?AUTHOR

Adolescent Unipolar Major Depression: Multisite Psychopharmacology Study

SPECIFIC AIMS

Evidence indicates that major depression (MDD) is prevalent in adolescence, affecting some 3% to 8% in this age group (Fleming & Offord, 1990; Lewinshohn, 1987). Similarly, longitudinal follow-up studies (Garber et al., 1988; Harrington et al., 1990; Kovacs et al., 1984; Strober et al., in press) indicate that depression recurs in a large proportion of child and adolescent cases, resulting in significant psychosocial morbidity and risk of self-harm and suicide (Brent et al., 1990; Kutcher & Marton, 1989).

The treatment of MDD in adolescents is an important clinical challenge. The efficacy of pharmacotherapy has been the subject of active interest, yet existing trials of tricyclic antidepressants (TCAs) are few in number and beset by methodological problems which cloud their interpretation. No adequate study has been conducted of other classes of antidepressants such as serotonergic compounds. It is to these questions that the present application is directed.

The primary objective of this proposal is to further our knowledge of the pharmacotherapy of major depression in adolescents. To address this goal, a multicenter, placebo controlled trial of two distinct compounds, imipramine and paroxetine, is proposed in nonpsychotic adolescents with unipolar Major Depression. The principal investigators and centers proposed for this study are: (1) Martin Keller, M.D., Brown University; (2) Rachel Klein, Ph.D. (PI) and Harold Koplewicz, M.D., (Co-PI), Columbia University, New York State Psychiatric Institute and Long Island Jewish Hospital; (3) Stanley Kutcher, M.D., University of Toronto; (4) Neal Ryan, M.D. (PI) and Boris Birmaher, M.D. (Co-PI), University of Pittsburgh; and (5) Michael Strober, Ph.D., University of California at Los Angeles. PIs

We propose to enroll 300 subjects in aggregate across all centers and treatments. Each of the five sites will enroll 12 to 15 subjects per year. Allowing for both a training/start-up period and for all the necessary time to complete the acute treatment phase of the last subject entered, we plan to complete the acute double-blind study within a five year period.

The current uncertainty about the efficacy of antidepressant drug therapy for adolescent depression forcefully illustrates the need for a collaborative endeavor of this scope. The evidence to be reviewed suggests that only through application of standardized diagnostic and assessment procedures across multiple sites will it be feasible to collect a clinical sample of sufficient size for investigating as yet unanswered questions regarding antidepressant treatment response in adolescents with nonpsychotic, nonbipolar Major Depression.

Primary specific aims are:

a. In adolescents with Major Depression we aim to determine the efficacy of:

(1) paroxetine
(2) imipramine

The above aim will be met by an 8 week double-blind study in which patients will be randomized to receive matching IMI, paroxetine, or a placebo.

b. Another primary aim is to assess the rate of relapse among IMI, paroxetine and placebo responders who are maintained on treatment for a period of 6 months beyond the randomized trial.

We hypothesize the following: INITIAL HYPOTHESIS

(1) Paroxetine will be significantly superior to placebo at the end of the 8 week treatment trial.
(2) IMI will be significantly superior to placebo at the end of the 8 week treatment trial.
(3) There will be fewer drop-outs and adverse events among patients on paroxetine compared to patients on imipramine.
(4) Responders to the 8 week experimental phase who are maintained on their study treatment for 6 months will experience significantly fewer MDD relapses on IMI and paroxetine than on placebo.

A secondary aim is to identify predictors of treatment outcome across clinical domains. The following indicators of differential response will be examined specifically, but no directional hypotheses are formulated: endogenous subtype, age of onset, number of prior episodes, duration and severity of current episode, comorbidity with separation anxiety disorder, attention deficit disorder, and conduct disorder. (Contrast among the latter two disorders will be a function of their frequency.)

Another secondary aim is to create a comprehensive profile of the patterns of course of psychopathology, psychosocial functioning, medical illness, and morbidity in all subjects after they complete or drop out of the randomized trial for any reason. This will be done by collecting interval data at 6 month intervals for a minimum of 2 years in all subjects.

BACKGROUND AND SIGNIFICANCE

Similarities between adolescent and adult depression in symptomatology, family history, and prospective course provide compelling rationale for investigating the efficacy of antidepressant drug therapy in young patients with affective disturbance. However, in neither open nor placebo controlled studies conducted thus far has solid evidence been adduced of robust changes in symptom severity, or of significant drug vs placebo differences.

1. Inpatient Studies

The first controlled study of a tricyclic (TCA) antidepressant evaluated the effect of amitriptyline (AMI; 200 mg/day) vs placebo in a very small sample (N=20) of inpatients with major depression (MDD) (Kramer & Feguine, 1983). There was no clear overall advantage of drug over placebo; however, our analysis of individual psychiatric rating scale items not examined in the original report indicates a significantly greater reduction in symptoms of sadness, concentration difficulties, and dysphoria in patients receiving AMI.

In an open study (Strober et al., 1990) of mainly endogenous (per RDC) depressed inpatients, 24 non-psychotic and 10 psychotic adolescents received up to 300 mg/day of imipramine (IMI) for six

weeks. Only 38% of nonpsychotic and 10% of psychotic patients were significantly improved. Plasma levels had no relationship to outcome. The authors concluded that IMI was only marginally effective in this sample. However, post-hoc analysis of these data conducted in support of this proposal indicates that all responders were characterized by core endogenous syndromal features of at least moderate severity (HAM-D scores $\geq$ 25)--the prototypic pattern in adult responders to TCAs.

