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Use of Selective Serotonin Reuptake Inhibitors in Pediatric Patients

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Childhood major depressive disorder (MDD) has become recognized as a serious and common illness affecting between 3 and 8% of children and adolescents.[1] The rate of major depressive disorder increases as age increases and it is estimated that 20% of adolescents have had at least one episode by the age of 18.[2] Similar to MDD in adult patients, the disease is more common in girls than boys. Problems associated with childhood depression include impaired development, feelings of worthlessness, low self-esteem, suicidal thoughts, and difficulty with concentration and motivation.[1] Furthermore, childhood depression is a positive predictor of adult depression and psychosocial impairment.[3]

Pediatric Use of Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are currently the most frequently prescribed antidepressants for children and adolescents with depression and/or anxiety.[4] Of the available SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), only fluoxetine is FDA-approved (January 2003) for the treatment of childhood depression for children older than seven years of age. Pfizer is currently seeking a similar indication for sertraline. Data supporting the effectiveness of SSRIs in the treatment of pediatric depression is limited. In addition, the results from the few clinical trials that have been published are not overwhelmingly favorable. Results from the major published trials are available in Table 1.

SSRI-Associated Adverse Events in Pediatric Patients

SSRIs are not benign medications. Common side effects include headache, nausea, vomiting, diarrhea, nervousness, and sleep disturbance. These drugs may also be associated with mania and disinhibition or activation particularly in young children. Recently, reports of an increased risk of suicide or suicidal behavior with the use of paroxetine in children and adolescents have raised concern regarding the use of this class of medication.

On June 19, 2003, The FDA issued a statement regarding the utilization of paroxetine in the pediatric population. In this Talk Paper, the FDA recommended that paroxetine not be used in children and adolescents for the treatment of MDD based on a possible increased risk of suicidal thinking and suicide attempts in children under the age of 18.[5] On October 27, 2003 the FDA issued a public health advisory to all health care professionals that stressed the need for additional data, analysis and public discussion of the incidence of suicide associated with the use of SSRI medications. The FDA emphasized three critical points.

(1) In the 20 placebo-controlled trials being considered for these 8 drugs, involving over 4100 pediatric patients, there have been no reports of completed suicides. However, FDA has not at this point been able to rule out an increased risk of suicidality for any of these drugs, including Paxil (paroxetine), which was the subject of a FDA Talk Paper on June 19, 2003.

(2) FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine). FDA recognizes that pediatric MDD is a serious condition for which there are few established treatment options, and that clinicians often must make choices among treatments available for adult MDD.

(3) FDA emphasizes that these drugs must be used with caution.[6]

On March 22, 2004, the FDA issued a statement to the manufacturers of ten antidepressant medications (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine) to include stronger cautions and warnings about the need to monitor patients for the emergence of worsening depression and suicidal ideation.

Prior to the recommendations released by the FDA, the United Kingdom Department of Health issued a press release stating that paroxetine (UK trade name Seroxat) must not be used for the treatment of depressive illness in children under the age of 18 (June and September 2003). This recommendation was based on a thorough review of data that demonstrated the benefits of paroxetine in children do not outweigh the risks of self harm and potentially suicidal behavior.[7] Based on the analyses conducted by the Committee on Safety of Medicines (CSM), it was found that the risk of self harm and suicidal behavior is increased 1.5 to 3.2 times over placebo.[8] In September, the same office issued a similar warning about the use of venlafaxine (UK trade name Efexor). Most recently, in a public health link issued December 10, 2003, the CSM reported on the completion of their review of the safety and efficacy of the SSRI class in the treatment of pediatric major depressive disorder. Their findings were as follows:

- *Paroxetine, venlafaxine, sertraline, citalopram and escitalopram are now* contraindicated *in paediatric MDD in the under 18s.*
- *There are no data on the safety and efficacy of fluvoxamine in paediatric MDD. Safety and efficacy in adults cannot be extrapolated to those under 18 and therefore this product* should not be used *in this age group.*
- *The balance of risks and benefits of fluoxetine in the treatment of MDD in under 18s appears to be favourable.*

The CSM recommends that prescribers (1) not start paroxetine, venlafaxine, sertraline, citalopram, escitalopram and fluvoxamine in children under 18 as new therapy, (2) complete planned treatment courses in patients who are successfully treated with these agents, and (3) consider switching to a safer alternative [e.g. fluoxetine] if patients are not doing well with any of these medications.[9]

The American Academy of Child and Adolescent Psychiatry (AACAP) has taken an opposing viewpoint. At a recent FDA committee meeting (February 2004), the AACAP made the following statement. "The AACAP supports the American College of Neuropsychopharmacology's report that the current research indicates that the evidence for the benefits of SSRI's -- as a treatment for depression -- outweigh their risks. Research findings to date point to the role of depression itself as the most likely cause of suicide. AACAP is adamant that continued research into SSRI use in children and adolescents to conclusively determine their effect."[10] The Academy did recognize, however, that only four of the twenty studies reviewed by the FDA were available for public evaluation.

