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

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Objective The current study quantitatively synthesized 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. Methods Meta-analysis was used to synthesize the results of 12 interventions to increase medication adherence in pediatric otitis media and streptococcal pharyngitis. Effect sizes were analyzed using homogeneity tests and an analog to the analysis of variance. Results 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. Conclusions 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.

Key words acute illness; adherence; intervention; medication; meta-analysis.

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 (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% (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. There is a large and growing literature on adherence to medication regimens for chronic illness, which has been comprehensively summarized elsewhere (Rapoff, 1999). Although chronic illnesses were not the focus of the current study, researchers should bear in the mind that interventions shown to be effective with chronic illnesses may generalize to adherence problems for acute illnesses as well.

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. As Rapoff (1999) outlined in a review of adherence interventions, interventions relevant to acute illnesses such as otitis media can be categorized as: (a) educational, (b) behavioral, or (c) 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). For example, a doctor may provide a family with a handout explaining the dosing schedule for the medication and the reasons for adhering to this schedule. Behavioral interventions provide families with methods for remembering to take medication and methods of addressing children’s refusal to take medication. For example, health care providers may teach families how to use time-out with children who refuse to take medication. 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. For example, a doctor’s office may provide a phone number families can call if they have difficulty in administering medication to their children (Cramer, 1991; Rapoff, 1999). Combinations of these three types of interventions may be used as well.

Measuring Adherence

As noted by Rapoff (1999), there are numerous ways to measure adherence to evaluate the effectiveness of interventions: direct measures (e.g., urine assays), indirect measures (e.g., pill counts), subjective measures (e.g., provider or patient estimate of adherence), and secondary measures (e.g., health outcome or attending a follow-up appointment). Because each measurement of adherence has benefits and drawbacks, there is currently no agreed-upon gold standard (Quittner, Espelage, Ievers-Landis, & Droter, 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 (Arnhold et al., 1970; Becker, Drachman, & Kirscht, 1972). The current study focused on the acute illnesses of pediatric otitis media and streptococcal pharyngitis for four reasons. First, adherence intervention research for pediatric acute illnesses has most often focused on these two illnesses (Rapoff, 1999). Second, these illnesses occur frequently in children; for example, acute otitis media is the most common pediatric bacterial infection in the US (Leibovitz, 2003), affecting 75% of children by the age of three (National Institute on Deafness and Other Communication Disorders, 2007). Third, 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). Fourth, 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 might 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 (Costello, Wong, & Nunn, 2004; Roter et al., 1998) although 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 medication adherence for specific acute illnesses and whether estimates of adherence differ depending on the method of measurement.

Method

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, and GoogleScholar. Searches in each database consisted of combinations of keywords 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. Together, these search terms produced 18 unique
combinations and each database was searched using them.

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. Second, if available, “forward searches” were conducted to identify reports that were published subsequent to and cite the initially found reports. Third, available conference proceedings for the years 1989 to 1993 and 2000 to 2007 for the following professional organizations were electronically or manually searched for relevant presentations, because oftentimes conference presentations are not subsequently published: The Society of Behavioral and Developmental Pediatrics (2006), Pediatric Academic Societies (1989–1993, 2000–2006), and the American Society of Pediatric Otolaryngology (2000–2002, 2005–2006). The year 1989 was chosen because it is the most recent publication date of a published report resulting from the electronic database literature searches. In addition, the years 2000 to 2007 were chosen to determine whether there were any reports in recent years concerning adherence interventions for these two illnesses.

Inclusion in the Meta-analysis

The meta-analysis included eligible reports from the inception of the databases through May 2007. 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 (ES) 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 ES of zero could be assigned based on a report of “non-significant results,” (g) if study participants included both adults and children, there was a way to calculate ES for the children alone, and (h) there was a comparison group. Comparison groups either did not receive an intervention or received an attention placebo (e.g., receiving education on the importance of wearing seatbelts).

