Key Words: child, adolescent, major depression, obsessive-compulsive disorder, social anxiety disorder, panic disorder, paroxetine

Paroxetine Treatment of Mood and Anxiety Disorders in Children and Adolescents

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ABSTRACT *~ This article provides an overview of the use of paroxetine in the treatment of mood and anxiety disorders in children and adolescents. Although not currently approved for use in patients younger than 18 years of age, the efficacy and safety of paroxetine have been studied in several pediatric mood and anxiety disorders. The epidemiology, diagnosis, and course of major depression, obsessive-compulsive disorder, social anxiety disorder, and panic disorder are discussed briefly. Current available data on the safety and efficacy of paroxetine based on double-blind, placebo-controlled trials and open-label studies for the treatment of mood and anxiety disorders in children and adolescents are reviewed. Clinical guidelines for the use of paroxetine in children and adolescents and recommendations regarding future directions of study are discussed.* Psychopharmacology Bulletin. *2003;37(Suppl 1):167-175.*

INTRODUCTION

Major depression in childhood is a serious disorder that significantly disrupts a child's overall functioning, including peer and family relationships and performance in school. In a follow-up study of depressed adolescents, the suicide rate in this population was reported to be approximately 8%.[1] Given the chronicity of major depression and its associated morbidity and mortality, it is essential to identify effective treatments for youngsters suffering from this disorder. Similarly, anxiety disorders such as obsessive-compulsive disorder (OCD) and social anxiety disorder may have a devastating impact on a child's development. Anxiety disorders often precede the development of depression in children and adolescents. Therefore, as is the case with major depression, it is important to identify efficacious and safe treatments for children with anxiety disorders.

Fortunately, there has been increasing interest in pharmacological studies of major depression and anxiety disorders in children and adolescents. However, at present, there are too few published controlled trials to enable a careful determination of

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whether these medications are more efficacious than placebo. This is of particular concern given the high rates of placebo response in pharmacotherapy studies of childhood disorders.

The literature being published about the use of paroxetine, a selective serotonin reuptake inhibitor (SSRI), in younger patients is growing. This article examines the literature on paroxetine and assesses the role of this agent in the treatment of mood and anxiety disorders in children and adolescents.

OVERVIEW OF MAJOR DEPRESSION AND ANXIETY DISORDERS IN CHILDREN AND ADOLESCENTS

Major depression is a common, chronic, and disabling condition in youth. The prevalence of major depression in children and adolescents ranges from 1.8% to 4.6%.[2,3] *The Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria are used to establish a diagnosis of major depression in children and adolescents. Many adolescents diagnosed with major depression have irritable rather than dysphoric mood. The mean length of an episode of major depression in children and adolescents is 9 months, or approximately 1 school year, and relapse rates are approximately 50%.[4] Continuity between depression in youth and adulthood has recently been demonstrated.[5] Development of serious untoward sequelae such as tobacco use, alcohol/substance use, teen pregnancy, suicidal behavior, functional impairment, and psychiatric comorbidity in patients whose depression is not treated or is inadequately treated underscores the importance of early diagnosis and aggressive treatment to full remission.

OCD is another common psychiatric disorder in young people, and the onset of this illness typically begins early in life or during young adulthood. The prevalence of OCD ranges from 2% to 4% in youths.[6,7] The *DSM-IV* criteria for OCD are the same in both children and adults, with the exception that, unlike some adults, children may not recognize that their obsessions or compulsions are unreasonable. The course of OCD in youths is chronic, and it often persists into adulthood.

Social anxiety disorder, also referred to as social phobia, is another common anxiety disorder in youngsters. The prevalence of social anxiety disorder is estimated to range from 0.9% to 7% of children and adolescents.[8,9] The *DSM-IV* diagnostic criteria for social anxiety disorder are similar for children and adults. Social anxiety disorder in children and adolescents is a chronic condition that often precedes and increases the risk of major depression.[9] Like major depression, social anxiety disorder during adolescence has been shown to continue into adulthood.[10]

Panic disorder has a prevalence rate in children and adolescents that ranges from 0.6% to 5% in the community and 0.2% to 9.6% in clinical

settings.[11] The *DSM-IV* diagnostic criteria for panic disorder in children and adolescents are the same as those in adults. Panic disorder is a chronic condition in youths, and there is continuity between childhood and adulthood panic disorder.[12]

REVIEW OF PAROXETINE DATA IN CHILDREN AND ADOLESCENTS

The efficacy and safety of paroxetine in the treatment of depressive and anxiety disorders in children and adolescents are demonstrated by a growing body of literature, which is reviewed below.

