Childhood and Early-Onset Anxiety: Treatment and Biomarker Studies

James T. McCracken, M.D.; John T. Walkup, M.D.; and Harold S. Koplewicz, M.D.

Increasing research attention is being applied to studies of early-onset anxiety, with a focus on its phenomenology, etiology, and strategies for treatment. The impetus for these studies includes well-confirmed findings from epidemiologic surveys clearly demonstrating that, as a group, the anxiety disorders represent the most highly prevalent form of psychopathology in children and adolescents. Overall rates of childhood anxiety disorders are estimated to be from 6% to 10%, depending upon categories included and strategies for ascertainment. New work is currently being conducted in the form of large-scale rigorous treatment studies, and new investigations explore etiopathophysiologic aspects of anxiety in children and adolescents. Significant progress is being made in this important clinical area that should translate to improved outcomes through refined diagnosis and empirically tested treatments.
(J Clin Psychiatry 2002;63[suppl 6]:8–11)

Increasing research attention is being applied to studies of early-onset anxiety, with a focus on its phenomenology, etiology, and strategies for treatment. The impetus for these studies includes well-confirmed findings from epidemiologic surveys clearly demonstrating that, as a group, the anxiety disorders represent the most highly prevalent form of psychopathology in children and adolescents. Overall rates of childhood anxiety disorders are estimated from 6% to 10%, depending upon categories included and strategies for ascertainment. New work relating to results of large-scale rigorous treatment studies is currently being conducted, and new investigations explore etiopathophysiologic aspects of anxiety in children and adolescents. This work demonstrates that significant progress is being made in this important clinical area that should translate to improved outcomes through refined diagnosis and empirically tested treatments.

From the Division of Child and Adolescent Psychiatry, UCLA Neuropsychiatric Institute, Los Angeles, Calif. (Dr. McCraken); the Division of Child and Adolescent Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Md. (Dr. Walkup); and the New York University Medical Center, New York, N.Y. (Dr. Koplewicz).

Presented at the symposium "Exploring the Boundaries of Obsessive-Compulsive Disorder and Other Anxiety Disorders: New Developments and Practical Approaches From the Fifth International OCD Conference," which was held March 29–April 1, 2001, in Sardinia, Italy, and supported by an unrestricted educational grant from Solvay Pharmaceuticals.

Corresponding author and reprints: James T. McCracken, M.D., Division of Child and Adolescent Psychiatry, UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024 (e-mail: jmccracken@mednet.ucla.edu).

PHARMACOLOGIC TREATMENT OF CHILDHOOD ANXIETY DISORDERS

The recently completed fluvoxamine trial[1] conducted by the Research Units on Pediatric Psychopharmacology (RUPP) network studied children and adolescents with separation anxiety disorder, social phobia, and generalized anxiety disorder. This study represented the first large-scale controlled trial completed by the RUPP network, which was funded by the National Institute of Mental Health in 1996 to foster rigorous psychopharmacologic research in child psychopathology. Participating sites included Johns Hopkins University (Baltimore, Md.), Columbia/New York State Psychiatric Institute (New York, N.Y.), New York University (New York, N.Y.), Duke University (Durham, N.C.), and the University of California Los Angeles (UCLA).

The study's authors recognized that in spite of some promising open-label treatment benefits seen with selective serotonin reuptake inhibitor (SSRI) medications in modest samples of children with selective mutism and anxiety and mixed anxiety populations[2,3] and a strong evidence base for SSRI efficacy in pediatric obsessive-compulsive disorder (OCD) and depression,[4–7] support for medication treatment of child anxiety disorders has been significantly lacking. Prior research with tricyclic antidepressant treatment of varying samples of children with school refusal and separation anxiety disorder had been conflicting, and other small controlled trials of clomipramine have been negative.[8,9] With the recognition of the extensive need for intervention for children with anxiety disorders, particularly given longitudinal data suggesting that childhood anxiety disorder diagnosis predicts increased

risk for anxiety and affective psychopathology in young adulthood,[10,11] the scientific justification to test pharmacologic treatments was very strong.

