

REVIEW AND EVALUATION OF CLINICAL DATA

**PLACEBO-CONTROLLED ANTIDEPRESSANT STUDIES IN
PEDIATRIC PATIENTS**

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EXECUTIVE SUMMARY

Several placebo-controlled trials of SSRI's and other modern antidepressant agents in children and adolescents have suggested an increased risk of suicidal ideation and suicide attempts in subjects randomized to drug compared to placebo. These findings were the topic of a meeting of the Psychopharmacological Drugs Advisory Committee on February 2, 2004, and the basis for the addition of WARNINGS statements to the labeling of these drugs shortly thereafter.

The potential for clinically important variation in the classification of these adverse events is considerable and, thus, the findings at that point were not considered definitive. To standardize the identification and classification of these experiences, all relevant adverse events from placebo-controlled pediatric trials with these agents were recently evaluated and classified using criteria developed at Columbia University by clinicians with expertise in the field of pediatric suicidality. These results of this effort are under analysis by Dr. Tarek Hammad, of the Safety Team in the Division of Neuropharmacological Drug Products at the FDA, with input from the Office of Drug Safety and the Office of Counter-Terrorism and Pediatric Drug Development.

This review was conducted in support in Dr. Hammad's analysis and comprised a review of each of 23 placebo-controlled studies of these drugs in the pediatric population, with the objectives of determining study pooling strategies for the analysis and identifying differences in study characteristics which might explain observed variation in suicidal risk between these studies.

As this review is purely descriptive in nature, no conclusions or recommendations are offered based on this information per se.

CLINICAL REVIEW

1.0 Background

1.1 Rationale

The FDA has been investigating a potential link between the use of SSRI's and other commonly used antidepressant agents and the emergence of suicidal ideation and suicide attempts in pediatric patients. Most recently, this investigation has focused on a careful classification and analysis of all events suggestive of suicidality from placebo-controlled pediatric clinical trials with these drugs. This analysis is being conducted by Dr. Tarek Hammad from the Safety Team within the Division of Neuropharmacological Drug Products with collaborative input from the Office of Drug Safety and the Office of Counter-Terrorism and Pediatric Drug Development.

The objective of this review was to describe and summarize the design characteristics of each placebo-controlled trial in order to provide some guidance in determining appropriate study pooling strategies in the analysis of these data and to identify factors that may explain different results among these trials.

1.2 Methodology

Dr. Hammad's analysis of suicidality encompassed 23 placebo-controlled pediatric trials conducted with the following nine agents: Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Luvox (fluvoxamine), Celexa (citalopram), Wellbutrin (bupropion), Effexor XR (venlafaxine extended-release), Serzone (nefazodone), and Remeron (mirtazapine).

This review entailed an examination of the study protocol, with amendments, and the final study report for each of 23 pediatric studies.¹

The following study characteristics were systematically documented:

- study initiation and completion dates.

¹ With one exception: there was no study report for study 75, a trial of Wellbutrin in patients with attention deficit disorder. A published report of this trial was utilized in lieu of a formal study report.

- study objective.
- number and location of study sites.
- total number of patients randomized.
- inclusion and exclusion criteria.
- screening and placebo lead-in procedures.
- randomization.
- active drug administration regimen.
- duration of double-blind treatment.
- assessments of depression and other efficacy measures.
- protocol-prohibited psychiatric medications.
- concomitant medication usage.
- incidence of protocol violations.
- study medication compliance rates.

Study features were then summarized in tabular form to facilitate comparisons between trials (see the Appendix to this review).

2.0 Review of Individual Clinical Trials

2.1 Prozac Studies

2.1.1 Study HCCJ

Fluoxetine versus Placebo in Adolescent Depressed Patients (March 1984-September 1987)

Study Objective

This study was conducted to compare the efficacy and safety of fluoxetine versus placebo in adolescent patients with major depressive disorder.

Patient Sample

Forty patients were enrolled from one Canadian site. According to the study report, 50 patients were to be entered into the study. However, the trial was terminated early due to slow enrollment and was not considered a supportive efficacy study by the sponsor due to its incomplete status.

Relevant patient selection criteria are summarized below.

Inclusion Criteria

- DSM-III major depressive disorder; unipolar; single or recurrent episode.

- HAM-D score at least 20 (version not specified).
- Raskin Depression Scale score at least 8.
- Raskin Depression Scale score must exceed the Covi Anxiety Scale score.
- ages 12-17 years, inclusive.
- outpatients.

Exclusion Criteria

- pregnant or sexually active females.
- lactating patients.
- serious suicidal risk.
- hypertensive patients treated with reserpine.
- significant illness that is not stabilized.
- mental retardation, organic brain disease, or history of seizures.
- schizophrenia or other psychosis.
- history of drug or alcohol abuse with one year.
- improvement during the placebo period (decrease in the HAM-D of 20% or more or below 20).

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

All patients received single-blind placebo for four to ten days (Study Period 1). Then, after randomization, double-blind fluoxetine or placebo was administered for six weeks (Study Period 2). Randomization methodology was not specified. Twenty-one patients were randomized to fluoxetine and 19 to placebo. Treatment consisted of 10mg fluoxetine capsules or matching placebo. Fluoxetine was dosed as follows:

	<u>AM</u>	<u>PM</u>
Days 1-3	10mg	10mg
Days 4-7	20mg	20mg
Weeks 2-6	10-30mg	10-30mg

The dose could be adjusted at the investigator's discretion by increasing the morning dose or decreasing the evening dose. If possible, the daily dose was to be equally divided. When feasible, the patient was to receive the maintenance dose established at week 2 of Period 2 during weeks 3-6.

The following scales were rated once each week during the trial: HAM-D, CGI, Raskin Depression Scale, Covi Anxiety Scale, SCL-58, PGI, Efficacy Index, and Adverse Experiences Form.

All patients who completed the trial could receive open-label fluoxetine for an additional 12 weeks under a separate protocol.

Concomitant Treatments

If deemed necessary by the investigator, chloral hydrate (0.5 or 1.0 g/day) was allowed for sleep during weeks 1 and 2 of Period 2. No other psychotropic medication was permitted.

Concomitant medication usage during the trial was not addressed in the study report.

Protocol Violations

No protocol violations were described in the clinical study report.

Compliance with study medication was not specifically addressed.

2.1.2 Study X065

Fluoxetine versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents (April 10, 1991 - February 28, 1995)

Study Objective

The primary study objective was to test the hypothesis that fluoxetine 20 mg/day is more effective than placebo in the treatment of children (age 8 to <13 years) and adolescents (age 13 to ≤18 years) diagnosed with DSM-III-R major depression after 8 weeks of treatment.

Patient Sample

This study was conducted at one U.S. site by Graham Emslie, M.D., of the University of Texas Southwestern Medical Center at Dallas. This study was not sponsored by Lilly but was supported by NIMH. It was not conducted under an IND.

A total of 108 patients entered this study. Relevant selection criteria are summarized below.

Inclusion Criteria

- female or male outpatients, age 8-18 years, with non-psychotic major depressive disorder by DSM-III-R; single or recurrent episodes.
- normal intelligence.

Exclusion Criteria

- diagnosis of bipolar I or II disorder.
- diagnosis of psychotic depression.
- history of bipolar I disorder in one or more first degree relatives.
- significant previous or concurrent medical illness.
- prior adequate treatment with fluoxetine.
- independent sleep disorder.
- history of alcohol or substance abuse.
- history of eating disorders.
- if sexually active, not using adequate birth control measures.

If a patient did not meet enrollment criteria and was inadvertently enrolled, the patient was discontinued unless there were ethical reasons to keep the patient in the trial.

Study Design

Patients underwent a rigorous 3-week diagnostic evaluation prior to inclusion in the acute treatment study. Patients were initially screened over the telephone and, if criteria for study entry were met, the patient and parent were scheduled for an initial evaluation. This initial assessment was performed by a clinician not involved in the treatment phase of the trial and included a structured psychiatric interview. Patient and parent were interviewed separately using a clinician-rated structured DSM-III-R-based interview schedule, the Diagnostic Inventory for Children (DICA) with parent and child versions.

Parents were interviewed using a modified family history Research Diagnostic Criteria (RDC) questionnaire. The medical history of each first and second degree relative was reviewed with regards to the presence of symptoms consistent with affective disorder, suicide, alcohol and

substance abuse, criminal behavior, schizophrenia, anxiety disorders, hysteria, and other psychiatric disorders. Additional information was obtained regarding functional impairment caused by the disorder and treatment. The parent and patient were interviewed together to complete the clinician-rated CDRS-R scale. In addition, several self-report measures were collected. If the patient met inclusion/exclusion criteria, he/she was scheduled for a repeat interview one week later.

At the second interview, the patient and family were interviewed by one of three primary investigators involved in the treatment phase of the study. DSM-III-R data collected with the DICA in the first interview were reviewed and the investigator rated the patient on the depressive items from the K-SADS, CDRS-R, CGAS, BID, and BPRS-C.² A third interview was scheduled one week after that.

The third interview was conducted by another of the three investigators and was independent from the previous assessments. DSM-III-R data from the DICA were reviewed and the K-SADS depressive items and CDRS-R were scored. Parent and patient self-report measures were repeated (CGAS, BID, and BPRS-C). The family history was also reviewed.

After completion of the three interviews, a consensus meeting was held. At this meeting, the investigators systematically reviewed data from interviews, parent and child self-report measures, and additional information (e.g., CDRS-R scores). The clinicians first reached consensus for the primary diagnosis of major depressive disorder. They then discussed the presence or absence of any secondary comorbid diagnoses for each patient. Onset dates for each diagnosis were estimated from parent's information.

If the patient met inclusion/exclusion criteria at all three interviews and the CDRS-R score was >40, the patient entered the treatment phase of the trial (Study Period I).

² Kiddie Schedule for Affective Disorders, Children's Depression Rating Scale-Revised, Children's Global Assessment Scale, Bellevue Index of Depression, and the Brief Psychiatric Rating Scale-Children, respectively.

During Study Period I, single-blind placebo medication was administered to patients for one to two weeks. One hundred and eight patients entered this phase. Patients took one placebo capsule each morning. This phase was intended to minimize the inclusion of placebo responders. After one week, if a patient's CDRS-R total score was >40, he/she proceeded to Study Period II. If a patient's CDRS-R score was ≤40, the patient was allowed to continue receiving placebo for an additional week. If, after two weeks, the CDRS-R score was still ≤40, the patient was considered a placebo responder and he/she was discontinued from the study.

During Study Period II, patients were randomized and double-blind medication was administered over an eight week period. Two-by-two stratified randomization was used based on age category (children age 8 to <13 and adolescents age 13 to ≤18) and gender. Ninety-six patients were randomized, 48 to each treatment arm. In each treatment group, there were 24 adolescents and 24 children.

Treatment consisted of fluoxetine 20mg or one matching placebo capsule every morning. If the dose was not well tolerated, patients were instructed to take one capsule every other day.

During Study Period II, patients were seen on a weekly basis. Psychiatric assessments (CDRS-R, BPRS-C, CGI, and BDI (if 13 or older) or CDI (if under 13)) were performed at each visit.³

The investigator followed patients for up to one year after completion of the acute phase of this trial in an uncontrolled, naturalistic setting.

Concomitant Treatments

Prohibited concomitant medications were not specifically delineated but all concomitant medications were monitored during the trial.

The only notable use of a concomitant substance occurred in three patients who reported smoking marijuana episodically during the study (two fluoxetine and one placebo patient).

³ BDI=Beck Depression Inventory and CDI=Children's Depression Inventory. Both are patient-rated scales that measure major symptom categories associated with depression.

Protocol Violations

Three patients entered the study in violation of entry criteria: one fluoxetine and one placebo patient who were age 7 at entry and one placebo patient diagnosed with alcohol abuse. These patients completed 8 weeks, 20 days, and 6 days of double-blind treatment, respectively.

A total of nine patients (four fluoxetine and five placebo) were not compliant with study medication in the judgement of the investigator based on direct questioning and pill counts. Non-compliance was retrospectively defined as failure to take study drug on more than 2 days within a visit interval. Seven of the nine (3 fluoxetine and 4 placebo) were deemed non-compliant at only one visit. Compliance information was not available for 14 fluoxetine patients and 17 placebo patients.

Four fluoxetine and two placebo patients missed one visit.

2.1.3 Study HCJE

Fluoxetine Versus Placebo in Childhood/Adolescent Depression (April 27, 1998 to December 16, 1999)

Study Objective

The primary objective is to test the hypothesis that fluoxetine 20mg is more effective than placebo in the treatment of children (age 8 to <13) and adolescents (age 13 to <18) with DSM-IV major depression.

Patient Sample

This trial was conducted by 15 investigators at 16 study sites in the U.S. Four hundred and twenty patients entered this study (Study Period I). Important selection criteria are listed below.

Inclusion Criteria

- male or female outpatients with a primary diagnosis of nonpsychotic major depressive disorder (single or recurrent episodes) by DSM-IV criteria.
- children (age 8 to <13) and adolescents (age 13 to <18) at the time of study entry.

- CDRS-R total score >40 and a CGI severity rating of moderate or greater.
- normal intelligence.

Exclusion Criteria

- pregnant or breastfeeding females.
- sexually active and not using medically acceptable contraception.
- serious illness that was not stabilized.
- abnormal thyroid function.
- seizure disorder with a seizure in the previous 6 months.
- any of the following by DSM-IV criteria: bipolar I or II disorder, sleep-wake disorder; lifetime history of psychotic depression, anorexia, or bulimia; borderline personality disorder or substance abuse disorder (last 6 months).
- one or more first degree relatives with bipolar I disorder.
- organic brain disease.
- previous failed response to adequate antidepressant treatment.
- serious suicide risk.
- receipt of any behavior-altering, centrally-acting, or excluded medication within 7 days of study entry.
- potential need to continue or initiate other treatments for depression, such a CBT.

Patients inadvertently enrolled in violation of entry criteria were to be discontinued.

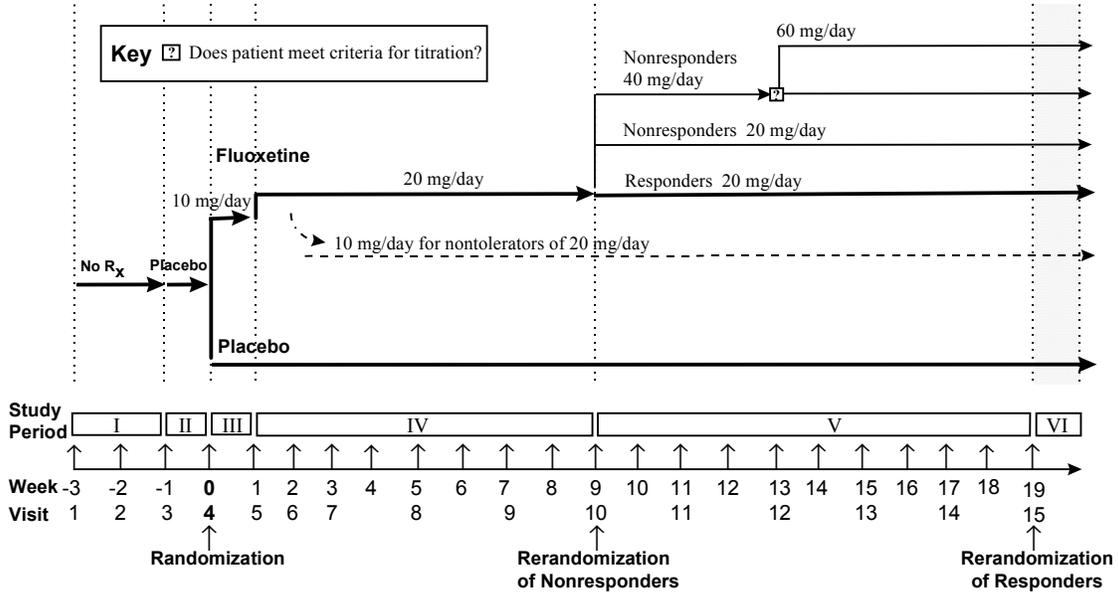
Study Design

Two general phases comprise this investigation: an acute randomized, double-blind, placebo-controlled treatment phase and a relapse prevention phase. Only the acute treatment phase will be addressed in this review.