Depression

Major Depressive Disorder. An early, open-label trial of paroxetine suggested efficacy and safety of this agent in children and adolescents with depression. In this study, treatment with paroxetine (mean daily dose, 16 mg) resulted in complete remission of symptoms after a mean of 8.4 months of treatment in 45 children and adolescents with major depressive disorder. Efficacy was assessed using the Clinical Global Severity (CGS) scale. At baseline, most patients were considered severely depressed (mean CGS score of 3). Mean CGS scores improved to 1.2 at 3 months, with full remission achieved by all patients after 8 months of treatment. Paroxetine was well tolerated in this population, and no patient was withdrawn because of adverse events.[13]

The findings of one of the largest randomized, double-blind, multicenter, controlled trials of an SSRI in the treatment of adolescents with major depression was reported by Keller and associates in 2001.[14] The efficacy and safety of paroxetine was demonstrated in 275 adolescent outpatients with major depression ranging in age from 12 to 18 years. Patients were randomized to paroxetine, imipramine, or placebo for an 8-week trial. Dose ranges for paroxetine were 20 to 40 mg per day, with a mean daily dose of 28 mg. Dose ranges for imipramine were 200 to 300 mg per day, with a mean daily dose of 205 mg. Paroxetine resulted in significantly greater rates of response (defined as Hamilton Rating Scale for Depression [HAM-D] score ≤8) compared with placebo in the last observation carried forward population. Response rates were higher for paroxetine (76%; P=.02), imipramine (64%), and placebo (58%) among those patients who completed the 8-week trial. There was no statistically significant difference between paroxetine or imipramine and placebo on the HAM-D total score at end point. However, there was a significantly greater increase in the Clinical Global Impression (CGI) improvement scores for the paroxetine group compared with the placebo group. Of patients in the paroxetine group, 66% were much or very much improved (P=.02 versus placebo) compared with 52% of patients in the imipramine group (P=.64 versus placebo) and 48% of patients in the placebo group.[14]

Paroxetine was better tolerated than imipramine, with discontinuation from the study because of adverse events occurring in 9.7% of paroxetine-treated patients, 31.5% of imipramine-treated patients, and 6.9% of placebo-treated patients. Adverse events most commonly reported for paroxetine were headache (34%), nausea (24%), dizziness (24%), dry mouth (20%), and somnolence (17%), which occurred at rates similar to those in the placebo group except for somnolence (3% in placebo group). The most common adverse events in the imipramine group were dizziness (47%), dry mouth (45%), headache (40%), nausea (24%), and tachycardia (19%). The lack of adverse cardiovascular events in the paroxetine group is notable, because approximately one third of patients in the imipramine group who were withdrawn prematurely from the study as a result of adverse events had treatment-emergent tachycardia, postural hypotension, or prolonged QT intervals.[14]

The effect of comorbid attention deficit hyperactivity disorder (ADHD) on response rates was assessed in a subset analysis[15] of the Keller and colleagues study. The presence of comorbid ADHD significantly reduced response rates in all of the treatment groups. Based on CGI improvement scores of 1 (very much improved) or 2 (much improved), the response rates among patients without ADHD were: paroxetine 71%, imipramine 64%, and placebo 59%. In the patients with ADHD, response rates were: paroxetine 25%, imipramine 31%, and placebo 13%.

In another multicenter, double-blind, placebo-controlled trial of paroxetine treatment of children and adolescents with major depression, there was no statistically significant difference in the response rates between the paroxetine and placebo groups (data on file, GlaxoSmithKline).

