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Clinical Advisory

and issue analysis

Regarding Antidepressant Use in Children and Adolescents

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IN VIEW of the complex issues, controversy and recent increased warnings and precautions announced by the U. S. Food and Drug Administration (FDA) regarding the use of antidepressants in children and adolescents, OMH has prepared this clinical advisory and issue analysis to assist practitioners and clinicians in psychiatric decision making.

This clinical advisory includes principles of practice and strategies for patient management, however, it is not intended to define the standard of care, nor is it inclusive of all methods of care. This advisory is based on an evaluation of currently available scientific literature and recent information from the FDA. The ultimate judgment regarding care of a particular patient must be made by the clinician in light of all the circumstances presented by the patient and his/her family and the diagnostic and treatment resources available.

I. Background:

- ◆ Beginning in June 2003 there has been increased concern about both the safety and effectiveness of 9 antidepressants in children and adolescents.
- ◆ The antidepressants include 6 serotonin reuptake inhibitors (SSRI) - Citalopram (Celexa); Escitalopram (Lexapro); Fluoxetine (Prozac); Fluvoxamine (Luvox); Paroxetine (Paxil); Sertraline (Zoloft); and 3 others - Bupropion (Wellbutrin); Mirtazapine (Remeron); Venlafaxine (Effexor)
- ◆ Since the Fall of 2003, the FDA has conducted a series of hearings regarding the safety and efficacy of antidepressants in children and adolescents. As part of this process, the data from all studies (N=24 placebo-controlled) involving the 9 antidepressant medications in children and adolescents (both published and unpublished) have been carefully reviewed and the data re-analyzed.
- ◆ In March 2004 the FDA required pharmaceutical companies to significantly strengthen the warning language with antidepressant medications to include monitoring for signs of suicidal thinking or behavior during treatment.
- ◆ In September 2004, after reviewing all the studies and as a result of the hearings the FDA's Advisory Committee recommended that the FDA require pharmaceutical companies to create a "black box warning" on all antidepressants about the medication-induced risk of increased suicidal thinking and behavior in children and adolescents.

They also recommended that a patient medication guide be provided to the patient/family with each prescription. The “black box warning” is the FDA’s strongest indication of risk with a particular medication.

- ◆ On October 15, 2004 the FDA announced that it would be requiring a “black box warning” on all antidepressants regarding their use in children and adolescents. This stronger warning applies to all antidepressants (the 9 listed above plus all tricyclic and MAO inhibitor antidepressants). Based on their analysis of the data, the FDA decided to strengthen safeguards for children and adolescents treated with antidepressants in view of the medication-induced risk of increased suicidal thinking or behavior. According to the FDA, the “black box warning” will also contain specific recommendations for monitoring of a patient as well as information to be provided to the patient and family. At this time the specific FDA language for the warning has not yet been made available.

II. Summary of Key Issues and Analysis of Data:

- ◆ Pediatric depression is a real illness and treatment is effective. In the United States, depression is responsible for over 500,000 suicide attempts by children and adolescents each year. Untreated depression carries significant rates of impairment and risk.
- ◆ Currently, fluoxetine (Prozac) is the only antidepressant approved (i.e. “labeled”) by the FDA for use in pediatric depression (i.e. children and adolescents). The prescribing of all other antidepressants in children and adolescents for any use is categorized as “off-label” use.
- ◆ To date, only fluoxetine (Prozac) has been shown to be clinically effective with depressed adolescents in two (2) carefully designed research studies.
- ◆ From the FDA’s review of the 24 SSRI antidepressant studies involving 4,400 children and adolescents, they concluded that all the SSRI (including fluoxetine) and other newer antidepressants can increase the risk of suicide-related thoughts and/or self-harming behavior in some children and adolescents (78 of 4,400 patients). The FDA analysis identified the average medication-induced risk to be 4% compared to 2% for a placebo. This means that statistically, 4 children and adolescents out of 100 patients treated might show increased suicidality due to the antidepressant medication. The medication-induced risk is greater when starting or adjusting the dose of these antidepressant medications.
- ◆ In the 24 studies reviewed involving children and adolescents taking SSRI antidepressant medications, there were no deaths. Also, none of the patients with increased suicidal ideation or behavior went on to commit suicide.
- ◆ New research in the treatment of adolescent depression (i.e. Treatment for Adolescents with Depression Study - TADS) demonstrates that the combination of therapy (cognitive behavioral therapy) and antidepressant medication (fluoxetine) results in successful treatment (71% of depressed adolescent patients responded positively to the combination treatment compared to 35% of patients on placebo).
- ◆ In spite of the “black box warning”, the FDA has not taken a position that SSRI and other new antidepressants are contraindicated in children and adolescents. Therefore, these medications (9 listed above) can continue to be prescribed for children and adolescents if rational prescribing principles are followed.

