A META-ANALYSIS OF INTERVENTIONS TO INCREASE ADHERENCE TO MEDICATION REGIMENS FOR PEDIATRIC OTITIS MEDIA AND STREPTOCOCCAL PHARYNGITIS

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Abstract

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Interventions to increase adherence to medication regimens for acute pediatric illnesses are important for both individual and public health outcomes. To date, there has not been a comprehensive, quantitative analysis of the effectiveness of interventions for acute pediatric illnesses. The current study used meta-analysis to quantitatively synthesize the adherence intervention literature for two common acute childhood illnesses and examined the magnitude of change in adherence as indicated by different outcome measures and the relationship between type of intervention and adherence outcome. Combination interventions were more effective than single strategy interventions. However, families receiving educational interventions alone did not demonstrate better adherence than control groups. Indirect measures of adherence showed more change in adherence than direct measures. The results of this meta-analysis suggest that further work is needed to develop effective interventions for improving adherence for the medication regimens required for short term illness and for optimizing health outcomes.

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A Meta-Analysis of Interventions to Increase Adherence to Medication Regimens for Pediatric Otitis Media and Streptococcal Pharyngitis

One of the earliest and most-cited definitions of compliance is "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes, 1979, p. 1). More recently, the term "adherence" has been used instead of "compliance." Although most initial adherence research concerned adult patients (e.g., Marston, 1970), later work focused on pediatric patients as well (e.g., Dickey, Mattar, & Chudzik, 1975). Pediatric adherence is perhaps even more complex than adult adherence, because depending on the age and abilities of the child, the family may play a significant role in illness care activities such as administering medications (Matsui, 1997).

Adherence to medication regimens has been of interest to researchers and clinicians because it is related to a variety of outcomes, such as illness remission, preventing recurrent infections, maintaining cost-effectiveness, and preventing the growth of antibiotic-resistant bacteria (Matsui, 1997; Rapoff & Barnard, 1991). The rise of antibiotic-resistant bacteria has received particular attention in recent years (e.g., Leibovitz, 2003), and it is thought that poor adherence to medications for common childhood illnesses such as otitis media and streptococcal pharyngitis contributes to the growth of these bacteria (Rapoff, 1999).

Rates of adherence vary between illness and age groups, definition of adherence used, and mode by which adherence is measured (Rapoff & Barnard,

1991). For pediatric acute illnesses such as otitis media and streptococcal pharyngitis, rates of adherence to antibiotic regimens range widely from 18% to 95%, and adherence to medication regimens may be better for streptococcal pharyngitis than for otitis media (Charney et al., 1967; Rapoff, 1999). The focus of the current study was adherence to medication regimens for the acute pediatric illnesses of otitis media and streptococcal pharyngitis. Although there are commonalities in adherence issues for acute and chronic illnesses, some issues may be unique to chronic illnesses due to complex, long-term treatments (e.g., Rapoff, 1999).

Nonadherence

Nonadherence to medication regimens can manifest in many forms, including failure to fill prescriptions, skipping doses, not finishing a full course of medication, and taking incorrect doses of medication (Matsui, 1997; Rapoff & Barnard, 1991). In pediatric patients, nonadherence may involve the child (e.g., refusing to take medication) and the family (e.g., parents not continuing to administer medication when symptoms remit; Matsui, 1997). There can be numerous underlying reasons that parents and their children do not adhere to medication regimens. For example, families may forget to administer medication at the correct times, they may not understand how to administer medication correctly or the importance of finishing the course of medication, and children may refuse to take medications because they do not like the taste (Matsui, 1997; Rapoff & Barnard, 1991). Of particular relevance to acute illnesses which are often treated with antibiotics, families may stop administering medication when children's symptoms remit (Matsui, 1997).

Interventions to Improve Adherence

Given the importance of adherence for health and economic reasons, clinicians and researchers have implemented a variety of interventions to improve adherence. Matsui (1997) recommended that interventions emphasize (a) collaboration and open communication between health care providers, patients, and their families, (b) simple medication regimens whenever possible, and (c) follow-up with families so that adherence can be improved if necessary. Interventions that are relevant to acute illnesses such as otitis media can be categorized as educational, behavioral, or organizational.

Educational interventions often aim to increase patients' and their families' knowledge about the illness, how to take medication, side effects of the medication, and the importance of adherence to the medication regimen. These interventions aim to improve adherence by equipping families with the knowledge of *why* adherence is important and *how* to adhere correctly (Cramer, 1991; Rapoff, 1999). Educational interventions may be delivered in verbal or written form, and may include demonstrations such as showing families how to correctly administer medication and allowing families to practice administering medication with the supervision of a health care provider (Rapoff, 1999; Rapoff & Barnard, 1991).

Behavioral interventions provide families with methods for remembering to take medication and methods of addressing children's refusal to take medication. For example, families may better remember to administer medications if medication is always given at dinnertime or if they use a beeping pill box. If children refuse to take

medications, families may use incentive systems or discipline strategies such as time-out (Cramer, 1991; Rapoff, 1999).

Finally, organizational strategies alter characteristics of the health care provider environment or interactions with patients so that families are more likely to and can more easily adhere to medication regimens. These strategies may include increasing contact with families between appointments, making the health care provider more available for questions about adherence, designing a medication regimen that is as simple as possible, and minimizing side effects of the medication itself (Cramer, 1991; Rapoff, 1999).

Combinations of these three types of interventions may be used as well. A previous meta-analysis indicated that combinations of interventions, specifically a combination of educational and behavioral techniques, are more effective than single-type interventions such as education alone (Roter et al., 1998). However, if only one type of intervention is to be used, educational and organizational strategies are viewed as the most effective (Rapoff & Barnard, 1991).

Measuring Adherence

There are numerous ways to measure adherence to evaluate the effectiveness of interventions: direct measures, indirect measures, subjective measures, and secondary measures. First, direct measures such as urine or blood assays can be used to determine how much medication has been ingested. Although these have the advantage of providing an estimate that is unbiased by reporting, direct measures cannot be considered to be a "gold standard" measurement (Rapoff, 1999). A gold

standard measurement must be error-free or as reasonably close to the true reading as can be expected (McGaghie, 1991). In the case of assays, other factors such as an individual's speed of digestion or metabolism may influence the readings. Also, drug assays provide a measure of medication levels for only a limited period of time, which limits the generalizability of the results to longer time periods (Matsui, 1997; Rapoff, 1999), particularly for medications with a short half-life.

Second, adherence can be measured indirectly with pill counts or measuring the volume of liquid medication left after a proscribed amount of time. More recently, electronic pill bottles such as the Medication Event Monitoring System (MEMS) have been used as indirect measures of medication adherence by providing information on how many times and when a bottle was opened. Unfortunately, both electronic measures and pill counts do not guarantee that medication has been ingested (Rapoff, 1999). Previous research indicates that indirect measures show greater changes in adherence following interventions than direct measures (Roter et al., 1998).

Third, subjective measures such as provider and patient estimates can be used to measure adherence. Provider estimates should be used cautiously particularly in regards to identifying nonadherent patients and families (Finney, Hook, Friman, Rapoff, & Christophersen, 1993). Patient estimates ranging from diaries to global ratings tend to overestimate adherence, although structured interviews may be more accurate than global ratings of adherence (Matsui, 1997; Rapoff, 1999). Finally, intervention studies may present health outcomes, such as the remission of illness or symptoms, or the making of or attendance at follow-up appointments, as measures of

adherence. These measures are considered to be secondary measures of adherence since they do not necessarily have a direct relationship with medication adherence (Matsui, 1997; Rapoff, 1999).

Because each measurement of adherence has benefits and drawbacks, there is currently no agreed-upon gold standard (Quittner, Espelage, Ievers-Landis, & Drotar, 2000) and thus a combination of methods to measure adherence may be used (Matsui, 1997; Quittner et al., 2000).

