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A Double-Blind, Placebo-Controlled Trial of Sertraline in Depressed Adolescent Alcoholics: A Pilot Study

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In order to preliminarily evaluate the efficacy, safety and tolerability of the serotonin reuptake inhibitor, sertraline, in the treatment of adolescents with a primary depressive disorder and a comorbid alcohol use disorder, a 12-week double-blind, placebo-controlled trial of sertraline plus cognitive behavior group therapy was conducted. Subjects were 10 outpatient treatment-seeking adolescents. Baseline assessment included the K-SADS, HAM-D, SCID, and the Time-Line Follow-Back. The HAM-D and the Time-Line Follow-Back were performed weekly thereafter. Both groups showed a significant reduction in depression scores with an average reduction between baseline and endpoint HAM-D score of $-9{\cdot}8$ ($F(1,8) = 26{\cdot}14$, $p \leqslant 0{\cdot}001$), although there were no significant group differences. There was an overall reduction in Percent Days Drinking (PDD); ($F(1,8) = 8{\cdot}90$, $p < 0{\cdot}02$) and in Drinks Per Drinking Day (DDD); ($F(1,8) = 20{\cdot}48$, $p < 0{\cdot}002$), however, there were no group differences. Depression responders tended to have higher baseline PDD than non-responders ($F(1,8) = 3{\cdot}9$, $p = 0{\cdot}08$) and change in HAM-D scores tended to correlate with change in PDD ($r = 0{\cdot}57$, $p = 0{\cdot}09$). Our data support that sertraline is safe and well tolerated in the treatment of adolescents with depression and alcohol dependence. Small sample size and cognitive behavior group therapy given to all subjects may limit the lack of group differences. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — adolescents; depression; alcohol use; sertraline

INTRODUCTION

Depression and alcoholism are major health problems in America; however, the relationship between the two is not clearly defined. This is especially true in the adolescent population. The coexistence of depression and alcoholism has been confirmed by many epidemiological studies, particularly in the adult population (Kessler *et al*., 1994). Comorbidity of depression and alcohol use disorders has also been found among adolescents in both inpatient (Deas-Nesmith *et al*., 1998; Grilo *et al*., 1995; Stowell and Estroff, 1992) and outpatient (Bukstein *et al*., 1989) settings.

The serotonin (5HT) system has been implicated in the treatment of depression as well as alcohol use disorders. Selective serotonin reuptake inhibitors (SSRIs) have been shown to be efficacious in the treatment of depression in adults (Grimsley and Jann, 1992; Murdoch and McTavish, 1992) as well as children and adolescents (Alderman *et al*., 1998; Apter *et al*., 1994; Boulos *et al*., 1992; Emslie *et al*., 1997; Jain *et al*., 1992; Simeon *et al*., 1990). In a double-blind placebo-controlled study of fluoxetine treatment of major depression in 40 adolescents, Simeon *et al*. (1990) demonstrated that improvements in the medication group significantly exceeded those of placebo. With the exception of the sleep disturbance factor of the HAM-D, the fluoxetine group of adolescents improved on all clinical variables. Similar efficacy of fluoxetine was demonstrated in a study of 15 adolescents and young adults (ages 16–24) with major depression who previously failed prior treatment with a tricyclic antidepressant (Boulos *et al*., 1992). More recently, in a double-blind, randomized, placebo-controlled trial of fluoxetine in 96 outpatient children and adolescents with depression, fluoxetine was demonstrated to be superior to placebo during the acute phase of treatment (Emslie *et al*., 1997). In addition, Alderman and colleagues (1998) reported that sertraline was both well tolerated and efficacious in children and adolescents with obsessive–compulsive disorder (OCD) or depression.

