

The Relevance of Pharmacokinetic Studies in Designing Efficacy Trials in Juvenile Major Depression

Robert L. Findling, M.D.,^{1,2} Nora K. McNamara, M.D.,^{1,2} Robert J. Stansbrey, M.D.,¹
Norah C. Feeny, Ph.D.,^{1,3} Christopher M. Young, M.D.,¹ Franco V. Peric, M.A.,¹ and
Eric A. Youngstrom, Ph.D.^{1,3}

ABSTRACT

Introduction: Identifying evidence-based dosing strategies is a key part of new drug development in pediatric populations. Pharmacokinetic (PK) studies can provide important information regarding how best to dose medications in children and adolescents. Utilizing scientifically supported dosing strategies provides the best chance for any given drug to demonstrate both efficacy and acceptable tolerability in definitive, placebo-controlled studies.

Methods: Results of both PK studies and randomized, placebo-controlled efficacy trials (RPCTs) in juvenile major depressive disorder (MDD) are reviewed. The degree to which the medication dosing strategies that were employed in the efficacy studies were supported by the extant PK data is considered. Medications that are reviewed include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, nefazodone, and mirtazapine.

Results: In many instances, the dosing paradigms that were used in the RPCTs differed, sometimes substantially, from the dosing strategies that would have been supported based on the results of PK studies.

Conclusions: Medication dosing regimens may have contributed to the failure of several RPCTs to show drug efficacy in the treatment of pediatric MDD. In addition, the doses of medication used in these RPCTs may also have contributed to the safety and tolerability concerns that have been raised with these drugs. PK and dose-ranging studies should be performed prior to the initiation of definitive efficacy trials so that empirically supported dosing strategies can be incorporated into the design of RPCTs of antidepressants in children and adolescents suffering from MDD.

INTRODUCTION

AS OF MARCH 2005, only fluoxetine has received approval from the U.S. Food and Drug Administration (FDA) as a pharmacological treatment for depressed youths (FDA 2003).

Interestingly, other agents have also been tested as potential treatments for juvenile depression in randomized, placebo-controlled trials (RPCTs). Most of these studies did not demonstrate superiority of active treatment when compared to placebo (Laughren 2004).

From the Departments of ¹Psychiatry, ²Pediatrics, and ³Psychology, University Hospitals of Cleveland/Case Western Reserve University, Cleveland, Ohio.

The reasons why many of these recently conducted studies have failed to show antidepressant efficacy have not been definitively elucidated. Although some of these antidepressants may truly be of no benefit to young people suffering from major depressive disorder (MDD), methodological issues also need to be considered when examining why some of these studies failed to show antidepressant efficacy. The field of child and adolescent psychopharmacology appears to be in a state similar to that point in time when studies of tricyclic antidepressants (TCAs) failed to demonstrate efficacy in youths with MDD. Methodological considerations that were raised at that time included adequate sample size, appropriate patient selection, duration of treatment, and empirically supported outcome measures (Jensen et al. 1992).

However, another key issue that needs to be considered when evaluating the safety and efficacy of any agent, including an antidepressant, is dosing (Atuah et al. 2004). Key parameters of dosing that should be empirically evaluated may include identifying an appropriate total daily dose and determining how frequently the medication needs to be administered each day. If a medication is not dosed properly, clinical efficacy might go undetected. Similarly, if a medication is not dosed properly, adverse events might occur that might otherwise have been avoidable with a different dosing strategy. As development-based differences in pharmacokinetics may be seen with drugs (Kearns et al. 2003), one of the means by which empirically based dosing strategies are derived in pediatric patients is through pharmacokinetic (PK) studies.

The aim of this paper is to consider what is known about the pharmacokinetics of the newer generation of antidepressants and then to consider whether or not the dosing strategies that could be supported by these PK data were actually employed in double-blind efficacy studies in juvenile depression.

Designs of the cited PK studies and the RPCTs are summarized in Tables 1 and 2. It should be noted that some of these trials incorporated a forced titration design. In such studies, a patient's treatment is increased to a predetermined target dose. In addition, several of the studies

utilized a dose-ranging design, which allowed for flexible dosing (within certain predetermined parameters) at the treating physician's discretion. Such trials can provide information about the optimal dosing for a compound within clinical settings. Furthermore, first- and multiple-dose PK studies were performed. This is an important consideration, because differences in PK parameter estimates may be observed at these two distinct time points. Finally, several of the PK studies included patients with different psychiatric diagnoses. Performing PK studies in patients with heterogeneous diagnoses does not reduce methodological rigor because drug biodisposition does not appear to be diagnosis-dependent.

Agents that will be considered herein include: Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, nefazodone, and mirtazapine. Although fluvoxamine has been shown to have efficacy in the treatment of pediatric obsessive-compulsive disorder (OCD) (Riddle et al. 2001) and several other pediatric anxiety disorders (Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001) and bupropion has been shown to have efficacy in the treatment of ADHD in children (Conners et al. 1996), these compounds will not be considered in this paper. This is because there are no adequately powered RPCTs with either agent in depressed youths.

Fluoxetine

Pharmacokinetic studies. Several PK parameter estimates were reported for fluoxetine, and its primary metabolite norfluoxetine, based on the results of a study in which 10 children and 11 adolescents participated (Wilens et al. 2002). These youths were diagnosed with either MDD or OCD and treated with fluoxetine at a dose of 20 mg per day for up to 60 days. Blood samples for PK analyses were obtained at predetermined time points between 8 and 12 hours after oral dosing.