Following up on these results, Strober et al. (1992) conducted a 3 week open study of lithium (Li) augmentation in 24 inpatients with MDD who were refractory to 6 weeks of IMI. Clinical effects were compared to those observed in a group of historical case controls, comprised of patients who received IMI monotherapy continuously for a minimum of 9 weeks in spite of minimal initial improvement. The effects of Li augmentation were modest at best; only 2 patients (8%) had clinically dramatic improvement. Analogous to the findings in the open label study of IMI, these two responders had prototypic melancholic features of marked severity (HAM-D scores of 28 and 32, respectively).

2. Outpatient Studies

In an open study of IMI in 34 subjects, Ryan et al. (1986) reported a clinical improvement rate of 44%. In contrast to observations made by Strober et al. (1990), endogeneity was associated with poor response, yet extensive comorbidity in this sample does not allow for straightforward conclusions. There was no relationship between IMI plasma levels and clinical response.

Geller et al. (1990) entered 52 adolescents in a 10 week trial involving a 2 week single-blind washout phase followed by 8 weeks of placebo or nortriptyline (NTP) in the non-responders to the initial placebo run-in. Drug was titrated to plasma levels of 80 $\pm$ 20 ng/ml. The final sample comprised 31 patients, 12 randomized to NTP, 19 to placebo. Improvement in the sample as a whole after 8 weeks was minimal with no statistically significant differeneces between the two groups. However, a noteworthy fact is that family history of bipolar illness was common, and a large proportion of subjects presented with concurrent antisocial conduct, each a potential confounding influence.

Boulos et al. (1991) entered 43 patients, ranging up to 20 years of age, in a 6 week placebo controlled trial of desipramine (DMI) at a fixed dose of 200 mg/day following a 1 week single-blind placebo washout. Thirty patients completed the trial: 12 on DMI, 18 on placebo. Nearly half had concurrent anxiety disorder, 20% had substance use disorder, and 7% had conduct disorder. Clinical response was defined operationally as a 50% or greater reduction in HAM-D score. Response was observed in 50% of patients receiving DMI compared to 33% rate of improvement in patients receiving placebo, a nonsignificant difference.

Klein et al. (1992) entered 28 patients with MDD into a 6 week trial of DMI at a dose of 300 mg/day by day 25 unless limited by side effects. Six patients were dropped from the protocol subsequent to randomization, leaving 11 patients on DMI and 11 on placebo. On a dichotomized global rating of improvement/lack of improvement, no advantage of active medication was obtained. Still, compared to placebo controls, patients receiving DMI were less likely to meet full criteria for MDD upon completion of the trial; were more likely to have a 50% or greater reduction in HAM-D score; and were less likely to still meet entry severity criteria on the HAM-D after six weeks. The lack of statistical significances of these differences may be due to the relatively small sample size. A post-hoc analysis was also conducted on DMI treated patients stratified by the presence vs absence of "atypical" features as defined by mood reactivity, intense lethargy, pathological sensitivity to rejection, hypersomnia, and overeating. While the sample was too small for a statistically meaningful

comparison, the results were consistent with recent adult findings (Liebowitz et al., 1989), with only 1 of 4 atypicals showing improvement compared to 5 of 7 nonatypicals.

Ryan et al. (1992) entered 31 subjects into an 8 week trial of AMI at doses of 5.0 mg/kg/day (maximum 300 mg/day) as limited by side effects only after a 7-10 day single-blind placebo washout period. Of those, 18 were on AMI and 13 on placebo. Both the 12-item depression rating scale from the K-SADS-P and the Hamilton depression rating scores, done week-by-week during the study, were analyzed using a random effects regression model. There was a highly significant improvement seen overall on both measures during the treatment (an effect of time, $P < .001$). There was no indication of a significant medication by time effect or a medication effect on either measure. Thus, this study did not confirm or lend support for the hypothesis that amitriptyline is superior to placebo in outpatient non-bipolar MDD.

Finally, Simeon et al., (1990) enrolled 40 adolescents in a 7 week double-blind, placebo controlled study of the serotonin reuptake inhibitor fluoxetine, following a one-week single blind placebo washout. A flexible dose design was employed with a target dosage of 60 mg/day. It is reported that symptom improvement was greater among patients receiving fluoxetine, however, none of the between-group comparisons were statistically significant. Regrettably, no descriptive data appear in the report and the approach employed to assess symptom change is not described fully.

3. Critique of Extant Data

At this juncture, in neither open-label nor randomized controlled clinical trials is there compelling evidence of efficacy of antidepressant drugs in the treatment of major depression in adolescents. However, it is our contention that such a judgment is premature. The following points underscore our position.

Thus far, existing studies have collectively evaluated drug efficacy in fewer than 200 patients, a number hardly adequate for reliable clinical or statistical inferences. No single trial has had sufficient sample size and statistical power to confirm or reject drug efficacy with confidence, especially in light of the known heterogeneity of depressive states and the possibility that clinical subtypes of depression (e.g., atypicals vs nonatypicals; unipolar vis bipolar) vary in their responsivity to TCAs (Liebowitz et al., 1984; Stewart et al., 1989; Thase & Himmelhoch, 1992). In essence, in the short span of ten years our knowledge of antidepressant effects in adolescents has moved from a near absence of objective data to an array of negative, but essentially inconclusive, results.

The difficulties of recruiting large numbers of adolescents into a clinical trial at any one site cannot be overstated. First, a large proportion of adolescent referrals, though clearly dysphoric, either do not exhibit unequivocal signs of functional impairment or have too variable or fluctuating a symptom presentation to qualify for study inclusion. Likewise, a sizeable proportion "improve" during the initial placebo washout phase thereby shrinking the pool of available subjects for randomization. Second, various nondiagnostic issues are problematic in this age group; these include inadequate parental supervision of medication, noncompliance with study protocol, etc. By the time all necessary exigencies are met, still fewer subjects that is ideal actually complete the trial, resulting in a nonrandomly truncated data set. Yet, to date, investigators have generally failed to take into account in the statistical analysis the outcome status of subjects who fail to adhere to the treatment protocol. The bias introduced from this censoring of subjects who deviate from protocol is addressed by Lavori (1992). We shall return to this point shortly.

