

Selecting an Antidepressant for the Treatment of Pediatric Depression

CHRISTOPHER J. KRATOCHVIL, M.D., BENEDETTO VITIELLO, M.D., DAVID BRENT, M.D.,
JEFF Q. BOSTIC, M.D., ED.D., AND MICHAEL W. NAYLOR, M.D.

FLUOXETINE AND PEDIATRIC DEPRESSION

When initiating pharmacotherapy for a child or adolescent with major depressive disorder, should fluoxetine always be the first antidepressant initiated? Should fluoxetine be the only antidepressant used in the treatment of pediatric depression?

Benedetto Vitiello, M.D.

When pharmacological treatment is deemed appropriate for a child or adolescent with major depressive disorder, I consider using fluoxetine first. Based on existing data, the efficacy of fluoxetine in pediatric depression is better documented than for any other

antidepressant as it is supported by three independent multisite clinical trials (Emslie et al., 1997, 2002; TADS Team, 2004). Fluoxetine is also the only antidepressant whose efficacy has been directly compared with that of cognitive-behavioral therapy, alone and in combination with fluoxetine (TADS Team, 2004), and the only medication that is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression in children and adolescents.

This position does not imply that fluoxetine is more effective or safer than other antidepressants, but only reflects the fact that the amount of data in support of fluoxetine efficacy in children and adolescents with major depression is, at this time, larger than for any other medication. Also, that fluoxetine should be considered first does not mean that it should be invariably prescribed first. There can be individual patient situations in which a second-line antidepressant may be preferred based on practical reasons. For example, if I encounter a family who has developed negative expectations from fluoxetine treatment because another close relative, such as a sibling or parent of the child, was unsuccessfully treated with fluoxetine, although they found another antidepressant helpful, I am inclined to follow the family's preference. Clinical experience has taught me that successful treatment decisions are based on applying scientific evidence to the individual patient context, expectations, and preferences.

Fluoxetine should not be the only antidepressant used in the treatment of children and adolescents with major depression. It is estimated that about 20%–40% of depressed youths treated with fluoxetine do not adequately improve on this medication, thus opening the question of what do to next. Although no

This is a case vignette created to exemplify a complex clinical problem and does not refer to any specific patient.

This column aims to discuss practical approaches to everyday issues in pediatric pharmacotherapy. The cases and discussions specifically target aspects of clinical care related to psychopharmacology for which we do not have adequate applicable controlled trials. Given the need to address symptoms in youths with complex, severe, and comorbid disorders, recommendations are likely to be "off label" from the perspective of the U.S. Food and Drug Administration. We fully appreciate that for virtually all disorders, medication is only one aspect of comprehensive care. This column focuses primarily on psychopharmacological management. The responses from the expert clinicians are not meant to be practice guidelines but rather examples of thought processes that may go into pharmacotherapy decision making.

Accepted November 2, 2005.

Dr. Kratochvil is with the Department of Psychiatry, University of Nebraska Medical Center, Omaha; Dr. Vitiello is with the National Institute of Mental Health, Bethesda, MD; Dr. Brent is with University of Pittsburgh Medical Center, Pittsburgh; Dr. Bostic is with Massachusetts General Hospital, Boston; and Dr. Naylor is with University of Illinois at Chicago.

Correspondence to Dr. Christopher J. Kratochvil, University of Nebraska Medical Center, 985581 Nebraska Medical Center, Omaha, NE 68198-5581; e-mail: ckratoch@unmc.edu.

0890-8567/06/4503-0371©2006 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.chi.0000197029.87378.1c

experimental data are currently available to address this question, adult data and clinical experience with youths suggest that a depressed patient who has not improved on one antidepressant has at least a 50% chance of improving on another one (Thase et al., 2001). Thus, if a youth is still depressed after an adequate trial of fluoxetine, I consider prescribing another selective serotonin reuptake inhibitor (SSRI) for which there is some evidence of efficacy from controlled clinical trials, such as citalopram or sertraline.

David Brent, M.D.

In clinical medicine, there are very few situations in which the answer includes the word “always.” All things being equal, fluoxetine is the medication for which there is the most consistent data for efficacy, so it is a logical first choice. However, some families and patients will refuse fluoxetine because of an adverse experience of a family member. For those patients, the use of another antidepressant for which some efficacy data exist, namely, sertraline or citalopram, is indicated. Another reason to avoid the use of fluoxetine is if there is concern about a possible adverse reaction, such as the triggering of mania. Although the treatment of pediatric depression in those with a bipolar diathesis is itself not well established, one may make the case the use of an antidepressant with a shorter half-life makes some sense, because in the event of mania, one can decrease the dose and available drug more quickly. For patients with a coagulation disorder, a drug with a shorter half-life might also be a safer choice. Fluoxetine is an inhibitor of the CYP2D6 isoenzyme, so for patients who are taking concomitant medications such as tricyclic antidepressants, opiates, and some neuroleptics, one might consider using a different agent, such as citalopram, which has a much lower potential for drug interactions.

Jeff Q. Bostic, M.D., Ed.D.