The authors found that steady-state levels of both fluoxetine and norfluoxetine were achieved by 4 weeks after the initiation of drug therapy. Although there was high intersubject variability, the concentrations of both moieties were

TABLE 1. RECENT PHARMACOKINETIC STUDIES OF SELECTED ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

Agent	N	Age range (years)	Daily doses studied	Key findings
<i>Fluoxetine</i>				
Wilens et al. (2002)	21	6–18	20 mg (once-daily)	After multiple 20-mg doses, concentrations of fluoxetine and norfluoxetine were approximately two times higher in the children than in adolescents. Population PK parameter estimates were similar to what had previously been described in adults.
<i>Sertraline</i>				
Alderman et al. (1998)	61	6–17	50 mg (single dose) and 200 mg (multiple doses). Once-daily dosing	After multiple 200-mg doses, children had higher C_{max} and systemic exposure when compared to either adolescents or to what had been previously reported in adults. At 200 mg, $t_{1/2}$ was similar for children, adolescents, and adults.
Axelson et al. (2002)	19	13–17	50 mg (single dose) and 50–150 mg (multiple doses)	$t_{1/2}$ was shorter than what had been previously noted in Alderman et al. (1998). Twice daily dosing for youths receiving < 200 mg/day might be optimal
<i>Paroxetine</i>				
Findling et al. (1999)	30	6–17	10 mg for 8 weeks or 10 mg for 4 weeks; then 20 mg for 4 weeks (once-daily dosing)	$t_{1/2}$ shorter after single 10-mg dose than previously reported in adults. Low intra-subject variability in drug concentrations after multiple doses. Non-linear increases in systemic exposure with increased dose
GlaxoSmithKline (2005a)	62	7–17	10 mg × 2 weeks; 20 mg × 2 weeks; 30 mg × 2 weeks (multiple doses)	Nonlinear relationship between systemic paroxetine exposure and paroxetine dose observed
<i>Citalopram</i>				
Gutierrez et al. (2000)	11	12–17	20 mg × 1 week; 40 mg × 3 weeks. Once-daily dosing.	After multiple 40-mg doses, PK parameters were similar in adolescents and adults
Axelson (unpublished)	17	9–17	20 mg (single and multiple doses)	$t_{1/2}$ for S-citalopram was shorter in adolescents when compared to adults
<i>Escitalopram</i>				
Periclou et al. (2003)	11	12–17	single 10-mg dose	$t_{1/2}$ shorter in adolescents when compared to adults

TABLE 1. RECENT PHARMACOKINETIC STUDIES OF SELECTED ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS (continued)

Agent	N	Age range (years)	Daily doses studied	Key findings
<i>Venlafaxine</i>				
Derivan et al. (1995)	12	6–15	2 mg/kg/day (multiple doses)	After multiple doses, overall systemic exposure to both venlafaxine and O-desmethylvenlafaxine was lower than reported in adults
<i>Nefazodone</i>				
Findling et al. (2000)	28	7–17	50 mg first dose; 100 mg × 1 week; 200 mg × 1 week (twice daily dosing)	Children had higher overall exposure and C _{max} of nefazodone and its three active metabolites when compared to adolescents
<i>Mirtazapine</i>				
Findling et al. (2001)	16	7–17	15 mg (single dose)	Significant increase in t _{1/2} with increasing weight and a decrease in C _{max} with increasing age observed.

PK = Pharmacokinetic; C_{max} = maximum concentration; t_{1/2} = half-life.

TABLE 2. SELECTED PLACEBO-CONTROLLED TRIALS IN JUVENILE MAJOR DEPRESSIVE DISORDER

Agent	N	Age range (years)	Daily dosing
<i>Fluoxetine</i>			
Simeon et al. (1990)	40	13–18	titrated up to 60 mg over the first 2 weeks
Emslie et al. (1997) ^a	96	7–17	20 mg
Emslie et al. (2002a) ^a	219	8–17	10 mg 1st week, 20 mg thereafter
TADS (2004) ^a	439	12–17	10 mg 1st week, then 20 mg. Could increase in 10-mg increments to a maximum of 40 mg
<i>Sertraline</i>			
Dubitsky (2004); Wagner et al. (2003); Laughren (2004) ^b	188	6–17	25 mg × 3 days, then 50 mg. Could be increased to a maximum of 200 mg. Once daily dosing.
Dubitsky (2004); Wagner et al. (2003); Laughren (2004) ^c	188	6–17	25 mg × 3 days, then 50 mg. Could be increased to a maximum of 200 mg. Once daily dosing.
<i>Paroxetine</i>			
Keller et al. (2001); Laughren (2004) ^c	275	12–18	20 mg with optional, subsequent increases in 10-mg increments to a maximum dose of 40 mg
Dubitsky (2004); Laughren (2004); GlaxoSmithKline (2005c) ^c	206	7–17	10 mg, with subsequent increases in 10-mg increments for a maximum dose of 50 mg allowed
Dubitsky (2004); Laughren (2004); GlaxoSmithKline (2005d) ^c	286	13–18	20 mg, subsequent increases allowable up to a maximum dose of 40 mg
<i>Citalopram</i>			
Wagner et al. (2004a) ^a	174	7–17	20 mg × 4 weeks with a subsequent increase to 40 mg allowed. Once daily dosing.

Dubitsky (2004); Laughren (2004) ^c	244	13–18	10 mg with subsequent increases in 10 mg increments to a maximum dose of 40 mg
<i>Escitalopram</i>			
Wagner et al. (2004b) ^c	264	6–17	10 mg × 4 weeks, with subsequent increase to 20 mg allowed. Once daily dosing.
<i>Venlafaxine</i>			
Mandoki et al. (1997) ^c	40	8–17	titrated up to 37.5 mg or 75 mg
Emslie et al. (2004); Dubitsky (2004); Laughren (2004) ^c	165	7–17	maximum dose of 112.5–225 mg
Dubitsky (2004); Emslie et al. (2004); Laughren (2004) ^c	196	7–17	maximum dose of 112.5–225 mg
<i>Nefazodone</i>			
Emslie et al. (2002b); Dubitsky (2004); Laughren (2004) ^b	206	12–17	Target dose 300–400 mg; maximum allowable dose 600 mg
Dubitsky (2004); Laughren (2004) ^c	284	7–17	Children low dose arm: maximum of 100 or 150 mg/day; children high dose arm: maximum of 200–300 mg/day; adolescent low dose arm: maximum of 300 mg/day; adolescent high dose arm: maximum of 400–600 mg/day
<i>Mirtazapine</i>			
Dubitsky (2004); Laughren (2004) ^c	126	7–17	Initial dose 15 mg; could increase by 15 mg increments. Max dose 45 mg
Dubitsky (2004); Laughren (2004) ^c	133	7–17	Initial dose 15 mg; could increase by 15 mg increments. Max dose 45 mg

^aStatistically significant difference between active drug and placebo on primary efficacy analysis.

^bStatistical trend for difference between active drug and placebo on primary efficacy analysis.