The 19 week acute treatment phase consisted of five study periods and is depicted in the diagram below.

Period I was a diagnostic evaluation phase during which three diagnostic interviews were held about one week apart, including the Diagnostic Interview for Children and Adolescents (DICA) and K-SADS (Kiddie Schedule for Affective Disorders and Schizophrenia). At each visit, child and parent were interviewed both separately and

together. Patients meeting entry criteria at the first interview were scheduled for a second interview one week later. The second interview was conducted by a different interviewer and was independent of the first interview. Again, patients meeting criteria for entry at the second visit were scheduled for a third visit one week later, which was conducted by a third interviewer independent of the previous interviews. The diagnostic evaluation required a consensus of the three independent interviewers.



Patients meeting inclusion/exclusion criteria entered Period II, a one week, single-blind, placebo washout phase. Patients who responded to placebo were discontinued. Response was defined as a $\geq 30\%$ decrease in the CDRS-R score during this phase or a CGI-improvement score of 1 or 2 at the end of this phase compared to the first visit of the study.

Patients not responding to placebo during this phase entered Period III, a one week adaptation phase during which patients were randomized to fluoxetine 10 mg/day (N=109) or placebo (N=110). Group assignment was determined by a computer-generated randomization sequence. Randomization was stratified by gender and age category (child and adolescent):

	<u>Fluoxetine</u>	<u>Placebo</u>
Children	61	61
Adolescents	48	49
Female	54	54
Male	55	56

Patients who could not tolerate study drug were discontinued from the study. Patients tolerating fluoxetine then entered Period IV, an eight week treatment phase in which fluoxetine 20 mg/day was given (N=109); if this dose was not tolerated, 10 mg/day was administered (N=0).⁴ Patients who had been randomized to placebo continued placebo treatment (N=109). Visits were scheduled weekly for the first two weeks of the period, then biweekly. Response status was assessed at the end of Phase IV.

This was followed by Period V, which lasted 10 weeks. Fluoxetine responders at the end of Period IV remained on fluoxetine 20 mg/day (N=61) in Period V. Response was defined as a $\geq 30\%$ decrease in CDRS-R score from baseline (end of placebo washout) to the end of Period IV. Non-responders were rerandomized to either remain on fluoxetine 20 mg/day (N=15) or receive 40 mg/day (N=14); if 40 mg/day was not tolerated, the dose could be decreased to a fixed dose of 20 mg/day. If patients did not respond to 40 mg/day after four weeks (based on the CGI-improvement score), the dose could be further increased to 60 mg/day (N=4); if these patients did not tolerate 60 mg/day, the dose could be reduced during the first two weeks at the high dose. Placebo patients continued on placebo (N=68). This design insured that all patients received a constant dose during the final four weeks of this phase.

During Period V, blinding was maintained through the use of an interactive voice response system which instructed site personnel to dispense study medication identified by package numbers based on the patient's CDRS/CGI scores and the randomization scheme. All patients received three capsules of study medication daily during all periods of the study.

⁴ Although this was designed as a flexible-dose treatment period, it was in actuality a fixed-dose period since no patients required dosage reduction.

Visits were conducted biweekly. Assessments included the CDRS-R, MADRS, CDI or BDI, HAM-A, and CGI.

Responders from Period V entered Period VI, a 32 week relapse prevention phase. Responders were rerandomized to continue their treatment from Period V or to placebo. Response required a CDRS-R score ≤ 28 at the last visit of Phase V.

It should be noted by the reader that the primary analysis of suicidality was based on data from only Periods III and IV of the study.

Concomitant Treatments

Prohibited concomitant medications included antidepressants, including St. John's Wort and MAOI's; CNS stimulants, anxiolytics, antipsychotics, antimigraine drugs, sedative/hypnotics, lithium, xanthine bronchodilators, pain medications, decongestants, antihistamines, cardiovascular medications, muscle relaxants, anorexiant, and all illicit drugs.

Patients could take over-the-counter or prescription medication not specifically excluded by protocol. Chloral hydrate or Ambien were permitted for sleep but use was to be limited to no more than five days within a four week time period.

A higher proportion of fluoxetine patients used at least one concomitant medication during the trial (84.4% vs. 71.8% of placebo patients; $p=0.033$).

No prohibited antidepressants were used during these phases.

Protocol Violations

One significant protocol violation was described: a patient experienced a response to placebo during Period II (placebo washout) but was inadvertently randomized. The patient was permitted to continue in the study under compassionate use guidelines.

Compliance was assessed by direct questioning and pill counts. Patients who missed study medication for three consecutive days at any time were deemed non-compliant.

Compliance rates by visit were consistently greater than 90% and balanced between the two treatment groups.

2.1.4 Study HCJW

Fluoxetine Versus Placebo in the Treatment of Children and Adolescents with Obsessive Compulsive Disorder (March 17, 1999 to February 1, 2000)

Study Objective

The primary study objective was to test the hypothesis that fluoxetine 20 to 60 mg/day is more effective than placebo in the acute treatment of children and adolescents with obsessive-compulsive disorder (OCD) during 13 weeks of double-blind therapy.

Patient Sample

This study was conducted at 21 centers in the U.S. One hundred and forty-eight patients entered the screening phase (Period I) of the study and, of these, 103 were randomized to treatment (Period II). Important selection criteria are listed below.

Inclusion Criteria

- male or female children (age 7 to <13) or adolescent (age 13 to <18) outpatients with a primary psychiatric diagnosis of DSM-IV OCD.
- OCD symptoms of at least moderate severity at Visits 1 and 2 defined as a rating of moderate or worse (≥ 4) on the CGI-severity scale and ≥ 16 on the CY-BOCS (Children's Yale-Brown Obsessive-Compulsive Scale). One of these symptoms must have been present for at least 6 months.
- baseline score ≥ 7 on the NIMH Global OCD scale.
- CDRS-R score ≤ 40 at study entry.
- educational level and degree of understanding such that the patient could communicate intelligibly with the investigator and study coordinator.

Exclusion Criteria

- previously completed or withdrawn from any fluoxetine study.
- pregnant females, females of childbearing potential not using medically acceptable contraception, or lactating females.

- any of the following coexisting conditions: major depressive disorder as a primary diagnosis, schizophrenia, bipolar disorder, neurological disorders including Tourette's syndrome, ADHD, autism or significant developmental disorder, eating disorder, panic disorder, separation anxiety disorder, PTSD, or borderline personality disorder. If present, depression must have been deemed to be secondary to OCD in the investigator's opinion.
- psychotic features.
- involved in or planning to initiate any ongoing therapy for OCD other than supportive psychotherapy.
- serious suicidal risk.
- previous treatment with a minimum dose of 40 mg/day of fluoxetine for more than four weeks.
- below the tenth weight percentile for age and gender.
- seizure disorder, with a seizure within the past year.
- history of alcohol or drug abuse in the past year.
- a first-degree relative with bipolar I disorder.

Study Design

This trial consisted of two periods. Study Period I was a screening phase lasting 3 to 14 days during which patients were assessed for eligibility to participate in the study. No study medication was administered. Evaluations conducted at the first visit included a physical examination and medical history, laboratory tests, ECG, interview utilizing the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL), CY-BOCS, NIMH Global OCD Scale, CGI, Multidimensional Anxiety Scale for Children (MASC), and CDRS-R. Patients who met eligibility criteria returned for a second visit to begin Period II.

Period II was a 13 week, double-blind treatment phase. Patients were randomly assigned to fluoxetine or placebo in a 2:1 ratio (N=71 and 32, respectively). Randomization was not stratified by age. The distribution of patients by treatment and age range (children 7-12 and adolescents 13-17) is shown below.

	<u>Fluoxetine</u>	<u>Placebo</u>
Children	51	24
Adolescents	20	8

Fluoxetine 10 mg/day was given for the first two weeks to allow acclimation to study drug. Fluoxetine 20 mg/day was then administered for two weeks. At week 4, response was evaluated using the CGI-improvement item. If improved, 20 mg/day was continued. If not changed or worse than baseline, the dose was increased to 40 mg/day. In these latter patients, response was again evaluated at week 7. If improved, 40 mg/day was continued. If not improved or worse and the 40mg dose was tolerated, the dose was increased to 60 mg/day for the remainder of the trial. If patients on a higher dose experienced intolerance, the dose could be decreased by 20mg and would remain at that level for the rest of the trial. Patients unable to tolerate fluoxetine 20 mg/day were discontinued.

During Period II, patients were seen weekly for the first 5 weeks (Visits 2 through 7) then biweekly for the next 4 weeks (Visits 8 and 9). The final visit (Visit 10) occurred 4 weeks after Visit 9. Assessments included the CY-BOCS, NIMH Global OCD Scale, CGI, and PGI (Patient's Global Impression of Improvement). Also, the CDRS-R and MASC were assessed at baseline and at weeks 5 and 10.

No provisions for a taper of study drug or continued treatment beyond Period II were described.

Concomitant Treatments

Psychotropic drugs were not permitted during the trial except for chloral hydrate and Ambien for sleep (use limited to no more than 5 days within a four week period). Over-the-counter and prescription drugs not excluded by protocol were allowed.

Three patients took excluded concomitant medications. One fluoxetine patient reported clonidine use at Visit 1; clonidine was stopped 2 days later and the patient completed the study. One placebo patient reported taking one dose of lorazepam at Visit 1 and another placebo patient reported smoking marijuana at Visit 5.

Protocol Violations

Five patient violated inclusion/exclusion criteria (two fluoxetine and three placebo patients). One placebo and one fluoxetine patient were below the required minimum weight. One fluoxetine patient had an insufficient washout

of an excluded medication (13 days versus the required 14 days). One placebo patient had a positive urine drug screen at screening. One placebo patient was taking melatonin and niacinamide at study entry but stopped at Visit 1.

One fluoxetine patient missed Visit 5 due to illness and was subsequently lost to follow-up.

Compliance with study medication was assessed by direct questioning and pill counts. Patients missing more than five consecutive days or more than 15 cumulative days of study medication were considered non-compliant. Compliance rates were consistently greater than 95% at each visit and balanced between the treatment groups.

2.2 Zoloft Studies

2.2.1 Study 498

Double-Blind Comparison of Sertraline and Placebo in Children and Adolescents with Obsessive Compulsive Disorder (August 7, 1991 to April 4, 1994)

Study Objective

The objective of this study was to evaluate the safety and efficacy of sertraline compared to placebo in children and adolescents with obsessive compulsive disorder (OCD).

Patient Sample

This trial was performed at twelve sites within the U.S. A total of 187 patients entered the double-blind phase of this study. Important selection criteria are delineated below.

Inclusion Criteria

- male or female outpatients between 6 and 17 years old.
- DSM-III-R OCD.
- a score of 7 or more on the NIMH Global Obsessive Compulsive Rating Scale at the end of washout (baseline).
- absence of major depression demonstrated by a 24-item HAM-D total score of 17 or less and an item 1 score of 1 or zero (doubtful depressed mood or not depressed).
- negative serum beta-HCG test on day 1 of washout for females of childbearing potential. Such females had to

agree to use medically acceptable contraception throughout the trial.

Exclusion Criteria

- pregnant or nursing females.
- organic mental disorder or organic brain syndrome.
- DSM-III-R primary diagnosis of depression (major, atypical, or dysthymic disorder), bipolar disorder (depressed or atypical), schizophrenic disorder, paranoid disorder, or psychotic disorder not elsewhere classified, anxiety states (including panic disorder, phobic disorder, and generalized anxiety disorder), Tourette's syndrome, ADD, or any personality disorder or developmental disorder of sufficient severity to interfere with the patient's ability to participate in the trial.
- history of schizophrenic disorder, paranoid disorder, or psychotic disorder not elsewhere classified.
- DSM-III-R abuse or dependence on any drug or alcohol within 6 months.
- required concomitant therapy with any psychotropic medication or any drug with a psychotropic component (e.g., Librax, Benadryl).

Study Design

This was a double-blind, placebo-controlled, parallel group study beginning with a one week, single-blind placebo lead-in to eliminate early placebo responders and to allow for washout of prior psychotropic medications.

Patients still fulfilling entry criteria at the end of washout were randomized to sertraline (N=92) or placebo (N=95) and received twelve weeks of double-blind, flexible dose treatment. Randomization was stratified into two age groups: children (6-12 years) and adolescents (13-17 years):

	<u>Sertraline</u>	<u>Placebo</u>
Children	53	54
Adolescents	39	41

All study medication was taken as a single dose with an evening meal. For children randomized to sertraline, daily dosing was as follows: 25mg days 1-3, 50mg days 4-7, 75mg days 8-10, 100mg days 11-14, 125mg days 15-17, 150mg days

18-21, 175mg days 22-24, and 200mg day 25 to the end of the study.

For adolescents randomized to sertraline, the dosing regimen was: 50mg days 1-7, 100mg days 8-14, 150mg days 15-21, and 200mg day 22 to the end of the study.

For both groups, the dose could be decreased at any time due to an adverse experience. Otherwise, dose changes were not to be implemented after the end of week 4.

The following were rated at baseline and at each visit: CY-BOCS, NIMH General Obsessive Compulsive Rating, and CGI. The 24-item HAM-D was completed only on the first day of washout and at baseline.

No taper phase or option for extended treatment after double-blind therapy is described in the study protocol.

Concomitant Treatments

Allowed and prohibited concomitant medications were specified in the study protocol. Concomitant antidepressants and other psychotropic agents were prohibited. Also, patients were not permitted to receive behavior therapy or any other form of psychotherapy as treatment for OCD during the trial.

Concomitant medications were used by 75.0% of sertraline patients and 69.5% of placebo patients during double-blind treatment. The use of concomitant psychotropic drugs appeared to be minimal: one sertraline patient used Ativan and one placebo patient used alprazolam during the study.

Protocol Violations

One sertraline patient was discontinued from the trial after 43 days of treatment due to a protocol violation. The specific violation was not mentioned in the study report.

Compliance was not addressed.

2.2.2 Study 1001

A Multicenter 10-Week Randomized Double-Blind Placebo-Controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents with Major Depressive Disorder (December 22, 1999 to May 17, 2001)

Study Objective

The objective of this trial was to evaluate the safety and efficacy of sertraline compared to placebo in children and adolescents (ages 6 to 17 years) with major depressive disorder.

Patient Sample

This study was conducted at 23 centers in the U.S. and four centers in India. One hundred and eighty-eight subjects were randomized to double-blind treatment. Important selection criteria were as follows.

Inclusion Criteria

- outpatients in the age range 6-17 years.
- current episode of major depression by DSM-IV criteria for at least six weeks at screening and confirmed at baseline. Diagnosis was determined by the K-SADS-PL.
- score ≥ 45 on the CDRS-R at screening, day 7, and baseline.
- CGI-severity score ≥ 4 at screening, day 7, and baseline.
- females of childbearing potential must have a negative serum beta-HCG test at screening and, if sexually active, must be using medically acceptable contraception.
- free of psychotropic medication for at least two weeks prior to baseline except for fluoxetine (free for four weeks).

Exclusion Criteria

- current primary DSM-IV diagnosis of ADHD, conduct disorder, obsessive-compulsive disorder, or panic disorder.
- current DSM-IV diagnosis or history of bipolar disorder (manic, mixed, or not otherwise specified(NOS)).
- current psychotic features or history of schizophrenia, autistic disorder, delusional disorder, schizophreniform disorder, or psychotic disorder NOS.
- current DSM-IV anorexia or bulimia nervosa.

- DSM-IV psychoactive substance abuse disorder, previous drug or alcohol dependence/abuse within six months, or a positive urine drug screen at screening day 7.
- patients who will undergo cognitive therapy during the study or other psychotherapy directed at issues of depression. Any psychotherapy must have been underway for at least two months prior to screening and cannot be terminated during study treatment. Psychotherapy must not be initiated during the study.
- failure to respond to clinically adequate dosing with an SSRI of at least six months duration.
- pregnant or breastfeeding females.
- requiring concomitant psychotropic therapy or drugs with a psychotropic component (e.g., Donnatal) except diphenhydramine or chloral hydrate for sleep.
- subjects who have previously attempted suicide or who would pose a serious suicidal or homicidal risk during the study.
- subjects requiring inpatient treatment of depression.