Conclusions and Appropriate Discontinuation of SSRI Treatment

In accordance with the recommendations from the FDA and the UK's CSM, it is recommended that SSRIs be continued in patients where effectiveness is apparent. For these patients, prescribers may be advised to inform parents of the potential risks associated with treatment and obtain informed consent. If, however, the SSRI is not effective, the prescriber may consider switching to a safer medication. At this time, only fluoxetine is FDA-indicated for the treatment of childhood depression.

SSRIs, like virtually all antidepressants (TCAs, MAOIs, venlafaxine, trazodone) can be associated with withdrawal symptoms if abruptly discontinued. The incidence of withdrawal side effects is least frequent with fluoxetine, most likely due to its longer half-life, and most frequent

with paroxetine. The signs and symptoms of this syndrome include dizziness, headache, nausea, vomiting, diarrhea, movement disorders, insomnia, irritability, visual disturbances, lethargy, anorexia, tremor, electric shock sensations, and lowered mood. Typically patients experiencing withdrawal from SSRIs will describe these symptoms as "flu-like." The discontinuation syndrome is best avoided with a slow taper of the medication. Generally a 25% per week taper will prevent most withdrawal symptoms, however, tapering schedules should be adjusted according to individual patient needs.

Reviewed by Keith Cheng, M.D., Trillium Family Services

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Table 1. Summary of Randomized Controlled Trials for SSRIs in Pediatric Depression

Study Description	Treatment/Method	Population	Results	Citation
Fluoxetine				
Randomized, double-blind, placebo controlled trial	- 1 week single-blind placebo both groups - followed by 7 weeks double-blind placebo or fluoxetine (up to 60mg/day)	- 22 female & 18 male patients randomized to fluoxetine or placebo - Age: 13-18 years - 16 placebo and 16 fluoxetine patients had follow-up data.	- No statistically significant differences were seen between the groups across the study weeks or at end-point. - There were no significant differences in long-term outcomes between the groups.	Simeon JG Prog Neuro Psychopharmacology and Biol Psychiatr 1990, 14:791-95
Randomized, double-blind, placebo controlled trial	- 1 week single-blind placebo both groups - followed by 7 weeks double-blind placebo or fluoxetine (up to 20mg/day)	- 48 patients randomized to each placebo and fluoxetine groups. - Age: 7-17 years.	- Significant differences seen in CGI and CDRS-R scales. NNT = 5 (intent to tx); NNT = 7 (completed trial) - No significant difference in BPRS-C, CGAS and self-reported depressive symptoms.	Emslie GJ Arch Gen Psychiatry 1997; 54:1031-37
Randomized, double-blind, placebo controlled trial	- 1 week single-blind placebo both groups - followed by 9 weeks double-blind placebo or fluoxetine (up to 20mg/day)	- 110 patients randomized to fluoxetine and 109 randomized to placebo. - Age: 8-18 years.	- Response defined as a 30% or greater improvement in CDRS-R score. - Difference between groups was not statistically significant. - Statistical significance was demonstrated for much or very much improved scores on the CGI. NNT = 7	Emslie GJ, et al J Am Acad Child and Adolesc Psych 2002; 41:1205-1216
Sertraline				
Randomized, double-blind, placebo controlled trial	- two multicenter, 10 week trials. - placebo vs sertraline (up to 200mg/day)	- 189 sertraline & 187 placebo. - Patients stratified into two age groups - age 6-11 years - age 12-17 years	- Statistically significant improvement in mean change of CDRS-R in adolescents only (≥12 years). NNT=10	Wagner KD, Ambrosini P, Rynn M, et al JAMA 2003; 290:1033-1041
Paroxetine				
Randomized, double-blind, placebo controlled trial	- 8-week trial comparing placebo to imipramine or paroxetine. - paroxetine doses were 20 to 40 mg/day.	- 275 patients randomized to one of three groups. - Age: 12-18 years.	- Primary outcomes: HAM-D ≤8 or 50% reduction and a change from baseline HAM-D total score. - A statistically significant difference was seen in the first, but not the second primary endpoint. NNT=6	Keller MB, Ryan ND, Strober M, et al J Amer Acad of Child and Adolesc Psych 2001, 40:762-
Venlafaxine				
Randomized, double-blind, placebo controlled trial	- 6-week trial comparing placebo to venlafaxine.	- 33 patients randomized to venlafaxine or placebo. - Age: 8-18 years	- no significant effect on any of the specific behaviors or symptoms in the treatment group.	Mandoki MW, Tapia MR, Tapia MA, et al Psychopharmacology Bulletin 1997, 33:149-154

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