Coding Procedures

Two coders, one of whom was the principal investigator, recorded intervention, adherence, study descriptor, and ES information for each report that met criteria for inclusion in the meta-analysis. Interventions to increase adherence to medication regimens were 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. 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 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 (SES)], (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.

Similar to procedures used in other meta-analyses (LeBlanc, Janowsky, Chan, & Nelson, 2001), coders resolved discrepancies through discussion, and the consensus rating was used for study analyses. Interrater reliability coefficients were calculated for coders’ independent ratings before discussion. All reliability analyses were computed using SPSS 11.0. Interrater reliability for categorical variables (κ = .88) and continuous variables (r = .99) was high.

Results

ES Estimates

Due to variations in study design across reports, logit odds ratio and Cohen’s d ES were calculated. Logit odds ratio ES were then converted to Cohen’s d ES so studies could be analyzed as a group.1 When more than one ES could be calculated for a given report, ES for a given study were averaged to maintain independence (Durlak, 2005; Lipsey & Wilson, 2001) and ES were weighted such that studies with larger sample sizes received greater weight in the analyses (see Table I for study ES).2 There were no outlying study ES (greater than three standard

1Converting the logit ES to Cohen’s d, a standardized mean difference ES: \( d = ES_{LOD}/1.83 \).

2Weighting the standardized mean difference ES entails multiplying the ES by its corresponding weight (w): \( w = 1/se^2 \)

\( se = \sqrt{(n_1 + n_2)/n_1 n_2 + ES^2/[2(n_1 + n_2)]} \) (Lipsey & Wilson, 2001)
deviations from the mean) that may have unduly influenced the analyses (Lipsey & Wilson, 2001).

**Homogeneity Analysis**

A homogeneity analysis using the Q-statistic determined whether the ES represented effects observed within the same population (Lipsey & Wilson, 2001). If the homogeneity analysis indicated heterogeneous ES, the analog to an analysis of variance (ANOVA; Hedges, 1982) was used to determine whether effectiveness in increasing adherence differed by intervention type. In the analog to ANOVA method, the Q-statistic is separated into two components: a Q-between, representing the variance in ES accounted for by intervention type, and a Q-within, representing the within-group error. If the Q-between is statistically significant and the Q-within is not significant, intervention type successfully accounts for the heterogeneity in ES (Lipsey & Wilson, 2001).

**Description of Reports**

Out of the 6,058 reports identified in the five electronic databases, 12 met criteria for inclusion in the meta-analysis (11 concerning otitis media and 1 concerning streptococcal pharyngitis). Excluded reports often addressed medical providers’ adherence to antibiotic-prescribing guidelines or basic science research on the effectiveness of antibiotics. All included reports were journal articles published between the years of 1972 and 1989 (median year published = 1986). Searches of conference proceedings yielded no eligible reports. Together, the 12 studies included 1,793 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 eight studies that reported sample attrition, the average rate of attrition was 19.2%. 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’ SES was reported in only three of the reports and none of the reports listed a complete SES breakdown.

**Study Design**

All studies took place in primary care clinics. Ten of the studies used random assignment to assign study participants to treatment or comparison groups and two studies used nonrandom assignment. For the comparison group, 10 of the studies used treatment as usual and two studies used an attention placebo. Six of the 12 studies employed an educational intervention (e.g., explaining to families and providing them with a handout about how to administer the medication and the importance of adhering to the medication regimen), two employed a behavioral intervention (e.g., asking patients to verbally agree to adhering to the medication regimen and giving patients a syringe for medication administration), one employed an organizational intervention (educating physicians on patient medication nonadherence and techniques to increase their adherence), one employed a combination of educational and behavioral interventions (educating families about adherence and providing them with a calendar to support on-time medication administrations), and two employed other combinations of interventions. One “other combination” intervention consisted of educational and organizational interventions, specifically providing patients with information about the