Another largely overlooked confound in existing studies is the failure to explicitly take into account known predictors of favorable and unfavorable response to TCAs in adults. These associations are obviously pertinent to the design and statistical analysis of randomized clinical trial data, particularly in the selection of diagnostic variables on which to stratify subjects for more fined-grained analysis of differential patterns of response.

This literature has been reviewed in detail (Bielski & Freidel, 1976; Klein & Gittelman-Klein, 1976; Nelson & Charney, 1981: Thase & Kupfer, 1987; Joyce & Paykel, 1989; Halpern & Hlassman, 1990). It suggests that the most substantial evidence of efficacy of TCAs is found in patients with endogenomorphic features (lack of consummatory pleasure; nonreactive mood; pathological guilt and brooding; cognitive dysfunction; psychomotor changes) of at least moderate severity. By the same token, placebo response tends to be modest at best in such patients, ranging, on average, from 15% to 35% (Raskin & Crook, 1976). Adult studies also suggest that resistance to TCAs is increased (or drug effects less robust) among patients with milder severity of illness, history of substance abuse or chronic personality problems, and bipolarity, and that patients with atypical or reversed neurovegetative features of depression may have slower time to remission during treatment with TCAs compared to patients with typical endogenous features (Thase & Kupfer., 1987).

Critically, it remains unclear to what extent the negative outcomes of adolescent studies are the result of these uncontrolled sources of response variance; the relatively limited scope of studies conducted to date precludes examination of the predictive significance of these variables. Nonetheless, it is noteworthy that family history of bipolar illness and comorbid conduct problems were usually common in subjects in the Geller (1990) NTP study, substance abuse was frequent in subjects studied by Boulos et al. (1991), and atypicality was prominent among subjects studied by Klein et al., (1992). We would argue therefore that the existing studies of antidepressants in adolescents MDD are marred by significant methodological confounds.

4. The Question of Placebo Response Reconsidered

Rationale for no wash-out.

The introductory placebo washout is a nearly routine design feature of controlled clinical trials of antidepressant drugs. This strategy assumes that the elimination of early remitters to placebo suppresses final placebo response rate and improves the chance of detecting a statistically significant effect of active treatment.

In point of fact, placebo response is not a stable individual characteristic; moreover, exclusion of placebo washout responders from clinical trials may actually confound results in ways entirely contrary to expectation. For example, Rabkin et al. (1986) observed depressive relapses among 20 of 45 subjects who were followed-up 3 months after initial improvement during a 10-day placebo washout trial. Reimherr et al. (1989), in reanalyzing data from a double-blind controlled trial of fluoxetine, imipramine, and placebo, showed that placebo response deteriorated over the six week trial and further demonstrated that elimination of initial placebo washout responders from this trial would not have suppressed final placebo response rate, and would have actually narrowed observed differences between the active treatment and placebo groups. And in a follow-up study of 6- to 12-year-olds with MDD recruited for a double-blind controlled study of nortriptyline, Geller et al. (1992), found that 4 of 11 placebo washout responders had relapsed within 4 weeks of initial "improvement" and continued to display significant affective morbidity over subsequent two to three-year follow-up.

Since it appears that a substantial number of subjects who receive placebo derive little sustained benefit, we decided not to include a placebo washout phase in the design of this protocol. Of equal importance, the issue of placebo response raises other salient points with regard to clinical trial methodology in adolescent MDD:

(1) If, as many experienced investigators believe, episodes of depression adolescence have a more reactive, fluctuating symptomatology as compared to depression in adulthood, initial improvement with placebo may be quite common in young patients.

(2) As is the case with adults, this placebo response, however robust initially, may be transitory. Indeed, we believe that many adolescent placebo responders remain in episode, even though asymptomatic at the completion of the acute treatment phase.

(3) It is crucial to emphasize that no objective data are presently available concerning the differential course of subjects receiving continued treatment with pharmacotherapy vs placebo. It is reasonable to ask therefore whether or not the temporal pattern of clinical remission of the pharmacologically treated episode of MDD in adolescents differ from that treated with placebo.

(4) Taking these points into account, if comparative trials of medication and placebo in adolescent MDD are to succeed in deconfounding short term placebo mediated improvement from more lasting pharmacologically induced suppression of the index episode, their design must focus explicit attention on the time course and stability of symptom improvement.

Accordingly, we are proposing to enter all medication and placebo responders (while maintaining the double-blind) into a 6-month continuation phase in order to objectively assess persistence of therapeutic gains across groups. We hypothesize that symptom recrudescence during the continuation phase will be less common amongst initial responders to medication compared to responders in the placebo group. Specifically, responders to paroxetine, and responders to imipramine, will demonstrate:

(a) fewer depressive symptoms;
(b) less overall functional impairment; and
(c) lower risk for relapsing into fully diagnosable MDD.

5. Why Study Two Antidepressants?

At present, there exists only one randomized, double-blind, placebo-controlled study of a specific serotonin reuptake inhibitor (SSRI) in adolescent depressives (Simeon et al., 1991); the limitations of this study have been noted. Several considerations, both theoretical and practical, argue for a joint examination of the efficacy and tolerance in an adolescent cohort of a TCA, and the newly available SSRIs.