Study Design

This was a randomized, double-blind, placebo-controlled, flexible dose study.

Double-blind treatment was preceded by a two week screening period. On screening day 1, assessments included a clinical interview and diagnostic evaluation using the K-SADS-PL. Also, the CDRS-R and CGI were performed.

On screening day 7, a physical examination, laboratory tests, and ECG were done as well as the CDRS-R and CGI.

On screening day 14 (baseline), diagnostic criteria were confirmed using the Affective Disorders Module of the K-SADS-PL and CDRS-R and CGI were repeated. Eligible patients were then randomized to sertraline (N=97) or placebo (N=91) with a 1:1 stratification of children (ages 6 to 11) to adolescents (ages 12 to 17). Randomization was done in blocks of two and stratification by age group:

	<u>Sertraline</u>	<u>Placebo</u>
Children	43	43
Adolescents	54	48

Double-blind treatment was continued for ten weeks. Sertraline was begun at 25 mg/day for the first three days followed by 50 mg/day until the end of the second week. Thereafter, the dose could be increased in increments of 50 mg/day at intervals of two weeks to a maximum of 200 mg/day. Dose increases above 50 mg/day were based on the clinical judgement of the investigator considering response and side effects. Dose reductions due to adverse experiences were to be done in increments of 50 mg/day to a minimum dose of 50 mg/day. The dose could be administered in either the morning or evening but divided dosing was not allowed.

The CDRS-R and CGI were performed at baseline and at the end of weeks 1, 2, 3, 4, 6, 8, and 10 of double-blind treatment.

The protocol did not provide for medication taper or continuation of treatment beyond the double-blind phase.

Concomitant Treatments

Allowed and prohibited concomitant medications are listed in the study protocol. Antidepressants, antipsychotics, sedative/hypnotics (except chloral hydrate or diphenhydramine for sleep), and other psychotropics were prohibited.

The overall incidence of concomitant drug use was similar in the two treatment groups (78.4% in sertraline and 78.0% in placebo patients). Only one patient took a concomitant antidepressant during the study (Prozac)(randomized treatment group for this patient was not specified).

Protocol Violations

Thirty-eight sertraline and 41 placebo patients deviated from the protocol. The most frequent deviations were lack of medication compliance (25 sertraline and 28 placebo patients were non-compliant at one or more visits) and use of different raters for a given patient throughout the study (10 sertraline and 11 placebo patients).⁵

⁵ Compliance was determined from pill counts and was defined as taking greater than 80% and less than 120% of the prescribed number of doses of study drug.

2.2.3 Study 1017

A Multicenter 10-Week Randomized Double-Blind Placebo-Controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents with Major Depressive Disorder (February 8, 2000 to March 26, 2001)

Study Objective

This study was designed to evaluate the safety and efficacy of sertraline compared to placebo in children and adolescents (6 to 17 years old) who are outpatients with major depressive disorder.

Patient Sample

This study was conducted at 14 sites in the U.S., 3 sites in Canada, one site in Costa Rica, one site in Mexico, and 5 sites in India. One hundred and eighty-eight patients were randomized to double-blind treatment. Important patient selection criteria are listed below.

Inclusion Criteria

- male or female outpatients age 6 to 17 years at baseline.
- current DSM-IV diagnosis of major depression for at least six weeks determined by the K-SADS-PL on screening day 1.
- CDRS-R score ≥ 45 and CGI-severity score ≥ 4 on screening days 1 and 7 and at baseline (screening day 14).
- females of childbearing potential must have a negative serum beta-HCG pregnancy test at screening day 7 and, if sexually active, must use medically acceptable contraception.
- meet all entrance criteria at baseline.

Exclusion Criteria

- current primary DSM-IV diagnosis of ADHD, conduct disorder, obsessive-compulsive disorder, or panic disorder.
- current DSM-IV diagnosis or history of bipolar disorder (mania, mixed, or not otherwise specified).
- current psychotic features or history of schizophrenia, autistic disorder, delusional disorder, schizophreniform disorder, or psychotic disorder NOS.
- DSM-IV anorexia or bulimia nervosa.
- DSM-IV psychoactive substance abuse disorder, drug or alcohol dependence within six months, or a positive urine drug screen at screening day 7.

- patients who would undergo cognitive therapy during the study. Other psychotherapy was allowed if it does not address issues of depression but it must have been in progress for at least two months prior to screening day 1 and must not have been terminated during the study. Psychotherapy could not be initiated during the trial.
- failure to respond to an adequate dose of an SSRI for at least six weeks.
- pregnant or breastfeeding females.
- history of a seizure disorder, neurological deficits that may impair the rating of the patient, or other cognitive disorders such as mental retardation.
- previous suicide attempt or patients who posed a serious suicide or homicide risk during the study.
- depression requiring inpatient treatment.

Study Design

This was a randomized, double-blind, placebo-controlled, flexible dose trial.

Double-blind treatment was preceded by a two week screening period. On screening day 1, assessments included a clinical interview and diagnostic evaluation using the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version). Also, the CDRS-R (Children's Depression Rating Scale-Revised) and CGI were performed.

On screening day 7, a physical examination, laboratory tests, and ECG were done as well as the CDRS-R and CGI.

On screening day 14 (baseline), diagnostic criteria were confirmed using the Affective Disorders Module of the K-SADS-PL and CDRS-R and CGI were repeated. Eligible patients were then randomized to sertraline (N=92) or placebo (N=96). Randomization was done in blocks of two and stratified by age category: children (ages 6 to 11) to adolescents (ages 12 to 17):

	<u>Sertraline</u>	<u>Placebo</u>
Children	43	48
Adolescents	49	48

Double-blind treatment was continued for ten weeks. Sertraline was begun at 25 mg/day for the first three days

followed by 50 mg/day until the end of the second week. Thereafter, the dose could be increased in increments of 50 mg/day at intervals of two weeks to a maximum of 200 mg/day. Dose increases above 50 mg/day were based on the clinical judgement of the investigator considering response and side effects. Dose reductions due to adverse experiences were to be done in decrements of 50 mg/day to a minimum dose of 50 mg/day. The dose could be administered in either the morning or evening but divided dosing was not allowed.

The CDRS-R and CGI were performed at baseline and at the end of weeks 1, 2, 3, 4, 6, 8, and 10 of double-blind treatment.

The protocol did not provide for medication taper or continuation of treatment beyond the double-blind phase.

Concomitant Treatments

Prohibited concomitant medications were listed in the study protocol and included antidepressants, antipsychotics, sedative/hypnotics (except chloral hydrate or diphenhydramine for sleep), and other psychotropics.

Usage of concomitant medication was similar between the two groups: 78.3% of sertraline and 74.2% of placebo patients used a concomitant medication. No use of concomitant psychotropic medication was reported.

Protocol Violations

Thirty-one sertraline and 42 placebo patients deviated from the study protocol. The most frequent deviations in both treatment groups were medication non-compliance at one or more visits (20 sertraline and 26 placebo patients) and use of different raters for a given patient throughout the study (11 sertraline and 15 placebo patients).⁶

⁶ Compliance was determined from pill counts and was defined as taking greater than 80% and less than 120% of the prescribed number of doses of study drug.

2.3 Paxil Studies

2.3.1 Study 329

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression - Acute Phase (April 20, 1994 to May 7, 1997)

Study Objective

The primary study objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

Patient Sample

This trial was conducted at 10 centers in the U.S. and 2 centers in Canada. A total of 275 patients were randomized. The following were important patient selection criteria.

Inclusion Criteria

- adolescents between the ages of 12 years 0 months and 18 years 11 months, inclusive.
- current episode of DSM-III-R major depression for at least 8 weeks. The diagnosis was made based on data from both the parent and child using the K-SADS-L. Both had to agree that the patient had a condition warranting treatment.
- severity score less than 60 on the Child Global Assessment Scale (C-GAS).
- score ≥ 12 on the 17-item HAM-D.
- IQ ≥ 80 on the Peabody Picture Vocabulary Test.

Exclusion Criteria

- current or lifetime DSM-III-R diagnosis of bipolar disorder, schizoaffective disorder, anorexia nervosa, bulimia, alcohol or drug abuse/dependence, obsessive-compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder.
- history of DSM-III-R PTSD within 12 months.
- an adequate antidepressant trial within 6 months.
- suicidal ideation with a definite plan, a suicide attempt within the current episode, or any suicide attempt by medication overdose.

- illicit drug use as documented by a drug screen within 2 weeks of the trial.
- epilepsy or mental retardation.
- pregnancy or lactation.
- sexually active females not using reliable contraception.

Although inpatients were not specifically excluded from this trial, only outpatients were actually enrolled.

Study Design

Patients were initially screened by telephone using the Screening for Youth Depression. Those who appeared likely to meet study criteria were promptly evaluated thereafter.

Diagnostic assessment utilized the K-SADS-L as well as the HAM-D and C-GAS. The parent and adolescent were interviewed separately and then the clinician formed a summary rating based on information from all sources. If there was a significant discrepancy between information obtained from the patient and parent, then the clinician, patient, and parent met to discuss the information and reach a conclusion. All K-SADS interview data was confirmed by a senior clinician who interviewed both the patient and the parent. Also, diagnostic interviews were audiotaped. Cases were reviewed by the principal or co-principal investigator to verify that each patient met entrance criteria.

If the patient met 6 or fewer of the DSM-III-R criteria for major depressive disorder or the investigator is uncertain of the diagnosis, the investigator must contact an investigator at another site to discuss the case. The external investigator reviewed the audiotape and rendered a decision. If the original investigator and external investigator disagreed, the external investigator's opinion prevailed.

After this initial assessment, the next 7-10 days were used to obtain prior treatment records, conduct other evaluations (e.g., physical examination), and document that depressive symptomatology was stable. Also, a family history was obtained from the mother or parent surrogate on all first-degree relatives. The mother's lifetime history was obtained using the SADS-L and the family history was obtained using the Family History Research

Diagnostic Criteria (FH-RDC). At the end of this interval, patients were re-evaluated.

Eligible patients were then randomized to one of three treatment arms: paroxetine (N=93), imipramine (N=95), or placebo (N=87). Treatments were randomized within blocks of six consecutive patients.

Treatment was administered under double-blind conditions for eight weeks. Additionally, this study included supportive psychotherapy. Weekly clinic visits consisted of a 45 minute session with the therapist.

There were six dosing levels (see table below). All patients were titrated to level 4 regardless of response. Levels 5 and 6 were optional for those not responding at level 4. Study drug doses were to be taken twice daily (morning and night).

LEVEL	STUDY DAYS	PAROXETINE	IMIPRAMINE
1	1-7	20mg	50mg
2	8-14	20mg	100mg
3	15-21	20mg	150mg
4	22-28	20mg	200mg
5	If needed	30mg	250mg
6	If needed	40mg	300mg

Assessments at each weekly visit included the following: HAM-D, depression section of the K-SADS-L, CGI, and adverse events. Blood samples were collected from all patients at baseline and after 4 and 8 weeks of treatment. These were analyzed for paroxetine, imipramine, and desipramine levels.

Responders at the end of 8 weeks of acute treatment continued blinded treatment on the final dose of paroxetine, imipramine, or placebo for an additional six months. Response was defined as a HAM-D score ≤ 8 or a decrease in the HAM-D total score $\geq 50\%$ from baseline. Non-responders were tapered off medication over a 7-17 day period and terminated from the study.

Concomitant Treatments

Other psychotropic medications were not allowed. Medications that are not psychotropic but that may have CNS

effects (e.g., antihistamines) were to be discouraged or used minimally.

Use of any concomitant medication was about equal across the three treatment groups (paroxetine 57.0%, imipramine 55.8%, and placebo 58.6%). Two placebo patients used concomitant psychotropic medication during double-blind acute treatment (diazepam for one day and lorazepam for 6 days). Additionally, two imipramine patients had a positive drug screen for cannabis during the trial.

Protocol Violations

There were two protocol violations that occurred in several patients each. Sixteen patients had a C-GAS score ≥ 60 at screening; 6 were in the paroxetine group, 5 in the imipramine group, and 5 in the placebo group. All 16 had a score in the range 61-70.

Compliance was defined as taking at least 80% and less than 120% of the prescribed number of capsules and was based on capsule counts at each visit. Over the eight week treatment period, 91.4% of paroxetine, 89.5% of imipramine, and 93.1% of placebo patients were considered compliant.

2.3.2 Study 377

A Double-blind, Multicentre Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Depression (April 26, 1995 to May 15, 1998)

Study Objective

The objectives of this trial were to compare the efficacy of paroxetine and placebo in the treatment of adolescents with unipolar major depression as well as to assess the safety and tolerability of paroxetine in these patients.

Patient Sample

This trial was conducted in 32 centers in Belgium, Italy, Spain, United Kingdom, Holland, Canada, South Africa, United Arab Emirates, Argentina, and Mexico. A total of 286 patients were randomized to double-blind treatment. Important patient selection criteria were as follows.

Inclusion Criteria

- male or female outpatients ages 13 years to 18 years 11 months at screening.
- current diagnosis of DSM-IV unipolar, major depression. Depression must not have occurred subsequent to OCD, panic disorder, social phobia, or PTSD.
- C-GAS (Child Global Assessment Scale) score under 69.
- MADRS score ≥ 16 .
- negative pregnancy test for females if required.

Exclusion Criteria

- patients who had not yet entered puberty.
- persistent conduct disorder in childhood or a history of non-compliance, autism or pervasive mental disorder, organic psychiatric disorder, schizophrenia, epilepsy, or serious suicidal ideation; OCD, panic disorder, social phobia, or PTSD which preceded the diagnosis of depression.
- previous response to psychotherapy for depression.
- patients scheduled to undergo long-term, formal psychotherapy. Short-term supportive psychotherapy or family supportive therapy was permitted.
- ECT in the previous three months or scheduled to undergo ECT during the study.
- current diagnosis or history in the previous six months of dependency on illicit drugs or alcohol.
- sexually active females not using reliable contraception.
- pregnant or lactating patients. Patients becoming pregnant during the study were to be withdrawn.

Study Design

Patients meeting inclusion/exclusion criteria were enrolled into a two week, single-blind placebo run-in phase.

Patients still meeting criteria at the end of run-in were randomized in a 2:1 ratio to paroxetine (N=187) or placebo (N=99) treatment for a 12 week period. Patients randomized to paroxetine received 20 mg/day during days 1-7. Thereafter, dosing was flexible in the range of 20-40 mg/day, with dose increases or decreases at weekly intervals of 10 mg/day.

Patients returned to the clinic for assessment after 7, 14, 21, 28, 42, 56, and 84 days of treatment. The MADRS and BDI (Beck Depression Inventory) were rated at each visit.

The CGI and MFQ (Mood and Feelings Questionnaire) were assessed less frequently during the trial.

Patients prematurely withdrawing from the study or completing 12 weeks of treatment were tapered off medication over a two week period.

Concomitant Treatments

Concomitant use of psychotropics was not permitted. Long-term use of other drugs with CNS activity (e.g., thyroxine) was prohibited; short-term use of such drugs was to be discouraged or used for a minimal duration of time.

Psychotropic medication was taken by 1.6% of paroxetine patients and no placebo patients.

Protocol Violations

Long-term psychotherapy was received by 9.6% of paroxetine and 8.1% of placebo patients.

Prohibited concomitant medication was taken by 4.8% of paroxetine and 5.1% of placebo patients.

In the paroxetine group, 2.7% of patient did not fulfill inclusion criteria versus no such placebo patients.

Compliance was determined from pill counts. Non-compliance was defined as taking <80% or >120% of the prescribed number of pills at each of two consecutive visits. Non-compliance rates were 1.6% in the paroxetine group and 3.2% in the placebo group.

2.3.3 Study 676

A 16 Week Double-Blind, Placebo Controlled Study to Investigate the Efficacy and Tolerability of Paroxetine in the Treatment of Children and Adolescents with Social Anxiety Disorder/Social Phobia (November 30, 1999 to October 19, 2001)

Study Objective

The primary objective was to investigate the efficacy of paroxetine in the treatment of social anxiety disorder/ social phobia in children and adolescents.

The secondary objective was to evaluate the safety and tolerability of paroxetine in this patient population.