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The serotonin (5HT) system has also been implicated in the control of alcohol intake in both animals (McBride *et al*., 1991; Svensson *et al*., 1993) and humans (Sellers *et al*., 1992). Serotonin agonists (Svensson *et al*., 1993) as well as the 5HT reuptake inhibitors (McBride *et al*., 1989; Meert, 1993) have been shown to promote reduced alcohol consumption in rats. The animal studies have prompted clinical trials in humans. Fluoxetine significantly decreased alcohol consumption in inpatient alcoholics (Gorelick and Paredes, 1992) and ondansetron, a 5HT3 antagonist, reduced alcohol consumption in nonseverely alcohol dependent males (Sellers *et al*., 1994). More recently, Cornelius *et al*. (1997) demonstrated efficacy of fluoxetine in alcoholics with comorbid major depression through reductions in both depressive symptoms and alcohol consumption.

Taken together, in adults the SSRIs have been shown to be efficacious in the treatment of depression, in the treatment of alcoholism, and in the treatment of alcohol use disorders comorbid with depression. In children and adolescents, only the former has been studied. That is, published studies have demonstrated the efficacy of SSRIs for depression in children and adolescents, but no clinical trials have studied the efficacy of SSRIs for alcohol use disorder or alcohol use disorders comorbid with depression. The study of pharmacotherapy for comorbidity of substance abuse and psychiatric disorders in children and adolescents, in general, has received very little attention aside from some open label trials (e.g. Riggs *et al*., 1996, 1997, 1998) and one recent controlled medication trial (Geller *et al*., 1998). Given the prevalence of comorbidity of psychiatric and substance use problems in this age group (Deas-Nesmith *et al*., 1998; Hovens *et al*., 1994; Stowell and Estroff, 1992), this is clearly an area that needs to be explored further.

The principle aim of this study was to preliminarily evaluate the efficacy, safety and tolerability of the serotonin reuptake inhibitor, sertraline, in the treatment of adolescents with a primary depressive disorder and a comorbid alcohol use disorder. The secondary aim was to explore the feasibility of doing studies of this type in this adolescent population.

METHODS

Subjects were 10 outpatient treatment-seeking adolescents at the Institute of Psychiatry, Medical University of South Carolina, Adolescent Substance Abuse/Dual Diagnosis Program. The Institutional Review Board (IRB) approved the study at the Medical University of South Carolina. Parents and/or guardian(s) were informed of the study at the time of the outpatient evaluation for the Adolescent Substance Abuse/Dual Diagnosis Program. The parent/guardian and adolescent signed informed consent and assent, respectively.

Subjects were assessed for psychiatric disorders using the Child Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers *et al*., 1985). Depression was also assessed with the HAM-D (Hamilton, 1976) and substance use disorder diagnoses were made using a modified version of the Structured Clinical Interview for DSM-IV (SCID-R) (American Psychiatric Association, 1994; Martin *et al*., 1995). Alcohol use data were obtained using the Time-Line Follow-Back (Sobell *et al*., 1988), a calendar-based instrument that measures daily amounts of alcohol and drug consumption for a specified period of time by patient self-report. A child/adolescent psychiatrist (DD) board certified in child/adolescent and addiction psychiatry administered the K-SADS, SCID-R and the HAM-D. The Time-Line Follow-Back was administered by a research assistant with a master's degree in psychology who was trained by the child/adolescent psychiatrist.

In addition to the structured psychiatric assessments and the Time-Line Follow-Back (TLFB), subjects received a medical review of systems, physical examination, and laboratory tests (complete blood cell and differential counts, liver panel, thyroid panel, urinalysis and electrocardiogram (EKG). Baseline assessments included: K-SADS, SCID-R, HAM-D, TLFB, EKG, and physical exam and laboratory test. Weekly follow-up assessments included the HAM-D, TLFB and the side-effects checklist.

