Lithium Carbonate Versus Cognitive Therapy as Sequential Combination Treatment Strategies in Partial Responders to Antidepressant Medication: An Exploratory Trial

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Background: Partial antidepressant response is associated with increased rates of relapse. Despite increasing evidence that full symptomatic remission is the optimal goal of antidepressant therapy, there have been few comparisons between disparate treatment approaches to achieve this goal.

Method: Forty-four patients with DSM-IV major depressive disorder (MDD) who had a partial response (17-item Hamilton Rating Scale for Depression [HAM-D-17] score of 8–15) during open-label antidepressant treatment for 8 to 14 weeks were randomly assigned to receive cognitive therapy (CT) or lithium augmentation (LA) for a further 8 weeks using a single-blind design. Antidepressant medication was continued throughout the study. Subjects were also reassessed 4 weeks after discontinuation of LA or CT. Patients were enrolled in this study beginning September 1996 and follow-up for all patients was completed in December 2000.

Results: Although LA or CT did not significantly decrease symptom severity during sequential combination therapy, there was a significant decrease in HAM-D-17 scores 4 weeks later in LA-treated subjects compared with CT-treated subjects ($p = .04$). This resulted in 32% of patients achieving remission status, although between-group differences were not significantly different (38% in the LA group compared with 26% in the CT group, $p = .39$).

Conclusion: Despite methodological limitations, this preliminary study provides justification for both combination treatments. An adequately powered, randomized, controlled trial to evaluate the relative merits of combination psychotherapy and augmentation of pharmacotherapy in patients with partially remitted MDD is required.

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Major depressive disorder (MDD) is a highly prevalent, chronic, and recurrent condition with enormous emotional and social costs. Estimates of lifetime risk for MDD are approximately 12% for men and 20% for women.[1,2] During a longitudinal evaluation over 12 years, patients met full criteria for MDD 15% of the time,[3] and the risk of recurrence increased steadily with each new episode.[4] This high prevalence and continuing risk of relapse and recurrence place depression among the leading medical causes of disability[5,6] and economic burden.[7]

The presence of residual symptoms following pharmacologic or psychological treatment is a sign of poor prognosis and a risk factor for relapse.[3,8–10] Despite these findings, data from clinical trials[11,12] and from natural practice settings[13] indicate that fewer than 50% of patients achieve a full remission of symptoms. Attempts to improve rates of remission (defined as achieving a score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression [HAM-D-17]) include "augmentation" (addition of a second agent that by itself does not have antidepressant effects), "combination" (addition of a pharmacologic or psychological agent), as well as "optimization" of the original treatment.[14] Although lithium augmentation (LA) and sequenced cognitive therapy (CT) have been independently shown to be effective in improving rates of remission, there are limited data on the relative merits of these treatments.

Paykel et al.[15] demonstrated that patients with "residual depression" who had CT sequentially added to antidepres-

sant medication displayed a reduced rate of relapse (29%) compared with those who only received maintenance antidepressant treatment (47%). Since de Montigny and colleagues[16] first reported a rapid response to LA in patients taking tricyclic antidepressants, 2 meta-analyses have shown that LA is effective, at least in enhancing rates of response, in approximately 60% of previously treatment-resistant patients.[17] CT has also been shown to enhance lithium prophylaxis in a small group of bipolar patients[18] and to reduce relapse rates in depressed patients with atypical features.[19,20]

In the absence of comparative studies between LA and CT as sequential combination treatments, clinicians are currently forced to choose either option based on anecdotal evidence or therapist preference and availability when treating patients who display a partial response to standard first-line antidepressant medications. The goal of this preliminary study was to explore the effectiveness of CT and LA as sequential combination treatments for 8 weeks in partially responsive depressed patients who had already received 8 to 14 weeks of standard antidepressant therapy. To our knowledge, this study is the first to compare the sequential addition of CT or lithium in this patient population.