Patient Sample

This trial was conducted in 22 centers in the U.S., 10 centers in South Africa, 4 centers in Canada, and 2 centers in Belgium.

A total of 322 patients were randomized to double-blind treatment (56.5% in the U.S., 31.1% in South Africa, 9.0% in Canada, and 3.4% in Belgium).

Important patient selection criteria are as follows.

Inclusion Criteria

- male or female outpatients with a primary diagnosis of DSM-IV social anxiety disorder/social phobia confirmed by the ADIS C/P (Anxiety Disorders Interview Schedule for DSM-IV-Child and Parent versions) structured clinical interview.
- age at least 8 and less than 18 years.

Exclusion Criteria

- another clinically predominant Axis I disorder.
- concurrent major depressive disorder.
- any history of a psychotic disorder, bipolar disorder, or pervasive developmental disorder.
- substance abuse or dependence within 3 months of screening.
- pregnant or lactating patients.
- ECT within 3 months of screening.
- serious suicide or homicide risk.
- receiving concurrent psychotherapy.
- testing positive for illicit drug use.

Study Design

This was a randomized, double-blind, placebo-controlled study. After a screening visit to assess study entrance criteria, eligible patients were randomized in a 1:1 ratio to receive either paroxetine (N=165) or placebo (N=157) for 16 weeks of double-blind treatment. An enumeration of ITT patients by treatment and age category is depicted below:

	<u>Paroxetine</u>	<u>Placebo</u>
Children	46	45
Adolescents	117	111

Paroxetine patients began treatment at a dose of 10 mg/day and maintained this dose for the first week. Then, according to clinical response and tolerability, the dose could be increased in 10 mg/day increments no more frequently than every seven days to a maximum of 50 mg/day. Dose reductions due to adverse events were permitted after the second week; patients requiring a dose reduction prior to the week 2 visit were discontinued. Doses could subsequently be increased. However, patients requiring more than one dose reduction were dropped from the trial.

Visits were conducted at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16. Assessments included the CGI, Social Phobia and Anxiety Inventory, Liebowitz Social Anxiety Scale-child version, Dalhousie Generalized Social Anxiety Disorder Scale for Adolescents (11-18 year olds), Children's Depression Rating Scale, and Global Assessment of Functioning.

For all patients completing the study or prematurely terminating, there was a gradual reduction of study medication dose. For paroxetine patients, the dose was decreased in increments of 10 mg/day per week over a maximum of four weeks.

Concomitant Treatments

Patients receiving psychotherapy or taking concomitant psychotropic medication were not to be enrolled in the trial. Previous medication was to be washed out for a minimum of 14 days before screening (4 weeks for MAOI's and fluoxetine and 12 weeks for depot neuroleptics).

A larger fraction of paroxetine patients used concomitant medication at least once during the trial (79.1% vs. 71.2% of the placebo group).

Nine paroxetine (5.5%) and six placebo (3.8%) patients took a prohibited psychoactive drug during the study.

Protocol Violations

The percentage of protocol violators was higher in the placebo group (28.8%) compared to the paroxetine group (22.7%).

Four paroxetine patients (2.5%) and one placebo (0.6%) patient were identified as having a concurrent major depressive episode prior to unblinding.

Compliance was determined from pill counts. Non-compliance was defined as missing >3 consecutive days of study medication, excluding the taper phase. In the total ITT population, 11.7% of paroxetine and 17.4% of placebo patients were non-compliant at some time during the trial.

2.3.4 Study 701

A Randomized, Multicenter, 8-Week, Double-Blind, Placebo-Controlled Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (March 20, 2000 to January 24, 2001)

Study Objective

The study objectives were to compare the efficacy, safety, and tolerability of paroxetine versus placebo in the treatment of children and adolescents with major depressive disorder.

Patient Sample

This study was conducted at 40 centers in the U.S. and one center in Canada. Three hundred and five patients were screened for this study. A total of 206 patients were randomized to double-blind treatment; 99 of the screened patients were not randomized, primarily due to failure to meet inclusion/exclusion criteria.

Relevant patient selection criteria are delineated below.

Inclusion Criteria

- male or female patients, age 7 years 0 months to 17 years 11 months, inclusive.
- DSM-IV major depressive disorder, single episode or recurrent, confirmed by the Kiddie Schedule for Affective

Disorders and Schizophrenia-Present and Lifetime semi-structured diagnostic interview.

- total raw score of 45 or greater on the Children's Depression Rating Scale-Revised (CDRS-R) at screening and baseline visits.

Exclusion Criteria

- clinically predominant Axis I disorder other than major depressive disorder.
- history of a psychotic episode or psychotic disorder.
- history of bipolar disorder.
- mental retardation or pervasive developmental disorder.
- substance abuse or dependence within 3 months of screening.
- positive test for an illicit drug.
- suicidal or homicidal risk.
- epilepsy.
- ECT within 3 months of screening.
- lactating or pregnant females.
- sexually active females not using reliable contraception.
- requiring concurrent psychotherapy.
- clear history of non-response to SSRI treatment for major depressive disorder (at least 2 different SSRI's at recommended doses for 4-6 weeks each).

Study Design

Patients underwent a screening visit (day -7 ±3 days) to determine eligibility based on inclusion/exclusion criteria.

Patients then returned for a baseline visit (day 0) about one week later. Patients who continued to meet eligibility criteria were randomized in a 1:1 ratio to paroxetine (N=104) or placebo (N=102) for 8 weeks of double-blind treatment.

The randomization scheme was stratified by age subgroup (children ages 7-11 and adolescents ages 12-17 years). Randomization was performed in blocks to ensure balance between treatment groups and each age subgroup was to account for at least 40% of the total number of randomized patients. Among children, 49 were randomized to paroxetine and 47 to placebo; among adolescents, 52 were randomized to paroxetine and 55 to placebo.

Paroxetine patients received 10 mg/day for the first week. Thereafter, the dose could be increased based on the investigator's judgement of efficacy and tolerability. Increases were to be in increments of 10 mg/day at frequencies of at least one week to a maximum of 50 mg/day. Dose could be reduced due to an adverse experience. Patients unable to tolerate 10 mg/day or requiring more than one dose reduction during the study were to be discontinued.

Visits were performed at weeks 1, 2, 3, 4, 6, and 8. Assessments included the CDRS-R, CGI, Global Assessment of Functioning, and the Kutcher Adolescent Depression Rating Scale.

Patients who completed the 8-week treatment phase or who dropped out were to undergo a gradual reduction in study medication over a period up to 4 weeks. Paroxetine was tapered in 10 mg/day increments each week of this phase.

Concomitant Treatments

The concomitant use of other psychotropic drugs or any form of psychotherapy was contraindicated during the study.

In the paroxetine group, 66.3% of the patients took at least one concomitant drug versus 57.8% of the placebo group.

In all, 4.0% of paroxetine patients and 3.9% of placebo patients took prohibited medication during the study. Several concomitant psychotropic agents were used during the trial (excluding taper): dexamphetamine, lithium, olanzapine, paroxetine, and risperidone. The number of patients taking each of these drugs was small (1-2).

Protocol Violations

A larger fraction of paroxetine patients were protocol violators (26.7% vs. 18.6% of placebo patients).

Compliance was determined from pill counts. Non-compliance was defined as missing >3 consecutive days of study medication, excluding the taper phase. Overall, 19.8% of paroxetine and 11.9% of placebo patients were non-compliant at some time during the trial.

2.3.5 Study 704

A Randomized, Multicenter, 10-Week, Double-Blind, Placebo-Controlled, Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Obsessive-Compulsive Disorder (OCD) (January 20, 2000 to July 3, 2001)

Study Objective

The objectives of this study were to assess the efficacy, safety, and tolerability of paroxetine versus placebo in the treatment of children and adolescents with obsessive-compulsive disorder (OCD).

Patient Sample

This trial was conducted at 37 centers in the U.S. and two centers in Canada. Two hundred and seven patients were randomized to double-blind treatment. Relevant patient selection criteria follow.

Inclusion Criteria

- male or female outpatients age 7 to 17 years, inclusive.
- DSM-IV OCD confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version semi-structured interview.
- history of OCD for at least two months.
- total score of 16 or greater on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) at screening and baseline.

Exclusion Criteria

- a clinically predominant Axis I disorder other than OCD.
- concurrent major depressive episode.
- pervasive developmental disorder or any history of a psychotic episode, including schizophrenia and bipolar disorder.
- substance abuse or dependence within 3 months of screening.
- positive test for illicit drug use.
- current suicidal or homicidal risk in the investigator's judgement.
- organic brain disease, epilepsy, or mental retardation.
- ECT within 3 months of screening.
- lactating or pregnant females.

- sexually active females not using reliable contraception.
- requiring psychotherapy.
- a clear history of non-response to SSRI treatment of OCD (at least two different SSRI's at recommended doses for 4-6 weeks each).

Study Design

Patients underwent a screening visit (day -7 ±3 days) to determine eligibility based on inclusion/exclusion criteria.

Patients then returned for a baseline visit (day 0) about one week later. Patients who continued to meet eligibility criteria were randomized in a 1:1 ratio to paroxetine (N=100) or placebo (N=107) for 10 weeks of double-blind treatment.

The randomization scheme was stratified by age subgroup (children ages 7-11 and adolescents ages 12-17 years). Each age subgroup was to account for at least 40% of the total number of randomized patients. Among children, 60 were randomized to paroxetine and 58 to placebo; among adolescents, 40 were randomized to paroxetine and 49 to placebo.

Paroxetine patients received 10 mg/day for the first week. Thereafter, the dose could be increased based on the investigator's judgement of response and tolerability. Increases were to be in increments of 10 mg/day at frequencies of at least one week to a maximum of 50 mg/day. Dose could be reduced due to an adverse experience. Patients unable to tolerate 10 mg/day or requiring more than one dose reduction during the study were to be discontinued.

Visits were performed at weeks 1, 2, 3, 4, 6, 8, and 10. Assessments included the CY-BOCS, CGI, and Global Assessment of Functioning.

Patients who completed the 10-week treatment phase or who dropped out were to undergo a gradual reduction in study medication over a period up to 4 weeks. Paroxetine was tapered in 10 mg/day increments each week of this phase.

Concomitant Treatments

The use of concomitant psychotropic medication was contraindicated in this trial.

In the paroxetine group, 62.2% of the patients took at least one concomitant drug versus 69.5% of the placebo group.

Prohibited psychoactive drugs were taken by 6.1% of paroxetine patients and 10.5% of placebo patients during the study. Several concomitant psychiatric agents were used during the trial (excluding taper): chlorpromazine, fluoxetine, fluvoxamine, imipramine, lorazepam, methylphenidate, and paroxetine. Few patients took these drugs (1-2 patients for each drug).

Protocol Violations

A slightly larger fraction of paroxetine patients were protocol violators (25.5% vs. 21.9% of placebo patients).

Two placebo patients (one child and one adolescent) had illicit drug use detected on drug screening.

Compliance was determined from pill counts. Non-compliance was defined as missing >3 consecutive days of study medication, excluding the taper phase. The overall rates of non-compliance (percentage of patients meeting the above criterion at any time during the study) by treatment and age group were as follows:

	<u>Paroxetine</u>	<u>Placebo</u>
Children	15.8%	19.3%
Adolescents	20.0%	16.7%

Overall, 17.5% of paroxetine and 18.1% of placebo patients were non-compliant at some time during the trial.

2.4 Luvox Study

2.4.1 Study 114.02.01

Fluvoxamine in the Treatment of Obsessive Compulsive Disorder: A Multicenter Double-Blind Placebo- Controlled Study in Outpatient Children and Adolescents (July 23, 1991 to August 17, 1994)

Study Objective

The primary objective of this study was to compare the safety and efficacy of fluvoxamine to placebo in the treatment of outpatient children and adolescents with obsessive-compulsive disorder (OCD).

Patient Sample

This trial was conducted at 20 centers in the U.S. One hundred and thirty-four patients were screened for this study, with 14 patients screened out for various reasons. Thus, a total of 120 patients were randomized.

Relevant patient selection criteria are listed below.

Inclusion Criteria

- male or female patients, ages 8-17, inclusive.
- DSM-III-R diagnosis of OCD which has been present for at least 6 months.
- females who have reached menarche must have a negative serum beta-HCG at screening and understand the potential risks of pregnancy during the study.
- body weight at least 25kg (55 lbs).
- Y-BOCS total score of at least 15 at screening and baseline.
- NIMH-OC Scale of at least 7 at screening and baseline with a score equal to or greater than the score on the NIMH Global Depression, Mania, Psychosis, or Anxiety Scale at these time points.
- CDRS-R 17-item total score no greater than 40 at screening and baseline.

Exclusion Criteria

- trichotillomania or nail-biting as the only compulsion.
- Tourette's disorder unless only by simple motor tics.

- schizophrenia, major depressive disorder, bipolar disorder, mental retardation, anorexia nervosa, bulimia nervosa, seizure disorder, or clinically significant neurological damage.
- ECT within three months.
- history of resistance to treatment for OCD with clomipramine, fluoxetine, sertraline, or paroxetine.
- require ECT or other psychotropic medication during the trial.

Study Design

This study was conducted in two phases: core and extension.

The core study comprised three periods: a screening period, titration period, and maintenance period. The extension phase consisted of open-label treatment for one year. These phases are further described below.

The 7-14 day screening period was used to evaluate study eligibility and allow for washout of prior psychotropic medication, if needed. Candidates meeting initial criteria for study entry received single-blind placebo during this time. A complete individual and family psychiatric and medical history was obtained.

At the conclusion of the screening period, baseline evaluations were performed and patients who continued to be acceptable were randomized to double-blind treatment with fluvoxamine (N=57) or placebo (N=63). Within each center, patients were assigned in approximately equal numbers to fluvoxamine or placebo according to a randomization schedule prepared by the sponsor. The distribution of patients by treatment and age group is depicted below.

	<u>Fluvoxamine</u>	<u>Placebo</u>
Children(8-12)	26	33
Adolescents(13-17)	31	30

Double-blind treatment lasted for ten weeks and consisted of a titration period and a maintenance period. During the 3-week titration period, the dose for fluvoxamine patients was gradually increased from 25 mg/day on days 1-3 to 200 mg/day by day 22. The dose could be decreased at any time in the event of an adverse experience but all patients had to receive at least 50 mg/day after day 4. Placebo

patients received an corresponding number of placebo capsules. Study medication was given at bedtime for the first week and twice daily (morning and bedtime) thereafter.

During the 7-week maintenance period, every attempt was made to maintain a constant dose. However, dose adjustments could be made if intolerable adverse experiences occurred.

Visits during this phase of the study occurred on study days 1 (baseline), 7, 14, 21, 28, 42, 56, and 70. Assessments performed during double-blind treatment included the Y-BOCS, NIMH-OC Scale, and CGI. The CDRS-R was administered only at screening, baseline, and final visits.

The extension phase allowed certain patients to continue fluvoxamine on an open-label basis for an additional year beyond the core phase. To be eligible, patient must have either completed the core study or have dropped out after at least 6 weeks of double-blind therapy due to lack of efficacy. All patients discontinued their treatment regimen after completing the core study and were re-titrated during the first 3 weeks of the extension phase using unblinded fluvoxamine.

Concomitant Treatments

All concomitant medication use was to be approved by the sponsor except for sleep medication (chloral hydrate or sedating antihistamine only), laxatives, antacids, or acetaminophen for headaches. Sleep medication was permitted only during the screening and titration phases.

Nonspecific supportive therapy and behavior therapy were permitted. However, the structure and content of such therapy was to remain constant during the course of the study.

At least one concomitant medication was taken by 59.65% of fluvoxamine patients and 50.79% of placebo patients during the double-blind treatment period of this trial.

The use of a psychiatric drug was reported by only one patient (sertraline in a patient from the placebo group).

Protocol Violations

Medication compliance was defined for each patient as taking at least 75% of all prescribed study medication based on pill counts. Among fluvoxamine patients, 91% were considered compliant versus 97% in the placebo group.

No other information on protocol violations was reported.

2.5 Celexa Studies

2.5.1 Study CIT-MD-18

A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression (January 31, 2000 to April 10, 2001)

Study Objective

The objective was to evaluate the safety and efficacy of citalopram in children (ages 7-11) and adolescent (ages 12-17) outpatients with major depressive disorder.