This study was a 12-week double-blind, placebo-controlled trial of sertraline plus group therapy. Following the baseline assessments, subjects were randomized using a computer-generated randomization table into sertraline or placebo groups. All of the medication was supplied by the study pharmacist and were identical in appearance. The adolescents were given a 10-day supply of medication, advised about the need for medication compliance, and given suggestions on how to remember to take their medication. They also were advised about possible side effects. The dosing schedule was 25-mg/day sertraline, increased weekly by 25 mg,

depending upon side effects, to a maximum dose of 100 mg in about 4 weeks. All patients were seen by the same psychiatrist weekly to assess side effects, to receive medication adjustments, to get another supply of medication, and to attend a non-manualized cognitive behavior group therapy (CBT). The cognitive behavior group therapy focused on relapse prevention, coping skills, anger management, modeling, role playing, etc. Cognitive behavior group therapy was administered to all adolescents participating in the study. The rationale for including CBT was that parents were more amenable to have their child participate if they knew other treatment was involved in light of the possibility of getting placebo.

Statistical analyses

Analysis of HAM-D scores. Baseline HAM-D scores were compared to the last HAM-D scores obtained during treatment (i.e. endpoint HAM-D scores) using a 2×2 split-plot analysis of variance (ANOVA) design with medication group (sertraline versus placebo) serving as the between-subjects variable and assessment time (baseline versus endpoint) functioning as the within-subjects factor.

Analyses of drinking outcomes. Both ANOVA and analyses of covariance were used to explore the relationship between medication group membership and drinking outcomes. Baseline percent days drinking (PDD) and drinks per drinking day (DDD) were computed based on the 90 days prior to study intake. Endpoint PDD and DDD measures were calculated using the last 21 days in which the patient participated in the treatment phase of the study. This 21-day calculation window allowed all subjects, including early terminators, to be included in the analyses. For each drinking outcome, a 2×2 split-plot ANOVA was conducted with medication group and assessment time as factors. An ANCOVA was also performed in which the endpoint drinking outcome was regressed on its baseline value along with a medication group factor.

Responder group analyses. Subjects were divided into those who experienced substantial improvement in their depressive symptoms (Responders) and those who did not (Nonresponders). The purpose of these analyses was to determine if remission of depressive symptoms, regardless of treatment, was associated with improved drinking outcome. Improvement was operationally defined as a 50 per cent decrease in HAM-D scores between baseline and endpoint assessments. A 2×2 split-plot ANOVA was conducted on drinking outcomes (i.e. PDD and DDD) where responder group served as the between-subjects factor and assessment time functioned as the within-subjects factor. ANCOVA models were also constructed where endpoint drinking outcome was regressed on the corresponding baseline measure and the responder group classification variable. Lastly, the correlation between change in HAM-D scores (baseline versus endpoint) and change in drinking outcome was also computed.

RESULTS

Sample characteristics

Table 1 provides characteristics of the patient sample. The sample was comprised of 10 subjects, of which 80 per cent were Caucasian and 80 per cent were males. At baseline assessment, subjects were drinking 29 per cent of the 90 days assessed and drank an average of 8·6 drinks per drinking day. Their overall HAM-D score at baseline averaged 20·6.

Medication group analyses

HAM-D scores. The mean baseline and endpoint HAM-D scores are given in Table 2 for the two medication groups. The ANOVA revealed a statistically significant time effect ($F(1,8) = 26{\cdot}14$, $p < 0{\cdot}001$) such that HAM-D scores decreased by 9·4 points on average regardless of medication group membership. Neither the main effect of medication group nor the medication group $\times$ time interaction was statistically significant.

Drinking outcomes. The mean baseline and endpoint drinking outcomes are also given in Table 2 and individual data are shown in Figures 1 and 2. An ANOVA on DDD revealed a statistically significant main effect of time ($F(1,8) = 20{\cdot}48$, $p < 0{\cdot}002$) such that subjects decreased the intensity of their drinking an average of 4·7 drinks from the baseline to endpoint assessments. There were no statistically significant medication group or medication group $\times$ assessment time effects. An ANCOVA which regressed endpoint DDD on baseline values and medication group did not reveal statistically reliable medication group effects, neither did a more complex ANCOVA model which

Table 1. Demographics

	Sertraline	Placebo	Overall
Age	16·4 ± 0·55 *n* = 5	16·8 ± 0·45 *n* = 5	16·6 ± 0·52 *n* = 10
Gender			
Male	4 (40%)	4 (40%)	8 (80%)
Female	1 (10%)	1 (10%)	2 (20%)
Race			
African–American	1 (10%)	1 (10%)	2 (20%)
Caucasian	4 (40%)	4 (40%)	8 (80%)
Baseline			
% Days drinking	27 ± 22	30 ± 32	29 ± 27
Drinks/drinking day	10·1 ± 6·0	7·2 ± 3·5	8·6 ± 4·9
HAM-D score	20·4 ± 5·5	20·8 ± 5·4	20·6 ± 5·5

* No significant differences were observed.