Paroxetine, structurally distinct from TCAs, has limited affinity for catecholaminergic or histaminergic receptors. As a result it produces significantly fewer of the side effects associated with TCAs. For this reason, paroxetine may have greater overall consumer acceptability with adolescents

thereby assuring improved compliance. Indeed, our collective experience in treating adolescent depressives with fluoxetine in open label studies indicates this is the case.

A second potential advantage of paroxetine is its limited cardiotoxicity. That it is far safer in overdose than TCAs argues for its special appropriateness in the pharmacologic management of adolescents, in whom rates of suicidal ideation and completed suicide are high (Rao et al., in press; Brent et al., 1990).

Theoretically, it is conceivable that, apart from uniformities in symptom picture and follow-up course, differences between adolescents and adults exist in the developmental pathophysiology of affective disturbance. For example, adolescent-onset depression has been associated with higher familial affective morbidity compared to adult-onset illness (Weissman et al., 1984; Kupfer et al., 1989). Genetic variation of this sort may have functional biological and neuropharmacologic implications as well, thus arguing for investigation of serotonergic compounds in this age group.

It is also conceivable that neurohormonal aspects of puberty and the ontogeny of brain neurotransmitter systems have important influences on the response of adolescents to specific classes of antidepressant drugs (Geller et al., 1990; Strober et al., 1990). For example, Strober et al., (1990) have speculated that increases in noradrenergic activity occurring with onset of puberty (Young et al., 1984) may contribute to a state of relative noradrenergic "activation" at this age that naturally inhibits, or blocks, the hypothesized TCA-induced down-regulation of B-adrenoreceptors thus limiting overall potency of this class of antidepressant. Analogously, one might be tempted to speculate that serotonergic antidepressants, which do not depend on down-regulation of B-adrenoreceptors for therapeutic effects, will have greater efficacy in this age group.

In sum, we believe the approach we have chosen, involving the systematic multi-stage study of two neuropharmacologically distinct antidepressants is theoretically and clinically important, and will ultimately have the broadest possible impact on research and clinical practice. Hence, by combining a placebo controlled study of the efficacy of imipramine and of paroxetine in a collaborative, multicenter proposal, definitive advances into the pharmacotherapy of adolescent depression are expected.

6. Why a 2 year prospective follow-up on all subjects after they have completed the randomized clinical trial?

The largest cohort of depressed adolescents followed to date prospectively has an N of 78 (Kovacs et al.). This study and a comparable study on 38 depressed adolescents (Keller et al, 1989) showed long durations of episodes of depression, high rates of relapse after recovery and substantial co-existing psychosocial and psychopathologic morbidity and co-morbidity. Collecting the proposed prospective follow-up data on this cohort would make it the largest sample of carefully diagnosed adolescent depressives followed in the history of psychiatry. These data will be unique and invaluable in enabling us to create a comprehensive profile on the natural history of affective disorders, analogous to the Adult NIMH Collaborative Depression Study and the Harvard/Brown Anxiety Disorder Research Program (HARP). Each of these programs has had a dramatic impact on our understanding of these major psychiatric disorders. This proposal will be similarly profound in increasing our knowledge of affective disorders in adolescents.

7. Summary

The possibility that adolescents with MDD do not respond as distinctively to antidepressants as adults is an intriguing hypothesis that remains unanswered. We contend that little can be concluded from studies conducted thus far due to a variety of methodological limitations and potential confounds. Morever, considering the difficulty of recruiting at any single site a large enough sample of adolescents with core endogenous features, and given the truly serious implications of failing to detect a modest treatment effect in this age group, we conclude that multicenter collaboration will be necessary for research on the pharmacotherapy of adolescent depression to have real potential. The large sample to be studied in this multicenter comparative trial wil allow for randomization of subjects to different active treatments, achieve the statistical power for documenting even modest treatment effects, and permit identification of predictors of response outcomes.

EXPERIMENTAL DESIGN AND METHODS

Overview

Adolescents from ages 13 years 0 months through 17 years 11 months inclusive who are currently in an episode of major depressive disorder (DSM-III-R) with a minimum duration of eight weeks and have a Hamilton severity score of 15 or greater will be included in this 8-week double-blind placebo-controlled three-cell study of the efficacy of paroxetine versus placebo and the efficacy of imipramine versus placebo. At the completion of the 8-week acute study, clinical responders will be blindly continued on the same medication in a 6-month extension study. Non-responders at the end of the 8-week acute study will be withdrawn and treated openly. Throughout the study, at each site, the number of subjects assigned to each cell will be approximately equal and each cell will be approximately group balanced for several potentially important covariates.

Inclusion Criteria

1. Diagnosis: The K-SADS-P semi-structured clinical interview will be administered in the fashion described in the instructions for that instrument and used to assess the presence or absence of each of the criteria symptoms for depression. The parent(s) and the adolescent are separately interviewed to assess each symptom. The clinician forms a summary rating based on best overall information combining all sources. For those symptoms where there is significant discrepancy between information provided by the adolescent and information provided by the parent(s), the clinician, adolescent and parent(s) all sit together and discuss the information provided by each source and reach a best consensus.

A diagnosis of major depressive disorder (MDD) using current DSM-III-R criteria is required for entry into the study. Since the adolescent is the person being treated, we will also require that the adolescent meet criteria for MDD using only the data provided by him/her. This is designed to rule out the occasional adolescent who denies symptoms in the face of a clear and convincing report of symptoms from the parent(s) and where this denial persists. Whether or not this occasional adolescent truly has a depression, clinical experience indicates that compliance problems are almost universal in those adolescents.