The effectiveness and tolerability of paroxetine (mean dose, 27 mg/d) for treatment of 7 adolescents with major depressive disorder and mild intellectual disability also were assessed in a 9-week, open-label trial. A significant reduction in depression scores was found at the end of the trial, and 57% of subjects no longer fulfilled *DSM-IV* criteria for a depressive episode at end point.[16]

Dysthymia. In an open-label trial of paroxetine treatment of 7 children and adolescents with dysthymia, 71% of the patients had a positive response during the course of the 3-month treatment period. Follow-up of 5 of these 7 patients showed sustained response at 6 months.[17]

Obsessive-Compulsive Disorder

Paroxetine treatment of OCD has been reported in 1 open-label study and in 2 larger, randomized, double-blind, placebo-controlled trials. In 1 early study, the efficacy of paroxetine in the treatment of OCD (10 to 60 mg/d) was suggested in a 12-week, open-label trial of 20 outpatients ranging in age from 8 to 17 years. In this small study, a significant

improvement in baseline obsessive-compulsive symptoms was observed at study end point.[18]

The efficacy and safety of paroxetine for treatment of OCD were further assessed in a large, multicenter, double-blind, placebo-controlled trial of 203 outpatient children and adolescents ranging in age from 7 to 17 years. Patients were randomized to paroxetine or placebo for a 10-week trial. The dose range for paroxetine was 10 to 50 mg per day, with a mean of 23 mg per day. There was a significantly greater reduction in Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) scores from baseline to end point for paroxetine compared with placebo. Response rates (≥25% reduction in CY-BOCS scores) were 64.9% in the paroxetine group and 41.2% in the placebo group (*P*=.002). The most common (≥10%) adverse events in the paroxetine group were headache, abdominal pain, nausea, respiratory disorder, somnolence, hyperkinesia, and trauma. Only hyperkinesia and trauma had incidences twice that of placebo.[19]

Another group of 335 outpatients, 7 to 17 years of age, with OCD participated in a multicenter, 16-week, open-label study of paroxetine (10 to 60 mg/d) followed by double-blind randomization of responders to paroxetine or placebo for an additional 16 weeks. The response rate (≥25% reduction in CY-BOCS scores) to paroxetine in the open-label phase was 68.7%. No significant difference in response rates was found between the paroxetine and placebo groups in the randomization phase. However, relapse rates were lower for patients treated with paroxetine (34.7%) than for patients who were switched from paroxetine to placebo (43.9%) during the double-blind phase.[20]

A post hoc analysis of the Emslie and colleagues[20] study of children and adolescents with OCD was conducted to assess the effect of comorbidity on response to paroxetine.[21] Response rates to paroxetine among patients with OCD, but no comorbid disorders, were 75%. In contrast, response rates for patients with OCD and comorbid ADHD, tic disorder, or oppositional defiant disorder were markedly lower: 56%, 53%, and 39%, respectively. Adverse events such as insomnia, nervousness, and hyperkinesia were also more common in patients with psychiatric comorbidity.[21]

Related Studies of Paroxetine in Children and Adolescents

The use of neuroimaging technology in the study of child and adolescent OCD offers insight into the effect of pharmacologic treatment. Clinical improvement of obsessive-compulsive symptoms in children and adolescents with OCD has been shown to be associated with reversal of some of the observed structural and functional brain abnormalities in this disorder. In 1 study using volumetric magnetic imaging, paroxetine decreased thalamic volumes in children and adolescents with OCD to

levels comparable to those in healthy controls, whereas thalamic volumes were significantly greater in treatment-naïve youths with OCD. Reduction was noted in obsessive-compulsive symptom severity for those patients with a decrease in thalamic volumes.[22] In another study, proton magnetic resonance spectroscopic examinations of the left caudate of children with OCD showed that caudate glutamatergic concentrations declined significantly after treatment with paroxetine to levels comparable to those in healthy controls. Decrease in caudate glutamatergic concentrations also was associated with a reduction in obsessive-compulsive symptom severity.[23]