Table 2. Means, standard deviations and cell sizes for reported analyses

Classification variable	Baseline assessment			Endpoint assessment		
	HAM-D	DDD	PDD	HAM-D	DDD	PDD
Medication						
Sertraline						
$\bar{X}$	20·40	10·06	27·11	12·00	4·99	5·71
s	5·55	6·04	21·67	4·95	4·48	3·98
n	5	5	5	5	5	5
Placebo						
$\bar{X}$	20·80	7·18	30·00	10·40	2·81	7·62
s	5·45	3·50	31·98	3·65	4·81	12·42
n	5	5	5	5	5	5
Depression						
Responder						
$\bar{X}$	21·17	8·62	40·00	8·50	4·27	7·14
s	6·52	6·13	27·30	2·66	5·58	11·17
n	6	6	6	6	6	6
Nonresponder						
$\bar{X}$	19·75	8·63	11·39	15·25	3·36	5·95
s	2·87	3·05	9·99	2·06	3·01	4·56
n	4	4	4	4	4	4
Overall						
$\bar{X}$	20·60	8·62	28·56	11·20	3·90	6·67
s	5·19	4·90	25·80	4·18	4·53	8·75
n	10	10	10	10	10	10

included baseline and endpoint HAM-D scores as additional covariates.

The analysis on per cent days drinking resulted in findings similar to those observed for DDD. Specifically, an ANOVA revealed a statistically significant main effect of time ($F(1,8) = 8{\cdot}90, p < 0{\cdot}02$), such that the PDD declined by 22 percentage points following treatment. However, there were no reliable effects of either medication group or its interaction with assessment time on PDD.

Additionally, there were no medication group effects when endpoint PDD was regressed onto the corresponding baseline values and the medication group factor. The addition of baseline and endpoint HAM-D scores to this ANCOVA model did not reveal a statistically significant medication group difference in endpoint PDD.

Responder group analyses

Six of the 10 patients exhibited improvement in their depression symptoms. Of these six patients, two were from the sertraline group, whereas four were from the placebo group. There was no reliable association between depression response classification and medication group as assessed with Fisher's exact test ($p = 0{\cdot}52$).

The split-plot ANOVA on DDD revealed a statistically significant main effect of assessment time ($F(1,8) = 20{\cdot}60$, $p < 0{\cdot}002$), but no reliable effects involving either responder group or its interaction with assessment time. (The former test result was expected given the main effect of assessment time in the Medication Group Analyses.) Similarly, the ANCOVA which regressed endpoint DDD on its baseline value and the responder group classification variable did not uncover any reliable responder group effects.

The results were slightly different for PDD. The split-plot ANOVA revealed a statistically significant interaction between responder group and assessment time ($F(1,8) = 5{\cdot}77$, $p < 0{\cdot}044$) along with the expected main effect of assessment time ($F(1,8) = 11{\cdot}25$, $p < 0{\cdot}010$). The interaction was such that responders tend to have higher baseline PDD values as compared to nonresponders ($F(1,8) = 3{\cdot}9$, $p = 0{\cdot}08$), but these differences attenuated by the end of treatment. However, when these baseline differences were partialled out of the endpoint PDD measure using the ANCOVA model, there was no statistically significant responder group difference. The correlation between raw change scores for HAM-D and PDD was equal to $+0{\cdot}57$ and reached statistical trend levels ($p < 0{\cdot}086$). Thus, decreases in depression symptomatology from baseline to endpoint assessments tended to coincide with decreases in PDD.