Patient Sample

This trial was conducted at 21 centers in the U.S. A total of 174 patients were randomized and received double-blind treatment.

Relevant patient selection criteria are presented below.

Inclusion Criteria

- male or female outpatients between 7 and 17 years of age.
- DSM-IV major depressive disorder of at least 4 weeks duration at baseline.
- CDRS-R score of 40 or greater at both screening and baseline.
- females of childbearing potential must have a negative serum beta-HCG at screening.

Exclusion Criteria

- primary psychiatric diagnosis other than major depressive disorder.

- DSM-IV ADHD, PTSD, bipolar disorder, pervasive developmental disorder, mental retardation, conduct disorder, or oppositional defiant disorder.
- presence of psychotic features.
- personality disorder of sufficient severity to interfere with study participation.
- history of substance abuse, including alcohol, within the past year.
- history of anorexia or bulimia within the past year.
- pregnancy or breastfeeding.
- females of childbearing potential not practicing or willing to practice a reliable method of birth control.
- history of a seizure.
- requiring treatment with any psychotropic medication (except zolpidem for sleep) or any drug with a psychotropic component (specified in Appendix II to the protocol, for example, anticonvulsants).
- previous failure to an adequate trial of citalopram or adequate trials of two other SSRI's.
- initiated psychotherapy or behavior therapy within three months of screening or those who plan to initiate or change such therapies during the course of the trial.
- unable to swallow tablets.
- considered a suicide risk (i.e., active suicidal ideation), a suicide attempt within the past year, or any history of hospitalization due to a suicide attempt.
- patients who might not be suitable for the study in the investigator's opinion.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study comparing flexible doses of citalopram (20-40 mg/day) to placebo.

The trial consisted of a one-week, single-blind placebo lead-in period. The diagnosis of DSM-IV major depressive disorder was confirmed at the screening visit using the K-SADS-PL.

Lead-in was followed by randomization to citalopram (N=89) or placebo (N=85) and eight-week double-blind treatment phase. The study population was to be equally stratified between children (ages 7-11) and adolescents (ages 12-17). Among the 89 citalopram patients, 45 were children and 44 were adolescents. Among the 85 placebo patients, 38 were children and 47 were adolescents.

Patients randomized to citalopram took 20mg each evening for the first 4 weeks (dosing could be switched to the morning if preferred). If, at the end of week 4 or thereafter, the clinician felt that the therapeutic response was not satisfactory and the patient was not experiencing dose-limiting adverse events, the dose could have been increased to 40mg, taken as a single daily dose. Dosage could be decreased due to adverse events but the minimum daily dose was 20mg and the maximum 40mg.

Clinic visits were conducted at screening, baseline, and at the end of weeks 1, 2, 4, 6, and 8. The CDRS-R and CGI were assessed at each visit beginning with the screening visit. The CDRS-R was administered separately to both the patient and identified parent or caregiver. If the latter did not accompany the patient, efficacy ratings were not performed. Also, at each visit after screening, the patient returned their medication bottle to the site to be inventoried.

A blood sample for steady-state citalopram plasma levels was obtained at the end of week 8 or at early termination.

Patients who completed this study were eligible to participate in a 24-week open-label extension study.

Concomitant Treatments

Psychotropic medication (except zolpidem) and other medication with a psychotropic component were prohibited during the trial.

Overall, 78.7% of citalopram patients and 74.1% of placebo patients received a concomitant medication during the study.

Prohibited concomitant medication was taken by 28% of citalopram and 22% of placebo patients. No patient received a concomitant antidepressant medication during double-blind treatment.

Protocol Violations

Due to a drug packaging error, nine patients were mistakenly dispensed medication that potentially unblinded their treatment assignment (i.e., different color coating

for citalopram and placebo). Five patients had been randomized to citalopram and four to placebo.

Four citalopram patients had citalopram and metabolite serum concentrations below the limit of quantification after double-blind treatment, indicating non-compliance. Otherwise, compliance with study medication was not addressed.

One citalopram and one placebo patient missed a clinic visit.

One citalopram patient performed a CDRS-R interview by telephone instead of in person.

2.5.2 Study 94404

A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in adolescents (November 19, 1996 to April 23, 2001)

Study Objective

The primary objective was to study the efficacy and tolerability of citalopram compared to placebo in adolescent patients suffering from major depression.

Patient Sample

This trial was conducted at 31 centers in 7 countries: 3 in Denmark, 2 in Estonia, 12 in Finland, 2 in Germany, 3 in Norway, 7 in Sweden, and 2 in Switzerland.

Two-hundred and forty-four patients were randomized. Relevant patient selection criteria follow.

Inclusion Criteria

- DSM-IV major depression with a duration of the current episode at least 4 weeks and at most one year.
- inpatients or outpatients.
- age 13-18 years, inclusive.
- Tanner Stage III (commencement of puberty).
- Beck Depression Inventory (BDI) score at least 21 for girls and at least 16 for boys.

- Global Assessment of Functioning (GAF) score 60 or less on any of the four rated items (activities, relationships, personal care, symptoms).

Exclusion Criteria

- bipolar disorder (including hypomania).
- ongoing DSM-IV ADD or disruptive behavior disorder.
- DSM-IV psychotic disorder.
- progressive neurological disorder.
- drug or alcohol abuse that influences daily functioning.
- primary anorexia nervosa or bulimia.
- attend special school for mentally retarded persons.
- pregnancy.
- ongoing pervasive developmental disorder.

Study Design

This was a randomized, double-blind, parallel group comparison of citalopram (10, 20, 30, or 40mg) versus placebo in the treatment of major depression in adolescents.

Patients were evaluated for study eligibility at a screening visit. The patient completed the BDI and GAF as well as a 5 minute interview with each parent which was recorded for subsequent analysis of expressed emotion (FMSS or Five Minute Speech Sample). The FMSS score was an exploratory variable in the primary efficacy analysis.

Then, patients meeting entry criteria were randomized in a 1:1 ratio to double-blind treatment with citalopram (N=124) or placebo (N=120) for a 12 week period. Randomization was done in blocks of four patients.

Treatment commenced after baseline assessments. For patients receiving citalopram, the initial dose was 10 mg/day for the first week. Dose increases could be made at the end of weeks 1, 2, 5, or 9 if any of the four GAF items decreased by 10 units or was unchanged from the last visit. The maximum dose increment was 10mg at each increase. The maximum daily dose was 40 mg/day. In case of intolerable adverse events, the dose could be lowered.

During double-blind treatment, visits occurred at the end of weeks 1, 2, 5, 9, and 12. Clinical assessments included the K-SADS-P, MADRS, BDI, and GAF. All investigators were

trained in the use of the K-SADS-P prior to starting the trial.

Adverse events were elicited by asking an open question; events were also rated on the UKU-checklist for adverse events (suicidal ideation was not included in this checklist).

Blood samples for the analysis of plasma citalopram and metabolite levels were taken at weeks 1 and 12.

Study medication dosing was abruptly stopped at the end of week 12.

Concomitant Treatments

The following concomitant medications were not allowed: antidepressants, buspirone, lithium, pimozide, phenytoin, sumatriptan, and oral anticoagulants.

In the citalopram group, 42% of patients continued concomitant medication and 54% started concomitant medication during the trial. In the placebo group, 47% of the patients continued and 47% started concomitant medication during the study period.

Prohibited concomitant medications were used by 1.7% of citalopram and 0.9% of placebo patients.

Protocol Violations

Deviations from inclusion, exclusion, and withdrawal criteria were noted in 13.2% of citalopram and 12.5% of placebo patients.

Three citalopram patients had serum concentrations of citalopram and metabolites below the level of quantification after double-blind treatment, indicating non-compliance. Blood samples were obtained in these patients after the supposed administration of 10, 20, and 40 mg/day. Otherwise, compliance with study drug was not addressed.

One citalopram patient mistakenly received 30mg of drug instead of 20mg for 7 days.

2.6 Wellbutrin Study

2.6.1 Study 75

A Double-Blind Comparison of the Efficacy and Safety of Bupropion versus Placebo in Children with Attention Deficit and/or Conduct Disorder (1984 to 1986)⁷

Study Objective

The primary objective of this study was to evaluate the efficacy and safety of bupropion compared to placebo in the treatment of children with attention deficit disorder (ADD).

Patient Sample

This study was conducted at four centers in the U.S. One-hundred and nine patients were randomized in this trial. Relevant patient selection criteria are presented below.

Inclusion Criteria

- age 6-12 years, inclusive.
- score of at least moderate illness severity on the Child Diagnostic Scale.
- physician diagnosis of DSM-III ADD (with or without hyperactivity) based on history and examination. A secondary diagnosis of conduct disorder was allowed.
- mean parent and teacher scores of at least 1.5 on the 93-item Connors Parent Questionnaire hyperactive-immature or restless-impulsive factors and the 39-item Connors Teacher Questionnaire hyperactivity factor.
- in good physical health and without evidence of laboratory, EEG, or ECG abnormalities.
- patients may be institutionalized or outpatients.

Exclusion Criteria

- WISC-R IQ <70.
- body weight <20kg. There was no upper weight limit.
- females who had attained menarche.

⁷ A study report for this trial was not available from the sponsor. Information regarding this investigation was based on the 8-21-84 protocol, the 4-18-85 protocol amendment, and the following publication: Connors CK, et al. Bupropion Hydrochloride in Attention Deficit Disorder with Hyperactivity. J. Am. Acad. Child Adolesc. Psychiatry, 1996;35(10):1314-1321.

- history of a seizure disorder, tic disorder, or head injury.
- any unstable medical condition.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study.

All patients underwent a single-blind placebo baseline phase for one week to identify placebo responders. Patients who scored much improved or very much improved on the CGI at baseline (day 0) were to be dropped from the study.

Eligible patients were then randomly assigned in a 2:1 ratio to bupropion (N=72) or placebo (N=37) for four weeks of double-blind treatment. Randomization methodology was not specified.

Dosing was accomplished using a flexible, ascending regimen depending on body weight as shown in the table below. Study medication was taken on a twice daily schedule (7AM and 7PM).

Study Days	Dose Level ^b	Total Daily Dose (mg) of Bupropion or Placebo			
		≈mg/kg ^c	Body Wt. (kg) ^d		
			20-30	>30-40	>40
-6 to 0	A	0	0	0	0
1 to 3	B	3	75(0)	100(0)	125(0)
4 to 7	C	4	100(0)	150(0)	175(0)
8 to 14	D	5	125(0)	175(0)	225(0)
15 to 28	E	6	150(0)	200(0)	250(0)
29 to 35	F	0	0	0	0

Assessments were conducted on days 3, 7, 14, 21, and 28 of double-blind treatment. The Connors Parent Questionnaire and Connors Teacher Questionnaire were completed at baseline and on days 14 and 28. The CGI and Brief Psychiatric Rating Scale for Children were assessed at each study visit.

Dosing was abruptly stopped after the day 28 dose. Patients were then assessed for possible discontinuation symptoms and/or deterioration in behavioral functioning during a one-week, placebo phase after double-blind treatment. The above measures plus assessment of adverse experiences and vital signs were evaluated on day 35.

Concomitant Treatments

All subjects had to be free of psychotropic medication for a minimum of 14 days prior to study entry.

Some adverse experiences were managed with concomitant medications (e.g., topical anesthetics and aspirin). No other information on concomitant drug use was available.

Protocol Violations

No information on protocol violations was reported.

Although pill counts were performed to monitor compliance with study medication, compliance rates were not reported.

2.7 Effexor XR Studies

2.7.1 Study 382

Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Major Depression (October 1997 to September 2000)

Study Objective

The objective of this study was to compare the antidepressant efficacy and safety of venlafaxine ER with placebo in children and adolescents with major depression.

Patient Sample

This study was conducted at 14 centers in the U.S. A total of 165 patients were randomized to double-blind treatment. Relevant selection criteria were as follows.

Inclusion Criteria

- age 7 through 17 years at entry.
- outpatient.

- meet DSM-IV and K-SADS criteria for major depression.
- CDRS-R score >40 at screening and baseline (study day -1) with no greater than a 30% decrease between these visits.
- symptoms of depression for at least one month prior to entry.
- CGI-severity score ≥ 4 at baseline.

Exclusion Criteria

- treatment with venlafaxine within 6 months.
- body weight <25kg.
- history of a seizure disorder other than a single childhood febrile seizure.
- history or presence of a psychotic disorder.
- history or presence of major depression with psychotic features.
- history or presence of bipolar disorder.
- history or presence of a mental disorder due to a general medical condition.
- acutely suicidal to a degree that requires precautions against suicide.
- history or presence of anorexia or bulimia.
- conduct disorder.
- panic disorder or OCD.
- at least one first-degree relative with bipolar I disorder (based on family history from a parent).
- lactating females or females of childbearing potential with a positive beta-HCG at screening. Females of childbearing potential must use a medically acceptable form of contraception during the study.
- ECT within 30 days.
- DSM-IV drug or alcohol dependence within one year.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study in depressed outpatients.

All patients underwent a single-blind, placebo screening phase for two weeks before double-blind treatment. This included a medical and psychiatric history, physical examination, laboratory tests, ECG, K-SADS, 21-item HAM-D, CDRS-R, and MADRS.

Patients who demonstrated significant improvement between screening and baseline (i.e., greater than 30% improvement

in the CDRS-R or a CDRS-R score ≤ 40) could have been rescreened within 4 \pm 3 days of baseline.

Eligible patients were then randomized to venlafaxine ER (N=80) or placebo (N=85). Medication was randomized in blocks of four patients and stratified by age group (children ages 7-12 and adolescents ages 13-17) as follows:

	<u>Placebo</u>	<u>Venlafaxine ER</u>
Children	47	42
Adolescents	38	38

Patients were treated with double-blind medication (on-therapy) for a maximum of eight weeks. All study medication was taken once daily in the morning. Dosing of venlafaxine ER was based on weight. On days 1-7, venlafaxine ER patients took 37.5 mg/day. On days 8-14, patients weighing 25-39kg could take 37.5 or 75 mg/day; larger patients took 75 mg/day. Beginning on day 15 if clinically indicated to improve response, patients weighing 25-39kg could take 75 mg/day, patients weighing 40-49kg could take 112.5 mg/day, and patients weighing greater than 50kg could take 150mg/day. Likewise, beginning on day 29 and if clinically indicated, the daily dose could be increased in these weight groups to 112.5mg, 150mg, and 225mg, respectively. Doses could be decreased at any time during the study to a minimum of 37.5 mg/day for patients weighing 25-39kg and 75 mg/day for other patients.

Visits during double-blind treatment were performed on study days 4, 7, 14, 21, 28, 42, and 56. Assessments at each visit included the HAM-D, CDRS-R, MADRS, and CGI.

Upon study completion or early termination, the medication was to be tapered over a period of at least 14 days.

Concomitant Treatments

The following treatments were prohibited: psychopharmacologic drugs, including other antidepressants; non-psychopharmacologic drugs with psychotropic effects, ECT, or the introduction or change in intensity of formal psychotherapy. Psychotherapy was allowed if well established prior to the study.

In this study, 74% of patients in both treatment groups received some type of concomitant therapy. No patients reported use of a concomitant antidepressant drug during the on-therapy treatment phase of the trial.

Protocol Violations

One placebo patient experienced a >30% decrease in the CDRS-R score between screening and baseline. One venlafaxine ER patient was discontinued from the study due to both parents having bipolar illness. Four placebo patients and one venlafaxine ER patient were dropped from the trial due to noncompliance with the study protocol.

Compliance with study drug was assessed by capsule counts at each visit. However, these counts were not recorded on the CRF's and compliance rates were not reported.

2.7.2 Study 394

Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Major Depressive Disorder (August 2000 to August 2001)

Study Objective

The objective of this study was to compare the antidepressant efficacy and safety of venlafaxine ER to placebo in children and adolescents with major depressive disorder.

Patient Sample

This study was conducted at 37 centers within the U.S. Two hundred and one patients were randomized to double-blind treatment. Relevant selection criteria were as follows.