Social Anxiety Disorder

The efficacy and safety of paroxetine have been assessed in a multicenter, double-blind, placebo-controlled trial of 319 outpatient children and adolescents with social anxiety disorder ranging in age from 8 to 17 years. The daily dose of paroxetine ranged from 10 to 50 mg, with a mean dose of 24.8 mg per day. The primary efficacy measure was the proportion of responders based on the CGI improvement score of 1 (very much improved) or 2 (much improved) at the week 16 end point in the last observation carried forward population. Paroxetine was significantly superior to placebo on the CGI improvement scores, with response rates of 77.6% and 38.3%, respectively ($P \leq .001$). There were statistically significant differences favoring paroxetine over placebo for a battery of secondary efficacy measurements, including the CGI severity of illness score, the Liebowitz Social Anxiety Scale for Children and Adolescents, the Dalhousie Generalized Social Anxiety Disorder Scale for Adolescents, the Social Phobia Anxiety Inventory, and the Global Assessment of Functioning Scale. There was no evidence of any statistically significant treatment-by-covariate interactions for age group, gender, or CGI Severity of Illness baseline scores. The most common (≥10%) adverse events reported in paroxetine-treated patients were headache, infection, respiratory disorder, abdominal pain, asthenia, insomnia, somnolence, rhinitis, and nausea. The most common adverse events in the placebo-treated group were headache, infection, respiratory disorder, and rhinitis. Only insomnia, decreased appetite, and vomiting occurred at an incidence greater than or equal to 5%, and occurred at least twice as frequently in patients on paroxetine as in those on placebo.[24]

Panic Disorder

The efficacy and safety of paroxetine treatment of panic disorder also have been suggested by the findings of a retrospective chart review of 18 child and adolescent outpatients. Patients ranged in age from 7 to 16 years, and were treated with paroxetine monotherapy for a mean

duration of 11.7 months. The dose range of paroxetine was 10 to 40 mg, with a mean daily dose of 23 mg per day. Fifteen patients (83%) achieved a CGI improvement score of 1 (very much improved) or 2 (much improved). The most common adverse events were nausea, tension-agitation, sedation, insomnia, palpitations, and headaches.[11]

ROLE OF PAROXETINE IN CHILD AND ADOLESCENT MOOD AND ANXIETY DISORDERS

A growing database has demonstrated that paroxetine is effective and safe for treatment of major depression in adolescents, OCD in children and adolescents, and social anxiety disorder in children and adolescents. These disorders are associated with significant morbidity for children and adolescents, and symptom reduction and resolution can significantly improve a child's overall functioning and educational and social achievement.

Dosage initiation for paroxetine is generally 10 mg, although starting dosages for very young children may be 5 mg. The dose should be increased as needed in 10-mg increments up to a maximal daily dose of 60 mg. For both major depression and anxiety disorders in children and adolescents, it is recommended that medication be continued for at least 1 year following symptom resolution.

In general, the treatment of mood and anxiety disorders in children and adolescents remains a remarkably understudied area. As such, the existing studies of paroxetine represent an excellent start. There remain a number of future directions for the study of paroxetine in youngsters. Controlled trials of paroxetine treatment for other anxiety disorders such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder are warranted. The efficacy of paroxetine in the treatment of bipolar depression in children and adolescents remains to be examined. In keeping with the goal of treating patients to full remission, studies of paroxetine in achieving remission and prevention of relapse in major depression and anxiety disorders for youths are needed. Maintenance studies also are necessary to guide optimal treatment duration with paroxetine.

The contribution of paroxetine treatment to the improvement of quality of life, academic achievement, peer relationships, and family function should be assessed in future controlled trials in children and adolescents with major depression and anxiety disorders. Neuroimaging studies of children who receive paroxetine monotherapy may help to further elucidate the neurobiologic underpinnings of these disorders, and may better clarify the clinical role of this SSRI. Controlled comparisons with other antidepressants of the efficacy of paroxetine for treatment of children with mood and anxiety disorders are needed to aid the clinicians in antidepressant selection.

CONCLUSION

In double-blind, placebo-controlled trials, paroxetine has demonstrated efficacy and safety in the treatment of major depression in adolescents, and in the treatment of OCD and social anxiety disorder in children and adolescents. Selective serotonin reuptake inhibitors such as paroxetine are currently the first-line treatment for children and adolescents suffering from major depression and anxiety disorders. Additional well-controlled studies are needed to further advance the treatment and outcome of children with depression and anxiety disorders. ✤

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