Rationale for Current Study

Some of the earliest studies of pediatric adherence and adherence interventions involved acute illnesses (e.g., Arnhold et al., 1970; Becker, Drachman, & Kirscht, 1972). Among the pediatric acute illnesses, otitis media and streptococcal pharyngitis have been the most studied (Rapoff, 1999). These illnesses occur frequently in children; for example, acute otitis media is the most common pediatric bacterial infection in the United States (Leibovitz, 2003), affecting 75% of children by the age of three (National Institute on Deafness and Other Communication Disorders, 2007). Furthermore, while these illnesses are usually successfully treated with short-term courses of antibiotics, recurrent infections can have potentially deleterious effects. Recurring otitis media has been linked with lower literacy skills, streptococcal pharyngitis has been linked with the onset of obsessive-compulsive disorder and tics in some cases, and partial adherence to medication regimens may lead to the growth of antibiotic-resistant bacteria (Rapoff, 1999; Snider & Swedo, 2003; Winskel, 2006). An understanding of the effectiveness of interventions to

improve adherence to the medication regimens for these illnesses is therefore important in order to increase children's and the public health. Furthermore, adherence research for certain acute illnesses can serve as a model for understanding the effectiveness of adherence interventions in other illnesses.

There have been qualitative and quantitative reviews of adherence intervention studies (e.g., Costello, Wong, & Nunn, 2004; Roter et al., 1998). Although both types of reviews are useful, quantitative reviews such as meta-analyses are unique in that they statistically summarize study findings so that treatment effects across studies can be described, independent of statistical significance (Durlak, 2005). Notably, there have been a limited number of meta-analyses of interventions to increase adherence for pediatric illness (Roter et al., 1998).

The current meta-analysis included study reports obtained from a broad search strategy to examine whether particular types of interventions are more effective in improving adherence for specific acute illnesses and whether estimates of adherence differ depending on the method of measurement. Based on previous reviews, combinations of types of interventions (e.g., educational and behavioral) were hypothesized to be more effective than one intervention alone (e.g., educational), and when only one type of intervention was used, educational and organizational strategies were hypothesized to be the most effective (Rapoff & Barnard, 1991). Also, based on previous literature, it was hypothesized that indirect measures of adherence (e.g., pill counts) would be associated with greater changes in estimates of adherence than direct measures (e.g., urine assays; Roter et al., 1998).

Method

Literature Searches

Several search strategies were used to identify reports eligible to include in the meta-analysis. Using combinations of search terms, the following electronic databases were used: PubMed, PsycINFO, ProQuest Dissertations and Theses, Educational Resources Information Center (ERIC), and GoogleScholar. PubMed and PsycINFO are comprehensive indexes of scientific literature in the medical and psychology fields. In addition, PsycINFO and ProQuest include dissertations and master's theses (the rationale for including theses and dissertations is discussed under *Inclusion in the Meta-analysis*). The ERIC database includes scientific reports, dissertations, book chapters, and conference proceedings in the education field. The education literature may provide eligible reports because a commonly-used intervention to improve adherence is providing educational materials to patients and their families. GoogleScholar includes peer-reviewed journal articles, theses, books, and articles from professional organizations and universities.

Searches in each database consisted of combinations of keywords. These keywords are frequently-used terms in the adherence literature. Keyword combinations were comprised of two terms joined by *AND*. The first term was the name of the acute illness: *otitis media* or *streptococcal pharyngitis*. The second term was related to adherence (*adherence* or *nonadherence* or *compliance* or *noncompliance* or *concordance*) or interventions (*education* or *intervention* or *strategy* or *instruction*). The wildcard symbol (*) was used to ensure that reports

containing variations of terms were identified. For example, *intervention* was entered as *interven** so that articles containing the words "intervention," "intervening," "intervenes," or "intervened" were identified in the database. Together, these search terms produced 18 unique combinations and each database was searched using them.

The meta-analysis includes eligible reports from the inception of the databases through May, 2007. PsycINFO includes reports starting in 1887, PubMed includes reports starting in 1950, Proquest includes reports starting in 1861, and ERIC includes reports starting in 1966. GoogleScholar searches included reports beginning in 1861.

As recommended by White (1994) and Reed and Baxter (1994), three additional methods were used to gather relevant reports. First, reference sections of each report identified in the search strategies were checked for other potentially eligible articles. Particular attention was given to the reference sections of review articles, previous meta-analyses, and books on adherence to medication regimens (e.g., Rapoff, 1999). Second, "forward searches" were conducted using the "articles citing" function in PsycINFO, the "cited in PMC" function in PubMed, and the "cited by" function in GoogleScholar. This process identified reports that were published subsequently and cite the initially identified reports. A similar function is not available in Proquest Dissertation and Abstracts or in ERIC. Third, available conference proceedings were searched for relevant presentations, because oftentimes conference presentations are not subsequently published (Lipsey & Wilson, 2001; Reed & Baxter, 1994).

Conference proceedings. The annual conference proceedings of the following professional organizations were electronically searched for potentially relevant reports: The Society of Behavioral and Developmental Pediatrics (2006), Pediatric Academic Societies (2000-2006), and the American Society of Pediatric Otolaryngology (2000-2002, 2005-2006). In addition, manual searches of the Pediatric Academic Societies conference proceedings for the years 1989-1993 were completed.[1]

Inclusion in the Meta-Analysis

In order to be included in the meta-analysis, a report fulfilled the following criteria: (a) it was in English, (b) the illness being studied was *otitis media* or *streptococcal pharyngitis*, (c) study participants were under the age of 18 years, (d) the study included at least one intervention to improve adherence to the medication regimen for one of the illnesses, (e) there was at least one measure of adherence, (f) effect size statistics could be calculated from the results presented in the report, from raw data solicited from study authors, or if neither of these was available, an effect size of 0 could be assigned based on a report of "non-significant results" (see section on *Effect Size Estimates* for the statistical information required), and (g) if study participants included both adults and children, there was a way to calculate effect sizes for the children alone.

As recommended by Durlak (2005) and Lipsey and Wilson (2001), unpublished master's theses and dissertations and unpublished conference presentations were included in the searches for eligible reports to allow a more

accurate representation of whether adherence interventions have an effect. Unpublished documents may be subject to publication bias or the "file drawer bias," or that they were not published because they reported negative results (Lipsey & Wilson, 2001). Also, statistical analyses to examine whether the file drawer bias influenced the meta-analytic results were conducted (see section on *Sensitivity Analyses*).

Description of Reports

Out of the 6,058 reports identified in the five electronic databases, 13 met criteria for inclusion in the meta-analysis (11 concerning otitis media and 2 concerning streptococcal pharyngitis). All were journal articles published between the years of 1972 and 1989 (median year published = 1985). Searches of conference proceedings yielded no eligible reports. Together, the 13 studies included 1,949 participants. On average, studies included 150 participants and sample sizes ranged from 30 to 512. For the eight studies that reported children's ages, the average age of the ill child was 2.25 years (*SD* = 1.41 years). For the nine studies that reported sample attrition, the average rate of attrition was 17.5%. On average, for the seven studies that reported the ethnicities of their participants, 52.4% of the samples were Caucasian. Other ethnicities represented included African-American, Native-American, and Hispanic. Participants' socioeconomic status (SES) was reported in only three of the reports and none of the reports listed a complete breakdown of the sample's SES.