^cNo statistically significant difference between active drug and placebo on primary efficacy analysis.

approximately two times higher in the children (ages 6–12) than in adolescents (ages 13–18). After weight normalization, drug and metabolite concentrations were found to be similar across the age groups. Population PK analysis of the collected samples yielded parameter estimates for absorption rate constant, oral clearance, and volume of distribution. These parameter estimates were found to be similar to what had previously been described in adults. Based on these findings, the authors suggested that 10 mg per day might be a rational initial dosing strategy for prepubertal children, whereas 20 mg per day might be a reasonable starting dose for adolescents (Wilens et al. 2002).

Efficacy studies. The first published RPCT examining the efficacy of fluoxetine in adoles-

cent MDD failed to show a difference between fluoxetine and placebo in a group of 40 adolescents (ages 13–18 years) during a 7-week trial (Simeon et al. 1990). In this study, fluoxetine was titrated to a dose of 60 mg/day over the first 2 weeks of treatment. It has been previously noted that methodological issues, such as small sample size, high placebo response rate, and the dosing strategy employed, may have contributed to this trial's failure to detect a difference between active treatment and placebo (Findling et al. 2002a).

Subsequently, Emslie et al. (1997) reported that fluoxetine was superior to placebo in the treatment of MDD in a cohort of 96 youths 7–17 years of age who participated in an 8-week randomized, double-blind study RPCT. In this trial, a fixed 20-mg dose of fluoxetine was used in the active treatment arm.

Fluoxetine was again found to be superior to placebo in another double-blind RPCT in which 122 children and 97 adolescents with MDD received treatment with either fluoxetine or placebo. In this study, patients who were randomized to active treatment initially received 10 mg of fluoxetine per day for the 1st week. These subjects then received 20 mg of fluoxetine per day thereafter for up to 8 more weeks (Emslie et al. 2002a).

In a follow-up trial to this study, patients who did not respond to 20 mg of fluoxetine were then randomized to maintenance (20 mg/day), 40 mg/day or 60 mg/day of fluoxetine (Hoog et al. 2001). Results suggest that doses of 40 or 60 mg per day of fluoxetine might be well tolerated, as well as superior to continued treatment with fluoxetine at 20 mg per day for those who do not adequately respond to 20 mg per day.

Finally, in a large multisite RPCT, 439 adolescents (ages 12–17) with MDD were randomized to receive cognitive behavioral therapy, fluoxetine, active combination therapy, or placebo for up to 12 weeks (Treatment for Adolescents with Depression Study [TADS] Team 2004). Again, treatment with fluoxetine was found to be superior to placebo in depressive symptom amelioration. In this study, fluoxetine was initiated at a dose of 10 mg per day. Fluoxetine was then increased to a dose of 20 mg per day after 1 week of treatment. Fluoxetine could then be increased in 10-mg increments to a maximum daily dose of 40 mg.

Interpretation. In the three studies showing fluoxetine to be more beneficial than placebo (Emslie et al. 1997; Emslie et al. 2002; TADS 2004), the starting dose of fluoxetine was either 10 or 20 mg per day. Notably, these were the doses suggested by the authors of the one PK study of fluoxetine (Wilens et al. 2002). There are also data (Hoog et al. 2001) to support the decision to allow for dose increases in fluoxetine above 20 mg per day, as was done in the TADS trial. However, it would have been interesting to see whether or not the RPCT results would have been affected if the younger children who participated in the RPCTs had received an initial 10-mg daily dose that did not have to be raised per study protocol.

Sertraline

Pharmacokinetic studies. The first PK study to examine sertraline included 29 children (ages 6–12 years) and 32 adolescent (ages 13–17 years) suffering from either OCD or MDD (Alderman et al. 1998). After receiving a single 50-mg dose, patients had their sertraline gradually increased to a final dose of 200 mg/day in either 25- or 50-mg increments. Sampling for PK analyses was done after the single 50-mg dose and after multiple 200-mg doses.

It was observed that children had higher maximum concentrations (C_{\max}) and systemic exposure to sertraline when compared to either adolescents or when compared to what had been previously reported in adults. The authors noted that differences in the PK parameters across the age groups were most likely the result of body-weight differences. In this study, the half-life ($t_{1/2}$) of sertraline exceeded 24 hours across age groups after multiple 200-mg doses.

In another study, the multiple-dose PK parameters of sertraline, when given at doses less than 200 mg to adolescents, were described (Axelson et al. 2002). After receiving multiple 50-mg doses, the authors noted that the $t_{1/2}$ of sertraline was 15.3 hours. After multiple 100- or 150-mg doses, it was noted that the $t_{1/2}$ of sertraline was 20.4 hours. As the $t_{1/2}$ was shorter than what had been previously noted in the study of Alderman et al. (1998) and was less than 24 hours, the authors suggested that it might be reasonable to dose sertraline initially in divided daily doses, and to consider divided daily dosing for those youths not responding to once-daily dosing. The authors did note that, for patients receiving 200 mg per day of sertraline, once-daily dosing might be appropriate.

Efficacy studies. There are two RPCTs in which the efficacy of sertraline was compared to placebo in the treatment of MDD in youths between the ages of 6 and 17 years. In these clinical trials, subjects received 10 weeks of double-blind treatment (Dubitsky 2004; Wagner et al. 2003). In one study, 97 patients received sertraline and 91 received placebo. In the other trial, 92 youths received sertraline and 96 were administered placebo. Sertraline treatment was initiated at a dose of 25 mg per day for 3 days, with the dose

of sertraline subsequently increased to a dose of 50 mg per day until the end of the 2nd week. Thereafter, the dose of sertraline could be increased in 50-mg-per-day increments to a maximum daily dose of 200 mg. Interestingly, divided dosing was not allowed in these efficacy studies (Dubitsky 2004). The mean dose of active sertraline given to patients across both trials was 131 mg/day. Although pooled analyses of both studies suggested superiority for sertraline over placebo (Wagner et al. 2003), each study, when considered individually, failed to demonstrate a statistically significant difference between active drug and placebo (Laughren 2004).