### Table I. ES for Primary and Secondary Outcome Measures of Adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Unweighted ES</th>
<th>Weighted ES</th>
<th>Unweighted ES</th>
<th>Weighted ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colcher and Bass (1972)</td>
<td>200</td>
<td>–</td>
<td>–</td>
<td>0.60</td>
<td>28.72</td>
</tr>
<tr>
<td>Mattar, Markello and Yaffe (1975)</td>
<td>233</td>
<td>1.33</td>
<td>34.05</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ellison and Altemeier (1982)</td>
<td>30</td>
<td>0.26</td>
<td>1.83</td>
<td>–0.43</td>
<td>−7.60</td>
</tr>
<tr>
<td>Reed, Lutz, Zazove, and Ratchlfe (1984)</td>
<td>290</td>
<td>−0.75</td>
<td>−50.73</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Casey, Rosen, Glowasly and Ludwig (1983)</td>
<td>92</td>
<td>0.79</td>
<td>5.22</td>
<td>0.33</td>
<td>7.45</td>
</tr>
<tr>
<td>Finney, Friman, Rapoff and Christophersen (1985)</td>
<td>73</td>
<td>0.51</td>
<td>6.27</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Williams et al. (1986)</td>
<td>60</td>
<td>0.28</td>
<td>3.41</td>
<td>−0.17</td>
<td>−2.49</td>
</tr>
<tr>
<td>Bertalik (1986)</td>
<td>59</td>
<td>0.00</td>
<td>0.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kulik and Carlino (1987)</td>
<td>41</td>
<td>0.00</td>
<td>0.00</td>
<td>0.57</td>
<td>5.59</td>
</tr>
<tr>
<td>Maiman, Becker, Liptak, Nazarian and Rounds (1988)</td>
<td>512</td>
<td>0.38</td>
<td>46.56</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Schwartz-lookinland, McKeever and Saputo (1989)</td>
<td>62</td>
<td>0.08</td>
<td>1.22</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Williams (1989)</td>
<td>141</td>
<td>–</td>
<td>–</td>
<td>−0.17</td>
<td>−6.05</td>
</tr>
</tbody>
</table>

Dashes (–) indicate an ES could not be calculated.
importance of adherence and calling patients two times before their next appointment. The second “other combination” intervention included educating families about the importance of adherence (educational intervention), providing families with a calendar to record medication administrations (behavioral intervention), and calling families before the next appointment to remind them of the importance of adherence (organizational intervention). The majority of the studies used one-time interventions. Nine out of the 12 studies used at least two measures of adherence, and four studies used three or more measures of adherence.

**Primary Outcome Measures of Adherence**

Primary outcome measures of adherence were direct, indirect, and subjective measures of adherence. The Q-statistic for primary outcome measures indicated that the study samples included in the analysis were not homogenous, or that they did not share a common ES, $Q_T = 109.72$, $p < .05$, $\chi^2 (9) = 16.92$.

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, which had to be collapsed into one group because of small sample sizes (one or two reports) in each of the other intervention categories. 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 was significant variability in ES within the group of educational interventions and within the group of all other interventions. Meanwhile, these groups were also significantly different from one another.

**Mean ES by Intervention Type**

The mean ES, Z-tests, and 95% CIs including the lower limit (LL) and upper limit (UL) for each intervention type are presented in Table II. Mean weighted ES 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 increased adherence to medication regimens, and a medium effect for organizational interventions.

**Secondary Outcome Measures of Adherence**

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 were not homogenous, $Q_T = 24.99$, $p < .05$, $\chi^2 (7) = 14.07$, meaning that they did not share a common ES.

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 ES, $Q_w = 24.74$, $p < .05$, $\chi^2 (7) = 14.07$; $Q_B = .26$, $ns$, $\chi^2 (1) = 3.84$. 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 ES of the two groups were not reliably different.

**Mean ES by intervention type**

The mean ES, Z-tests, and 95% CIs including the LL and UL for each intervention type are presented in Table II. All mean weighted ES, however, were not statistically significant as indicated by Z-tests.