Medication compliance and group therapy attendance

Medication compliance was measured by self-report and pill counts. Subjects were dispensed enough medications to last for 10 days and asked to return unused medications at each weekly visit. None of the subjects reported non-compliance with medications, although two subjects reported occasionally forgetting to take medications at the scheduled time and subsequently took medications 2–3 h later.

Subjects attended weekly cognitive behavioral group therapy. The average number of group therapy sessions attended during the 12-week treatment period was 8·2 and 10·6 for the sertraline and the placebo group, respectively. An independent sample *t*-test revealed no significant difference between the two groups ($t(1,8) =$, $p = 0{\cdot}347$). A treatment completer was defined as attending at least eight sessions. All five of the subjects in the placebo group met the criterion for treatment completion, while three out of the five subjects in the sertraline group met the criterion. These rates were not statistically different ($p = 0{\cdot}444$).

Adverse events

In general, there were few reported adverse events. One of the five subjects from the sertraline group reported insomnia, palpitations, and decreased appetite. On the other hand, fatigue was reported by one of five subjects in the placebo group. The adverse effects were mild and transient.

DISCUSSION

Our pilot study indicates that: it is feasible to conduct a 12-week medication trial in a dually diagnosed adolescent sample; adolescents can tolerate sertraline and cognitive behavior group therapy; sertraline is safe in alcohol dependent adolescents. However, the efficacy of sertraline in the treatment of adolescents with comorbid depression and alcohol dependence is questionable given our results. With treatment completion defined *a priori* as eight sessions, there was an overall 80 per cent treatment completion rate for the entire sample. There was no significant difference between groups. Subjects tolerated sertraline without serious adverse effects. One subject reported transient insomnia, palpitations and decreased appetite.

There was a correlation between change in HAM-D scores and change in drinking outcome from baseline to endpoint. These subjects were primary depressed as determined on initial assessment with the K-SADS and SCID-R which delineated the onset of symptoms. Depression was found to

