination of other MTA variables showed no significant ethnic differences in acceptance of or compliance with either medication or behavioral treatments. The discrepancy between our current saliva findings and our previously reported adherence rates may be because our earlier findings concerning ethnicity were based on the definition of medication adherence as “80% or greater attendance” at the 14 months of medication-monitoring visits.

To the extent that our saliva assays were a fair representation of the child’s having taken medication on the day that parents reported compliance, concordance in Table 3 between parental reports of compliance and physiological measures was only fair, suggesting that parents overreport their child’s actual medication-taking behavior. Given recent research on factors related to nonadherent behavior, the present discrepancy between parental reports and saliva levels may have resulted from both intentional (purposeful actions) and unintentional (patterned behaviors, such as forgetting) variables. Parents may misreport their child’s medication-taking behavior to satisfy their physicians’ expectations and to project a favorable impression. Relatedly, one study of youths’ adherence to human immunodeficiency virus therapy found that many participants viewed their health care providers as powerful authorities and admitted to giving them inaccurate adherence information to avoid blame and criticism. Recent literature has similarly demonstrated the impact of the therapeutic relation on adherence reports and behaviors, suggesting that a more positive parent–therapist relationship predicts greater treatment acceptability and persistence. Further research on the development of a collaborative doctor–patient relationship and methods for increasing parents’ comfort in candid disclosure might lead to improvements in actual medication adherence or at least more accurate information about the degree of actual adherence.

Stigma associated with medication therapy may also contribute to the discrepancy between self-report and biological measures of adherence. Previous research...
indicates that inaccurate information about treatment, embarrassment, and anticipated disapproval from family and peers can lead patients or parents to skip medication doses or prematurely discontinue treatment.\(^\text{37,39}\) Moreover, parents of children with ADHD are reported to consider medication treatments less socially acceptable than psychosocial or combination interventions.\(^\text{40}\) Stigma reduction programs may be needed to nullify stereotypes about ADHD care and encourage treatment adherence among youths and their parents.

To the extent that unintentional barriers to adherence, such as lifestyle factors, busyness, or simply forgetting, might play a role in adherence, parents of children with ADHD and long-term pharmacotherapy regimens may benefit from medication recall tools, such as pill boxes or treatment tracking systems, as well as simplified (single daily dose) medication regimens.\(^\text{41}\)

The current study provides new insights into the potential causes of ADHD medication “nonresponse” and suggests that clinicians should assess medication adherence in patients with a poor response before altering dosage or changing medications. The physician should consider asking about adherence in a fashion that makes full and candid disclosure more likely such as saying, “Many parents have concerns about the medication, or find it hard to remember doses, sometimes during the week, or sometimes on weekends. Or some parents cut the dose because they are worried about side effects, or because of something they read about medicine that troubled them. What’s been the biggest problem for you, in either remembering to give it, or cutting the dose?”

Generally, our findings seem to suggest that adherence may be more important for patients whose only treatment is medication (MedMgt) than for those who have additional behavioral therapy (Comb). Possibly, in the Comb group, the added benefit of behavioral therapy allowed a good outcome even when medication adherence was low, whereas the MedMgt outcomes were more fully dependent on medication adherence.

Because our current findings, as well as previous reports, have shown that medication adherence is associated with children’s outcomes and because parent reports may often be incomplete, it is worth the clinicians’ time to focus on strategies for enhancing adherence at treatment outset and throughout treatment duration. Such approaches might include encouraging parents to adopt a regular time and routine for medication, encouraging parents to monitor and reinforce children’s pill taking carefully, using long-acting formulations to reduce the number of times the family needs to remember medication, enlisting cooperation of both child and parent, using a medication diary or log (perhaps as simple as a calendar), putting the family at ease so they candidly report adherence, and giving the child a chance privately to talk about adherence and his/her feelings about medication. Research on these adherence strategies, as well as studies of medication adherence across different psychiatric disorders or using different methods (such as drug urine dipstick tests), are sorely needed. In particular, studies are needed to identify adherence strategies that actually work, including whether they can improve children’s outcomes. Such strategies are especially important for children who seem unresponsive to medication and where adherence is of potential concern.

The NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial involving six clinical sites. Collaborators from the National Institute of Mental Health: Peter S. Jensen, M.D. (currently at Columbia University), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Joanne B. Severe, M.S. (Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Benedetto Vitello, M.D. (Child and Adolescent Treatment and Preventive Interventions Research Branch), Kimberly Hoagwood, Ph.D. (currently at Columbia); previous contributors from NIMH to the early phase: John Richters, Ph.D. (currently at National Institute of Nursing Research); Donald Vereen, M.D. (currently at National Institute on Drug Abuse). Principal investigators and coinvestigators from the clinical sites are as follows: University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, Ph.D., M.D. (San Francisco); Duke University: C. Keith Conners, Ph.D., Karen C. Wells, Ph.D., John March, M.D., M.P.H., Jeffry Epstein, Ph.D.; University of California, Irvine/Los Angeles: James Swanson, Ph.D. (Irvine), Dennis P. Cantwell, M.D., (deceased, Los Angeles), Timothy Wigal, Ph.D. (Irvine); Long Island Jewish Medical Center/Montreal Children’s Hospital: Howard A. Abikoff, Ph.D. (currently at New York University School of Medicine), Lily Hechman, M.D. (McGill University); New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill, M.D. (Columbia), Jeffrey H. Newcorn, M.D. (Mount Sinai School of Medicine); University of Pittsburgh: William E. Pelham, Ph.D. (currently at State University of New York, Buffalo), Betsy Hoza, Ph.D. (currently at University of Vermont), Brooke Molina, Ph.D. Original statistical and trial design consultant: Helena C. Kraemer, Ph.D. (Stanford University). Follow-up phase statistical collaborators: Robert D. Gibbons, Ph.D. (University of Illinois, Chicago), Sue Marcus, Ph.D (Mt. Sinai
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