During the planning stages of the RUPP trial, several scientific and methodological issues were addressed. One initial choice related to sample, with the decision to define the treatment sample broadly to include children with separation anxiety disorder, social phobia, or generalized anxiety disorders. This decision to enroll a broader group rather than a narrow group was based on the following: (1) extensive comorbidity across DSM-IV categories of childhood anxiety disorders, (2) family studies suggesting reduced specificity of familial transmission of anxiety disorders, and (3) treatment data, sparse as they were, suggesting a broad efficacy for SSRIs for anxiety in children. A second methodological challenge was to identify a clinician rating instrument for pediatric anxiety suitable for use in the context of a clinical trial. This search resulted in the development of a new instrument, the Pediatric Anxiety Rating Scale (PARS). The PARS subsequently has been shown to demonstrate excellent psychometric properties for use in the assessment of a variety of non-OCD anxiety disorders in children.[12,13] Another primary outcome measure for the trial was the Clinical Global Impressions-Improvement scale (CGI-I) score, and secondary measures included the Multidimensional Anxiety Scale for Children (MASC) and the Screen for Child Anxiety Related Emotional Disorders as a self-report. In addition, the Children's Global Assessment Scale (CGAS) and the Hamilton Rating Scale for Anxiety were also employed.

The choice of design for the trial took several factors into consideration. A significant issue that entered into the design choice included the prior observations of high placebo response rates in earlier placebo-controlled trials of childhood anxiety disorders.[14] In an effort to identify and reduce the inclusion of those children who might prove to be highly responsive to a moderate amount of support and brief psychosocial intervention, all subjects meeting eligibility criteria initially were entered into an open-label psychosocial intervention with education provided about anxiety in children and support and advice for strategies to manage anxiety. Only those children who remained symptomatic after completing 3 weeks of the psychosocial intervention were entered into the 8-week controlled trial. The trial consisted of a randomized, double-blind, placebo-controlled, parallel-arm design testing fluvoxamine versus placebo with a one-to-one randomization. Children randomly assigned to active treatment were begun on treatment with 25 mg/day of fluvoxamine, which was titrated within the first 6 weeks up to a maximum of 250 mg/day or 300 mg/day. A total of 128 children were enrolled in the trial

According to the CGI-I results, 76% of children randomly assigned to active medication were rated as responders versus 29% of children who received placebo. Dimensional ratings of anxiety also showed a robust improvement in the drug group versus the placebo group as well; the mean PARS severity score fell from 18.7 to 9.0 in children taking fluvoxamine, representing greater than 50% reduction in symptomatology, versus only a 15% reduction in symptom severity scores for children taking placebo. Mean daily dose was 137 mg per day for active treatment. Regardless of clinical measure, whether improvement on the CGI-I or PARS, active treatment with fluvoxamine was robustly superior to placebo for the treatment of anxiety in this population.

In addition, fluvoxamine appeared to be well tolerated in spite of the aggressive dosing schedule. Two adverse events appeared to be more common with active drug treatment than placebo: stomachaches and increased motor activity. Dropout rates were low in the fluvoxamine-treated group, reflecting the excellent tolerability of the medication.

Overall, the efficacy of fluvoxamine surpassed the initial expectations; the effect size approached 1.0. This effect size is clearly superior to effect sizes commonly observed in controlled antidepressant trials in children (0.4–0.5) and the efficacy of SSRIs in the treatment of pediatric OCD (0.4–0.5). While the active treatment effect was robust for all measures of anxiety, there was only a limited reduction in measures of depressive symptom scores on the CGAS, reflecting the low rate of comorbid depression in the study. Therefore, the efficacy of the SSRIs, including fluvoxamine, in child anxiety disorders appears to be due to a primary effect on anxiety.

Additional studies to follow up the primary RUPP efficacy trial will include an examination of long-term benefits as seen in open-label treatment in an extension phase, and additional reports will extensively examine safety data.

PRELIMINARY STUDY OF CO_2 SENSITIVITY IN PEDIATRIC ANXIETY

Pilot data on studies of CO_2 sensitivity in pediatric anxiety disorders have been reported.[15] The purpose of the study was to examine the question of whether shared vulnerability features exist across the range of anxiety disorders including separation anxiety disorder, generalized anxiety, and social phobia. Data from adult samples of outpatients with panic disorder and other anxiety disorders have reliably observed hypersensitivity to CO_2 exposure, but the examination of whether this hypersensitivity exists in children has only just begun.[16,17]

The study[15] recruited children aged 9 to 17 years; one group of children met DSM-IV criteria for separation anxiety disorder, generalized anxiety disorder, or social phobia and the other included children screened to be free of any Axis I psychopathology. The reported pilot sample included 50 healthy children and 18 children with anxiety disorders. The procedure involved placement of the child in a large plastic canopy for approximately 30 minutes with an initial

exposure of 15 minutes to room air plus 5% CO_2. Dependent measures included a variety of respiratory, cardiovascular, and symptom variables. Data examining a modified version of the Acute Panic Inventory were reported.