Interpretation. The dosing strategy used in the sertraline efficacy studies diverged from the dosing strategies that could be best justified, based on the results of the PK studies. The extant data suggest that for subjects being treated at doses of sertraline less than 200 mg per day, divided daily dosing might be more effective than once-daily dosing. However, as already noted, the efficacy studies did not permit split daily dosing. These studies also did not force-titrate subjects to a 200-mg-per-day dose level (the level at which once-daily dosing is best supported). It is possible that if the dosing schema in the two sertraline efficacy studies were different, the distinctions between active treatment and placebo that were noted only through a pooled series of analyses (Wagner et al. 2003) might have been more readily detectable.

Paroxetine

Pharmacokinetic studies. There are two pharmacokinetic studies of paroxetine in children and adolescents. The 1st-dose pharmacokinetics of paroxetine were described in a cohort of 30 children and adolescents with MDD (Findling et al. 1999). Intensive blood sampling for PK analyses occurred after a single 10-mg dose. Subsequently, subjects were treated with open-label paroxetine for 8 weeks, with a starting dose of 10 mg per day. After 4 weeks of open treatment, those patients with persistent depressive symptomatology could have their dose of paroxetine increased to 20 mg per day.

The investigators found that the average $t_{1/2}$ of a single 10-mg dose of paroxetine was 11.1

hours with wide intersubject variability. In addition, they noted that several PK parameters correlated with cytochrome P450 2D6 (2D6) phenotype. There was also a trend for catechol-*O*-methyltransferase (COMT) activity to correlate with first dose $t_{1/2}$.

Plasma concentrations of paroxetine also were measured weekly during the course of the study. Drug concentrations for individual subjects who were maintained on 10 mg of paroxetine generally remained consistent during the course of the study. However, an almost 7-fold increase in paroxetine concentration was noted in the subjects who had their paroxetine dose raised ($n = 8$) owing to insufficient clinical benefit. Similar to adults, this finding demonstrated that paroxetine has nonlinear PKs in youths.

Overall, the study medication was well tolerated and associated with salutary effects, with most subjects responding adequately to the 10-mg-per-day dose. There were only 2 early discontinuations from the trial. In both instances, this was because of the development of hypomania. In addition, there were 2 poor metabolizers with respect to 2D6 phenotype. Interestingly, the subject with the least amount of 2D6 activity was the patient who discontinued earliest from the study. Based on these observations, the authors raised the question of whether or not being a poor metabolizer with respect to 2D6 activity conferred a vulnerability to paroxetine intolerance in this patient population.

In addition, the authors noted that treatment with 10 mg of paroxetine was associated with substantial reductions in platelet-rich plasma serotonin concentrations. Similarly, paroxetine also causes reductions in whole-blood serotonin levels when it is administered to adults (Marsden et al. 1987). These data suggest that paroxetine exerts pharmacodynamic effects on serotonin in children that are similar to that seen in adults (Findling et al. 2002b).

Based on these findings, the authors suggested that paroxetine at a dose of 10 mg per day appears to be an appropriate starting dose. For those who do not respond to this treatment, a dose increase to 20 mg/day may be a reasonable strategy.

The other PK study was a 6-week, open-label trial in patients with either MDD or OCD.

Twenty-seven (27) children between the ages of 7 and 11 years and 35 adolescents between the ages of 12 and 17 years were initially treated with 10 mg of paroxetine per day for 2 weeks. These patients then received 20 mg of paroxetine a day for 2 weeks, and were subsequently treated with 30 mg of paroxetine per day for 2 more weeks. Blood sampling for PK analyses was then performed at the end of the 2-week treatment period for each dose (GlaxoSmithKline 2005a).

Results of this study confirmed the nonlinear relationship between systemic paroxetine exposure and paroxetine dose. In addition, the children in this study were noted to generally have higher systemic exposure to paroxetine than the adolescents who participated. The data from this trial suggest that children might be able to be treated with a lower initial paroxetine dose than adolescents.

Efficacy studies. In a study in which 275 youths 12–18 years of age were randomized to receive paroxetine, imipramine, or placebo in a double-blind fashion, paroxetine was found not to be superior to placebo on the two primary outcome measures (Keller et al. 2001). However, paroxetine was shown to be associated with greater symptom reduction than placebo on several secondary outcome assessments. In this study, patients were initially treated with 20 mg/day of paroxetine given as a single daily dose. Subjects could subsequently have their dose of paroxetine increased in 10-mg increments to a maximum total daily dose of 40 mg/day, with doses of 30 or 40 mg/day given in divided doses, based on the treating physicians' discretion. Of the 93 youths treated with paroxetine, 42 remained on 20 mg/day, with the rest having their dose increased to 30 or 40 mg/day (GlaxoSmithKline 2005b).

In an 8-week study of 206 youths between the ages of 7 and 17 years (Dubitsky 2004; GlaxoSmithKline 2005c), no statistically significant difference between paroxetine and placebo was found (Laughren 2004; GlaxoSmithKline 2005c). Of note, all patients were started on a dose of 10 mg per day for the 1st week of treatment. After 1 week of treatment, paroxetine could be increased at 10-mg increments to a maximum daily dose of 50 mg/day. Notably,

only 5% of patients remained on the 10-mg paroxetine dose throughout the trial. In addition, approximately 60% of patients were treated with doses of paroxetine greater than 20 mg/day (GlaxoSmithKline 2005c).

In a 12-week study of 286 adolescents between the ages of 13 and 18, paroxetine was again not found to be superior to placebo (Laughren 2004; GlaxoSmithKline 2005d). In this study, paroxetine was initiated at a dose of 20 mg per day. Subjects could be treated with a maximum dose of 40 mg of paroxetine per day (Dubitsky 2004). Fifty-six percent (56%) of subjects did not have their dose of paroxetine raised from the 20-mg/day level (GlaxoSmithKline 2005d).

Interpretation. The doses of paroxetine employed in the RPCTs generally exceeded the doses of paroxetine that would be recommended, based on the results of the PK studies. As the systemic exposure to paroxetine is not proportional to dose, the effects of this decision could be substantial. Of particular interest is the finding that in a recent review by the FDA of antidepressant trials, paroxetine was found to have the highest risk of treatment-emergent agitation or hostility (Hammad 2004). It is interesting to speculate whether or not the same rates of agitation or hostility, as well as improved efficacy, would have been observed if more conservative dosing strategies had been employed in the MDD RPCT.