Inclusion Criteria

- age 7 through 17 years at entry and able to swallow capsules.
- outpatient.
- meet DSM-IV and Kiddie-SADS-PL criteria for major depression.
- CDRS-R score >40 at screening and baseline (study day -1) with no greater than a 30% decrease between these visits.
- CGI-severity score ≥4 at screening and baseline.

- symptoms of depression for at least one month prior to entry.
- sexually active females must use medically acceptable contraception.

Exclusion Criteria

- treatment with venlafaxine within 6 months.
- body weight <25 kg (55 lbs).
- history of a seizure disorder other than a single childhood febrile seizure.
- history or presence of a psychotic disorder.
- history or presence of major depression with psychotic features.
- history or presence of bipolar disorder.
- presence of a mental disorder due to a general medical condition.
- acutely suicidal to a degree that requires precautions against suicide.
- history or presence of anorexia or bulimia.
- conduct disorder.
- panic disorder or OCD.
- at least one first-degree relative with bipolar disorder (based on family history from a parent).
- lactating females or females with a positive serum beta-HCG at screening.
- ECT within 30 days.
- DSM-IV drug or alcohol abuse or dependence within one year.

Study Design

This was a randomized, double-blind, placebo-controlled, flexible dose trial.

The treatment phase was preceded by a 7±3 day single-blind placebo lead-in period. This included a screening medical and psychiatric history, physical examination, laboratory tests, ECG, Kiddie-SADS-PL, 21-item HAM-D, CDRS-R, MADRS, and CGI-severity rating.

Patients who demonstrated significant improvement between screening and baseline (i.e., greater than 30% improvement in the CDRS-R or a CDRS-R score ≤40) could have been rescreened within 4±3 days of baseline.

Following this, 201 eligible patients were randomized to treatment with either venlafaxine ER or placebo. Five randomized patients failed to return after the baseline visit and, thus, only 196 patients (102 venlafaxine ER and 94 placebo patients) provided data during the double-blind treatment phase. Medication was stratified by age group (children ages 7-12 and adolescents ages 13-17) as follows:

	<u>Placebo</u>	<u>Venlafaxine ER</u>
Children	54	57
Adolescents	40	45

Patients were treated with double-blind medication (on-therapy) for a maximum of eight weeks. All study medication was taken once daily in the morning. Dosing of venlafaxine ER was based on weight. On days 1-7, venlafaxine ER patients took 37.5 mg/day. On days 8-14, patients weighing 25-39kg could take 37.5 or 75 mg/day; larger patients took 75 mg/day. Beginning on day 15 if clinically indicated to improve response, patients weighing 25-39kg could take 75 mg/day, patients weighing 40-49kg could take 112.5 mg/day, and patients weighing greater than 50kg could take 150mg/day. Likewise, beginning on day 29 and if clinically indicated, the daily dose could be increased in these weight groups to 112.5mg, 150mg, and 225mg, respectively. Doses could be decreased at any time during the study to a minimum of 37.5 mg/day for patients weighing 25-39kg and 75 mg/day for other patients.

Visits during double-blind treatment were performed on study days 7, 14, 21, 28, 42, 49, and 56. Assessments at each visit included the HAM-D, CDRS-R, and CGI.

Upon study completion or early termination, the medication was to be tapered over a period of at least 14 days.

Concomitant Treatments

The following treatments were prohibited: psychopharmacologic drugs, St. John's wort or any other herbal products, ECT, introduction or change in the intensity of formal psychotherapy, and non-psychopharmacologic drugs with psychotropic effects taken for less than one month before double-blind treatment. Psychotherapy was permitted if it was well established before the study.

In the venlafaxine ER treatment group, 87% of patients received some type of concomitant therapy versus 82% of placebo patients. No patient took a concomitant antidepressant agent during the double-blind treatment phase.

Protocol Violations

One venlafaxine ER patient failed to undergo a placebo lead-in due to a site error. One placebo patient and one venlafaxine ER patient failed to meet inclusion criteria for the CDRS and CGI-severity rating, respectively. One placebo patient was discontinued due to non-compliance with study drug.

Compliance with study drug was assessed by capsule counts at each visit. However, counts were not documented in the CRF's and compliance rates were not reported.

2.7.3 Study 396

Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Generalized Anxiety Disorder (August 2000 to September 2001)

Study Objective

The objective of this study was to compare the anxiolytic efficacy and safety of venlafaxine ER to placebo in children and adolescents with generalized anxiety disorder (GAD).

Patient Sample

This study was conducted at 37 centers in the U.S. One hundred and sixty-five patients were randomized to double blind treatment. Relevant patient selection criteria are listed below.

Inclusion Criteria

- outpatient.
- age 6 through 17 years at study entry and able to swallow capsules.
- DSM-IV and Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD subsection (C-Kiddie-SADS GAD) criteria for GAD.

- total score of at least 20 on the Severity component of the C-Kiddie-SADS GAD at screening and baseline (study day -1).
- a total score of at least 7 on the Impairment component of the C-Kiddie-SADS GAD at screening and baseline.
- total score of at least 4 on the following three items of the C-Kiddie-SADS GAD severity component at screening and baseline: severity of anxiety and worry, difficulty controlling the worry, and severity of associated symptoms.
- score of at least 4 on the following two items from the Severity component of the C-Kiddie-SADS GAD at screening and baseline: frequency during the average week of the severity of anxiety and worry and the frequency during the average week of the severity of associated symptoms.
- score of at least 4 on the global impairment in functioning item of the Impairment component of the C-Kiddie-SADS GAD at screening and baseline.
- Childhood Depression Rating Scale-Revised (CDRS-R) <45 at screening and baseline.
- CGI-Severity score ≥ 4 at screening and baseline.
- anxiety symptoms for at least 6 months prior to study entry.
- sexually active females had to use medically acceptable contraception.

Exclusion Criteria

- weight less than 25 kg (55 lbs).
- history of seizure disorder other than a single childhood febrile seizure.
- presence of major depressive disorder, social anxiety disorder, separation anxiety disorder, PTSD, anxiety predominantly related to situational factors, panic disorder with or without agoraphobia, and OCD.
- specific phobia with severity and impairment that exceed those of GAD symptomatology.
- conduct disorder.
- history or presence of any psychotic disorder, bipolar disorder, anorexia, or bulimia.
- presence of a mental disorder due to a general medical condition.
- acutely suicidal and requiring precautions against suicide.
- at least one first-degree relative with bipolar disorder (based on family history from a parent).
- lactating females or females with a positive serum beta-HCG during screening.

- ECT within 30 days of double-blind treatment.
- history of drug or alcohol dependence or abuse within one year by DSM-IV criteria.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group, flexible dose trial.

Double-blind treatment was preceded by a 7±3 day single-blind placebo lead-in. The screening evaluation included a medical and psychiatric history, physical examination, laboratory tests, and ECG. The diagnosis of GAD was confirmed utilizing the C-Kiddie-SADS GAD subsection and DSM-IV criteria for GAD. The Kiddie-SADS-PL Anxiety (excluding GAD), CDRS-R, and CGI were also assessed during the prestudy evaluation.

Following this lead-in period, 165 eligible patients were randomized to double-blind treatment. One patient had no post-baseline data; thus, only 164 patients (80 on venlafaxine ER and 84 on placebo) were studied. Randomization was done in blocks of four patients and was stratified by age group (children age ≤11 and adolescents age >11):

	<u>Placebo</u>	<u>Venlafaxine ER</u>
Children	47	45
Adolescents	37	35

Patients were treated with double-blind medication (on-therapy) for a maximum of eight weeks. All study medication was taken once daily in the morning. Dosing of venlafaxine ER was based on weight. On days 1-7, venlafaxine ER patients took 37.5 mg/day. On days 8-14, patients weighing 25-39kg could take 37.5 or 75 mg/day; larger patients took 75 mg/day. Beginning on day 15 if clinically indicated to improve response, patients weighing 25-39kg could take 75 mg/day, patients weighing 40-49kg could take 112.5 mg/day, and patients weighing greater than 50kg could take 150mg/day. Likewise, beginning on day 29 and if clinically indicated, the daily dose could be increased in these weight groups to 112.5mg, 150mg, and 225mg, respectively. Doses could be decreased at any time during the study to a minimum of 37.5 mg/day for patients weighing 25-39kg and 75 mg/day for other patients.

Assessments were performed at baseline and on study days 7, 14, 21, 28, 42, 49, and 56 and included the C-Kiddie-SADS GAD, PARS (Pediatric Anxiety Rating Scale), and CGI. The HAM-A and Self-Report for Childhood Anxiety Related Disorder (SCARED) Parent and Child Forms were also rated on days 28 and 56.

Venlafaxine and metabolite levels were obtained on study day 56.

On study completion or premature termination, the study drug was to be tapered over a period of up to two weeks.

Concomitant Treatments

The following treatments were prohibited during the trial: psychopharmacologic drugs, herbal products, ECT, introduction or change in the intensity of formal psychotherapy, and non-psychopharmacologic drugs with psychotropic effects taken for less than one month before double-blind treatment. Psychotherapy was permitted if it was well established before the study.

In the venlafaxine ER group, 71% of patients received some type of concomitant therapy compared to 74% of placebo patients. One venlafaxine ER patient received a concomitant psychopharmacologic agent (Adderall) during the study; this use was for only one day.

Protocol Violations

One venlafaxine ER patient scored less than 4 on the Severity item of the C-Kiddie-SADS GAD during screening. Several patients did not meet inclusion criteria on this scale at baseline (five venlafaxine ER and four placebo patients).

Two venlafaxine ER patients had higher than permitted scores on the CDRS-R at screening and baseline.

One placebo was underweight during the study.

Four venlafaxine ER patients and two placebo patients were dropped from the study for other reasons, generally non-compliance.

At each visit, compliance with study medication was assessed by capsule counts. But, counts were not documented in the CRF's and compliance rates were not available.

2.7.4 Study 397

Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Generalized Anxiety Disorder (April 2000 to August 2001)

Study Objective

The objective of this trial was to compare the anxiolytic efficacy and safety of venlafaxine ER with placebo in children and adolescents with generalized anxiety disorder (GAD).

Patient Sample

This trial was conducted at 29 centers within the U.S. A total of 158 patients were randomized to double-blind treatment. Relevant selection criteria are presented below.

Inclusion Criteria

- outpatient.
- age 6 through 17 years at study entry and able to swallow capsules.
- DSM-IV and Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD subsection (C-Kiddie-SADS GAD) criteria for GAD.
- total score of at least 20 on the Severity component of the C-Kiddie-SADS GAD at screening and baseline (study day -1).
- a total score of at least 7 on the Impairment component of the C-Kiddie-SADS GAD at screening and baseline.
- total score of at least 4 on the following three items of the C-Kiddie-SADS GAD severity component at screening and baseline: severity of anxiety and worry, difficulty controlling the worry, and severity of associated symptoms.
- score of at least 4 on the following two items from the Severity component of the C-Kiddie-SADS GAD at screening and baseline: frequency during the average week of the severity of anxiety and worry and the frequency during the average week of the severity of associated symptoms.

- score of at least 4 on the global impairment in functioning item of the Impairment component of the C-Kiddie-SADS GAD at screening and baseline.
- CDRS-R <45 at screening and baseline.
- CGI-Severity score ≥ 4 at screening and baseline.
- anxiety symptoms for at least 6 months prior to study entry.
- sexually active females had to use medically acceptable contraception. Additionally, condoms were encouraged.

Exclusion Criteria

- weight less than 25 kg (55 lbs).
- history of seizure disorder other than a single childhood febrile seizure.
- presence of major depressive disorder, social anxiety disorder, separation anxiety disorder, PTSD, anxiety predominantly related to situational factors, panic disorder with or without agoraphobia, and OCD.
- specific phobia with severity and impairment that exceed those of GAD symptomatology.
- conduct disorder.
- history or presence of any psychotic disorder, bipolar disorder, anorexia, or bulimia.
- presence of a mental disorder due to a general medical condition.
- acutely suicidal and requiring precautions against suicide.
- at least one first-degree relative with bipolar disorder (based on family history from a parent).
- lactating females or females with a positive serum beta-HCG during screening.
- ECT within 30 days of double-blind treatment.
- history of drug or alcohol dependence or abuse within one year by DSM-IV criteria.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group, flexible dose trial.

Double-blind treatment was preceded by a 7 \pm 3 day single-blind placebo lead-in. The screening evaluation included a medical and psychiatric history, physical examination, laboratory tests, and ECG. The diagnosis of GAD was confirmed utilizing the C-Kiddie-SADS GAD subsection and DSM-IV criteria for GAD. The Kiddie-SADS-PL Anxiety

(excluding GAD), CDRS-R, and CGI were also assessed during the prestudy evaluation.

Following this lead-in period, 158 eligible patients were randomized to double-blind treatment. Two patients had no post-baseline data; thus, only 156 patients (77 on venlafaxine ER and 79 on placebo) were studied. Randomization was done in blocks of four patients and was stratified by age group (children age 6-11 and adolescents age 12-17):

	<u>Placebo</u>	<u>Venlafaxine ER</u>
Children	43	40
Adolescents	36	37

Patients were treated with double-blind medication (on-therapy) for a maximum of eight weeks. All study medication was taken once daily in the morning. Dosing of venlafaxine ER was based on weight. On days 1-7, venlafaxine ER patients took 37.5 mg/day. On days 8-14, patients weighing 25-39kg could take 37.5 or 75 mg/day; larger patients took 75 mg/day. Beginning on day 15 if clinically indicated to improve response, patients weighing 25-39kg could take 75 mg/day, patients weighing 40-49kg could take 112.5 mg/day, and patients weighing greater than 50kg could take 150mg/day. Likewise, beginning on day 29 and if clinically indicated, the daily dose could be increased in these weight groups to 112.5mg, 150mg, and 225mg, respectively. Doses could be decreased at any time during the study to a minimum of 37.5 mg/day for patients weighing 25-39kg and 75 mg/day for other patients.

Assessments were performed at baseline and on study days 7, 14, 21, 28, 42, 49, and 56 and included the C-Kiddie-SADS GAD, PARS (Pediatric Anxiety Rating Scale), and CGI. The HAM-A and Self-Report for Childhood Anxiety Related Disorder (SCARED) Parent and Child Forms were also rated on days 28 and 56.

Venlafaxine and metabolite levels were obtained on study day 56.

On study completion or premature termination, the study drug was to be tapered over a period of up to two weeks.

Concomitant Treatments

The following treatments were prohibited during the trial: psychopharmacologic drugs, herbal products, ECT, introduction or change in the intensity of formal psychotherapy, and non-psychopharmacologic drugs with psychotropic effects taken for less than one month before double-blind treatment. Psychotherapy was permitted if it was well established before the study.

In the venlafaxine ER group, 64% of patients received some type of concomitant therapy compared to 73% of placebo patients. One venlafaxine ER patient used valium for one day during the study.

Protocol Violations

Six patients (four venlafaxine ER and two placebo patients) were discontinued from the study due to protocol violations (three for non-compliance, one for placebo response at baseline, one who was unable to swallow capsules, and one for prednisone usage for asthma).

Several patients did not meet C-Kiddie-SADS entry criteria: at screening, five venlafaxine ER and two placebo patients did not meet criteria and, at baseline, five patients in each group failed to meet criteria.

Also, three venlafaxine ER and one placebo patient did not meet the entry criteria for the CDRS-R (<45).

Three patients failed other inclusion criteria: concurrent social phobia diagnosis (placebo), baseline CGI <4 (venlafaxine ER), and unknown duration of current GAD episode (venlafaxine ER).

Compliance with study medication was monitored at each visit by capsule counts. However, capsule counts were not documented in the CRF's and compliance rates were not reported.

2.8 Serzone Studies

2.8.1 Study CN104141

A Multicenter, Double-Blind, Placebo-Controlled Trial of Nefazodone in Depressed Adolescents (October 29, 1998 to September 19, 2001)

Study Objective

The study objective was to evaluate the safety and efficacy of nefazodone in depressed adolescents.

Patient Sample

This trial was conducted at 15 centers in the U.S. Two hundred and six patients were randomized to double-blind treatment. Relevant selection criteria are shown below.

Inclusion Criteria

- healthy adolescents, age 12-17 years (inclusive).⁸
- primary diagnosis of DSM-IV major depression.
- CDRS-R (Childhood Depression Rating Scale-Revised) total score ≥ 45 at the end of baseline.
- women of childbearing potential must have a negative pregnancy test and, if sexually active, utilize adequate contraceptive measures.