III. Rational Prescribing Principles for Any Psychiatric Medication:

OMH recommends the following principles whenever any psychiatric medication is being prescribed for a child or adolescent:

1. Psychiatric medication(s) should not be prescribed until a thorough psychiatric assessment is conducted by a qualified professional.
2. Psychiatric medication(s) should rarely be used as the sole treatment modality or intervention for a child or adolescent with a mental disorder.
3. Selection of a specific psychiatric medication for a particular psychiatric or behavioral problem should be based on support from the scientific literature and evidence base (when it exists).
4. Each decision to use a psychiatric medication must be carefully individualized by the prescribing physician. The decision should be based on a discussion between the physician, parents and patient of the potential benefits and the potential risks (including side-effects) of using a particular medication as well as alternative treatments.
5. The risks associated with “non-treatment” must also be considered. Failure or refusal to treat significant psychiatric and behavioral problems in children and adolescents (including reluctance or failure to use medication) can also carry risk.
6. Prescribing physicians must work with the parents/guardians to carefully assess for response (or non-response) to treatment, and emergence of side-effects during the course of treatment with a medication. Regular communication between the physician and parents/guardians is essential. Symptoms and side-effects are best tracked using standardized rating scales or other quantifiable measures.
7. A decision to stop or change the dose of any psychiatric medication must involve a discussion between the psychiatrist or physician, patient and parents/guardians.

IV. Specific Recommendations re: SSRI and Other New Antidepressants and Depression:

OMH has the following specific recommendations regarding the use of the 9 newer (6 SSRI and 3 others) antidepressants in depressed children and adolescents:

1. Based on an evaluation of the current research evidence, first line treatments for moderate to severe depression in adolescents (ages 13-18 years) include the antidepressant fluoxetine, cognitive behavioral therapy (CBT), and the combination of fluoxetine and CBT. Interpersonal psychotherapy (IPT) has also been shown to be effective.

Note: In view of the limited availability of CBT and IPT in some clinical settings, other forms of psychotherapy may be considered. However, in spite of their widespread use in clinical practice, there is very limited research evidence that these other forms of psychotherapy are effective in depressed adolescents.

2. SSRI antidepressants can be prescribed for moderate to severe depression in adolescents (ages 13-18 years) since there is some research evidence of their clinical effectiveness.
3. Current evidence for the safety and efficacy of the SSRI antidepressants in children (under 13 years of age) is much weaker. Therefore, a clinical decision to use SSRI antidepressants for an individual child must be based on a careful evaluation of potential risk versus potential benefit.
4. Whenever antidepressants are prescribed, parents, families and patients should receive complete written information about the specific medication. The FDA will be defining the content of this information. The written information should include a list of suicidal symptoms, such as increased suicidal ideas or thoughts and self-harming behaviors. Parents/guardians should be advised to immediately contact the prescribing physician if suicidal ideation or self-harming behavior occurs.

5. For the first 4 weeks of treatment with SSRI antidepressants, patients should be followed weekly (in-person or by telephone) to monitor severity of depression, response to treatment and possible emergence of side-effects (including suicidal ideation, self-harming behavior). During the monitoring contacts, the physician should ask the patient and family specifically about any new or increased suicidal ideation or occurrence of self-harming behavior.
6. For weeks 5-8 of treatment (2nd month) of treatment with SSRI antidepressants, patients should be followed at least biweekly (preferably in-person) to monitor severity of depression, response to treatment and possible emergence of side-effects (including suicidal ideation, self-harming behavior).
7. For continuing treatment (3rd month and beyond) with SSRI antidepressants, patients should be followed at least monthly (in-person) to monitor severity of depression, response to treatment and possible emergence of side-effects (including suicidal ideation, self-harming behavior). Additional monitoring should be arranged as needed.
8. When adjusting doses (higher or lower) of SSRI antidepressants, patients should be followed weekly (in-person or by telephone) to monitor severity of depression, response to treatment and possible emergence of side-effects (including suicidal ideation, self-harming behavior) during the first month.
9. Patients and families should also be educated about the possible appearance of the following symptoms with these antidepressants: anxiety, agitation, panic attacks, insomnia, irritability; hostility/aggressiveness, impulsivity, restlessness (akathisia) and hypomania or mania. Parents/guardians should be advised to contact the prescribing physician when any of these symptoms occurs.
10. When starting an antidepressant, the prescribing physician should develop a "crisis/safety plan" with parents, families and patients with specific steps to follow so problems or concerns could be immediately communicated "after hours".
11. Children and adolescents currently taking SSRI antidepressants should not suddenly stop their use or abruptly be taken off these antidepressant medications. Serious side effects can emerge (including suicidal ideation and self-harming behavior) with sudden discontinuation of these medications.
12. More careful research is needed to clarify the risk of suicidal behavior or thinking and the overall clinical effectiveness of antidepressant medications in depressed children and adolescents. Clinicians should continue to stay informed as new information on these issues becomes available from both research studies and the FDA.
13. The principles of practice and strategies for patient management contained in this advisory are not intended to define the standard of care, nor are they inclusive of all methods of care. The ultimate analysis and decision regarding the specific treatment of a particular child or adolescent patient must consider all the circumstances presented by the patient and his/her family and the diagnostic and treatment resources available.