Citalopram

Pharmacokinetic studies. The first PK study of citalopram examined 11 adolescents (ages 12–17 years) and 7 adults (18–45 years) with MDD (Gutierrez et al. 2000). These patients were treated with citalopram at a dose of 20 mg/day for 1 week, followed by 3 weeks of treatment with citalopram at a dose of 40 mg/day. After 4 weeks of treatment, subjects had blood sampling performed for subsequent pharmacokinetic analyses. The authors found that the PK parameters of citalopram were similar in the adolescents and adults. The $t_{1/2}$ of citalopram in adolescents was 38.4 hours and the $t_{1/2}$ of citalopram in adults was 44 hours.

In a PK study of adolescents between the ages of 9 and 17 years, Axelson et al. (2002)

treated patients with 20 mg of citalopram per day (Perel et al. 2001; Findling et al. 2004). Intensive sampling for PK-parameter estimation was performed after both a single 20-mg dose ($n = 9$), as well as after multiple daily doses of citalopram. As part of this study, the authors examined S-citalopram concentrations.

S-citalopram, now marketed in the United States as escitalopram, is the S-enantiomer of racemic citalopram. It has been suggested that the S-enantiomer of the isomer is responsible for the salutary effects of the compound and that the R-enantiomer is clinically inactive (Aronson and Delgado 2004).

The authors found a substantial correlation between CYP 2C19 activity and S-citalopram concentration after treatment with multiple daily doses of citalopram. The authors also observed that the $t_{1/2}$ for S-citalopram after a single 20-mg dose (16.9 hours), and the half life of S-citalopram after multiple 20 mg daily doses (19.2 hours) were both shorter in the adolescents they examined when compared to what had been previously observed in adults. Based on these data, the authors raised the question whether or not citalopram, when given at a dose of 20 mg per day, should be dosed twice-daily in adolescents in order to obtain optimal therapeutic effectiveness.

Efficacy studies. In an 8-week MDD study (Wagner et al. 2004a), 174 youths between 7 and 17 years were treated with an initial dose of 20 mg/day of citalopram. After 4 weeks of treatment, subjects could have this dose increased, based on the treating physician's discretion, to a dose of 40 mg/day. Overall, at an average dose of 24 mg/day, the medication was found to be generally well tolerated, with those patients randomized to active treatment receiving superior benefit to those randomized to receive placebo.

In another multisite, placebo-controlled study, 244 youths between 13 and 18 years of age with MDD were treated with citalopram at doses ranging between 10 and 40 mg per day for up to 12 weeks. The starting dose of citalopram was 10 mg/day. This could be increased in 10-mg increments, based on clinical response and tolerability (Dubitsky 2004). In this study, treatment with citalopram was not found to be

superior to treatment with placebo (Laughren 2004). However, it should be noted that this study is different from the other multisite study of citalopram in methodology. This study permitted inpatients as subjects and allowed the use of concomitant psychoactive medications (Dubitsky 2004). It is possible that these two factors may have contributed to the discrepant results between these two citalopram trials.

Interpretation. The dose of citalopram examined in both efficacy studies did not exceed the doses of citalopram that were examined in the PK studies. Based on the extant data, it appears that, for patients receiving 20 mg of citalopram per day, a twice-daily dosing strategy might be reasonable. Whether or not evidence for improved efficacy for citalopram might have been found in the two RPCTs if a twice-daily dosing schema had been employed for patients receiving less than 40 mg per day of citalopram remains an empiric question. Interestingly, one of the RPCTs (Wagner et al. 2004a) enrolled children and adolescents. However, based on the finding that the $t_{1/2}$ of the active isomer of citalopram might be shorter in adolescents than adults (suggesting possible age-related effects on PK parameters), it is particularly unfortunate that there is an absence of available PK data for citalopram in children.

Escitalopram

Pharmacokinetic studies. There is one PK study of escitalopram in youths. In this study, a single 10-mg dose was given to 11 adolescents (12–17 years) and 12 adults (ages 18–35 years) (Periclou et al. 2003). The authors found that the $t_{1/2}$ of escitalopram was 19.0 hours in adolescents and 28.9 hours in adults. It was also observed that the overall systemic exposure was approximately 15% greater in adults than in adolescents.

Efficacy studies. There is one RPCT of escitalopram in juvenile MDD (Wagner et al. 2004b). In this study, 264 youth between the ages of 6 and 17 years, were randomized to receive either escitalopram or placebo for up to 8 weeks after a 1-week placebo lead-in. The starting dose of escitalopram was 10 mg/day and could be

increased to 20 mg/day at the end of week 4 of active treatment. Overall, no statistically significant difference between the two treatment arms was found. However, post hoc analyses suggested that among adolescents (ages 12–17 years) who completed the study, those who received escitalopram had greater symptom amelioration than those who received placebo.

Interpretation. It is interesting to note that the results of Periclou et al. (2003) with escitalopram in adolescents are very similar to those of Axelson et al. (see above) with citalopram. As with citalopram, it is possible that improved efficacy might have been seen if twice-daily dosing of escitalopram had occurred when doses less than 20 mg per day were administered in the RPCT. In addition, it appears that escitalopram might be more effective in adolescents than children when the dosing strategies employed in the RPCT are utilized. Unfortunately, in the absence of PK data in children, the extent to which a development-based difference in escitalopram drug disposition might have contributed to this observation remains unknown.

Venlafaxine

Pharmacokinetic studies. One PK study has been conducted with venlafaxine. The multiple-dose PK of venlafaxine was examined in 6 children and 6 adolescents who were administered a dose of approximately 2 mg per kg each day (Derivan et al. 1995). The authors observed that the overall systemic exposure to both venlafaxine and its active metabolite, *O*-desmethylvenlafaxine, was lower than that seen in adults when a similar dosing strategy was used.

Efficacy studies. Three RPCTs have examined the efficacy of venlafaxine. In the first (Mandoki et al. 1997), 40 patients with MDD between the ages of 8 and 17 years were randomized to receive either venlafaxine or placebo as an adjunct to psychotherapy for 6 weeks. Patients between the ages of 8 and 12 years had their venlafaxine titrated to a dose of 12.5 mg thrice-daily over the course of the 1st week of the study. The older subjects had their dose of venlafaxine gradually increased during the 1st

week of the study to a target dose of 25 mg thrice-daily. Overall, the authors found that benefit was equivalent across both treatment arms and that the study treatments were generally well tolerated. This study lacked a placebo-only arm and randomized a small number of subjects. These methodological considerations may have substantially contributed to the finding that active treatment was not superior to placebo coupled with psychotherapy.