Study design. Almost all (12) of the studies took place in primary care clinics; one study took place in a private practice. Ten of the studies used random assignment to assign study participants to treatment or control groups. One study did not utilize a control group, and two studies used nonrandom assignment. For the control group, 10 of the studies used treatment as usual, two studies used an attention placebo, and one study did not have a control group. Seven of the 13 studies employed an educational intervention, 2 employed a behavioral intervention, 1 employed an organizational intervention, 1 employed a combination of educational and behavioral interventions, and 2 employed other combinations of interventions (i.e., educational and organizational; educational, organizational, and behavioral). The majority of the studies used one-time interventions; however, two studies employed interventions that took place over a longer period of time. Nine out of the 13 studies used at least two measures of adherence, and five studies used three or more measures of adherence.

Coding Procedures

Two coders, one of whom was the principal investigator, recorded intervention, adherence, study descriptor, and effect size information for each report that met criteria for inclusion in the meta-analysis (see Appendixes A and B for coding sheets). The second coder received training on the adherence intervention literature, meta-analytic methods, and the rationale for the current study. Such education is one way to maximize reliability and validity of the information to be coded (Lipsey & Wilson, 2001). For purposes of training and refining the coding

protocol, the two coders coded three reports together (Stock, 1994). After establishing reliability, coders independently coded the remaining reports (Lipsey & Wilson, 2001). Coders resolved discrepancies through discussion, and the consensus rating was used for study analyses. All reliability analyses were computed using SPSS 11.0. Interrater reliability for categorical variables (κ = .88) and continuous variables (r = .99) was high.

Study-Related Variables

Intervention variables. Interventions to increase adherence to medication regimens were recorded and identified as educational, behavioral, organizational, or a combination of strategies. In studies where there was more than one intervention group, the only intervention coded was the group that was the focus of the study or the group that was hypothesized to have the best adherence outcome due to the intervention.

Adherence measures. Measures of adherence were recorded and coded into the following categories: (a) direct measures, (b) indirect measures, (c) subjective measures, and (d) secondary measures of adherence (health outcomes and appointment making or keeping).

Study characteristics. Study characteristics that were recorded, if available, were: (a) publication type (e.g., journal article), (b) sample size and attrition, (c) participant demographics (mean age, percent female, race, socioeconomic status), (d) illness (otitis media or streptococcal pharyngitis), (e) study setting (e.g., primary care

clinic), (f) method of assigning to intervention or control group, and (g) number of intervention sessions.

Effect Size Estimates

An effect size is a quantitative measure of the magnitude of a treatment effect (Lipsey & Wilson, 2001). As applied to the current meta-analysis, an effect size is a measure of an intervention's effectiveness in increasing adherence to a medication regimen for otitis media or streptococcal pharyngitis.

The following information, if available, was recorded for each report so that effect size statistics could be calculated: (a) when adherence was measured (e.g., pre-treatment, post-treatment), (b) group means (e.g., mean adherence for the intervention group), (c) group sample sizes, (d) group standard deviations or variances, (e) proportion of individuals with a successful outcome, (f) type and result of statistical analysis used in the report, and (g) significance levels (see Appendix B for the Effect Size coding sheet).

The effect size statistics used in the current meta-analysis were the logit odds ratio, the logit proportion, and Cohen's *d*. For reports comparing a treatment and control group measured on a dichotomous outcome variable (e.g., adherent versus nonadherent), the logit odds ratio effect size was used. For reports involving dichotomous outcome variables and no control group, the logit proportion effect size was used. Cohen's *d*, a standardized mean difference, was used for reports where the outcome measure was continuous in nature (see Appendix C for effect size formulas).

If non-significant results were reported in the absence of exact statistical information, and if data could not be solicited from authors, an effect size of zero was assigned (as prescribed by Rosenthal, 1995), which downwardly biased these effect sizes. These studies were included because non-significant results suggest that an intervention did not improve adherence to medication regimens. Furthermore, including these studies is one way to minimize the file drawer bias (Lipsey & Wilson, 2001). An analysis of whether mean effect sizes changed when these studies were included in the meta-analysis was completed (see section on *Sensitivity Analyses*).

Weighting effect size estimates. Studies with larger sample sizes are considered to be more accurate estimations of population effects than studies with smaller sample sizes. As a result, effect size estimates of larger studies, which have a smaller standard error, should carry more weight in the analysis of mean effect size across studies. This was achieved by weighting each effect size with an inverse variance, which is based on the standard error (see Appendix C for formulas; Hedges & Olkin, 1985; Lipsey & Wilson, 2001).

Independence of Effect Size Estimates

In a meta-analysis, independence between effect size estimates must be maintained. That is, each report included in the meta-analysis must contribute independent effect sizes to the analysis. If more than one effect size can be calculated for any one given report (e.g., if there is more than one measure of adherence), there are two recommended strategies to maintain independence. One strategy is to choose one of the effect sizes for use in the final analysis. The choice may be made at

random, or by deciding which effect size relates most directly to the outcome variable, or by choosing the effect size that uses the most widely-accepted measure of the outcome. In the current meta-analysis, however, all effect sizes pertained to adherence, and there is no consensus in the adherence literature as to the "best" measure of adherence. Therefore, when more than one effect size could be calculated for a given report, the second recommended strategy of averaging all effect sizes for a given study was used (Durlak, 2005; Lipsey & Wilson, 2001).

Homogeneity Analysis

Before analyzing effect sizes as a group, it was necessary to determine using a homogeneity analysis whether the reports were drawn from the same population. In other words, it was necessary to determine whether the effect sizes represented effects observed within the same population. The null hypothesis of this analysis is that the samples in the reports were drawn from the same population and that any variation between effect sizes can be accounted for by random sampling error (Lipsey & Wilson, 2001).

The homogeneity analysis was conducted using the *Q* statistic, which is calculated from the effect sizes, the weights of the effect sizes, and the mean effect size (see Appendix C for formulas). The *Q* statistic was then compared with a critical value, the chi-square value for one less than the number of effect sizes included in the meta-analysis. A *Q* statistic greater than or equal to this chi-square value indicates heterogeneous effect sizes. This would suggest that there were other factors, beyond

random sampling error, that accounted for differences between effect sizes (Lipsey & Wilson, 2001). In this case, there are two ways to analyze the effect sizes.

One method is to assume a random effects model. The random effects model assumes that the variability in effect sizes can be accounted for by random sampling error and an unknown random error between studies (Lipsey & Wilson, 2001). Random effects analyses allow one to generalize the conclusions of a meta-analysis to other studies that were not included in the analysis (Hedges & Vevea, 1998). However, this method is not suitable when a meta-analysis includes a small number of studies (Hedges & Vevea, 1998). Thus, another method that accounts for known sources of variability was used in the present study.

The fixed effects model assumes that there are known variables that influence the differences between effect sizes, in addition to random sampling error. One way to utilize the fixed effects model in the analysis of categorical variables such as type of intervention, is to use a technique analogous to an analysis of variance (ANOVA; Hedges, 1982). In this technique, the *Q* statistic is separated into two components: a *Q*-between, representing the variance in effect sizes accounted for by the variable of interest, and a *Q*-within, representing the within-group error. If the *Q*-between is statistically significant and the *Q*-within is not significant, the variable of interest successfully accounts for the variance between effect sizes (Lipsey & Wilson, 2001).

Sensitivity Analyses

Sensitivity analyses were conducted in order to measure how robust the findings were to different subsets of the data (Greenhouse & Iyengar, 1994). Three

sensitivity analyses were performed. First, a sensitivity analysis was performed to assess whether results differed if studies of streptococcal pharyngitis were excluded. Previous research indicates that adherence rates before intervention may differ for these two illnesses (Charney et al., 1967), and thus adherence rates following intervention may significantly differ as well. In addition, preliminary literature searches and previous reviews (Rapoff, 1999) indicated that there have been fewer studies of streptococcal pharyngitis. If this is the case, the results of streptococcal pharyngitis studies may be less reliable than those of otitis media. Second, a sensitivity analysis was performed to assess whether mean effect size estimates changed when studies with an effect size estimate of zero, as determined by a reporting of "non-significant results," were excluded.

