SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PEDIATRIC PSYCHOPHARMACOLOGY: A REVIEW OF THE EVIDENCE

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Treatment decisions are increasingly being guided by research-based evidence[1] rather than by expert opinion or clinical experience. Following the lead from other disciplines, recent efforts to use an evidence-based approach have been made in pediatric psychiatry.[2,3] In view of the great responsibility involved in prescribing psychoactive agents to minors, evidence-based efficacy information and accurate safety data must be accessible to the pediatric practitioner.

We used an evidence-based approach to review the extant literature on selective serotonin reuptake inhibitors (SSRIs) used in pediatric psychopharmacology, attending to both the quality of individual studies and the strength of the entire body of evidence. Due to the quality and number of controlled studies, this review focuses on the use of SSRIs in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD), with reference to their use in non-OCD anxiety disorders. We weigh the benefit observed in these studies against the risks regarding the safety of SSRIs in pediatric patients. Although nonpharmacologic interventions are widely used in children with both anxiety and depression and have substantial supporting evidence, this review is largely limited to the safety and efficacy of the SSRIs. SSRIs currently available in the United States include citalopram (Celexa©), escitalopram (Lexapro©), fluoxetine (Prozac©), fluvoxamine (Luvox©), paroxetine (Paxil©), and sertraline (Zoloft©). At this time, only fluoxetine (to treat depression and OCD), fluvoxamine (to treat OCD), and sertraline (treat OCD) have been approved by the Food and Drug Administration (FDA) for use in children.

METHODS

We conducted a PubMed search (to January 2005) to locate primary references, using the following search terms: SSRI, the generic names of each specific SSRI, psychopharmacology, and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnoses MDD and OCD. Our search included only English-language publications and was limited to the pediatric age group inclusive of age 18 years. Additional topics regarding safety and clinical use of SSRI received a broader search with no restriction by age (eg, "suicide," "switching"). Abstracts, including presentations at national meetings (eg, of the American Academy of Child and Adolescent Psychiatry [AACAP]), were also reviewed. To further expand the search, all primary and secondary references were vetted in an iterative fashion to identify other citations. We used the Agency for Healthcare Research and Quality (AHRQ) guidelines[4] to undertake a systematic examination. As described by the AHRQ, key quality domains of a controlled trial include a description of the study population, randomization, blinding, interventions, outcomes, statistical analysis, and sources of funding.

In addition, we surveyed websites and reports including the AACAP, the American Psychiatric Association (APA), the American College of Neuropsychopharmacology (ACNP), the FDA Center for Drug Evaluation and Research and Office of Drug

AACAP	American Academy of Child and Adolescent Psychiatry	DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ACNP	American College of Neuropsychopharmacology	FDA	Food and Drug Administration
AHRQ	Agency for Healthcare Research and Quality Guidelines	GI	Gastrointestinal
		HR	Hazard ratio
APA	American Psychiatric Association	MAOI	Monoamine oxidase inhibitor
CBT	Cognitive-behavioral therapy	MDD	Major depressive disorder
CDA	Centers for Disease Control	NSAIDS	Nonsteroidal anti-inflammatory drugs
CDRS	Children's Depression Rating Scale-Revised	OCD	Obsessive-compulsive disorder
CGI	Clinical Global Improvement	PAE	Psychiatric adverse event
CI	Confidence interval	RCT	Randomized controlled trial
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale	SSRI	Selective serotonin reuptake inhibitor
		TCA	Tricyclic antidepressant

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Safety, and the United Kingdom Committee on Safety of Medicines to obtain the latest bulletins and advisories on safety and efficacy in pediatric populations. Pharmaceutical company websites that have posted data and analysis of unpublished studies were also surveyed. Also included in this review were August 2004 documents from the FDA, including a meta-analysis of neuropharmacological drug products, the audit of the Columbia Suicidality Classification Methodology, and the follow-up consult from the FDA's Division of Drug Risk Analysis.

RESULTS

The total number of MEDLINE citations for each individual SSRI was as follows: fluoxetine, 674; paroxetine, 337; fluvoxamine, 197; sertraline, 273; and (es)citalopram, (133)160. The key word "psychopharmacology" alone yielded 337 citations, whereas "selective serotonin uptake inhibitors" yielded 435 references. The number of citations for the individual DSM diagnoses, delimited by adding "and selective serotonin uptake inhibitors) (shown in parentheses) were 1632 (58) for MDD and 1780 (65) for OCD. Controlled clinical trials of SSRIs in pediatric MDD were reviewed, inclusive of the data on 24 studies as recently reviewed by the FDA. More than 19 controlled clinical trials of SSRIs in pediatric OCD were reviewed, along with 5 controlled studies of SSRIs in mixed pediatric anxiety disorders.