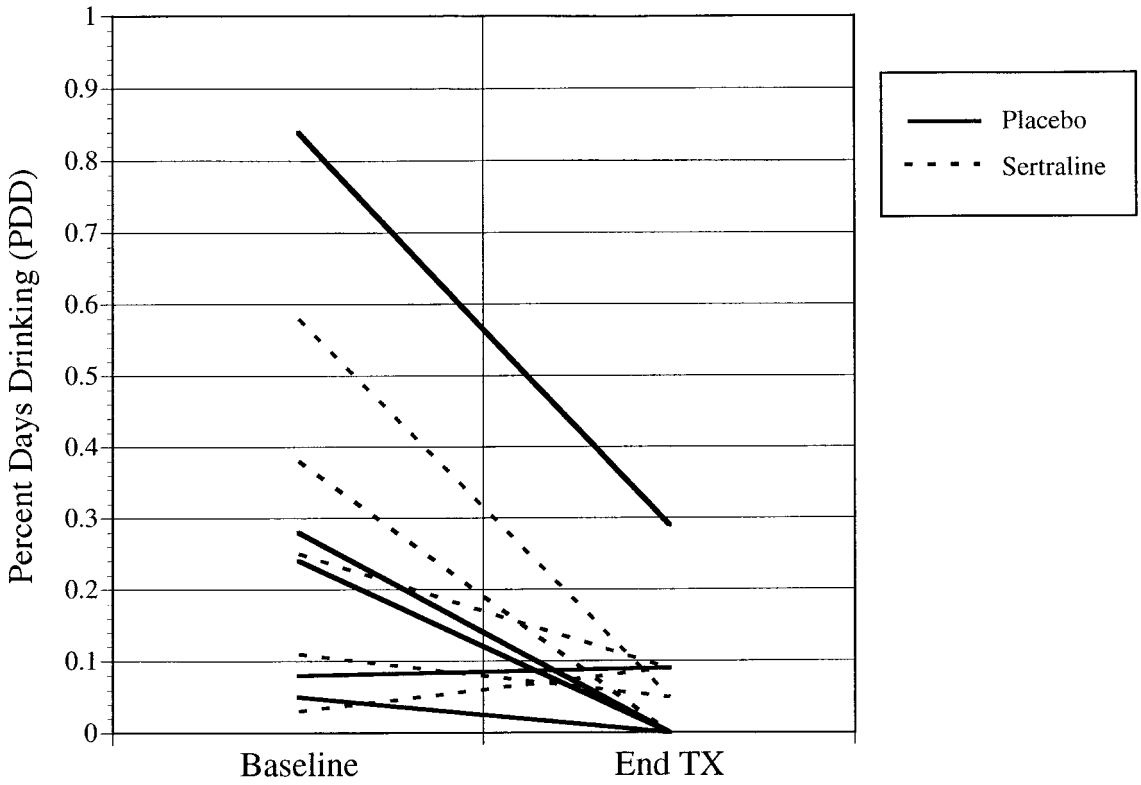

Figure 1. Individual-level results PDD

have predated the alcohol use. Depressive symptoms are likely to decrease over time in primary alcoholics without the use of psychotropics (Brown *et al.*, 1995; Schuckit, 1983). Since these subjects were primary depressives, the value of the use of an antidepressant may be noted by the correlation of change in depression scores and drinking outcome. Additionally, well documented primary–secondary diagnoses in an adolescent substance-abusing population may prove beneficial in preventing the worsening of a substance abuse problem and other related consequences, especially if pharmacotherapy is used.

Regardless of group assignment (medication versus placebo), depression significantly improved over time (baseline to end of treatment). The possibility of a placebo response in this sample of depressed adolescents should be considered given the rates of positive placebo response in populations of depressed adolescents. High rates of positive placebo response in the adolescent population (Puig-Antich *et al.*, 1987; Simeon *et al.*, 1990) are especially challenging. Nonetheless, it appears that the response rates in our study may be due, in part, to the active adjunctive group therapy. It should be underscored that in addition to medication or placebo, all subjects received weekly cognitive behavioral group therapy. Cognitive behavior therapy (CBT) has been demonstrated to be effective in the treatment of adolescent depression (Brent *et al.*, 1997). The improvement of depression over time regardless of group may be reflective of the effects of CBT. These results suggest a systematic relationship between change in depression symptomatology and frequency of drinking. The extent to which CBT led to a reduction in depression symptoms cannot be determined from these data. However, given the aforementioned relationship, CBT may be indirectly related to decreased drinking frequency.

Drinking outcomes (PDD and DDD) showed a significant main effect of time; however, there were no medication group differences. The lack of medication group differences may also be attributed to the adjunct *treatment* of cognitive behavior group therapy. Adolescents participated in therapy with much enthusiasm and in many cases indicated that