The third set of sensitivity analyses assessed whether the file-drawer bias may have impacted the effect size analyses. This sensitivity analysis estimates how influential "hidden" studies may be, and how likely that there is a substantial number of "hidden" studies. Because there is no consensus on which of two methods should be used for this type of sensitivity analysis (Greenhouse & Iyengar, 1994; Lipsey & Wilson, 2001), both methods were used. One method is a modification of Rosenthal's fail-safe *n.* This analysis indicates the number of studies reporting no effect that would appreciably reduce the mean effect size. If the number of "hidden" studies seems unlikely given the number of studies included in the meta-analysis, then it is likely that publication bias has not greatly affected the estimation of the significance of mean effect sizes (Lipsey & Wilson, 2001).

The second method used was the funnel plot, a plot of effect sizes by sample sizes (Light & Pillemer, 1984). The scattering of data points should resemble a funnel, with a larger number of points scattered in the lower part of the plot. The rationale is that studies with smaller sample sizes should have a wider range of effect sizes. Deviations from a funnel shape suggest the presence of publication bias.

Data Analysis Plan

1) Weighted and unweighted effect sizes were calculated for each report. Logit odds ratio effect sizes were converted to Cohen's *d* effect sizes. Converting logit odds ratio effect sizes to a standardized mean difference effect size such as Cohen's *d* is recommended when two conditions are met: (a) the outcome is an inherently continuous variable (i.e., adherence) and (b) the studies artificially dichotomized the construct (i.e., adherent vs. nonadherent; Lipsey & Wilson, 2001). If there was more than one effect size for a report, effect sizes for the report were averaged so that each report contributed only one effect size to the analyses.
2) Effect sizes were examined for outliers.
3) Primary outcome measures: The homogeneity (*Q*) statistic was calculated and compared with the appropriate chi-square test statistic for primary outcome measures. The analog to ANOVA was used to determine whether effect sizes might differ as a result of intervention type. Mean effect sizes, *Z*-tests, and 95% confidence intervals were calculated.

4) Secondary outcome measures (illness remission and appointment making or keeping): Weighted and unweighted effect sizes were calculated. Effect sizes were averaged within each study if there was more than one secondary outcome measure in a study. The homogeneity statistic was compared with the appropriate chi-square test statistic. The analog to ANOVA method was used to determine whether effect sizes might differ as a result of intervention type. Finally, mean effect sizes, *Z*-tests, and 95% confidence intervals based on "illness remission" versus "appointment making or keeping" were calculated.
5) Mean unweighted and weighted effect sizes, *Z*-tests, and confidence intervals for the categories of adherence measures (direct, indirect, subjective, and secondary outcome measures) were calculated.
6) Sensitivity analyses were performed by excluding studies with an artifactual effect size of zero, excluding studies of streptococcal pharyngitis, and analyzing publication bias using Rosenthal's fail-safe *n* and the funnel plot.

Results

Effect Sizes

Due to variations in study design across reports, several types of effect sizes were used and for some studies, more than one type of effect size was calculated. Logit odds ratio effect sizes were calculated for 12 studies, Cohen's *d* was calculated for one study (which also had logit odds ratio effect sizes), and logit proportion effect sizes were calculated for one study. Logit odds ratio effect sizes were converted to Cohen's *d* effect sizes so studies could be analyzed as a group (see Table 1).

Table 1

Effect Sizes (ES) for Primary and Secondary Outcome Measures of Adherence

		Primary outcome measures		Secondary outcome measures	
Study first author (year)	Sample size	Unweighted ES	Weighted ES	Unweighted ES	Weighted ES
Leistyna (1966)	156	-	-	-	-
Colcher (1972)	200	-	-	0.60	28.72
Mattar (1975)	233	1.33	34.05	-	-
Ellison (1982)	30	0.26	1.83	-0.43	-7.60
Reed (1984)	290	-0.75	-50.73	0.00	0.00
Casey (1985)	92	0.79	5.22	0.33	7.45
Finney (1985)	73	0.51	6.27	0.01	0.13
Williams (1986)	60	0.28	3.41	-0.17	-2.49
Bertakis (1986)	59	0.00	0.00	-	-
Kulik (1987)	41	0.00	0.00	0.57	5.59
Maiman (1988)	512	0.38	46.56	-	-
Schwartz-Lookinland (1989)	62	0.08	1.22	-	-
Williams (1989)	141	-	-	-0.17	-6.05

Dashes (-) indicate an ES could not be calculated

Using Cohen's (1988) criteria, a small effect is less than or equal to .20, a medium effect is less than or equal to .50, and a large effect is less than or equal to .80. In addition, a positive effect size indicates that the intervention group had better adherence than the control group and a negative effect size indicates that the control group had better adherence than the intervention group. See Figures 1 and 2 for stem-and-leaf plots of weighted effect sizes for primary and secondary outcome measures.

Figure 1

Weighted Effect Sizes for Primary Outcome Measures

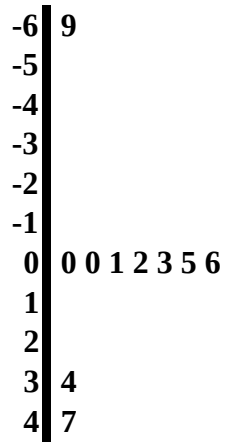
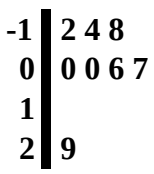


Figure 2

Weighted Effect Sizes for Secondary Outcome Measures



The study with proportion effect sizes (i.e., the study classified participants as adherent or nonadherent and the study did not employ a control group) utilized both primary and secondary outcome measures. The mean unweighted and weighted proportion effect sizes were .94 for primary outcome measures (95% confidence interval for mean weighted effect size: .90 to .96) and .95 for the secondary outcome measure (95% confidence interval for mean weighted effect size: .90 to .97) indicating that in this study, approximately 94% to 95% of participants were adherent to their medication regimen following an educational intervention. No further analyses were conducted for the logit proportion effect sizes because of the small number of studies in this category (i.e., one) and the fact that these effect sizes could not be transformed into Cohen's *d* effect sizes (Lipsey & Wilson, 2001).

Outliers

The distribution of the Cohen's *d* effect sizes was visually examined using stem-and-leaf plots to determine whether there were any outliers (greater than three standard deviations from the mean) that may unduly influence the analyses (Hedges & Olkin, 1985; Lipsey & Wilson, 2001). Inspecting stem and leaf plots of the weighted and unweighted effect sizes for primary and secondary outcome measures separately, there were no outlying effect sizes.

Primary Outcome Measures

Homogeneity analysis. The *Q* statistic for primary outcome measures (direct, indirect, and subjective measures of adherence) indicated that the study samples

included in the analysis are not homogenous, or that they do not share a common effect size, $Q_T = 109.72$, $p < .05$, $\chi^2(9) = 16.92$.

Analog to ANOVA. One factor that may have contributed to the heterogeneity is the type of intervention the study employed. The analog to ANOVA was used to compare educational interventions with all other interventions.[2] After partitioning the Q_T into the between-groups and within-groups variances, there was significant within-group heterogeneity ($Q_w = 42.59$, $p < .05$, $\chi^2(8) = 15.51$) and significant between-group heterogeneity ($Q_B = 67.13$, $p < .05$, $\chi^2(1) = 3.84$). Thus, there is a significant variability in effect sizes within the group of educational interventions and within the group of all other interventions. Meanwhile, these groups are also significantly different from one another.

Mean effect sizes by intervention type. The mean effect sizes, *Z*-tests, and 95% confidence intervals for each intervention type are presented in Table 2.