There are two larger-scale, double-blind, placebo-controlled studies in which children and adolescents between the ages of 7 and 17 years suffering from MDD were treated for up to 8 weeks with either extended-release venlafaxine or placebo after either a 1- or 2-week single-blind placebo run-in phase (Emslie et al. 2004). In the first study, 165 youths were randomized to receive active treatment or placebo. In the second study, 196 youths were randomized (Dubitsky 2004). In each of these trials, subjects had the opportunity of having their venlafaxine increased to a maximum dose of 112.5–225 mg/day, depending on their body weight. Some subjects could receive treatment that exceeded 4 mg/kg/day per protocol. When considered separately, both studies failed to show overall efficacy of venlafaxine when compared to placebo (Laughren 2004). A post hoc analysis of the pooled data from the adolescents randomized ($n = 161$) across both studies suggested that there was superior benefit for active medication when compared to placebo in this subpopulation (Emslie et al. 2004). As far as tolerability is concerned, a relatively high number of patients (10%) who were randomized to receive active drug were discontinued from these studies because of adverse events (Emslie et al. 2004).

Interpretation. There seems to be very little empiric basis for the doses of medications used in the placebo-controlled efficacy trials. In the study of Mandoki et al., it appears that the subjects received lower doses of venlafaxine than might be recommended. However, in the two larger-scale studies, it appears that some of the study subjects could have received substantially higher doses of venlafaxine than what might be supported by the extant PK data. It is interesting to note that, based on the results of

the two larger, multisite venlafaxine trials, venlafaxine was found to be the antidepressant associated with the highest risk of suicidal behavior and suicidal ideation in MDD trials (Hammad 2004). It is possible that improved tolerability, reduced suicidality, and improved efficacy might have been found if a different dosing strategy had been employed in these trials.

Nefazodone

Pharmacokinetic studies. A PK study was conducted in which 28 depressed children and adolescents (ages 7–17 years) were treated with nefazodone (Findling et al. 2000). Blood sampling for PK analysis was done at three separate time points during the first 2 weeks of treatment—after the first 50-mg dose, after 1 week of treatment at 50 mg twice-daily, and after 1 subsequent week of treatment at 100 mg twice-daily.

When compared to adolescents, children were noted to generally have higher overall exposure and maximum concentrations (C_{\max}) of nefazodone and its three active metabolites. In addition, the $t_{1/2}$ of nefazodone and two of its metabolites appeared to be shorter in children and adolescents than what had been previously reported in adults.

After the 1st 2 weeks of the trial, patients were treated with open-label flexible doses of nefazodone for 6 more weeks. Children (7–12 years old) could have their dose increased to a maximum dose of 300 mg/day in order to optimize both clinical benefit and tolerability. Adolescents could have their dose increased to a maximum dose of 600 mg/day. The mean final doses for nefazodone were 233 mg/day for children and 342 mg/day for adolescents. Overall, the authors noted that the nefazodone treatment was generally well tolerated and associated with substantial degrees of symptomatic response. It was also suggested that doses of medication that might be best for children may be lower than what may be optimal for adolescents.

It should also be mentioned that an attempt was made to identify whether or not there was a subgroup of patients who might be at-risk for not tolerating nefazodone therapy. One of

nefazodone's active metabolites, *meta*-chlorophenylpiperazine (*m*CPP) is metabolized by cytochrome P450 2D6 (CYP 2D6) (Barbhaiya et al. 1996). For that reason, the authors examined whether or not being a poor metabolizer with respect to 2D6 was associated with reduced nefazodone tolerability. It is interesting to note that results suggested that being a poor metabolizer with respect to CYP 2D6 was not associated with a reduced ability to tolerate nefazodone therapy.

Efficacy studies. In one study, 206 youths between the ages of 12 and 17 years with MDD were randomized to receive either nefazodone or placebo for 8 weeks (Emslie et al. 2002b; Dubitsky 2004). Patients were initially treated with 50 mg of nefazodone twice-daily and could then have their dose of medication increased to a target dose of 300–400 mg/day. If there was insufficient clinical response, patients could receive a maximum daily dose of 600 mg/day. Results of this study suggested a trend for nefazodone being superior to placebo in the treatment of adolescents with MDD (Emslie et al. 2002b; Laughren 2004).

In another multicenter, placebo-controlled efficacy study, treatment with nefazodone was not found to be superior to treatment with placebo (Laughren 2004). In this study, children (ages 7–11 years) and adolescents (age 12–17 years) with MDD received either double-blind treatment with nefazodone ($n = 190$) or placebo ($n = 94$) for 8 weeks (Dubitsky 2004). Subjects were randomized to receive placebo, “low-dose” nefazodone, or “high-dose” nefazodone in approximately equal numbers. Children randomized to the “low dose” arm had their nefazodone gradually increased to a maximum dose of 100 or 150 mg/day, and children randomized to the “high dose” arm had their nefazodone dose gradually increased to 200–300 mg/day. Adolescents randomized to the “low dose” group could receive up to 300 mg/day of nefazodone, whereas adolescents in the “high dose” group received between 400 and 600 mg/day of active drug.

Interpretation. In the study of adolescents in which the dosing of nefazodone was based on the PK data for the compound, a trend for drug

superiority to placebo was found. Interestingly, in the study of children and adolescents in which the dosing was not based on PK data, no indication of therapeutic efficacy for nefazodone was observed.

Mirtazapine

Pharmacokinetic studies. Findling et al. (2001) examined the pharmacokinetics of mirtazapine after a single 15-mg dose in a cohort of 16 youths 7–17 years of age with MDD. The results of this study showed that there was a significant increase in $t_{1/2}$ with increasing weight with the values of $t_{1/2}$ for the individual patients ranged between 17.8 and 48.4 hours. The investigators also note that there was a decrease in maximum concentration (C_{max}) with increasing age.

Efficacy studies. There are two studies of mirtazapine in juvenile MDD (Dubitsky 2004). Both involved youths between the ages of 7 and 17 years. In one study, 126 subjects were randomized. In the other study, 133 subjects were randomized. Per protocol, the randomization ratio of mirtazapine to placebo was 2:1. The double-blind treatment period was 8 weeks in length. Subjects were treated at an initial dose of 15 mg/day. Subjects could subsequently have their dose of mirtazapine increased in 15-mg increments to a maximum daily dose of 45 mg. Both studies failed to show that active treatment was superior to placebo (Laughren 2004).