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MDD. In contrast to the literature on adult mood disorder, the only controlled evidence of efficacy in pediatric unipolar depressive disorders is found in studies with SSRI medications. There is no controlled evidence targeted at pharmacologic treatment of suicidality in depressed youth.[5] Open-label studies suggest variable response rates to SSRIs in children and adolescents with MDD,[6-8] higher than the rates observed in controlled studies (40% to 70%). Placebo response rates are also high in controlled trials (30% to 60%), indicating that overall effect sizes are modest and that underpowered studies are unlikely to demonstrate statistically significant efficacy.

Several randomized controlled trials (RCTs) have nonetheless demonstrated the efficacy of SSRIs for the acute management of MDD in youth. Emslie and colleagues[9,10] demonstrated a significant benefit of acute fluoxetine in treating children and adolescents with depression. These studies demonstrated a 40% to 65% response rate to 20 mg/day of fluoxetine, compared with a 20% to 50% placebo response rate in the acute phase. A multivariate post hoc analysis did not identify any variables to predict a positive response to fluoxetine.[11] In a recent 32-week relapse-prevention phase after an acute controlled trial,[12] 20 patients continued to receive fluoxetine (F/F group), and another 20 patients were switched to placebo (F/P group). Mean time to relapse was longer in the F/F group than in the F/P group ($P = .046$). Relapse occurred in an estimated 34% of the F/F group and 60% of the F/P group (primarily within the first 8 weeks). This is the first reported study of the benefit of long-term treatment for children and adolescents with MDD.[12]

An important National Institutes of Mental Health–sponsored 12-week multicenter RCT of 439 adolescents with DSM-IV MDD evaluated fluoxetine (10 to 40 mg/day), cognitive-behavioral therapy (CBT), and placebo.[13] Rates of a priori defined clinical global improvement (CGI) response in the 2 fluoxetine groups at endpoint were statistically superior to those of CBT alone and placebo: 71% for fluoxetine and CBT (95% confidence interval [CI] = 62% to 80%), 61% for fluoxetine alone (95% CI = 51% to 70%), 43% for CBT alone (95% CI = 34% to 52%), and 35% for placebo (95% CI = 26% to 44%).

Expert panels, including the 1999 Report of the Texas Consensus Conference Panel on Treatment of Childhood MDD[14] and the recent 2004 task force convened by the ACNP, have recommended several SSRIs besides fluoxetine for treating youth with MDD. Although the ACNP identified fluoxetine, citalopram, sertraline, and paroxetine as significantly more effective than placebo in at least 1 RCT, the panel did acknowledge that paroxetine and citalopram have also registered negative findings.[15] However, a recent FDA review of SSRIs in depressed pediatric populations led to the endorsement of fluoxetine only.[16]

Although a study from the United Kingdom did not find significant efficacy of citalopram in adolescents with MDD,[15] Wagner et al[17] recently published the results of an 8-week, randomized, double-blind, placebo-controlled study of citalopram and placebo in the treatment of 174 children and adolescents with MDD. Mean Children's Depression Rating Scale—Revised (CDRS) scores decreased significantly from baseline with citalopram (24 mg/day) compared with placebo, but the overall difference in change scores (−22 for citalopram vs −17 for placebo) was modest. Defined response rates at week 8 were 36% for citalopram and 24% for placebo ($P < .05$).

Two multicenter randomized, double-blind, placebo-controlled trials of sertraline were conducted at 53 sites in the US and internationally between 1999 and 2001.[18] A total of 376 youth (age 6 to 17 years) with DSM-IV MDD of moderate or worse severity were entered. Sertraline was more effective than placebo; statistically greater improvement was seen as early as week 3 of treatment. The magnitude of response for sertraline in this trial (mean CDRS change, −23 for sertraline vs −20 for placebo) can be compared with that found in an earlier trial of fluoxetine (mean CDRS change, −22 for fluoxetine vs −15 for placebo).[10] Although these trials were not powered to detect age group differences, the treatment effect was demonstrated in the adolescent group.[19]

Paroxetine (20 to 40 mg/day) also demonstrated superiority over placebo (secondary outcome measures) and comparability to the serotonergic tricyclic antidepressant (TCA) clomipramine (75 to 150 mg/day) in RCTs of adolescent MDD.[20,21] In the latter trial, in a sample of 121 patients (age 12 to 20 years) with DSM-IV MDD, based on intent-to-treat analysis, paroxetine and clomipramine had similar efficacy; using the CGI scale and the Montgomery and Asberg Depression Rating Scales (MADRAS), 48% and 58% of