Table 2

Mean Unweighted Effect Sizes (UES) and Weighted Effect Sizes (WES) by Intervention Type

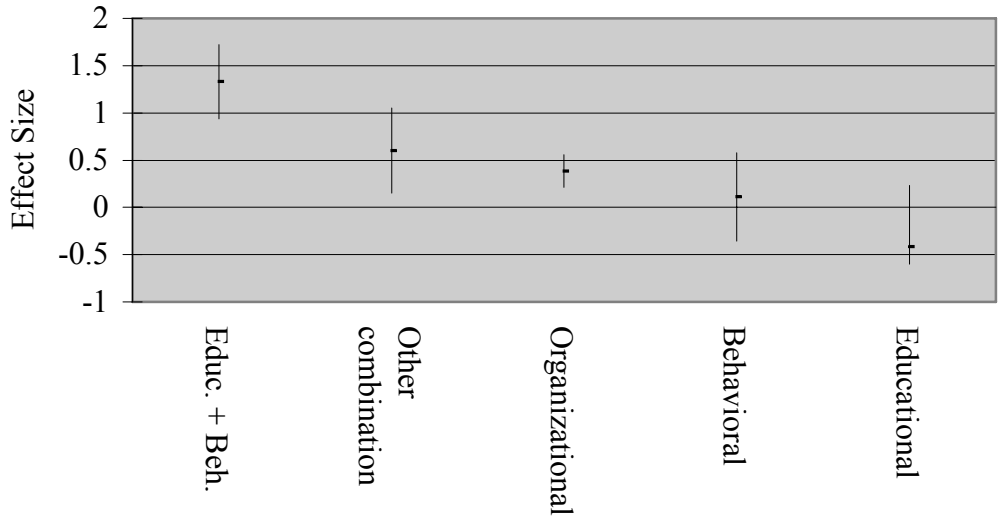
Intervention	N studies	Primary outcome measures					N studies	Secondary outcome measures				
		95% CI			*Z*-test	UES		95% CI			*Z*-test	UES
		LL	WES	UL				LL	WES	UL		
Educational	4	-0.60	-0.42	0.23	4.39	-0.10	4	-0.03	0.12	0.27	1.55	0.07
Behavioral	2	-0.36	0.11	0.58	0.44	0.13	2	-0.45	-0.07	0.30	0.38	0.07
Organizational	1	0.21	0.38	0.56	4.22	0.38	0		-		-	-
Educational & Behavioral	1	0.94	1.33	1.72	6.73	1.33	0		-		-	-
Other Combination	2	0.15	0.60	1.05	2.62	0.65	2	-0.12	0.21	0.54	1.27	0.17

Dashes (-) indicate that the intervention type was not used

See Figure 3 for a visual plot of mean weighted effect sizes and 95% confidence intervals.

Figure 3

Primary Outcome Measures:
Mean Weighted Effect Sizes with 95% Confidence Intervals



Mean unweighted effect sizes ranged from a large effect for the combination "educational and behavioral" interventions to a small effect in favor of the control group for educational interventions indicating that educational interventions did not increase adherence. There is also a large effect for the "other combination" interventions suggesting that these interventions successfully increase adherence to medication regimens. There are medium and small effects for organizational and behavioral interventions, respectively, indicating some success in increasing adherence, particularly for organizational interventions.

Mean weighted effect sizes ranged from a large effect for the combination "educational and behavioral" interventions to a medium effect of educational interventions favoring the control group, indicating that they did not successfully increase adherence. There was a large effect in favor of the "other combination" interventions suggesting that these interventions successfully increase adherence to medication regimens, and a medium effect for organizational interventions. The mean effect size for behavioral interventions was not statistically significant.

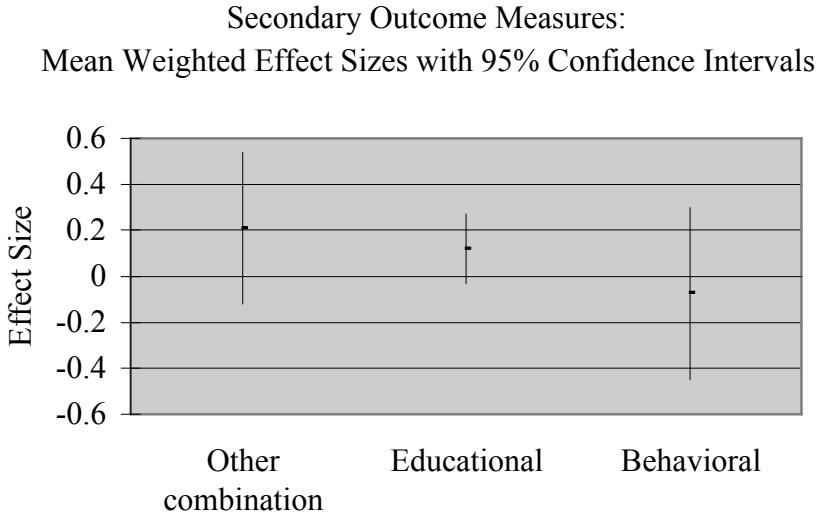
Secondary Outcome Measures

Homogeneity analysis. The Q statistic for secondary outcome measures (illness remission or follow-up appointment making or keeping) indicated that the study samples included in this analysis are not homogenous, $Q_T = 24.99$, $p < .05$, $\chi^2(7) = 14.07$.

Analog to ANOVA. Again, the analog to ANOVA was used to compare educational interventions with all other interventions. The results indicated that grouping the studies into educational interventions versus all other interventions did not successfully account for the heterogeneity in effect sizes, $Q_w = 24.74$, $p < .05$, $\chi^2(7) = 14.07$; $Q_B = .26$, *ns,* $\chi^2(1) = 3.84$. In other words, there was significant variability within the group of educational interventions and within the group of all other interventions. In addition, the mean effect sizes of the two groups were not reliably different.

Mean effect sizes by intervention type. The mean effect sizes, *Z*-tests, and 95% confidence intervals for each intervention type are presented in Table 2. See Figure 4 for a visual plot of mean weighted effect sizes and 95% confidence intervals.

Figure 4



The mean unweighted effect sizes for secondary outcome measures were small, with the "other combination" interventions superior to educational only and behavioral only interventions. The mean weighted effect sizes ranged from a small effect for behavioral interventions in favor of the control group to a small effect for "other combination" interventions. All mean weighted effect sizes, however, were not statistically significant as indicated by *Z*-tests.

Comparison of Adherence Measures

To determine mean effect sizes for each adherence measure, effect sizes were separated into direct, indirect, subjective, and secondary adherence measures. The

unweighted and weighted mean effect sizes, 95% confidence intervals, and *Z*-tests are presented in Table 3.

Table 3

Mean Weighted Effect Sizes (WES) and Unweighted Effect Sizes by Adherence Measure

Type of Adherence Measure	N studies	95% CI			*Z*-test	Unweighted Mean ES
		LL	WES	UL		
Direct	5	-0.66	-0.46	-0.25	4.45	0.00
Indirect	8	0.36	0.49	0.63	7.19	0.55
Subjective	2	0.18	0.33	0.49	4.16	0.20
Secondary	10	-0.02	0.11	0.24	1.69	0.09

Mean unweighted effect sizes ranged from a large effect for indirect measures to no effect for direct measures. Indirect measures showed the greatest change in adherence following intervention, followed by subjective measures and secondary measures. Mean weighted effect sizes ranged from a medium effect for indirect measures in favor of the treatment group to a medium effect for direct measures in favor of the control group, indicating that direct measures did not demonstrate an improvement in adherence for families receiving an intervention. All weighted mean effect sizes for type of adherence measure were statistically significant except for secondary outcome measures.