Interpretation. As can be seen from previously discussed PK studies, differences may be observed when single- and multiple-dose PK parameters are examined for a given drug. As multiple doses of mirtazapine were used in the placebo-controlled efficacy trials, it is unfortunate that the one PK study of mirtazapine did not examine the multiple-dose PKs of the drug.

DISCUSSION

In many instances, the dosing strategies that were employed in the placebo-controlled efficacy studies in juvenile MDD are not supported by the data available from PK studies. In addition,

there are cases in which there is inadequate evidence to either support or to refute the dosing strategies employed in some of the placebo-controlled MDD studies. This is unfortunate because identification of an evidence-based dosing strategy is generally considered to be a pivotal aspect of pediatric drug development (Atuah et al. 2004).

Inappropriate drug dosing may have contributed to the failure to detect efficacy for some antidepressant studies. Similarly, dosing may have contributed to the suboptimal tolerability seen with some of these drugs.

It should be remembered that there are limits to PK studies. Although PK data can provide vital information about how to dose a drug in a given population, age-related differences in pharmacodynamics are important considerations that can also substantially influence drug efficacy and tolerability (Vitiello and Jensen 1995). In addition, some of the PK studies that were reviewed in this paper were not designed to determine effective dosing ranges for youths, but to make comparisons with what was known about PK-parameter estimates in adults. Although such data can be used to provide rational dosing strategies for clinical trials, only methodologically stringent treatment studies can inform clinicians about the safety, tolerability, and efficacy of a given drug.

There is a need to develop evidence-based dosing strategies before studying any drug in children. This may be particularly important for antidepressants for several reasons. Firstly, other methodological factors, such as high placebo response rates, can make it difficult to detect efficacy for an agent in the treatment of MDD. In addition, antidepressants can be associated with serious side effects when they are prescribed to children and adolescents. Thus, in order for a drug to be studied in a way in which it has the best chance to adequately evaluate both efficacy and optimal tolerability, empirically based dosing strategies are needed.

As children may respond to medications differently than adults, data derived from adults may not be applicable to youths (Wiznitzer and Findling 2003). For this reason, it is important that PK, PD, and RPCT studies be performed in children and adolescents. The feasibility of successfully completing RPCTs in pediatric

MDD has been demonstrated. Because of the challenges and the large sample sizes employed in such efficacy trials, some might believe that open-label, dose-ranging, and PK studies may not be important or as "rigorous" as placebo-controlled trials. However, the results of this review suggest that PK (first- and multiple-dose trials) and dose-ranging studies may be key steps that should be completed prior to the initiation of any definitive efficacy trial. Data from these open-label trials can ultimately provide important information regarding both minimally effective and maximally-tolerated drug dosing.

CONCLUSIONS

In short, in order to optimally study both the safety and efficacy of a given drug, it is vital that the drug is dosed properly. Methodologically sound, data-supported dosing paradigms should be incorporated into RPCT efficacy studies in pediatric MDD. By not employing scientifically based dosing strategies in efficacy trials of pediatric MDD, investigators risk the possibility of not being able to test whether or not these compounds are either safe or truly have efficacy.

DISCLOSURES

Dr. Robert L. Findling receives or has received research support, acted as a consultant or served on a speaker's bureau for Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Synthelabo, Shire, Solvay, and Wyeth. Dr. Norah C. Feeny has received research support from Pfizer. Dr. Nora K. McNamara, Dr. Robert J. Stansbrey, Dr. Christopher M. Young, and Franco Peric have no financial ties to disclose. Dr. Eric A. Youngstrom has received research support from Abbott and AstraZeneca.

REFERENCES

Alderman J, Wolkow R, Chung M, Johnston HF: Sertraline treatment of children and adolescents

with obsessive-compulsive disorder or depression: Pharmacokinetics, tolerability, and efficacy. *J Am Acad Child Adolesc Psychiatry* 37:386-394, 1998.

Aronson S, Delgado P: Escitalopram. *Drugs Today (Barc)* 40:121-131, 2004.

Atuah KN, Hughes D, Pirmohamed M: Clinical pharmacology: Special safety considerations in drug development and pharmacovigilance. *Drug Safety* 27:535-554, 2004.

Axelsson DA, Perel JM, Birmaher B, Rudolph GR, Nuss S, Bridge J, Brent DA: Sertraline pharmacokinetics and dynamics in adolescents. *J Am Acad Child Adolesc Psychiatry* 41:1037-1044, 2002.

Barbhaiya R, Buch A, Greene D: Single- and multiple-dose pharmacokinetics of nefazodone in subjects classified as extensive and poor metabolizers of dextromethorphan. *Br J Clin Pharmacol* 42:573-581, 1996.

Conners CK, Casat CD, Gualtieri CT, Weller E, Reader M, Reiss A, Weller RA, Khayrallah M, Ascher J: Bupropion hydrochloride in attention-deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 35:1314-1321, 1996.

Derivan A, Aguiar L, Upton GV, Martin P, D'Amico D, Troy S, Ferguson J, Preskorn S: A study of venlafaxine in children and adolescents with conduct disorder. New Orleans (Louisiana), Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 1995.

Dubitsky GM: Review and evaluation of clinical data: Placebo-controlled antidepressant studies in pediatric patients. Online document at: www.fda.gov/ohrms/dockets/ac/04/briefing/20044065b1-08-TAB06-Dubitsky-Review.pdf / Accessed on January 24, 2005.

Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J: A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54:1031-1037, 1997.

Emslie GJ, Findling RL, Rynn MA, Marcus RN, Fernandes LA, D'Amico MF, Hardy SA: Efficacy and safety of nefazodone in the treatment of adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 12:299, 2002b.

Emslie G, Findling R, Yeung P, Kunz N, Durn B: Venlafaxine XR in the treatment of children and adolescents with major depressive disorder. *Int J Neuropsychopharmacol* 7:S351, 2004.

Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG: 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, 2002a.