2. Duration of episode of eight weeks or greater.

3. Age 13 years 0 months to 17 years 11 months inclusive at the time of entrance into the protocol.

4. Severity of affective episodes: A score of 15 or greater on the 17 item Hamilton Depression Rating Scale (HDRS) is required.

5. Subjects must be medically healthy as determined by a physical examination, medical history, and laboratory screening.

6. IQ $\geq$ 80 by Peabody Picture Vocabulary Test.

7. Informed Consent signed by adolescent and parent.

Exclusion Criteria

1. Other psychiatric disorders: Patient with a current or lifetime DSM-III-R diagnosis of bipolar disorder, delusional depression, schizophrenia or schizo-affective disorder, anorexia, bulimia, alcohol or drug abuse/dependence, obsessive/compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder will be excluded. Patients with a current diagnosis of post traumatic stress disorder (DSM-III-R) are excluded.

2. Subjects who have had an adequate trial of antidepressants within the six months prior to beginning this study will be excluded. An adequate trial is defined as a treatment of at least four weeks or more with imipramine, desipramine, or amitriptyline at a dosage of 150 mg per day or greater, with nortriptyline at a dosage of 50 mg per day or greater, or with fluoxetine at a dosage of 20 mg per day or greater during the entire four week period.

3. Suicidality: Subjects who have suicidal ideation with a definite plan, who have made a suicide attempt within the current episode, or who have ever made a suicide attempt by medication overdose will be excluded from the study.

4. Medical illness: Patients with medical illness which contraindicates the use of heterocyclic antidepressants will be excluded (e.g. cardiovascular disease).

5. Concomitant medication: Subjects using (1) psychotropic medications including anticonvulsants, anxiolytics, neuroleptics, lithium carbonate, (2) illicit drugs as documented by a drug screen within two weeks of starting the study, or (3) medications with CNS effects (e.g. thyroid replacement or steroids) will be excluded.

6. Organic brain disease, epilepsy or mental retardation.

7. Pregnancy.

7. Sexually active girls not using reliable methods of contraception.

Recruitment and Initial Screening

Subjects will initially be screened by telephone at each site. All sites will use the Screening for Youth Depression. This screen will review depressive syndrome criteria and major inclusion and exclusion criteria. Subjects who appear likely to meet criteria will be evaluated promptly thereafter.

Diagnostic assessment will be done using the K-SADS-P (for present episode) and K-SADS-E (for lifetime episodes) with both the adolescent and parent(s). All K-SADS interview data will be directly confirmed by a senior clinician (psychiatrist or psychologist) who will interview both the adolescent and parent(s) and will confirm each of the positive criteria symptoms for depression by direct interview. The psychiatrist or psychologist will also review each of the items of the Hamilton Depression Rating Scale.

Diagnostic interviews will be audiotaped. Cases will be reviewed by Principal Investigator or Co-Principal Investigator at the local site who will confirm that each patient meets entrance requirements. Each potential case will be reviewed by phone by a senior investigator at another site who will have available the audiotape in the event of diagnostic questions. A random 20% subsample of all audiotaped initial interviews will be reviewed in detail by a senior investigator at another site.

Following initial assessment of an adolescent who meets inclusion criteria and signs informed consent, the subsequent seven to ten days will be used to obtain baseline laboratory work, to request and obtain medical or psychiatric records of prior treatment where indicated, and to document that the depressive symptomatology is stable after the initial psychiatric contact. At the end of this interval, the adolescent will return to the clinic and will be re-evaluated using the K-SADS-P sections for affective disorder (Mini-K-SADS) and the Hamilton Depression Rating Scale. Only subjects continuing to meet inclusion criteria (DSM-III-R major depression and a Hamilton Depression Rating Scale of 15 or greater) will be included. This seven-to-ten-day pretreatment period closely mirrors our clinical practice.

Informed consent

Informed consent will be obtained from both the adolescent and parent(s) or guardian(s). Adolescents who are excluded from participation in the study or who do not give consent will be referred for treatment at another appropriate program within our institution or in the community.

Randomized assignment of subjects to treatments

Assignment of equal number of subjects to each of the three treatment arms, imipramine, paroxetine, and placebo, will be done on a per site basis using Efron's biased coin design (1978, 1980) to approximately balance the three groups on severity of illness, presence/absence of melancholia, sex, and age. This technique consists of giving a greater than proportionate chance of assigning a particular subject to the cell where he/she will most improve the overall balance across multiple balancing characteristics, considering all subjects recruited at that site up to that point in time. With subjects presenting sequentially, an exact match on multiple covariates is not possible, however, if a wholly random assignment scheme is used severe imbalances (with respect to a particular covariate) tend to occur with high probability. Therefore, Efron's biased coin design will be utilized in order to prevent severe imbalances. We have a computer program designed by Satish Iyengar, Ph.D., currently used in another study (NIMH R01 MH45424, "Imipramine Treatment of School Refusal") which automates this procedure.

Only statistical and pharmaceutical personnel at Smith Kline will know the status of the medication/placebo assignment of each subject. Statistical personnel there will instruct the investigators at the specified site to use a numerically labelled pill pack such that correct assignment after biased randomization as described above is accomplished. At each site there will be a sealed envelope available 24 hours per day which may containing the drug assignment information for each individual case which may be opened only in the event of emergency. Opening such an envelope for a subject will necessitate termination of that subject in the study (except for the proposed long-term follow-up component).