Exploratory Analyses

There were two types of secondary outcome measures employed in the reports: illness remission and follow-up appointment keeping or making. Effect sizes based on illness remission and those based on follow-up appointment making or keeping were analyzed separately. The mean unweighted effect sizes for illness remission and follow-up appointments were .17 and -.09, respectively. The mean weighted effect sizes were .12 (95% confidence intervals: -.01 to .24) and -.06 (95% confidence intervals: -.21 to .10), respectively, however the *Z*-tests (1.83 and .73, respectively) indicated non-statistically significant findings (i.e., $p > .05$).

Sensitivity Analyses

Excluding studies. Sensitivity analyses were completed to see if the results of effect size analyses changed when studies of streptococcal pharyngitis were excluded (two studies). Only one of the two studies had contributed to the effect size analyses. The study was included only in the secondary outcomes of adherence analyses. When this study was excluded from the homogeneity analysis, the results indicated the samples were homogenous, $Q_w = 10.55$, *ns,* $\chi^2(6) = 12.59$. The overall unweighted mean effect size was .02, the weighted mean effect size was -.02, the *Z*-test value was .22, and the 95% confidence interval was -.16 to .13. After excluding this study from the analog to ANOVA comparing educational interventions with the other interventions as a group, the mean effect size of the educational intervention changed considerably. Before excluding the study, the mean weighted effect size of the educational intervention was .12, and after excluding the study, the mean weighted

effect size was -.07 (*Z*-test = .77, 95% confidence interval: -.25 to .11). Similarly, when the two types of secondary outcome measures (illness remission and follow-up appointment making and keeping) were compared, the weighted mean effect size of the illness remission group changed considerably from .12 to 0.00 (*Z*-test = .02, 95% confidence interval: -.14 to .14). These mean effect sizes should be interpreted with caution because they were not statistically significant.

Another set of sensitivity analyses were completed excluding studies with an effect size coded 0 because non-significant results were reported (with no further statistical information) and study authors were unable to provide the raw data needed to calculate effect size statistics. When the three studies were excluded from the homogeneity tests for primary and secondary outcome measures, the results did not change. When the two studies that contributed to primary outcome analyses were excluded, the mean weighted effect size for behavioral interventions changed from .11 to .26 indicating a medium effect in favor of the treatment group when studies with non-significant results were excluded. Excluding the third study from comparisons of effect sizes across secondary outcome measures yielded a change in the mean weighted effect size for illness remission (from .12 to .27), again indicating a medium effect in favor of the treatment groups. No other results changed considerably after exclusion of the studies.

File-drawer analysis. A modification of Rosenthal's fail-safe sample size analysis was used to determine the number of "file-drawer" studies needed to reduce the mean weighted effect sizes for primary and secondary outcome measures to .04.

For primary outcome measures, the number of studies needed would be 33 and for secondary outcome measures, the number of studies needed would be 14. Given that only 13 reports were eligible for the current meta-analysis after a comprehensive search, it is unlikely that 14 or more studies remain "hidden."

Funnel plot. A lack of publication bias renders a funnel shape, such that larger sample sizes are associated with a narrow range in effect sizes and smaller sample sizes are associated with a wide range in effect sizes. Deviations from the funnel shape suggest the possibility of publication bias. For both plots, there is a range in effect sizes for larger sample sizes (see Figures 5 and 6).

Figure 5

Funnel Plot for Primary Outcome Measures

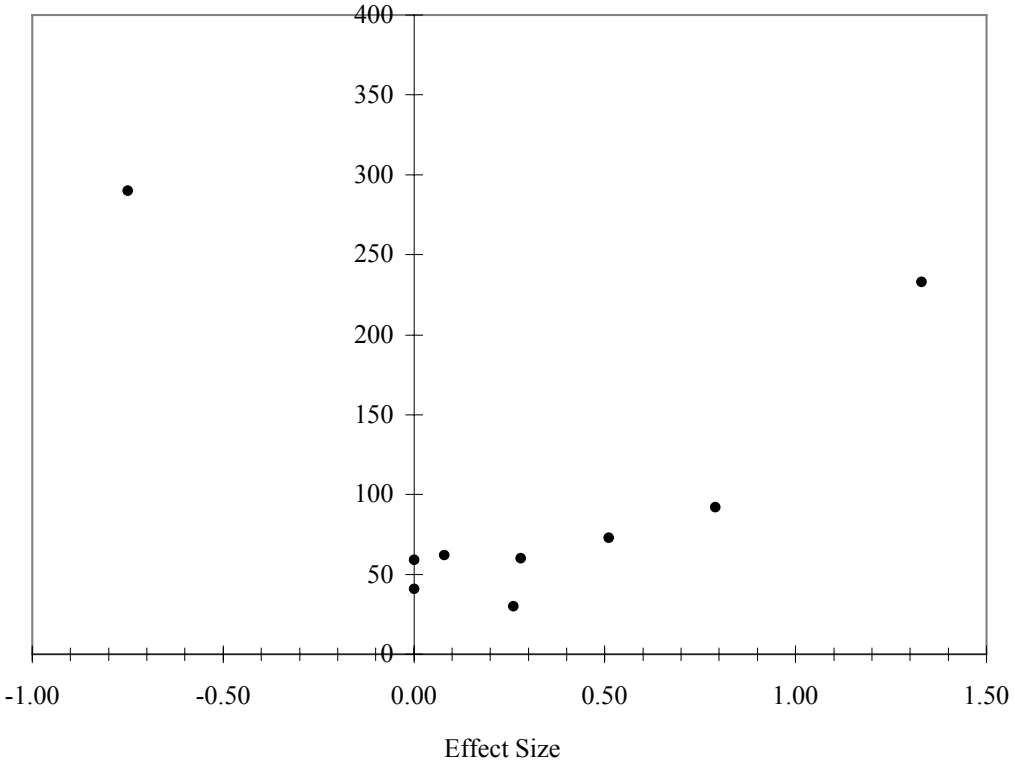
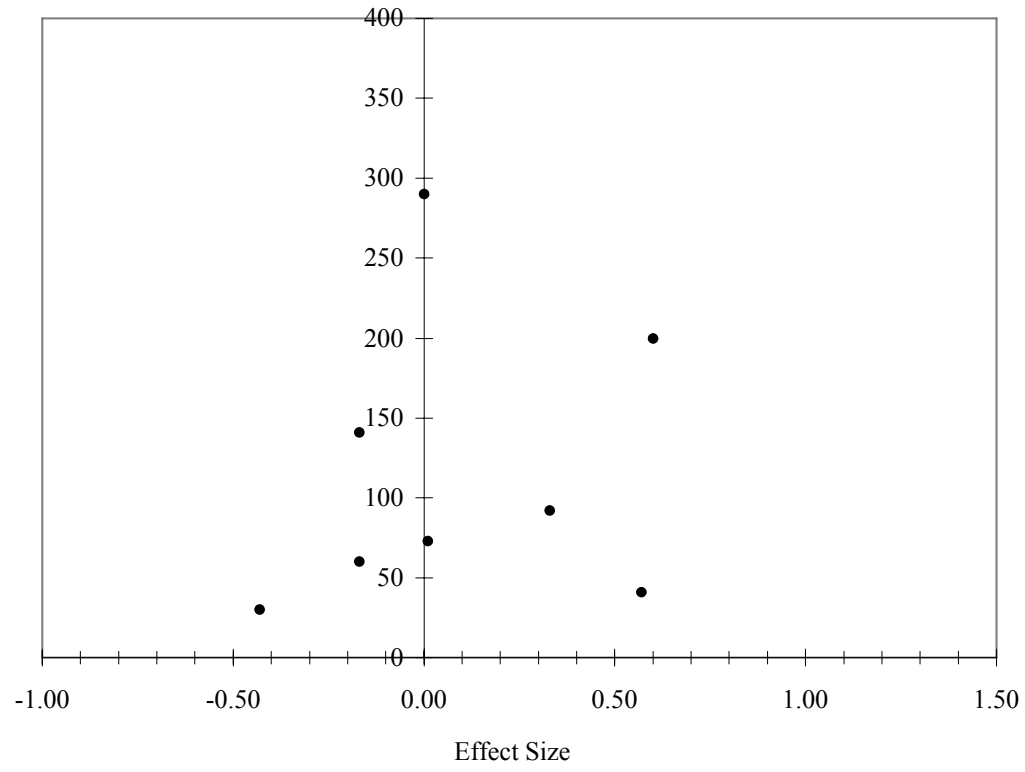


Figure 6

Funnel Plot for Secondary Outcome Measures



Although this suggests the possibility of publication bias, the non-funnel shape may also be an artifact of the small number of studies included in the meta-analysis (Lipsey & Wilson, 2001).