Findling R: The relevance of pharmacokinetic studies of antidepressants. In: 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACA-

- PAP). Edited by Remschmidt H, Belfer M. Berlin, Germany: Steinkopff Verlag Darmstadt, 2004, p 75.
- Findling RL, Feeny NC, Stansbrey RJ, Delperto-Bedoya D, Demeter C: Somatic treatment for depressive illnesses in children and adolescents. *Child Adolesc Psychiatr Clin NA* 11:555–578, 2002a.
- Findling RL, Myers C, O’Riordan MA, Branicky LA, Pettigrew A, Reed MD, Blumer JL: An open-label dosing study of paroxetine in depressed youths. *Curr Ther Res* 63:588–601, 2002b.
- Findling RL, Preskorn SH, Marcus RN, Magnus RD, D’Amico F, Marathe P, Reed MD: Nefazodone pharmacokinetics in depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry* 39:1008–1016, 2000.
- Findling RL, Reed MD, Blumer JL, Boyle KR, van den Heuvel MW: Mirtazapine pharmacokinetics in depressed children and adolescents. Honolulu (Hawaii), Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2001.
- Findling RL, Reed MD, Myers C, O’Riordan MA, Fiala S, Branicky LA, Waldorf B, Blumer JL: Paroxetine pharmacokinetics in depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38:952–959, 1999.
- GlaxoSmithKline: Paroxetine and Pediatric and Adolescent Patients, Pharmacokinetics Study 715. Online document at: www.gsk.com/media/paroxetine.htm / 2005a. Accessed on January 31, 2005.
- GlaxoSmithKline: Paroxetine and Pediatric and Adolescent Patients, Unipolar Major Depression Study 329. <http://www.gsk.com/media/paroxetine.htm> / 2005b. Accessed on January 31, 2005.
- GlaxoSmithKline: Paroxetine and Pediatric and Adolescent Patients, Major Depressive Disorder Study 701. Online document at: www.gsk.com/media/paroxetine.htm / 2005c. Accessed on January 31, 2005.
- GlaxoSmithKline: Paroxetine and Pediatric and Adolescent Patients, Unipolar Major Depression Study 377. Online document at: www.gsk.com/media/paroxetine.htm / 2005d. Accessed on January 31, 2005.
- Gutierrez M, Chou T, Tiseo P, Sherman T, Abramowitz W: The pharmacokinetic profile of citalopram in adolescents and adults with major depressive disorder (MDD). New York (NY), Annual Meeting of the American Academy of Child & Adolescent Psychiatry, October, 2000.
- Hammad TA: Review and evaluation of clinical data. Online document at: www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf / Accessed February 7, 2005.
- Hoog SL, Heiligenstein JH, Wagner KD, Findling RL, Ernest DE, Nilsson M, Jacobson JG: Fluoxetine treatment 20 mg versus 40–60 mg for pediatric fluoxetine 20 mg nonresponders. New Orleans (Louisiana), American Psychiatric Association Annual Meeting New Research Abstracts, October, 2001.
- Jensen PS, Ryan ND, Prien R: Psychopharmacology of child and adolescent major depression: Present status and future directions. *J Child Adolesc Psychopharmacol* 2:31–45, 1992.
- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE: Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 349:1157–1167, 2003.
- Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP: Efficacy of paroxetine in the treatment of adolescent major depression: A randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 40:762–772, 2001.
- Laughren TP: Memorandum to members of PDAC and Peds AC: Background comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC). www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-04-Tab02-Laughren-Jan5.pdf / Accessed on January 24, 2005.
- Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL: Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull* 33:149–154, 1997.
- Marsden CA, Tyrer P, Casey P, Seivewright N: Changes in human whole blood 5-hydroxytryptamine (5-HT) and platelet 5-HT uptake during treatment with paroxetine, a selective 5-HT uptake inhibitor. *J Psychopharmacol* 1:244–250, 1987.
- Perel J, Axelson D, Rudolph G, Birmaher B: Stereoselective PK/PD of \pm citalopram in adolescents: Comparisons with adult findings. *Clin Pharmacol Ther* 69:30, 2001.
- Periclou A, Rao N, Sherman T, Ventura D, Abramowitz W: Single-dose pharmacokinetic study of escitalopram in adolescents and adults. Atlanta, (Georgia), Annual Meeting of the American College of Clinical Pharmacy, November, 2003.
- Research Unit on Pediatric Psychopharmacology Anxiety Study Group: Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 344:1279–1285, 2001.
- Riddle MA, Reeve EA, Yaryura-Tobias JA, Yang HM, Claghorn JL, Gaffney G, Griest JH, Holland D, McConville BJ, Pigott T, Walkup JT: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: A randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry* 40:222–229, 2001.

- Simeon JG, Dinicola VF, Ferguson HB, Copping W: Adolescent depression: A placebo-controlled fluoxetine treatment study and follow-up. *Progr NeuroPsychopharmacol Biol Psychiatry* 14:791–795, 1990.
- Treatment for Adolescents with Depression Study (TADS) Team: Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized, controlled trial. *J AMA* 292:807–820, 2004.
- U.S. Food and Drug Administration: FDA approves Prozac for pediatric use to treat depression and OCD. Online document at: www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html
- Vitiello B, Jensen PS: Developmental perspectives in pediatric psychopharmacology. *Psychopharmacol Bull* 31:75–81, 1995.
- Wagner KD, Ambrosini P, Rynn M, Wohlberg C, Yang R, Greenbaum MS, Childress A, Donnelly C, Deas D, for the Sertraline Pediatric Depression Study Group: Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: Two randomized, controlled trials. *J AMA* 290:1033–1041, 2003.
- Wagner KD, Jonas J, Bose A, Tourkodimitris S: Controlled trial of escitalopram in the treatment of pediatric depression. Washington (DC), Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October, 2004b.
- Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE: A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry* 161:1079–1083, 2004a.
- Wilens TE, Cohen L, Biederman J, Abrams A, Neft D, Fairs N, Sinha V: Fluoxetine pharmacokinetics in pediatric patients. *J Clin Psychopharmacol* 22:568–575, 2002.
- Wiznitzer M, Findling RL: Why do psychiatric drug research in children? *Lancet* 361:1147–1148, 2003.

Address reprint requests to:

Robert L. Findling, M.D.
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, Ohio 44106–5080

E-mail: Robert.Findling@uhhs.com

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.