The best interests of the patient should always be our first priority. Fluoxetine certainly deserves “first-line consideration” for any child suffering across multiple life domains with depression. But fairy dust it is not. Whether we sprinkle fluoxetine or another SSRI, we do not really know which one will work the most magic for a given patient—indeed, at least eight adult studies clearly indicate a person may respond poorly to one SSRI, then fabulously to another. Our best efforts

remain matching the patient’s unique constellation of symptoms, along with other variables (other medications, comorbid conditions, family history [of psychopathology and of reactions to medications]) to the best fitting treatment.

In addition to the clinical picture, many of our patients and their families have opinions about living in a “Prozac Nation.” In each case, we have at least two people to adhere to a treatment. Discerning each patient’s and family’s thoughts and preferences about various SSRIs, irrational as they might be, is often essential to allying them toward any treatment.

Trying to make sense out of a particular case, I find out as much as feasible about the patient’s clinical circumstances and the patient’s and family’s perceptions about any medication treatment and offer them choices. “Prozac is FDA-indicated for depression, although Lexapro is less likely to interact with Hubert’s other medications, and Zoloft was the agent that helped Aunt Gertie finally go outside the house.” Partnering with the child and family around treatment decisions may take precedence over allegiance to an erratically obtained and disparately motivated and measured database. The FDA investigation of SSRI suicidality concerns will likely best be remembered for advancing standardized, consistent methodologies and reporting of child psychopharmacology trials. Meanwhile, partnering with families by providing honest input on what we know about each agent and which ones might best “fit” their child favors each child’s best interests.

Michael W. Naylor, M.D.

I consider several factors when determining which antidepressant to prescribe in the treatment of a depressed child or adolescent. For example, has the patient had an antidepressant trial in the past? If so, was it of adequate duration and at an adequate dose? How well was the medication tolerated? Why was it discontinued? If the medication was well tolerated and effective, I would reinstate treatment with that medication. In addition, I consider family history in making the decision about which medication to initiate. Recent research suggests that a family history of medication response can predict a patient’s response to that same medication (Duffy et al., 2002).

That said, I believe that children and adolescents with new-onset nonpsychotic unipolar depression, no

previous antidepressant medication trials, and a non-contributory family history to inform medication choice should be treated with fluoxetine preferentially. There are several arguments in favor of using fluoxetine as the drug of first choice for the treatment of pediatric depression. In a meta-analysis of randomized, controlled studies of SSRIs published in peer-reviewed journals and unpublished studies reviewed by the Committee on Safety of Medicines, Whittington et al. (2004) showed that only fluoxetine had a favorable risk-benefit profile. Additionally, fluoxetine is the only SSRI approved by the FDA for the treatment of pediatric depression. Although off-label use of medications is legal and may represent the standard of care for certain disorders, FDA approval may offer clinicians greater legal protection in the event of a serious adverse reaction. Finally, fluoxetine is available in generic form, not a small consideration in these days of spiraling health costs. Some clinicians argue that the long half-life of fluoxetine may be problematic in the event that the medication must be discontinued abruptly because a serious side effect. Although that may be true, fluoxetine is less likely to result in potentially catastrophic rebound symptoms of depression that have been described in SSRIs with shorter half-lives.

In initiating fluoxetine, I would start at a low dose, 2.5–5 mg for young children and 10 mg for older children and adolescents. I would increase the dose every 7–14 days, given its long half-life. I have found that slower titration can prevent some of the akathisia and activation seen with SSRIs. I aim for a maximum dose of 10–20 mg for younger children and 40 mg in

adolescents, although I would go higher if the patient was tolerating the medication well and had a partial response. It is important to monitor the patient closely for suicidal ideation and self-harm behavior after initiating treatment with fluoxetine. I recommend weekly follow-ups for 4 weeks, two biweekly follow-ups, then monthly follow-ups as needed.

Disclosure: Dr. Kratochvil has received grant support from, is a consultant to, and/or member of the speaker's bureau of Eli Lilly, GlaxoSmithKline, Forest, Shire, Cephalon, Novartis, McNeil, Organon, AstraZeneca, and Pfizer. Dr. Bostic has received grant support and/or honoraria from Abbott, Forest, GlaxoSmithKline, Eli Lilly, and Pfizer. The other authors have no financial relationships to disclose.

REFERENCES

- Duffy A, Alda M, Kutcher S et al. (2002), A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. *J Clin Psychiatry* 63:1171–1178
- Emslie GJ, Heiligenstein JH, Wagner KD et al. (2002), Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41:1205–1215
- Emslie GJ, Rush AJ, Weiberg WA et al. 1997), A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54:1031–1037
- TADS Team (2004), The Treatment for Adolescents with Depression Study (TADS): short-term effectiveness and safety outcomes. *JAMA* 292:807–820
- Thase ME, Feighner JP, Lydiard RB (2001), Citalopram treatment of fluoxetine nonresponders. *J Clin Psychiatry* 62:683–687
- Whittington CJ, Kendal IT, Fonagy P, Cottrell ID, Cotgrove A, Boddington E (2004), Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 36:1341–1345
- Zimmerman R (2001), Child play: pharmaceutical firms win big on plan to test adult drugs on kids. *Wall Street Journal* Feb 5:A1.