Titration of Medication

Medication will be titrated upwards as limited by side effects and cardiac safety limits but entirely independent of clinical response according to the following schedule:

DAY	IMIPRAMINE	PAROXETINE
1 - 3	25 mg	20 mg
4 - 7	50 mg	20 mg
8 - 10	75 mg	20 mg
11 - 14	125 mg	20 mg
15 - 17	150 mg	20 mg
18 - 21	200 mg	20 mg
22 - 24	250 mg	20 mg
25 - 28	300 mg	20 mg
29 - 42	300 mg	30 mg
43 - 56	300 mg	40 mg

Assessment Instruments and Their Scheduling

The following assessment instruments will be used at time of initial evaluation: Kiddie-SADS-P (with parent and child), Kiddie-SADS-E (with parent and child), and Clinical Global Assessment Scale.

The Kiddie-SADS-P (Present episode, 1986 version) (Puig Antich & Ryan, 1986) is a diagnostic instrument for the semistructured assessment of an ongoing episode of psychiatric disorder in children and adolescents 6-17 years of age. It includes an interview with the parent and an interview with the child (Chambers et al., 1985). The K-SADS-P facilitates the systematic recording and integration of clinical data from a number of sources gathered during a child psychiatric evaluation, characterizes the symptomatology and measures the severity of the different diagnoses during the current episode of disorder.

The semistructured interview section of the K-SADS-P is composed of four sections, each section of which addresses the symptoms of four major categories of child and adolescent psychiatric disorders (i.e., affective, anxiety, conduct, and psychotic disorders). The final section is for rating behaviors manifested during the interview with the child. The parent is interviewed first using an unstructured format to establish a chronology of the evolution of progress of the current episode of disorder, the onset, predominant symptoms, and the period during the episode of the greatest severity or intensity of symptoms. Then the parent is interviewed using the semistructured portion of the protocol. The child is then interviewed, generally with only the child and the interviewer present (unless the child is unable to tolerate separation from the parent). In a test-retest reliability study of mother-child pairs (N=52), the diagnoses of major and non-major depression and conduct disorder, as well as several related additive scales proved to be highly reliable (Chambers et al, 1985) with a mean test-retest intraclass R of 0.60 for the fourteen diagnostic symptoms for major depressive disorder.

The Kiddie-SADS-E (epidemiologic version, with 1983 modifications) is a semistructured diagnostic instrument to characterize retrospectively the symptomatology of past episodes of disorder in children and adolescents (Orvaschel et al, 1982). The K-SADS-E follows a very similar format and method to the K-SADS-P. It is very accurate in characterizing past episodes of depression.

Overall global functioning will be assessed using the Child Global Assessment Scale (C-GAS) (Shaffer D, Gould M, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S, 1983).

At the end of the assessment period the following will also be obtained: Autonomous Functioning Checklist, Self Perception Profile for Adolescents, and Sickness Impact Scale (described below).

At the end of the assessment period and at each weekly visit, each subject will be assessed with the depression section from the K-SADS-P, HDRS, Side Effects Scale (SES), and the Clinical Global Impression and Clinical Global Improvement Scales.

During the assessment interval, a family history will be obtained on all first degree family members using the mother as informant (or other parent or parents surrogate if required). The mother will be interviewed about her own lifetime history using the SADS-L (Spitzer RL, Endicott J, 1978) and family history of all other first degree relatives using the Family History-Research Diagnostic Criteria (FH-RDC), (Andreasen, 1986).

Cardiovascular functioning

Cardiovascular functioning will be assessed at baseline by obtaining a 12 lead EKG, heart rate, and blood pressure. At each clinic visit, each subject will have a repeat EKG rhythm strip, blood pressure sitting and standing and heart rate assessment. Cardiovascular limits to titration will be as follows using criteria developed by Boris Birmaher, M.D. and James Zuberbuhler, M.D.

resting heart rate < 100
resting systolic BP < 140
resting diastolic BP < 85
PR interval < 0.21
QRS interval < 0.12 and less than 150% of baseline
QTc < 0.48

Cardiovascular parameters slightly outside those described above will result in decreasing medication dosage by one tablet per day.

Study Drop-outs

In order to get as complete data as possible on each subject whether or not they must be withdrawn from the study or decide to withdraw on their own, all subjects will be paid an honorarium of $10/visit and an honorarium of $50 for completion of interview schedules at the scheduled time of last visit. Experience by several of the principal investigators suggest that, especially with adolescents who may at some weeks be ambivalent about coming and whose parents may otherwise occasionally be tempted to have the adolescent skip a week or two, this modest token payment will meaningfully increase the quality of completeness of data collection.

The standard basis of inference in clinical trials is the principle of "intention to treat" (ITT). This principle demands that all patients' outcomes be assigned to the original randomization group, regardless of protocol adherence or extra-protocol treatments (Peto et al., 1977). The ITT principle requires that patients' outcomes be ascertained regardless of protocol status (Lavori, 1992) since otherwise the analysis is not possible. Alternatives to the ITT principle ("last value carried forward", "adherers", "evaluables") are not well defined statistically, and do not preserve the causal strength of the randomization.

The ITT analysis permits a rigorous comparison of the treatment "policies," in a "pragmatic" analysis (Pocock, 1983), while the "exploratory" goal of detecting the causal effects of treatments are feasible only when the experiment remains "in control," with so few protocol violations that all analyses will yield the same result. Thus, if there is a little dropout, the issue is moot, while with substantial dropout the prognostic ITT analysis is the only statistically supportable analysis.

Early Termination for Medical Reasons

It is anticipated that in a few subjects the study will be terminated early because of medication side effects. Potential reasons for early termination include cardiovascular side effects beyond those permitted (see above), allergic reaction to medications, etc. Decisions for early study termination for medical or other reasons should be the responsibility of the principal investigator at each site. In all cases, subjects terminated early for any reason including medical reasons will be included in data analysis. Decision to terminate or not will be made blind to actual medication/placebo status--the blind will be broken only after termination is decided.