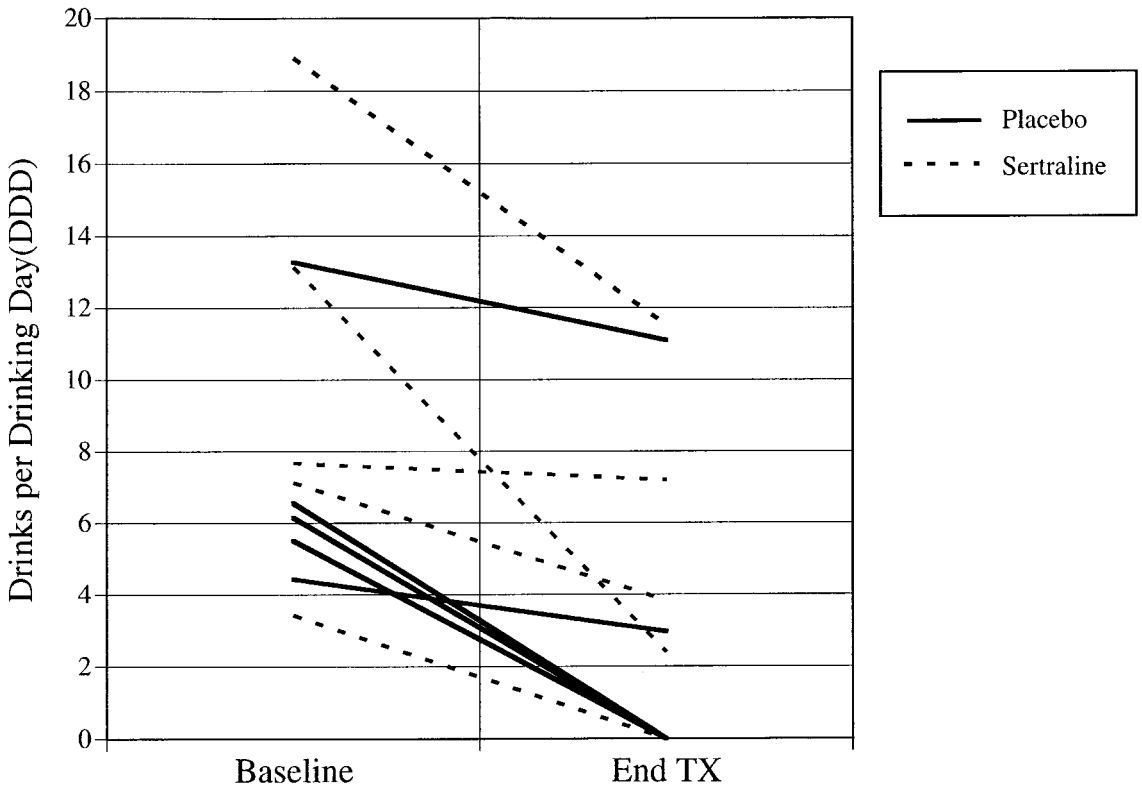

Figure 2. Individual-level results DDD

the group was helpful. The cognitive behavioral group therapy may have played a role in 'washing-out' the medication effect. Perhaps a less effective intervention (i.e. education group for encouraging compliance) may have provided a clear distinction between the medication group and placebo. Likewise, CBT group therapy has been demonstrated to be effective in reducing substance use in an adolescent sample (Kaminer *et al*., 1998). Thus the decreases in per cent days drinking and drinks per drinking day over time may be due to the CBT group. It is also unknown whether higher doses of sertraline (i.e. 200 mg) would have shown differential responses between the groups. The results of this study suggest that sertraline is safe and tolerated in an adolescent alcohol-abusing population. Side effects of sertraline within this sample were transient and did not lead to dropouts. While a maximum dose of 100 mg sertraline was utilized, it has been demonstrated that children and adolescents can tolerate up to 200 mg, doses typically used in adult populations (Alderman *et al*., 1998).

Study limitations include a very small sample size, which limits the ability to generalize to other populations or to draw general conclusions. The question of compliance with medications in this substance-abusing sample of adolescents also may be an issue. Although self-report and pill counts were used as compliance indicators, it is unknown whether these adolescents manipulated medications to appear compliant. Although self-report of substance use may be an issue, it has been reported that the use of self-report is a valid way of assessing adolescents with alcohol and other substance use problems (Winters *et al*., 1991) as well as dually diagnosed adults seen as outpatients (Weiss *et al*., 1998). An additional limitation is the potential restriction of medication effects because cognitive behavioral group therapy was given to all subjects.

Preliminarily, there is no significant difference in patient outcomes between depressed adolescent alcoholics treated with placebo or sertraline. It is premature to make conclusions about sertraline given the limitations of the study. Future studies with less intensive adjunct therapy, large sample sizes, compliance enhancement and compliance

markers are warranted. Since subjects were not followed after the 12-week trial, it is unknown whether the improvement seen in both the placebo and sertraline groups was sustained. Such profound improvement in both depression and drinking is worth noting and suggests that this population can improve markedly if treated with group CBT. The present study does, however, demonstrate the feasibility of conducting pharmacotherapy trials in adolescents with comorbid depression and alcohol dependence over a 12-week period.

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