Overall, both groups experienced some increase in reported anxiety in response to CO_2 exposure. However, the degree of increase in reported anxiety symptomatology appeared much more significant in children meeting current criteria for an anxiety disorder than in those free of Axis I disorders. The apparent magnitude of the anxiety response to CO_2 exposure was deemed to mirror that seen in adults as well as children at risk for anxiety disorders. In addition, there was no apparent difference in anxiety response to CO_2 based on current DSM-IV anxiety disorder type, although this comparison was difficult to assess owing to the small sample size. The possible links among childhood anxiety disorders such as separation anxiety disorder, generalized anxiety disorder, and social phobia remain to be clearly examined, and refined classification schemes for children may be needed.

Many of these subjects underwent a CO_2 challenge prior to and after an 8-week trial of fluvoxamine.[15] Results showed that after fluvoxamine treatment, some anticipatory anxiety increases were seen with reexposure to the experimental CO_2 challenge protocol; however, sensitivity to CO_2 exposure appeared significantly reduced in patients who had received fluvoxamine treatment. In general, these results suggest that fluvoxamine treatment may have decreased CO_2 sensitivity and raise other questions regarding the association of CO_2 response with prediction of treatment and outcome.

Future directions for research in this area include expansion of the sample in order to firmly ascertain differences in CO_2 sensitivity between patients and controls and similarly to expand the pretreatment and posttreatment samples. The study group plans to examine other comparisons including CO_2 responsiveness in these patient groups versus groups at risk for anxiety. Exaggerated CO_2 sensitivity may represent a general anxiety vulnerability marker and as such could have additional importance in recognition and diagnosis of anxiety disorders in children. Additionally, a whole host of contextual variables may be central to determining anxiety response, and other developmental influences may emerge from future studies of larger samples and repeated measurements.

IMMUNE FUNCTION OF CHILDREN AND ADOLESCENTS WITH OCD AND TIC DISORDER

Preliminary findings from an ongoing study of immune response in children and adolescents with OCD and Tourette's disorder have been reported.[18] The study attempted to replicate and extend the published observations of the possible association between the exposure to infectious pathogens and the onset or worsening of OCD and Tourette's disorder in children and teenagers.[19–22] This model of pediatric OCD and Tourette's disorder suggests that exposure to pathogens, especially group B streptococcus, may elicit OCD or Tourette's with Sydenham chorea as an analog. In essence, this subtype of OCD and Tourette's disorder represents an autoimmune disorder, which has important implications in understanding heterogeneity seen in family genetic studies and treatment studies as well as outcome.

In addition, a strong association between D8/17 lymphocyte antigen expression and pediatric OCD and Tourette's disorder has been observed.[21] The D8/17 lymphocyte antigen may also be associated with rheumatic fever vulnerability in families, and, although indirect, the observations of elevated D8/17 expression in children and adolescents with OCD and Tourette's formed an intriguing link between immune function and neuropsychiatric symptoms. However, a gap in the autoimmune model includes the absence of any direct evidence of immune activation in patients with OCD and Tourette's, particularly those thought to represent the PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) subtype.

The design of the ongoing study described by McCracken et al.[18] involves recruitment of children and adolescents between the ages of 6 and 17 years who meet the DSM-IV criteria for OCD and/or Tourette's disorder as part of a comprehensive research evaluation using a variety of rating scales, including the Anxiety Disorders Interview Schedule, the MASC, the Childhood Yale-Brown Obsessive Compulsive Scale, and the Child Depression Index. In keeping with the Murphy et al.[21] report, children were enrolled with or without active treatment. A control group of children free of current psychopathology with a family history negative for OCD or Tourette's in first-degree relatives was recruited after the completion of comparable research assessments.

The initial sample included 28 children, 24 with OCD, and 4 with Tourette's disorder. Nine controls were examined for comparison. In contrast to reports, a relatively low rate of expression of the D8/17 antigen was observed in the patient sample with mean expression values similar in the OCD group and controls. An examination of the typically applied threshold of 11% showed no group difference.

In addition, 3 plasma measures of immune system activation were recorded. These measures have been noted to reflect activation resulting from infectious causes, autoimmune causes, and immune-mediated activation and include neopterin, IL-2R, and TNF-α concentrations. Overall, levels of neopterin increased in some children and provided some support for activation in the combined group of children with OCD and Tourette's disorder. Review of IL-2R and TNF-α concentrations showed no significant group differences but did show slight increases in the direction of patients higher than controls. Correlational

analysis between D8/17 antigen and expression and immune activation markers found no significant correlations.