Should a patient decide to terminate the study early, a discontinuation taper will be strongly recommended. If this is accepted by the family, the medication will be tapered off in a linear fashion over approximately five to seven days.

Serum Levels

Blood samples for analysis of serum levels of imipramine, desipramine and the 2-OH metabolites of each will be obtained on all subjects no matter to which treatment they are assigned. Blood will be collected in a uniform manner. Serum will be extracted and stored at -20° Centigrade until completion of the study. All plasma levels will be done by a single central laboratory.

Medical Management -- Psychotherapy

Experience by several of the principle investigators doing similar protocols in adolescents suggest that patients and families expect psychotherapy and are reluctant to consider a course of medication treatment alone, especially where the medication may be solely placebo. On the other hand, a provision of treatment with a psychotherapy which, in retrospect, turned out to be extraordinarily efficacious might well preclude the demonstration of a real, significant, and clinically-meaningful medication effect. There are currently several research groups beginning the process of examining different specific psychotherapies (e.g. cognitive behavioral and interpersonal) for adolescent depression. As of yet, however, there are no completed controlled studies which would suggest a "reference" psychotherapy treatment. We will include supportive psychotherapy, similar to the medication management as described by Fawcett (ref), which has been modified by our group to address issues specific to adolescents.

Weekly visits will consist of a 45 minute visit with the therapist. In unusual circumstances, emergency contact of greater duration where permitted. Duration of all contact including phone calls will be systematically documented.

Definition of "responders" and "non-responders" at end of eight-week acute treatment study

To be classified as a "responder" and continue to the continuation phase a subject must:

1. Have a Hamilton Depression rating not greater than 8.

2. Have no more than one positive criterion symptom for major depression as assessed by the K-SADS-P interview (rating of 3 or greater on an item counts as positive).

3. Have no present suicidal ideation as assessed by the K-SADS-P.

4. Have no evidence of mania or hypomania as assessed by K-SADS-P.

Termination at end of acute study for non-responders

At the end of the acute phase subjects who are "non-responders", as defined above, will be terminated from the study. We will taper medication/placebo off over a five to seven day period at which time their care will be transferred to clinical personnel who are not part of this study. In general, the patient and family, all clinical personnel, and all research personnel will remain blind to medication assignment of all subjects even after termination of the acute phase. In some subjects, for ethical reasons, it may be necessary for the clinical personnel to be informed which medication the subject was on. The decision to unblind the clinical personnel will be made jointly with clinical personnel at the site and clinical personnel at Smith Kline each of whom will be unassociated with any personnel involved in this study. In all cases, study personnel will remain blind until the final study subject across all sites has completed the acute phase of the protocol.

Six-Month Blind Continuation

Subjects who are "responders" at the end of the double-blind acute study will be blindly continued on the current (final) dose of imipramine/paroxetine/placebo for an additional six months. We estimate that 65% of subjects in both active treatment will be "responders" and 40% of subjects on placebo will be a "responder".

The aims of the six-month continuation phase are test our hypotheses that: (1) Responders to the 8 week experimental phase who are maintained on their study treatment for 6 months will experience significantly fewer MDD relapse on IMI and paroxetine than on placebo; and (2) During the 6 month continuation phase the side effect profile of paroxetine will continue to be more favorable than that of placebo.

Procedure for 6-month follow-up:

1. Maintain last medication/placebo dose blindly.

2. Monthly brief psychiatric and side effect assessments:
   a) affective section of K-SADS-P interview
   b) Hamilton depression rating scale
   c) Side effect scale (SES)
   d) Clinical Global Assessment Scales
   e) EKG rhythm strip, blood pressure, and heart rate assessment

3. Assessment at Termination of 6-month follow-up:
   a) Full K-SADS-P and K-SADS-E for interval
   b) Hamilton Depression rating scale
   c) Side effect scale (SES)
   d) Clinical Global Assessment Scales
   e) EKG rhythm strip, blood pressure, and heart rate assessment

Prospective Naturalistic Follow-up

In all subjects whether or not they enter the six-month blind continuation phase we will obtain the following at 6, 12, 18, and 24 months after completion of the acute phase study:

a) LIFE
b) Clinical Global Assessment Scales
c) Autonomous Functioning Checklist
d) Self Perception Profile for Adolescents
e) Sickness Impact Scale

Instruments

L.I.F.E.: The Longitudinal Interval Follow-up Evaluation (LIFE) is an integrated system for assessing the longitudinal course of psychiatric disorders. It consists of a semistructured interview, an instruction booklet, a coding sheet, and a set of training materials. An interviewer uses the LIFE to collect detailed psychosocial, psychopathologic, and treatment information for a six-month follow-up interval.

Family History Screen (FHE), Subject Version: The Family History Screen is a brief computer-scorable instrument which collects a pedigree and screens for DSM-III-R diagnoses in family members. The instrument has been shown to have good levels of sensitivity and specificity for adults reporting on themselves. (Lish et al)

Self Perception Profile for Adolescents: This scale (Harter, 1987) is an upward extension of the Self Perception Profile for Children which in turn is based on the Perceived Competence Scale (Harter, 1985). It is a measure of "self" as a dimension of competence in the proposed research. It consists of 45 item self report questionnaire, assessing perceived competence in 9 domains: scholastic, social, athletic, physical appearance, job, romantic, conduct/morality, close friendship, and global self-worth. Psychometric information regarding this scale is available for a parochial school population. Subscale reliability is generally very high. Validity of the perceive competence scale has been supported by a number of recent studies (Cauce 1987; Nottelman 1987). Scores do not correlate with age.