Exclusion Criteria

- pregnant or lactating females.
- concurrent Axis I diagnosis of delirium, dementia, amnestic, or other cognitive disorders; schizophrenia, delusional disorder, or psychotic disorder not otherwise specified; bipolar disorder, eating disorder, OCD, conduct disorder, and pervasive developmental disorder.
- borderline personality disorder.
- delusions or hallucinations during the current episode.
- first-degree biological relative with bipolar I disorder.
- likely to require prohibited treatment during the study.
- DSM-IV criteria for any significant substance use disorder within six months.
- significant risk of suicide based on history or mental status examination.

⁸ Patients age 18 were included prior to a June 15, 2000, protocol amendment. Seven nefazodone and four placebo patients were 18 years old at baseline.

- thyroid pathology with treatment not stabilized for at least three months.
- seizure disorder.
- refractory to two or more adequate courses of antidepressant medication.
- individual psychotherapy started within two months of the beginning of baseline.
- patients with attention deficit disorder requiring prohibited medication.⁹

Study Design

This was a randomized, double-blind, placebo-controlled outpatient trial.

After a preliminary determination that entry criteria were met, patients entered a 2-4 week baseline period to fully assess study eligibility and evaluate the stability of symptoms. A medical and psychiatric history was obtained and a physical examination, laboratory tests, ECG, and K-SADS (Schedule for Affective Disorders and Schizophrenia-Children's version) interview were performed at the start of baseline.

At the end of the baseline period, patients returned for final evaluations before entering the study. This assessment included the CGI, CDRS-R, HAM-D, and CGAS (Clinical Global Assessment Scale).

Eligible patients were randomized in a 1:1 ratio to either nefazodone (N=106) or placebo (N=100) for eight weeks of double-blind acute treatment. Randomization utilized a fixed block scheme. Approximately equal numbers of patients were assigned to each treatment group at each study site.

Study medication was taken on a BID schedule. Patients randomized to nefazodone initially received nefazodone 100 mg/day (50mg BID). At the end of the first week, the dose was increased to 200 mg/day (100mg BID). In the absence of dose-limiting adverse experiences, the dose was further escalated in 100 mg/day increments each week until the target dose of 300-400 mg/day was achieved. If there was no adequate clinical response (CGI improvement rating of 1 or 2), the dose could be increased to a maximum of 600

⁹ Prior to a March 13, 2001, protocol amendment, all patients with attention deficit disorder were excluded.

mg/day. The dose could be decreased although investigators were encouraged to maintain patients at a dose of at least 200 mg/day and to increase the dose to the maximum tolerated level. The minimum allowable dose was 100 mg/day.

Clinical visits were held weekly. Each visit entailed rating on the CGI and CDRS-R. The HAM-D and CGAS were rated every two weeks.

Patients who were at least minimally improved after eight weeks of treatment could have continued double-blind treatment for up to an additional 26 weeks. For other patients, there was no apparent provision for a taper of study medication.

Concomitant Treatments

The concomitant use of clonidine, benzodiazepines, stimulants, or other antidepressants was not permitted during the acute phase of this trial. Psychotherapy could not be initiated or intensified during the short-term phase of the study.

Seventy-five percent of nefazodone and 76% of placebo patients took at least one concomitant medication.

Two nefazodone patients reported use of prohibited concomitant medications. One patient reported concomitant participation in a trial of tomoxidine for ADHD but stated that he discontinued nefazodone prior to starting the ADHD trial. The other patient took butal-apap-caf for migraine during the study.

Protocol Violations

One patient was assigned to nefazodone but received a supply of placebo instead.

Four patients in each treatment group underwent a baseline evaluation period that was either too long or too short.

Tablet counts were used to monitor treatment compliance and medication usage was recorded in the CRF's. Three nefazodone patients and five placebo patients missed greater than two consecutive doses of study medication during the study.

2.8.2 Study CN104187

A Multicenter, Double-Blind, Placebo-Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children and Adolescents with a Major Depressive Episode (October 23, 2000 to November 15, 2001)

Study Objective

The primary study objective was to demonstrate the efficacy of nefazodone at two dose ranges compared to placebo in the treatment of children and adolescents with non-psychotic major depression.

Patient Sample

This study was conducted at 28 centers within the U.S. A total of 284 patients were randomized to double-blind treatment. Relevant patient selection criteria are listed below.

Inclusion Criteria

- physically healthy children (ages 7-11) and adolescents (ages 12-17).
- primary diagnosis of DSM-IV major depression.
- CDRS-R (Childhood Depression Rating Scale-Revised) total score ≥ 45 at the end of baseline.
- women of childbearing potential must have a negative serum or urine pregnancy test.

Exclusion Criteria

- concurrent Axis I diagnosis of delirium, dementia, amnesic, or other cognitive disorders; schizophrenia, delusional disorder, or psychotic disorder not otherwise specified; bipolar disorder, eating disorder, OCD, conduct disorder, and pervasive developmental disorder.
- borderline personality disorder.
- delusions or hallucinations during the current episode.
- first-degree biological relative with bipolar I disorder.
- DSM-IV criteria for any significant substance use disorder within six months of the start of baseline.
- significant risk of committing suicide based on history or mental status examination.
- depressive symptoms which are unstable in the opinion of the investigator.

- refractory to two or more adequate courses of antidepressant medication.
- individual psychotherapy which started within two months of randomization or planning to begin psychotherapy during the acute phase of the study.
- females who are pregnant or lactating.
- likely to require treatment with prohibited medication.
- thyroid pathology not stabilized for at least three months.
- seizure disorder.

Study Design

This was a randomized, double-blind, placebo-controlled outpatient trial using two discrete dose ranges of nefazodone.

After a preliminary determination that entry criteria were met, patients entered a 2-4 week baseline period to fully assess study eligibility and ensure washout of prohibited pharmacotherapy. A medical and psychiatric history was obtained and a physical examination, laboratory tests, ECG, CDRS-R, and K-SADS interview were performed at the start of baseline.

At the end of the baseline period, patients returned for final evaluations before entering the study. This assessment included the CGI, CDRS-R, vital signs, and pregnancy test for post-menarche females.

Eligible patients were randomized to one of the following treatments: low dose nefazodone (N=95), high dose nefazodone (N=95), or placebo (N=94) for eight weeks of double-blind acute treatment. Randomization used a fixed block schedule designed to allocate patients among the three treatment arms. Treatment group assignment was stratified by age group (children ages 7-11 and adolescents ages 12-17) so that approximately equal numbers of patients were randomized within each age group:

	<u>Low Dose</u>	<u>High Dose</u>	<u>Placebo</u>
Children	46	50	40
Adolescents	49	45	54

There was some imbalance in the proportion of children across dose groups (low dose 48%, high dose 53%, and placebo 43%).

Study medication was taken on a BID schedule. The nefazodone dosing regimen was based on treatment group (high vs. low dose), age group, and, for children, body weight. Dosing is described below.

Low Dose Children

Children randomized to the low dose group began treatment at 50 mg/day for the first week. At week 2, the dose was increased to 100 mg/day. Children under 70 lbs continued this dose for the remainder of the 8 week trial. Children 70 lbs or heavier received 150 mg/day (50mg qAM and 100mg qPM) at week 3, based on tolerability; the dose could have been decreased to 100 mg/day if needed.

High Dose Children

Children randomized to the high dose group took 50 mg/day for the first week, 100 mg/day for the second week, 150 mg/day for the third week, and 200 mg/day for the fourth week. Children under 70 lbs received this dose for the remainder of the trial. Children 70 lbs or heavier had their dose increased to 250 mg/day at week 5 and to 300 mg/day at week 6, based on tolerability. For weeks 6-8, the dose could have been adjusted between 200 and 300 mg/day in 50mg increments.

Low Dose Adolescents

Adolescents randomized to the low dose group took 100 mg/day for week 1, 200 mg/day for week 2, and, based on tolerability, 300 mg/day on week 3. For weeks 3-8, the dose could have been adjusted in the range of 200-300 mg/day.

High Dose Adolescents

Adolescents randomized to the high dose group received 100 mg/day for week 1, 200 mg/day for week 2, 300 mg/day for week 3, and 400 mg/day for week 4. At week 5, the dose could have been increased to 500 mg/day and, at week 6, to 600 mg/day, based on tolerability. For weeks 6-8, the dose

could have been adjusted between 400 and 600 mg/day in 50mg or 100mg increments.

Clinical visits were held weekly. Each visit entailed rating the CGI and CDRS-R.

Patients who completed eight weeks of acute treatment could have continued open-label treatment for up to an additional 26 weeks. For other patients, there was no apparent provision for a taper of study medication.

Concomitant Treatments

The following concomitant drugs were prohibited during the study: clonidine, benzodiazepines, herbal preparations with potential psychoactive properties, stimulants, and other antidepressants. Patients on stable medication for ADD were to be excluded from participation. Psychotherapy was not to be started or intensified during the acute phase of this trial.

No patients received a prohibited medication during this study.

Protocol Violations

Four patients (three low dose and one high dose patient) had a baseline evaluation period that was either too long or too short.

Pill counts were documented to verify compliance and accountability. Five patients (two low dose, two high dose, and one placebo patient) did not take study drug as specified in the protocol, generally resulting in under dosing for variable periods within the first few weeks of the study. Fifteen other patients (five low dose, three high dose, and seven placebo patients) missed greater than two consecutive doses of study drug.

Several patients (five low dose, nine high dose, and two placebo patients) were dosed with a greater number of tablets per day than specified in the study protocol.

2.9 Remeron Study

2.9.1 Study 45

A multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron in outpatient children and adolescents with major depressive disorder (February 1999 to November 2000)

Study Objective

This study was intended to demonstrate the safety and efficacy of Remeron therapy over placebo in the treatment of children and adolescents with major depression.

Patient Sample

According to a September 14, 1999, protocol amendment, centers were added to the original protocol so that this trial could be structured as two studies: Study 1 and Study 2. The first 17 centers comprised Study 1 and the second 17 centers comprised Study 2. All 34 centers were located within the U.S.

In Study 1, a total of 126 patients were randomized; 133 patients were randomized in Study 2.

Relevant patient selection criteria were as follows.

Inclusion Criteria

- at least 7 and less than 18 years old at baseline.
- females must be non-pregnant and, if fertile and sexually active, using acceptable birth control.
- primary diagnosis of DSM-IV major depression (non-psychotic, chronic or recurrent) on the Kiddie-SADS-PL.
- score ≥ 15 on the first 17 items of the 21-item HAM-D at baseline.
- score < 70 on the CGAS (Children's Global Assessment Scale) at baseline.
- score ≥ 40 on the CDRS-R.

Exclusion Criteria

- history of seizures (other than childhood febrile seizures) or taking anticonvulsants to prevent seizures.
- SGOT or SGPT values on screening labs ≥ 1.25 times the upper limit of normal.

- requiring treatment with concomitant psychotropic medications (including melatonin).
- history of DSM-IV drug or alcohol abuse within 90 days before first screen visit.
- bipolar (I or II) disorder or a parent with bipolar I disorder.
- any history of an eating disorder.
- concurrent diagnosis of obsessive-compulsive disorder or schizophrenia.
- serious suicide attempt during the current major depressive episode or any suicide attempt that resulted in hospitalization.
- failed more than two adequate trials of antidepressants.

Study Design

This was a randomized, double-blind, placebo-controlled outpatient study.

All patients underwent a screening visit 14 days prior to baseline. Assessments at that time included a medical history, physical examination, Kiddie SADS, CGAS, 21-item HAM-D, and CDRS-R. This was followed by a second screening visit 7 days before baseline which entailed an ECG, vital signs, pregnancy test, drug/alcohol screen, CDRS-R, SCARED (Self-Report for Childhood Anxiety-Related Disorders), and Connors Global Index.

After completion of the second screening visit, baseline assessments were performed (Kiddie SADS, CGAS, HAMD, CGI, CDRS-R, vital signs). Eligible patients were randomized, roughly in a 2:1 ratio, to Remeron or placebo for eight weeks of double-blind treatment.

Patients randomized who took at least one dose of study drug are enumerated below by study, treatment group, and age category (children 7-11 years and adolescents 12-17 years). (One patient randomized to placebo in Study 2 received no study medication.)

	Study 1		Study 2	
	Remeron (N=82)	Placebo (N=44)	Remeron (N=88)	Placebo (N=44)
Children	30	19	41	18
Adolescents	52	25	47	26

Remeron patients began at a dose of 15mg taken each evening with the option to increase the dose to a maximum of 45mg in 15 mg/day increments each week up to study day 28. On and after day 28, there were to be no more dose adjustments.

During double-blind treatment, visits were scheduled on days 7, 14, 21, 28, 35, 42, 49, and 56. The visits on days 35 and 49 were optional and could have been skipped at the discretion of the investigator. Assessments at each visit included the HAM-D, CDRS-R, and CGI.

Blood samples for mirtazapine plasma levels were collected on study days 28 and 56 (or the subject's last treatment day).

There were no provisions for administration of study medication beyond eight weeks of double-blind treatment.

Concomitant Treatments

Concomitant use of other psychotropic drugs was not allowed during the trial.

Patients could not begin formal psychotherapy during the study period. Supportive care was permitted as defined below:

- discussion of the understanding of the illness.
- discussion of improvement or lack of improvement.
- discussion of reaction to pharmacologic treatment.
- other interventions included in an acceptable level of care for patients beginning a new therapy.

A total of two patients (one Remeron in Study 1 and one placebo patient in Study 2) used disallowed concomitant medication post-baseline.

Protocol Violations

Compliance was computed from the ratio of the total number of tablets taken, based on pill counts, to the total number of tablets prescribed over the entire duration of the treatment period. A few patients were classified as major protocol violators because they were less than 75% compliant with the intake of study medication overall:

	<u>Remeron</u>	<u>Placebo</u>
Study 1	3.7%	0%
Study 2	0%	2.2%
Studies 1+2	1.8%	1.1%

Larger fractions of the patient sample were found to be non-compliant during any visit interval (26% of Remeron and 30% of placebo patients in the combined study population).

Overall, there were no major differences between treatment groups for other reported protocol violations.

3.0 Summary of Findings

Study characteristics are summarized in the Appendix to this review.

All 23 trials utilized a randomized, double-blind, placebo-controlled, flexible-dose, parallel group design. Most of these trials (15) studied patients with major depression. Of the other eight trials, four studied patients with obsessive compulsive disorder, two evaluated patients with generalized anxiety disorder, one examined social anxiety disorder patients, and one enrolled patients with attention deficit disorder.

The following differences among these trials were noted:

- One study was prematurely terminated (Prozac study HCCJ).
- Two studies were conducted during the 1980's (Prozac study HCCJ and Wellbutrin study 75). All other studies were performed during the 1990's and early 2000's.
- Two studies were single-center (Prozac studies HCCJ and X065).
- Two studies were conducted entirely outside of the United States (Paxil study 377 and Celexa study 94404).
- Two studies allowed the enrollment of inpatients (Celexa study 94404 and Wellbutrin study 75).
- One trial was conducted entirely in children (ages 6-12)(Wellbutrin study 75). Five trials were conducted only in adolescents and the remaining 17 studies enrolled both children and adolescents.
- Of the 17 trials enrolling both children and adolescents, the age group distributions of two were markedly skewed (73% children in Prozac study HCCJ and 71% adolescents in Paxil study 676).

- Three studies utilized a more extensive screening process (Prozac studies X065 and HCJE and Paxil study 329). For example, these studies required verification of diagnosis and study eligibility by at least two independent clinicians.
- Five studies did not specifically exclude patients deemed to be at risk for suicide (Prozac study X065, Zoloft study 498, Luvox study 114.02.01, Celexa study 94404, and Wellbutrin study 75).
- One study did not exclude patients with a personal history of bipolar disorder (Wellbutrin study 75).
- Two studies allowed patients with psychotic symptoms (Paxil study 329 and Wellbutrin study 75).
- One study included an active control group (imipramine in Paxil study 329).