Binomial Effect Size Display (BESD)

The BESD provides the "real-world" significance of the effect size findings through a comparison of the treatment and control groups in terms of their "success rate" in improving adherence (Lipsey & Wilson, 2001). This comparison is based on the correlation effect size, which can be computed from Cohen's *d*. The success rates

for the groups are calculated as: .50 - *r*/2 for the control group and .50 + *r*/2 for the treatment group (Lipsey & Wilson, 2001). Because of the small sample sizes for all intervention types except educational interventions, the only BESD calculated was for educational interventions. For primary outcome measures, the BESD indicated that there is a 60% success rate in improving adherence for the control group and a 40% success rate in improving adherence for the treatment group (a 20% difference in favor of the control group). For secondary outcome measures, the BESD indicated that there is a 47% success rate in improving adherence for the control group and a 52% success rate for the treatment group (a 5% difference in favor of the treatment group).

Discussion

The results provided mixed support for the hypotheses regarding the effectiveness of interventions and the magnitude of adherence change indicated on outcome measures. On primary outcome measures, ill children and their families who received combination interventions, particularly the combined educational and behavioral intervention, had the best adherence. Similarly, previous reviews have indicated that combination interventions are more effective than single interventions (Roter et al., 1998).

Among the single interventions, families receiving organizational interventions demonstrated the best adherence outcome. In fact, families who received education alone demonstrated significantly worse adherence than control groups receiving treatment as usual. This is likewise reflected in the binomial effect

size display for educational interventions. The exception to these findings are the results of the study that was not included in the group analyses (due to an incompatible effect size type). This study indicated that approximately 94% of study participants were adherent to their medications following an educational intervention. However, there was no control group and the illness studied was streptococcal pharyngitis, whereas the majority of the other studies concerned otitis media. Previous meta-analyses of interventions for adults and children have also found no effect or a small effect for educational interventions (DiMatteo, 2004; Morrison & Wertheimer, 2004; Peterson, Takya, & Finley, 2003). In general, the mean weighted effect sizes by intervention type in the current meta-analysis were small to moderate, which confirms findings in previous reviews of interventions to increase medication adherence in adults and children (McDonald, Garg, & Haynes, 2002; Roter et al., 1998). However, mean weighted effect sizes in the current meta-analysis should be interpreted with caution given that heterogeneity was maintained after grouping by intervention type (educational interventions versus all other interventions).

The mean weighted effect sizes for secondary outcome measures were not statistically significant, perhaps due to the small sample sizes in each group. The binomial effect size display for secondary outcome measures indicated that families who received the educational intervention had a 5% higher success rate of better adherence than the control group. Unfortunately, because of the small number of studies, a limited number of statistical comparisons between intervention types could be made.

In comparing the four types of adherence measures (direct, indirect, subjective, and secondary), the results summarized previous findings that indirect measures of adherence showed the greatest change in adherence following intervention, particularly when compared with direct measures of adherence (DiMatteo, 2004; Roter et al., 1998). On direct measures of adherence such as urine assays, the control group had a significantly higher degree of medication adherence than the treatment group. This may be explained in part by attrition of families who did not return for follow-up appointments when urine assays were taken, and that families who returned for follow-up appointments may also have been motivated to adhere to the medication taking instructions.

Contrary to the results of a previous meta-analysis (Roter et al., 1998), the secondary outcome measures indicated that interventions did not have a statistically significant effect on adherence outcomes. This suggests that even if adherence is improved through intervention, health outcomes may not be affected. Further work is needed to elucidate the impact of adherence interventions on both short and long-term health outcomes.

The results of the sensitivity analysis excluding the study of streptococcal pharyngitis from the secondary outcome analyses suggest that some interventions might be less effective for otitis media and more effective for streptococcal pharyngitis. Specifically, when the streptococcal pharyngitis study was removed, the mean weighted effect size for educational interventions decreased. In addition, the results of the proportion effect size study indicated that following an educational

intervention, approximately 94% of children with streptococcal pharyngitis were adherent to medication regimens. Thus, educational interventions may be more effective for streptococcal pharyngitis than for otitis media. However, these results need to be interpreted with caution because the sensitivity analysis was based on the exclusion of one study alone, whose results could be spurious or outlying. As may be expected, the second sensitivity analysis excluding studies with an artifactual effect size of 0 resulted in higher mean effect sizes across analyses.

The results of the current meta-analysis should be interpreted with some limitations in mind. The 13 studies varied widely in terms of study design. For example, studies used different definitions of medication adherence (e.g., greater than 60% of medication taken versus greater than 80% of medication taken). Furthermore, "treatment as usual" varied between studies, and even interventions within the same category (e.g., educational) were different. These variations may account for some of the heterogeneity in the effect sizes. Unfortunately, because of the small number of studies eligible for inclusion in the meta-analysis, it was not possible to elucidate potential moderators of the heterogeneity. With additional research on adherence interventions for acute illness, future meta-analyses need to address potential moderators of adherence outcomes such as the use of random assignment, SES, attrition, and study setting so that health care provider and family factors related to adherence and the effectiveness of interventions for acute illnesses can be identified (Rapoff, 1999; Rapoff & Barnard, 1991). Unfortunately, only a subset of the studies

included in the meta-analysis provided information on potential moderators such as attrition and SES.

Although the possibility of sampling bias is always of concern for meta-analyses, Rosenthal's fail-safe sample size suggests that the current meta-analysis was not greatly affected by sampling bias. Definitive conclusions about sampling bias based on funnel plots cannot be made because of the small sample size, but it is encouraging that there were some negative effect sizes reported.

Despite these limitations, the results of the current meta-analysis are a quantitative synthesis of interventions to increase adherence for two common, childhood acute illnesses. Some interventions, particularly combination interventions, can be effective in increasing adherence, but may not improve health outcomes. However, because of the relatively small number of studies completed thus far, it is still inconclusive as to what interventions are the most effective and how interventions can be tailored to the needs of individual children and families. Interestingly, it appears that within the last two decades, research on interventions to increase adherence for otitis media and streptococcal pharyngitis has stopped. The problem of nonadherence, however, has not stopped and the rise of antibiotic-resistant bacteria emphasizes that renewed attention to adherence to medication regimens for acute illness is manifestly necessary. In order to facilitate the development of more effective interventions to increase adherence and ultimately improve health outcomes, a greater number of studies is needed and studies should more consistently report information such as demographics of participants and rates

of attrition so that future interventions can be better tailored to individual needs. Nevertheless, the current body of research provides some useful ideas for interventions to increase adherence in these and other acute pediatric illnesses, particularly those requiring short-term medication.