Autonomous Functioning Checklist: The AFC is a parent-completed checklist designed to measure behavioral autonomous functioning in adolescents between the ages of twelve and eighteen. It contains seventy-eight items and is subdivided into four conceptually distinct subscales: Self-and Family Care, Management, Recreational Activity, and Social and Vocational Activity. Each item in the first three subscales is a short description of a behavior. The parent rates the adolescent in relation to each item on a five-point scale ranging from 0 (does not do) to 4 (does every time there is an opportunity). The items on the fourth subscale, Social and Vocational Activity, are rated by the parent on a dichotomous, yes/no scale. For each scale, high scores indicate that the adolescent routinely performs many of the acitivities listed.

Kiddie-SADS-P (fourth working draft, Puig-Antich & Ryan, 1986) and **Kiddie-SADS-E-Revised** (Orvaschel & Puig-Antich, 1987) are semi-structured interviews of both the adolescent and parent obtaining present episode and lifetime data respectively for all axis I disorders including affective disorder, psychosis, drug and alcohol abuse. They have demonstrated good reliability for affective disorders.

The Sickness Impact Profile (SIP) is a behaviorally based measure of health-related dysfunction that was developed to provide a measure of health status useful in the assessment of individuals or populations with both chronic and acute illnessess. It may be either interviewer or self administered and is scored as a total SIP score or as two dimensions, physical and psychological. It has undergone extensive field testing and has demonstrated good reliability (internal consistency, Cronbach's alpha, ranges from 0.94 to 0.97; overall reproducibility score ranges from 0.88 to 0.92) and validity (SIP to self assessment of sickness ranges from 0.54 to 0.69 and dysfunction ranges from 0.52 to 0.69; SIP to NHIS ranges from 0.55 to 0.61). It is easily understood by patients and the version used in this study has been modified for an adolescent population and has been piloted in an adolescent outpatient affective disorders clinic where it has demonstrated good utility. (Bergner et al., 1976; ibid. 1985).

Data Management and Statistical Analysis

All data will be entered on standardized forms and will be double-checked for completeness and accuracy. A second staff member will then check that patient name and ID information are entered and are correct on the form which will then be copied. The copy will remain at the local site and the original will be forwarded to Smith Kline for data entry. Immediately after data entry and verification, all data except information about medication/placebo assignment will immediately be made

available by electronic form (tape, electronic file transfer, etc.) to the data procession/biostatistical personnel at the various sites.

planned analysis date

Analysis of the 8 week double-blind study will occur immediately after completion of the 8 week acute phase of the last subject entered (prior to completion of the continuation study for some subjects). At that point the biostatistical team at the sites will be given the medication assignment data (they should already have all other data relevant to this analysis). Data analysis of the acute treatment study will be done as a collaborative enterprise between the statistical personnel at the sites and statistical personnel at Smith Kline.

The primary analysis of the 8 week double-blind study will use analysis of variance methods including pre-treatment depression severity, presence/absence of melancholia, sex, and age as covariates. There are two pre-planned comparisons (IMI vs. placebo and paroxetine vs. placebo) so appropriate statistical adjustment will be made (e.g. Dunnett's test) to account for the use of a single placebo control group as comparison for both active treatments. The analysis will be on an "intent to treat" basis with all subjects entered into the blind phase of the study included. We will also use other methodologies, such as random effects models, as secondary analyses of the double-blind study. Final plans for the exact statistical methodology to be used for this main analysis of the double-blind study will be jointly established and documented in a collaboration between Smith Kline and our statistical personnel before entering the first subject.

This study is designed to have adequate power to detect even relatively small effect sizes in the two active comparison groups. We calculate that using conservative statistical assumptions (Bonferroni correction) we have power greater than 0.80 to detect an effect size of 0.30 or greater ($alpha_2 = 0.05$) in either active medication vs. placebo comparison.

Longitudinal data comparing rates of side effects or other adverse consequences will use standard Chi-square or Fisher's exact statistics. Assuming that about 60-65% of subjects in each of the active cells will enter the extension phase and about 40% of subjects on placebo will enter this phase (which requires clinical remission at the end of the acute study) we will have power of 0.80 to detect differences of effect size of 0.55 or greater in this component. Longitudinal data comparing rates of relapse between different treatments during the extension phase will be performed using standard life table methodologies. Such comparisons will have slightly more power than the categorical comparisons.

Administrative Organization

Collaborative research programs involving institutions in different cities require a well organized administrative structure and clearly defined procedures including all phases of research design, training of interviewers, data collection, laboratory studies, data processing, and data analysis. The proposed administrative organization is presented:

A. Steering Committee: Boris Birmaher, M.D., Satish Iyengar, Ph.D., Martin Keller, M.D. (permanent chair of steering committee), Rachel Klein, Ph.D., Harold Koplewicz, M.D., Stanley Kutcher, M.D., Philip Lavori, Ph.D., Neal Ryan, M.D., and Michael Strober, Ph.D.

In general, matters coming to the steering committee will be decided by consensus. In the event of a failure to reach a consensus, matters will be decided by a vote with each site having one

vote. Martin Keller will be chairperson of this committee. In the event of a tie vote which cannot otherwise be resolved, Dr. Keller will break the tie.

B. Subcommittees

Clinical Psychopathology: Michael Strober, Martin Keller, Rachel Kline, and Boris Birmaher

Psychopharmacology: Neal Ryan, Doug Robbins, Stan Kutcher, and Harold Koplewicz

Psychotherapy: Douglas Robbins, Stan Kutcher, David Brent

Data Processing/Biostatistics: Satish Iyengar

Training and Reliability: Martin Keller, Boris Birmaher, and Tracie Shea

Medical Management: Boris Birmaher, Douglas Robbins, and Stan Kutcher

External Oversight Committee: To be determined

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