**Comparison of Adherence Measures**

The mean unweighted and weighted ES, 95% CIs including the LL and UL, and Z-tests for the four types of adherence measures are presented in Table III. Mean weighted ES 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 ES for type of adherence measure were statistically significant except for secondary outcome measures.

**Publication Bias**
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 ES 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 12 reports were eligible for the current meta-analysis after a comprehensive search, it is unlikely that 14 or more studies remain “hidden” (Lipsey & Wilson, 2001).

**Discussion**
The results indicate that some interventions are effective in increasing medication adherence for pediatric otitis media and streptococcal pharyngitis. 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. Previous meta-analyses of interventions for adults and children have similarly found no effect or a small effect for educational interventions (DiMatteo, 2004; Morrison & Wertheimer, 2004; Peterson, Takiya, & Finley, 2003). The finding that educational interventions are not effective when used alone is particularly notable given the widespread use of educational interventions, especially in pediatric primary care settings. Educational interventions are easy to implement, but their efficacy as the sole intervention to increase medication adherence is not yet established. The current results suggest that combination interventions (e.g., education and behavioral interventions) are more effective in increasing adherence to medication regimens for pediatric acute illness. Clinicians and researchers need to better disseminate and implement effective combination interventions (Rapoff, 1999).

In general, the mean weighted ES by intervention type in the current meta-analysis were small to moderate, which confirms previous findings for adults and children (McDonald, Garg, & Haynes, 2002; Roter et al., 1998). However, mean weighted ES in the current meta-analysis should be interpreted with caution given that heterogeneity was maintained after grouping by intervention type (educational interventions vs. all other interventions). Examining the mean weighted ES within a particular category of interventions (e.g., organizational) may provide guidance as to the more effective interventions; however, these types of comparisons are confounded by differences in definitions of adherence and measures used to assess adherence across studies. Unfortunately, because of the small number of studies, statistical comparisons between all intervention types could not 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. Perhaps accounting for the difference in adherence between these methods of measurement is that each adherence measure assesses different aspects of adherence. For example, direct assays may be better measures of short-term adherence over a few days while indirect measures may be better measures of adherence over a longer period of time. Future research should address the relationships and differences between these methods of measurement.

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

<table>
<thead>
<tr>
<th>Type of Adherence Measure</th>
<th>N studies</th>
<th>LL WES UL</th>
<th>Z-test</th>
<th>UES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>5</td>
<td>-0.66 -0.46 -0.25</td>
<td>4.45</td>
<td>0.00</td>
</tr>
<tr>
<td>Indirect</td>
<td>8</td>
<td>0.36 0.49 0.63</td>
<td>7.19</td>
<td>0.55</td>
</tr>
<tr>
<td>Subjective</td>
<td>2</td>
<td>0.18 0.33 0.49</td>
<td>4.16</td>
<td>0.20</td>
</tr>
<tr>
<td>Secondary</td>
<td>10</td>
<td>-0.02 0.11 0.24</td>
<td>1.69</td>
<td>0.09</td>
</tr>
</tbody>
</table>
significant effect on adherence outcomes. This finding 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 current meta-analysis should be interpreted with some limitations in mind. The 12 studies varied widely in terms of study design and these variations may account for some of the heterogeneity in the ES. For example, studies used different definitions of medication adherence (e.g., > 60% of medication taken vs. > 80% of medication taken). Unfortunately, due to the small number of studies eligible for inclusion in the meta-analysis and inconsistent reporting of sample characteristics, it was not possible to elucidate other potential moderators of the heterogeneity (e.g., use of random assignment, SES of participants, attrition, and study setting). 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.

Despite the 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 how interventions differ in their effectiveness 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 suggestions of methods to increase adherence in these and other acute pediatric illnesses, particularly those requiring short-term medication.

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Conflicts of interest: None declared.

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References


References marked with an asterisk indicate studies included in the meta-analysis.