Footnotes

1. 1989 was chosen because it is the most recent publication date of a report included in the current meta-analysis. Three years beyond 1989 were also searched to see if relevant research was presented in conferences but not published during those years. Conference proceedings for 1989-1993 for the other three professional organizations were not available for manual or electronic searches.
2. All other types of interventions besides educational interventions had to be collapsed into one group because of small sample sizes (one or two reports) in each of the other intervention categories.

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Appendix A

Study Descriptor Coding Sheet

Study ID: _____ **Coded by:** _____

Type of Publication:

1) journal article	4) conference paper
2) book chapter	5) other (specify)
3) dissertation/thesis	

Publication Year: _____ (99: missing)

Illness: 1) otitis media 2) streptococcal pharyngitis

Mean age: _____ **Standard deviation age:** _____ (99: missing)

Final sample size (used for analyses): Tx _____ Control _____

- ***Beginning of study***
  Treatment group *n*: _____ Control group *n*: _____

- ***End of study***
  Treatment group *n*: _____ Control group *n*: _____

% attrition tx group: _____ % attrition control: _____

% White: _____ (99: missing)

Predominant Race:

1) greater than 60% White	5) greater than 60% Native American
2) greater than 60% Black	6) mixed, none more than 60%
3) greater than 60% Hispanic	7) mixed, cannot estimate proportion
4) greater than 60% Asian	99) cannot tell/not reported

Non-White groups represented:

_____

% Male: _____ (99: missing)

Primary socioeconomic status of study sample:

1) Lower class	3) Higher middle class
2) Lower middle class	4) Upper class

Assignment to experimental/control groups

1) random, after matching/stratification…	4) nonrandom, other (specify)
2) random, simple	5) other (specify)
3) nonrandom, posthoc matching	99) missing

Study design:

1) between-subjects
2) within-subjects
3) single-subject

Control group: _____

1) treatment as usual, no intervention	4) no control group
2) wait list, delayed intervention	5) alternative intervention: _____
3) attention placebo	99) missing

Setting of intervention:

1) primary care clinic (family practice)	4) phone
2) hospital	5) private practice
3) patient's home	99) missing

Interventions (circle all that apply)

Educational	***Organizational***
1) mail	11) increase accessibility to healthcare
2) home visits; explicitly educational	12) increase consumer friendliness
3) oral	13) health care provider phone contact
4) telephone education	14) change regimen to make adherence easier (e.g., simplify regimen)
5) visual	15) physician education
6) written	16) nurse education
7) tailored to individual needs	17) other: _____
8) audiovisual	***Behavioral***
9) computer program	18) Calendar
10) other: _____	19) Contracting or verbal agreement
	20) Demonstration dose
Other	21) Family problem-solving training
32) _____	22) Feedback
	23) Increased parental supervision
Intervention type	24) Memory aids (including stickers)
1) educational	25) Obtrusive pill count

2) behavioral	26) Pill boxes
3) organizational	27) Reminder (mail)
4) other (single intervention): _____	28) Reminder (telephone)
5) educational and behavioral	29) Rewards/consequences
6) other (combination): _____	30) Time-out
	31) Other: _____

How many times the intervention was given (by nurse, doctor, etc.):
_____

(99: missing)

Adherence outcome measures (circle all that apply)

1) assay (direct measure)	7) parent-report (subjective measure)
2) observational measure	8) provider rating (subjective measure)
3) health outcome/illness remission: including another prescription of antibiotics (secondary)	9) diary/record keeping (subjective meas.)
4) electronic measure (indirect measure)	10) appointment keeping (secondary)
5) pill count (indirect measure)	99) missing
6) child-report (subjective measure)	

Specify _____

Medication(s) used in study (circle all that apply)

1) penicillin	4) unspecified antibiotic
2) amoxicillin	99) other: _____
3) erythromycin & sulfisoxazole (Pediazole)	

Appendix B

Effect Size Coding Sheet

****Use one of these coding sheets per effect size in a study. (For example, a study with 3 adherence outcome measures will need at least 3 effect size coding sheets. You may need more than 3 effect size coding sheets if there are more than two groups in the study.)****

Coded by: _____

Study ID: _____ **Effect Size # (within *this* study):**

_____

This effect size compares:

_____

* list the groups that this ES compares

Effect size type:
1) post-test comparison

2) other _____

Outcome Measure this ES captures:

_____

Type of statistical information presented in the report:

1) means, standard deviations	5) frequencies or proportions, polychotomous
2) *t* or *F* or *r*	6) other (specify): _____
3) chi-square	99) missing
4) frequencies or proportions, dichotomous	

Page number for effect size statistics: _____

Raw difference favors OR if no raw difference provided (no means provided), circle the group that does better as reported in the study:

1) treatment group A	3) control group A
2) treatment group B	4) control group B
99) missing	5) none

For all items below, if the information is not available in the report, code 99:

If means/standard deviations (SD) reported:

_____ Treatment group A sample size _____ Control group A sample size

_____ Treatment group A mean _____ Control group A mean

_____ Treatment group A SD _____ Control group A SD

_____ Treatment group B sample size _____ Control group B sample size

_____ Treatment group B mean _____ Control group B mean

_____ Treatment group B SD _____ Control group B SD

If proportions/frequencies can be estimated:

_____ *n* of treatment group A with successful outcome

_____ proportion of treatment group A with successful outcome

_____ *n* of treatment group B with successful outcome

_____ proportion of treatment group B with successful outcome

_____ *n* of control group A with successful outcome

_____ proportion of control group A with successful outcome

_____ *n* of control group B with successful outcome

_____ proportion of control group B with successful outcome

If other statistics are reported:

_____ *t*-value _____ *p*-value

_____ *r*-value _____ *p*-value

_____ *F*-value _____ *p*-value

_____ chi-square value _____ *p*-value

Were the results reported statistically significant?
1) Yes 2) No

Significance level (p-value): _____

Calculated effect size (by hand or Excel program): _____

Appendix C

Formulas

Logit odds ratio effect size:

$ES_{LOR} = \ln(ad/bc)$

	Frequencies	
	Success	Failure
Treatment Group	*a*	*b*
Control Group	*c*	*d*

Cohen's *d* effect size:

$$\mathbf{d} = \frac{\bar{X}_1 - \bar{X}_2}{s_p} \qquad s_{pooled} = \sqrt{\frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}}$$

Logit proportion effect size:

$ES_l = \ln [p/(1-p)]$ p = proportion of subjects in category of interest
n = total number of subjects

Standard error of the effect size:

For logit odds ratio

$$se = \sqrt{(1/a)+(1/b)+(1/c)+(1/d)}$$

For Cohen's *d*

$$se = \sqrt{[(n_1+n_2)/n_1n_2] + ES^2/[2(n_1+n_2)]}$$

For logit proportion

$$se = \sqrt{(1/np) + 1/[n(1-p)]}$$

Weighting the effect size:

$$w = \frac{1}{se^2}$$

Weighting for logit proportion effect size:

$w = np(1-p)$

Weighted mean effect size:

$$\overline{ES} = \frac{\sum(w \times ES)}{\sum w}$$

Standard error of the mean effect size:

$$se = \sqrt{1 / \sum w}$$

Homogeneity (*Q)* statistic:

$$Q = \sum(w \times ES^2) - \frac{[\sum(w \times ES)]^2}{\sum w}$$

Z-test for the Mean ES:

$$Z = \overline{ES} / se$$

95 % confidence interval for Mean ES:

$$Lower = \overline{ES} - 1.96(se)$$
$$Upper = \overline{ES} + 1.96(se)$$

Fixed effects model analog to ANOVA:

Within group homogeneity

$Q_W = Q_{Group\_1} + Q_{Group\_2}$ $\quad df = k - j$ $\quad k$ = number of effect sizes, j = number of groups

Between group homogeneity:

$Q_B = Q_T - Q_W$ $\quad df = j - 1$ $\quad Q_T$ = full group Q statistic