Time-Lag Bias in Trials of Pediatric Antidepressants: A Systematic Review and Meta-Analysis

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Objective: To determine whether there is evidence of a time-lag bias in the publication of pediatric antidepressant trials. **Method:** We conducted a meta-analysis of published and unpublished randomized placebo-controlled trials of serotonin reuptake inhibitors (SRIs) in subjects less than 18 years of age with major depressive disorder. Our main outcomes were (1) time to publication of positive versus negative trials, and (2) proportion of treatment responders in trials with standard (<3 years after study completion) versus delayed publication. **Results:** We identified 15 randomized, placebo-controlled trials of SRIs for pediatric depression. Trials with negative findings had a significantly longer time to publication (median years ± standard deviation = 4.2 ± 1.9) than trials with positive findings (2.2 ± 0.9; log-rank $\chi^2 = 4.35$, $p = .037$). The estimated efficacy in trials with standard publication time (number needed to treat = 7, 95% CI = 5–11) was significantly greater than those with delayed publication (17, 95% CI = 9–∞; $\chi^2 = 4.98$, $p = .025$). The inflation-adjusted impact factor of journals for published trials with positive (15.33 ± 11.01) and negative results (7.54 ± 7.90) did not statistically differ ($t = 1.4$, $df = 10$, $p = .17$). **Conclusions:** Despite a small number of trials of SRIs for pediatric antidepressants, we found a significant evidence of time-lag bias in the publication of findings. This time-lag bias altered the perceived efficacy of pediatric antidepressants in the medical literature. Time-lag bias is not unique to child psychiatry and reflects a larger problem in scientific publishing. J. Am. Acad. Child Adolesc. Psychiatry, 2011; 50(1):63–72. **Key words:** publication bias, antidepressant agents, serotonin reuptake inhibitors, meta-analysis, child and adolescent psychiatry

Publication bias is a well-described form of bias that can affect the estimated efficacy of interventions.[1,2] Publication bias occurs when studies with positive results are published more frequently than those with unfavorable findings, thus creating an overrepresentation of efficacious findings in the medical literature.[3] For example, previous research demonstrated that only 51% of the antidepressant trials registered with the US Food and Drug Administration (FDA) had been positive.[4] By contrast, as many as 94% of trials published in the peer-reviewed literature evaluating antidepressant agents were positive.[4] A meta-analysis published in 2004 suggested that this type of bias may have affected our estimates of the risk/benefit profile of antidepressant use in children.[5] A larger meta-analysis conducted after the publication of several trials subsequent to the FDA Black Box Warning indicated that this effect of publication bias may have dissipated.[6] The problem of publication bias is by no means unique to psychiatry. A recent systematic review in the field of internal medicine suggests that trials with positive results were nearly twice as likely to be published compared with trials with negative results.[7]

Time-lag bias is another form of bias that can also affect perceived efficacy of interventions, although it has been much less well studied in the scientific literature. Time-lag bias occurs when the results of negative trials take substantially longer to publish than positive results of trials.[8] For example, one study assessing efficacy trials of human immunodeficiency virus (HIV) treatments concluded that the time from study enrollment to publication was significantly longer for negative trials than that for positive trials.[9] Likewise, of the phase 3 randomized con-

trolled trials presented at the annual American Society of Clinical Oncology meetings, as many as 81% of those with positive findings were published within 5 years of presentation, whereas only 68% of negative trials were published within this time period.[10] Individual medical practices are potentially vulnerable to research results that are readily disseminated and accessible to clinicians. Time-lag bias is a particularly important form of bias that creates an environment in which treatments may be inaccurately portrayed as efficacious in a shorter period of time, amid the existence of negative, although not yet published, data.

To our knowledge, there have been no studies investigating time-lag bias in the child psychiatry literature. The purpose of this study was to examine time-lag bias in pediatric antidepressant trials. We examined published and unpublished randomized controlled trials of serotonin reuptake inhibitors (SRIs) for the treatment of major depressive disorder in children and adolescents to determine the following: (1) whether time-lag bias existed (i.e., whether negative antidepressant trials took significantly longer to be published than positive trials); (2) whether time-lag bias affected estimates of the efficacy of SRIs in the treatment of pediatric depression; and (3) whether trials with positive results were published in higher impact journals than trials with negative findings.

METHOD

Search Strategy for Identification of Studies

Two reviewers (M.M.R. and K.E.P.) searched PubMed (between June 2009 and July 2009) for relevant studies using the search strategy: (serotonin uptake inhibitors (MeSH) or SSRI or citalopram or duloxetine or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or venlafaxine) AND (depressive disorders (MeSH) or depress* or dysthymi*). The search was further limited to randomized, placebo-controlled clinical trials, meta-analyses, and reviews involving children and adolescents (0–18 years). Randomized clinical trials were examined for eligibility for inclusion in this meta-analysis. The references of included articles, as well as review articles and meta-analyses in this area, were searched for citations of further relevant published and unpublished research. We further searched the FDA Center for Drug Evaluation and Research online database on approved drug products (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA) for additional trials in "Approval History, Letters, Reviews, and Related Documents" related to medications included in this review. To identify additional eligible trials, we also searched the U.S. National Institutes of Health (NIH) clinical trials database (http://www.clinicaltrials.gov), searching with the following search terms: serotonin uptake inhibitors or SSRI or citalopram or duloxetine or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or venlafaxine combined with interventional studies, age group: child, and depression or dysthymia.

Selection of Studies

The titles and abstracts of studies obtained by this search strategy were scrutinized by two reviewers (M.M.R. and K.E.P.) to determine whether these publications were potentially eligible for inclusion in this review. Eligibility for the study was based upon scrutiny of the full articles for the following inclusion criteria: (1) they were randomized, clinical trials comparing an SSRI or serotonin-norepinephrine reuptake inhibitors (SNRI; duloxetine or venlafaxine) with placebo in the treatment of depression symptoms; and (2) participants included were children and adolescents less than 18 years of age. The studies were excluded if they were unpublished, compared our antidepressants of interest with another active medication (i.e., another antidepressant agent, mood stabilizer, antipsychotic agent or stimulant), or if they were discontinuation studies. We also excluded placebo-controlled trials of other antidepressant agents such as 5-HT2 antagonists (mirtazapine, trazadone, or nefazodone), tricyclic antidepressants, monoamine oxidase inhibitors, and bupropion to eliminate as much noise from heterogeneity of effect between agents as possible.

Data Analysis: Meta-Analytic Procedure

Our first a priori analysis was whether time to publication differed between trials with positive versus negative outcomes. A trial was considered positive when any of the primary outcomes defined in the study manuscript demonstrated a statistically significant benefit of a medication compared with placebo. We used the Kaplan–Meier life-table method of survival analysis to analyze these results using the LIFETEST procedure command in SAS 9.2. Time to publication was computed in months by subtracting publication date of a manuscript from the date of study completion. The date of study completion was identified from date reported (in order of preference) from the following: (1) published manuscript, (2) FDA report,[11] (3) NIH clinical trials online database study completion date (http://www.clinicaltrials.gov), (4) FDA Center for Drug Evaluation and Research online database (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA), (5) company Web site, or (6) correspondence with the primary author or principal investigator of a study.