Overall, these data, though preliminary, suggest the possibility of a large sample difference among reports of patients examined for D8/17 lymphocyte antigen expression. Effects of treatment are less clear based on this initial negative report.[18] Differing rates of streptococcal exposure and types of streptococcus may also figure prominently in differences in D8/17 results or in children with possible PANDAS subtype. Furthermore, assay performance may show appreciable differences over time.

Differences in the neopterin concentration suggest the possibility that some patients display immune activation in association with their psychopathology. The cause or relationship cannot be determined from this study, of course, but future studies should examine possible relationships between immune activation and clinical features, natural history, and treatment response of anxiety disorders such as OCD and Tourette's disorder. D8/17 might be a nonspecific or general indicator of vulnerability for psychopathology, but more intensive tests of immune function are indicated as well as longitudinal studies of epidemiologic samples.

CONCLUSION

The study of mental disorders in children presents many medical and ethical challenges, yet it is essential that these disorders be studied. Childhood anxiety disorders cause distress for both the child and his or her family and are associated with a higher risk for later psychiatric disorders and hospitalization.[9,10] Although recent studies of anxiety in children and adolescents represent a step forward in the field, much more research is needed to determine the causes, progression, and best treatments for these diseases to improve outcome.

Drug name: fluvoxamine (Luvox).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, fluvoxamine is not approved by the U.S. Food and Drug Administration for the treatment of child/adolescent anxiety.

REFERENCES

1. Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med 2001;344:1279–1285
2. Fairbanks JM, Pine DS, Tancer NK, et al. Open fluoxetine treatment of mixed anxiety disorders in children and adolescents. J Child Adolesc Psychopharmacol 1997;7:17–29
3. Birmaher B, Waterman GS, Ryan N, et al. Fluoxetine for childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry 1994;33:993–999
4. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA 1998;280:1752–1756. Erratum 2000;283:1293
5. Labellarte MJ, Ginsburg GS, Walkup JT, et al. The treatment of anxiety disorders in children and adolescents. Biol Psychiatry 1999;46:1567–1578
6. Emslie GJ, Walkup JT, Pliszka SR, et al. Nontricyclic antidepressants: current trends in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999;38:517–528
7. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031–1037
8. Popper CW. Psychopharmacologic treatment of anxiety disorders in adolescents and children. J Clin Psychiatry 1993;54(5, suppl):52–63
9. Bernstein GA, Borchardt CM, Perwien AR. Anxiety disorders in children and adolescents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1996;35:1110–1119
10. Pine DS, Cohen P, Gurley D, et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry 1998;55:56–64
11. Costello EJ, Angold A, Keeler GP. Adolescent outcomes of childhood disorders: the consequences of severity and impairment. J Am Acad Child Adolesc Psychiatry 1999;38:121–128
12. Greenhill LL, Pine D, March J, et al. Assessment issues in treatment research of pediatric anxiety disorders: what is working, what is not working, what is missing, and what needs improvement. Psychopharmacol Bull 1998;34:155–164
13. Walkup JM, Davies M. The Pediatric Anxiety Rating Scale (PARS): a reliability study. In: Scientific Proceedings of the 46th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 19–24, 1999; Chicago, Ill. Abstract NR78
14. Klein RG, Koplewicz HS, Kanner A. Imipramine treatment of children with separation anxiety disorder. J Am Acad Child Adolesc Psychiatry 1992;31:21–28
15. Pine D, Klein R, Abikoff, H, et al. CO_2 sensitivity in children with anxiety disorders. Presented at the 5th International Obsessive-Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
16. Pine DS, Rachel RG, Coplan JD, et al. Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. Arch Gen Psychiatry 2000;57:960–967
17. Pine DS, Coplan JD, Papp LA, et al. Ventilatory physiology of children and adolescents with anxiety disorders. Arch Gen Psychiatry 1998;55:123–129
18. McCracken JT, Piacentini J, Bergman RL, et al. Immune markers in childhood OCD and TS. Presented at the 5th International Obsessive-Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
19. Swedo SE. Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders [clinical conference]. JAMA 1994;272:1788–1791
20. Swedo SE, Leonard HL, Kiessling L. Speculations on antineural antibody-mediated neuropsychiatric disorders of childhood. Pediatrics 1994;93:323–326
21. Murphy TK, Goodman WK, Fudge MW, et al. B Lymphocyte antigen D8/17: a peripheral marker for childhood-onset obsessive-compulsive disorder and Tourette's syndrome? Am J Psychiatry 1997;154:402–407
22. Giedd JN, Rapoport JL, Garvey MA, et al. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. Am J Psychiatry 2000;157:281–283