Systematic Review and Meta-Analysis: Early Treatment Responses of Selective Serotonin Reuptake Inhibitors in Pediatric Major Depressive Disorder

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological treatment for pediatric major depressive disorder (MDD). We conducted a meta-analysis to examine the following: the time-course of response to SSRIs in pediatric depression; whether higher doses of SSRIs are associated with an improved response in pediatric depression; differences in efficacy between SSRI agents; and whether the time-course and magnitude of response to SSRIs is different in pediatric and adult patients with MDD.

Method: We searched PubMed and CENTRAL for randomized controlled trials comparing SSRIs to placebo for the treatment of pediatric MDD. We extracted weekly symptom data from trials to characterize the trajectory of pharmacological response to SSRIs. Pooled estimates of treatment effect were calculated based on standardized mean differences between treatment and placebo groups.

Results: The meta-analysis included 13 pediatric MDD trials with a total of 3,004 patients. A logarithmic model indicating that the greatest benefits of SSRIs occurred early in treatment best fit the longitudinal data (log [week] = 0.10, 95% CI = 0.06–0.15, $p < .0001$). There were no significant differences based on maximum SSRI dose or between particular SSRI agents. SSRIs were demonstrated to have a smaller benefit in pediatric compared to adult MDD.

Conclusion: Treatment gains in pediatric MDD are greatest early in treatment and are, on average, minimal after 4 weeks of SSRI pharmacotherapy in pediatric MDD. Further research is needed using individual patient data to examine the power of early SSRI response (e.g., 2–4 weeks) to predict outcomes in short-term pharmacological trials.

Key Words: MDD, meta-analysis, serotonin reuptake inhibitors

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Pediatric depression affects roughly 3% of children and 8% of adolescents.[1] The lifetime prevalence of major depressive disorder (MDD) is estimated to be around 15%.[2-4] Selective serotonin reuptake inhibitor (SSRI) pharmacotherapy is a commonly used treatment intervention that is currently a recommended first-line treatment option in moderate-to-severe pediatric depression. Supportive and more specialized forms of psychotherapy (cognitive-behavioral therapy [CBT] and interpersonal therapy) remain other useful treatment options that may be preferred to or used in combination with selective serotonin reuptake inhibitors (SSRIs) for the treatment of pediatric depression.

Systematic reviews and meta-analyses regarding SSRI pharmacotherapy in pediatric depression have been common.[5-9] These meta-analyses have demonstrated that SSRI pharmacotherapy is effective for pediatric depression. SSRIs as a class provide around a 25% greater chance of responding over the short-term when compared to placebo and have a number needed to treat (NNT) of 10.[6,8] Meta-analysis of response rates in pediatric antidepressant trials are high (61%), but so is the response rate to placebo (50%).[8] Systematic reviews have demonstrated that treatment estimates of SSRI efficacy were previously exaggerated by publication bias and time-lag bias in the distribution of negative trial results.[5,9]

Regarding the use of SSRIs in pediatric depression, the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter recommends that "patients should be treated with adequate and tolerable doses for at least 4 weeks.[2] Clinical response should be assessed at 4-week intervals, and if the child has tolerated the antidepressant, the dose may be increased if a complete response has not been obtained.[10,11] At each step, adequate time should be allowed for clinical response, and frequent, early dose adjustments should be avoided. However, patients who are showing minimal or no response after 8 weeks of treatment are likely to need alternative treatments. Furthermore, by about 12 weeks of treatment, the goal should be remission of symptoms, and in youths who are not remitted by that time, alternative treatment options may be warranted."[2] These AACAP recommendations mimic American Psychiatric Association (APA) Practice Guidelines in adults with MDD.[12]


Clinical guidance is available at the end of this article.


Supplemental material cited in this article is available online.

Despite the plethora of systematic reviews and meta-analyses in the area of pharmacotherapy for pediatric depression, several important clinical questions that affect practice guidelines have not been answered sufficiently with evidence-based data. Important clinical questions include the following: how quickly SSRIs typically work in pediatric depression; whether higher doses of SSRIs are more efficacious in treating pediatric depression; and whether pediatric patients and adults with depression exhibit different treatment responses to SSRIs. A similarly conducted meta-analysis performed in adults with MDD found that SSRIs begin to have significant beneficial effects compared to placebo in depression after the first week of treatment. Furthermore, more than three-fourths of the treatment gains observed in adult SSRI trials are evident within the first month of treatment.[13] Meta-analyses examining the dose–response relationship of SSRIs in adult MDD have been equivocal.[14,15] To our knowledge, no such analyses of weekly treatment responses to SSRIs have been performed in the pediatric population. A meta-analysis examining longitudinal treatment response within existing placebo-controlled SSRI trials could potentially answer these questions with data.

The objective of this meta-analysis is to examine weekly treatment response data in pediatric MDD trials to examine the course and magnitude of treatment response to SSRIs in pediatric depression, and to clarify whether higher doses are more effective than lower doses in pediatric MDD. We also compare the longitudinal trial data of SSRIs in pediatric and adult depression to determine whether the magnitude and course of SSRI response is different with age.

METHOD

Search Strategy and Study Selection

A literature search was conducted on December 9, 2014, using the following: PubMed and CENTRAL, The Cochrane Collaboration database of controlled trials (in the Cochrane Library); reference lists of identified RCTs; and reference lists of other systematic reviews and meta-analyses.[5-9] Published, randomized controlled trials comparing all SSRIs versus placebo in short-term treatment of unipolar depression in pediatric populations were sought by 2 reviewers (A.L.V. and C.C.), using MeSH keywords *SSRI* or *fluoxetine* or *fluvoxamine* or *citalopram* or *escitalopram* or *sertraline* or *paroxetine* and the key words *placebo* and *depression*. Trials were excluded if they met the following criteria: were limited to adults >18 years; included a cross-over design; studied psychiatric diagnosis other than MDD or a dual diagnosis (substance use appearing most commonly); did not study an SSRI; were not randomized; were not placebo controlled; or provided adjunctive psychotherapy to active or control group. Trials were included if efficacy data were available for both SSRI and placebo-treated participants for at least 1 time point other than baseline and endpoints, and if they used standardized, validated outcome measurements. Trials identified through this search that met all criteria except being pediatric studies were included in comparisons examining the efficacy of SSRIs for adult compared to pediatric MDD.

Data Extraction

Included trials provided weekly data points reported in a variety of validated depression outcome measurements. The primary measure of efficacy reported in pediatric depression trials included the Children's Depression Rating Scale–Revised (CDRS-R),[16] Hamilton Rating Scale for Depression (HAM-D),[17] Montgomery–Asberg Depression Rating Scale (MADRS),[18] and the Schedule for Affective Disorders and Schizophrenia for School Aged Children–Present

FIGURE 1 Selection of studies and search strategy. Note: MDD = major depressive disorder; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.