4.0 Conclusions and Recommendations

Since the objective of this review was simply to provide information in support of the primary analysis of suicidality conducted by Dr. Hammad, no definitive conclusions or recommendations are offered here. The reader is referred to Dr. Hammad's review for the results of his analysis, conclusions, and recommendations.

Gregory M. Dubitsky, M.D.
August 6, 2004

cc: NDA 18-936/SE5-064 (Prozac)
NDA 19-839/SE5-044 (Zoloft)
NDA 20-031/SE5-037 (Paxil)
NDA 20-243/SE2-021 (Luvox)
NDA 20-822/SE5-016 (Celexa)
NDA 18-644/000-000 (Wellbutrin)
NDA 20-699/SE5-030 (Effexor XR)
NDA 20-152/SE5-032 (Serzone)
NDA 20-415/SE5-011 (Remeron)
HFD-120/Division Files
HFD-120/GDubitsky
 /TLaughren
 /RKatz
 /PAndreason
 /JRacoosin
 /THammad
 /AHughes
 /PDavid

APPENDIX

Summary of Pediatric Trial Characteristics

The following tabulation of clinical trial features is self-explanatory for the most part. The following study features (column headings) merit some comment.

- **Indication:** MDD=major depressive disorder, OCD=obsessive compulsive disorder, SAD=social anxiety disorder, ADD=attention deficit disorder, GAD=generalized anxiety disorder.
- **Drug:Placebo Ratio:** randomization ratio to drug and placebo, respectively. For trial 329, 1 to 1 to 1 signifies that patients were equally distributed to Paxil, placebo, and an active control agent (imipramine).
- **Placebo Lead-in:** length of any single-blind placebo lead-in period prior to randomization.
- **Excl. Plac. Responders:** indicates whether responders (by various criteria) during the placebo lead-in were excluded from randomization.
- **Extensive Screening:** three studies were distinguished from the other trials by virtue of a more extensive diagnostic and eligibility screening process (e.g., requiring corroboration of diagnosis by independent clinicians).
- **Incl. Crit. Depression:** for MDD trials, the minimum depression score required for randomization; for non-MDD trials, the maximum depression scale score allowed for randomization in order to exclude patients with significant depressive symptomatology.
- **Exclude TX Resistant:** indicates whether patients with a history of treatment-resistance for the primary disorder were excluded from the study.
- **Depression Scale Monitored:** the depression scale evaluated during the course of double-blind treatment.
- **Balance/Compliance:** indicates whether the treatment groups were reasonably balanced in terms of study medication compliance (i.e., there was no gross imbalance between groups).
- **Balance/Prot. Violations:** indicates whether the treatment groups were reasonably balanced in terms of protocol violations.
- **Balance/Concom. Meds:** indicates whether the treatment groups were reasonably balanced in terms of concomitant medication use.

Drug	Study	Indication	Dates	Location(#Centers)	Inpt/Outpt	N	Drug:Placebo Ratio	Ages (yrs)
Prozac	HCCJ	MDD	1984-1987	Canada(1)	Outpt	40	1 to 1	12 to 17
	X065	MDD	1991-1995	US(1)	Outpt	108	1 to 1	8 to 18
	HCJE	MDD	1998-1999	US(16)	Outpt	420	1 to 1	8 to 17
	HCJW	OCD	1999-2000	US(21)	Outpt	103	2 to 1	7 to 17
Zoloft	498	OCD	1991-1994	US(12)	Outpt	187	1 to 1	6 to 17
	1001	MDD	1999-2001	U.S.(23)/India(4)	Outpt	188	1 to 1	6 to 17
	1017	MDD	2000-2001	N.America(19)/India(5)	Outpt	188	1 to 1	6 to 17
Paxil	329	MDD	1994-1997	U.S.(10)/Canada(2)	Outpt	275	1 to 1 to 1	12 to 18
	377	MDD	1995-1998	Non-US(32)	Outpt	286	2 to 1	13 to 18
	676	SAD	1999-2001	U.S.(22)/Foreign(16)	Outpt	322	1 to 1	8 to 17
	701	MDD	2000-2001	U.S. (40)/Canada(1)	Outpt	206	1 to 1	7 to 17
	704	OCD	2000-2001	US(37)/Canada(2)	Outpt	207	1 to 1	7 to 17
Luvox	114.02.01	OCD	1991-1994	US(20)	Outpt	120	1 to 1	8 to 17
Celexa	CIT-MD-18	MDD	2000-2001	US(21)	Outpt	174	1 to 1	7 to 17
	94404	MDD	1996-2001	Europe (31)	Inpt/Outpt	244	1 to 1	13 to 18
Wellbutrin	75	ADD	1984-1986	US(4)	Inpt/Outpt	109	2 to 1	6 to 12
Effexor XR	382	MDD	1997-2000	US(14)	Outpt	165	1 to 1	7 to 17
	394	MDD	2000-2001	US(37)	Outpt	201	1 to 1	7 to 17
	396	GAD	2000-2001	US(37)	Outpt	165	1 to 1	6 to 17
	397	GAD	2000-2001	US(29)	Outpt	158	1 to 1	6 to 17
Serzone	CN104141	MDD	1998-2001	US(15)	Outpt	206	1 to 1	12 to 17
	CN104187	MDD	2000-2001	US(28)	Outpt	284	2(high&low dose) to 1	7 to 17
Remeron	45	MDD	1999-2000	US(34)	Outpt	259	2 to 1	7 to 17

Drug	Study	Indication	Strat Randomization	% by Age Group	Placebo Lead-In	Excl. Plac. Responders	Screen DSM Version
Prozac	HCCJ	MDD	No	N/A	SB 4 to 10 days	Yes	DSM-III
	X065	MDD	Age & Gender	50% 8-12/50% 13-18	SB 1 to 2 wks	Yes	DSM-III-R
	HCJE	MDD	Age & Gender	56% 8-12/44% 13-17	SB 1 wk	Yes	DSM-IV
	HCJW	OCD	No	73% 8-11/27% 12-17	No	N/A	DSM-IV
Zoloft	498	OCD	Age	57% 6-12/43% 13-17	SB 1 wk	Yes	DSM-III-R
	1001	MDD	Age	46% 6-11/54% 12-17	No	N/A	DSM-IV
	1017	MDD	Age	48% 6-11/52% 12-17	No	N/A	DSM-IV
Paxil	329	MDD	No	N/A	No	N/A	DSM-III-R
	377	MDD	No	N/A	SB 2 wks	Yes	DSM-IV
	676	SAD	No	29% 8-11/71% 12-17	No	N/A	DSM-IV
	701	MDD	Age	47% 7-11/53% 12-17	No	N/A	DSM-IV
	704	OCD	Age	57% 7-11/43% 12-17	No	N/A	DSM-IV
Luvox	114.02.01	OCD	No	49% 8-12/51% 13-17	SB 1-2 wks	Yes	DSM-III-R
Celexa	CIT-MD-18	MDD	Age	48% 7-11/52% 12-17	SB 1 wk	Yes	DSM-IV
	94404	MDD	No	N/A	No	N/A	DSM-IV
Wellbutrin	75	ADD	No	N/A	SB 1 wk	Yes	DSM-III
Effexor XR	382	MDD	Age	54% 7-12/46% 13-17	SB 2 wks	Yes	DSM-IV
	394	MDD	Age	57% 7-12/43% 13-17	SB 1 wk	Yes	DSM-IV
	396	GAD	Age	56% 6-11/44% 12-17	SB 1 wk	Yes	DSM-IV
	397	GAD	Age	53% 6-11/47% 12-17	SB 1 wk	Yes	DSM-IV
Serzone	CN104141	MDD	No	N/A	No	N/A	DSM-IV
	CN104187	MDD	Age	48% 7-11/52% 12-17	No	N/A	DSM-IV
Remeron	45	MDD	No	42% 7-11/58% 12-17	No	N/A	DSM-IV

Drug	Study	Indication	Extensive Screening	Incl. Crit. Depression	Exclude TX Resistant	Excl. Current Suicide Risk
Prozac	HCCJ	MDD	No	HAMD 20	No	Yes
	X065	MDD	Yes	CDRS-R>40	No	No
	HCJE	MDD	Yes	CDRS-R>40	Yes	Yes
	HCJW	OCD	No	CDRS-R 40	No	Yes
Zoloft	498	OCD	No	24-item HAMD 17	No	No
	1001	MDD	No	CDRS-R 45	No	Yes
	1017	MDD	No	CDRS-R 45	Yes	Yes
Paxil	329	MDD	Yes	17-item HAMD 12	No	Yes
	377	MDD	No	MADRS 16	No	Yes
	676	SAD	No	Exclude by DX	No	Yes
	701	MDD	No	CDRS-R 45	Yes	Yes
	704	OCD	No	Exclude by DX	Yes	Yes
Luvox	114.02.01	OCD	No	CDRS-R 40	Yes	No
Celexa	CIT-MD-18	MDD	No	CDRS-R 40	Yes	Yes
	94404	MDD	No	BDI 21(F) 16(M)	No	No
Wellbutrin	75	ADD	No	None	No	No
Effexor XR	382	MDD	No	CDRS-R>40	No	Yes
	394	MDD	No	CDRS-R>40	No	Yes
	396	GAD	No	CDRS-R<45	No	Yes
	397	GAD	No	CDRS-R<45	No	Yes
Serzone	CN104141	MDD	No	CDRS-R 45	Yes	Yes
	CN104187	MDD	No	CDRS-R 45	Yes	Yes
Remeron	45	MDD	No	CDRS-R 40,HAMD 15	Yes	Yes

Drug	Study	Indication	Excl. H/O Suicide Attempt	Excl. Homicide Risk	Excl. Bipolar D/O	Excl. FH Bipolar D/O	Excl. Psychosis
Prozac	HCCJ	MDD	No	No	Yes	No	Yes
	X065	MDD	No	No	Yes	Yes	Yes
	HCJE	MDD	No	No	Yes	Yes	Yes
	HCJW	OCD	No	No	Yes	Yes	Yes
Zoloft	498	OCD	No	No	Yes	No	Yes
	1001	MDD	Yes	Yes	Yes	No	Yes
	1017	MDD	Yes	No	Yes	No	Yes
Paxil	329	MDD	Yes (if OD)	No	Yes	No	No
	377	MDD	No	No	Yes	No	Yes
	676	SAD	No	Yes	Yes	No	Yes
	701	MDD	No	Yes	Yes	No	Yes
	704	OCD	No	Yes	Yes	No	Yes
Luvox	114.02.01	OCD	No	No	Yes	No	Yes
Celexa	CIT-MD-18	MDD	Yes	No	Yes	No	Yes
	94404	MDD	No	No	Yes	No	Yes
Wellbutrin	75	ADD	No	No	No	No	No
Effexor XR	382	MDD	No	No	Yes	Yes	Yes
	394	MDD	No	No	Yes	Yes	Yes
	396	GAD	No	No	Yes	Yes	Yes
	397	GAD	No	No	Yes	Yes	Yes
Serzone	CN104141	MDD	Yes	No	Yes	Yes	Yes
	CN104187	MDD	Yes	No	Yes	Yes	Yes
Remeron	45	MDD	Yes	No	Yes	Yes	Yes

Drug	Study	Indication	Excl. Alcohol/Drug	Excl. Borderline	Excl. Eating	Dose (mg/day)	Active Control
			Abuse	PD	D/O		
Prozac	HCCJ	MDD	Yes	No	No	20 to 60	No
	X065	MDD	Yes	No	Yes	20	No
	HCJE	MDD	Yes	Yes	Yes	20 or 10	No
	HCJW	OCD	Yes	Yes	Yes	20 to 60	No
Zoloft	498	OCD	Yes	Yes	No	25 to 200	No
	1001	MDD	Yes	No	Yes	50 to 200	No
	1017	MDD	Yes	No	Yes	50 to 200	No
Paxil	329	MDD	Yes	No	Yes	20-40 (imi 200-300)	Yes
	377	MDD	Yes	No	No	20 to 40	No
	676	SAD	Yes	No	Yes	10 to 50	No
	701	MDD	Yes	No	Yes	10 to 50	No
	704	OCD	Yes	No	Yes	10 to 50	No
Luvox	114.02.01	OCD	No	No	Yes	50 to 200	No
Celexa	CIT-MD-18	MDD	Yes	No	Yes	20 to 40	No
	94404	MDD	Yes	No	Yes	10 to 40	No
Wellbutrin	75	ADD	No	No	No	150 to 250	No
Effexor XR	382	MDD	Yes	No	Yes	37.5 to 225	No
	394	MDD	Yes	No	Yes	37.5 to 225	No
	396	GAD	Yes	No	Yes	37.5 to 225	No
	397	GAD	Yes	No	Yes	37.5 to 225	No
Serzone	CN104141	MDD	Yes	Yes	Yes	100 to 600	No
	CN104187	MDD	Yes	Yes	Yes	100 to 600	No
Remeron	45	MDD	Yes	No	Yes	15 to 45	No

Drug	Study	Indication	DB TX Duration (wks)	Depression Scale Monitored	Balance/Compliance	Balance/Prot. Violations
Prozac	HCCJ	MDD	6	HAMD	Not reported	Not reported
	X065	MDD	8	CDRS-R	Yes	Yes
	HCJE	MDD	9	CDRS-R/MADRS	Yes	Yes
	HCJW	OCD	13	CDRS-R	Yes	Yes
Zoloft	498	OCD	12	None	Not reported	Yes
	1001	MDD	10	CDRS-R	Yes	Yes
	1017	MDD	10	CDRS-R	Yes	Yes
Paxil	329	MDD	8	HAMD	Yes	Yes
	377	MDD	12	MADRS	Yes	Yes
	676	SAD	16	CDRS	Yes	Yes
	701	MDD	8	CDRS-R	Yes	Yes
	704	OCD	10	None	Yes	Yes
Luvox	114.02.01	OCD	10	CDRS-R	Yes	Not reported
Celexa	CIT-MD-18	MDD	8	CDRS-R	Not reported	Yes
	94404	MDD	12	BDI,MADRS,K-SADS	Not reported	Yes
Wellbutrin	75	ADD	4	None	Not reported	Not reported
Effexor XR	382	MDD	8	CDRS-R, HAMD, MADRS	Not reported	Yes
	394	MDD	8	CDRS-R,HAMD	Not reported	Yes
	396	GAD	8	None	Not reported	Yes
	397	GAD	8	None	Not reported	Yes
Serzone	CN104141	MDD	8	CDRS-R, HAMD	Yes	Yes
	CN104187	MDD	8	CDRS-R	Yes	Yes
Remeron	45	MDD	8	CDRS-R, HAMD	Yes	Yes

Drug	Study	Indication	Balance/Concom. Meds	Continuation TX	Other Remarkable Characteristics
Prozac	HCCJ	MDD	Not reported	OL fluoxetine	Terminated early D/T slow recruitment
	X065	MDD	Yes	OL fluoxetine	
	HCJE	MDD	Yes	DB acute TX	Wk 1 DB TX=Low dose adaptation, non-tol. D/O'd
	HCJW	OCD	Yes	None	
Zoloft	498	OCD	Yes	None	Also HAMD item 1 zero or one for inclusion
	1001	MDD	Yes	None	
	1017	MDD	Yes	None	
Paxil	329	MDD	Yes	DB acute TX	About 1/3 w/melancholic SX;supportive TX for all pts
	377	MDD	Yes	2 wk taper	Previous psychotherapy responders excluded
	676	SAD	Yes	4 wk taper	MDD in 2.5% par/0.6% plac
	701	MDD	Yes	4 wk taper	
	704	OCD	Yes	4 wk taper	
Luvox	114.02.01	OCD	Yes	OL fluvoxamine	
Celexa	CIT-MD-18	MDD	Yes	OL citalopram	
	94404	MDD	Yes	None	About 1/3 H/O suicide attempt;16% drug/12% plac inpt
Wellbutrin	75	ADD	Not reported	None	No study report available; 90% male
Effexor XR	382	MDD	Yes	2 wk taper	
	394	MDD	Yes	2 wk taper	
	396	GAD	Yes	2 wk taper	
	397	GAD	Yes	2 wk taper	
Serzone	CN104141	MDD	Yes	DB acute TX	
	CN104187	MDD	Yes	OL nefazodone	
Remeron	45	MDD	Yes	None	

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/s/

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8/6/04 09:41:31 PM
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