METHOD

Subjects

Eligible subjects (aged 18–65 years) were those who met criteria for partial response after receiving 1 of 4 standard antidepressant medications—moclobemide, paroxetine, sertraline, or venlafaxine—to maximum tolerated doses for 8 to 14 weeks at the Depression Clinic, Centre for Addiction and Mental Health, University of Toronto. The choice of antidepressant was at the discretion of the treating psychiatrist and reflected current practices as well as patients' prior treatment history. All subjects had initially met DSM-IV criteria for a major depressive episode (MDE) derived from the Structured Clinical Interview for DSM-IV (SCID)[21] and had a score of 16 or greater on the HAM-D-17 and at least one prior MDE. Patients were classified as "remitters" (HAM-D-17 score ≤ 7), "partial responders" (HAM-D-17 score 8–15), or "nonresponders" (HAM-D-17 score ≥ 16). Outcomes of this phase of treatment have been reported elsewhere.[13]

All subjects gave their written informed consent. The study received approval from the Research Ethics Board at the Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto. Patients were ineligible if they met criteria for any of the following conditions: major medical disorder, organic brain syndrome, schizophrenia or schizoaffective disorder, bipolar disorder, MDD with psychotic features, or substance/alcohol use or dependence within the past 6 months.

Design and Measures

During the first phase of treatment, moclobemide, 300 to 600 mg/day, paroxetine, 20 to 40 mg/day, sertraline, 50 to 200 mg/day, or venlafaxine, 75 to 225 mg/day, were prescribed. Dose adjustments were permitted during the first 6 weeks. Following assessment at week 8, those patients who met criteria for a partial response were randomly assigned to receive either lithium or CT as sequential combination therapies using a single-blind design beginning in September 1996. Subjects who did not meet entrance criteria after 8 weeks (i.e., full responders or nonresponders) continued standard antidepressant treatment and were reassessed after 14 weeks. Subjects who met criteria for partial response at this assessment were also eligible for enrollment. Follow-up for all patients randomly assigned to treatment with LA or CT was completed in December 2000. Antidepressant therapy continued after the sequential treatments were discontinued.

Trained research staff, who were blind to treatment allocation, administered the HAM-D-17 at randomization and every 4 weeks including the endpoint assessment. The Beck Depression Inventory (BDI)[22] was also completed by all subjects at each visit. During the course of both treatment strategies, an attempt was made to maintain constant antidepressant dosage. Where intolerable side effects emerged, one decrement in the dosage was permitted. Any further need to adjust medication required termination within the study.

Lithium augmentation. Subjects who were randomly assigned to the LA group (N = 21) received a routine blood screen including complete blood count, electrolyte levels, serum creatinine levels, and thyroid-stimulating hormone levels. Lithium carbonate, 600 mg/day, was prescribed as a single nighttime dose. Serum lithium levels were measured every 2 weeks (with a target blood level of ≥ 0.4 mEq/L) to provide additional information about compliance and to allow comparison with previous reports. Clinicians were permitted to increase lithium dosing by 300 mg/day after 2 or 4 weeks based on clinical response, tolerability, and serum levels. Subjects were seen every 2 weeks for routine clinical management. Lithium was administered for 8 weeks and then tapered in decrements of 300 mg/day every 3 days over the following week.

Cognitive therapy. Subjects who were randomized to the CT group (N = 23) received 12 sessions over 8 weeks under the supervision of one of us (Z.S.). When used in combination with ongoing pharmacotherapy, fewer sessions of CT are typically offered than when CT is the sole acute intervention (e.g., 16–20 sessions).[23] In order to standardize procedures, we developed a session-by-session protocol based on a modification of the treatment manual by Beck et al.[24] This protocol emphasized acquisition and implementation of a number of core cognitive

Table 1. Characteristics of Subjects Randomly Assigned to the LA or CT Group[a]

Characteristics	LA (N = 21)	CT (N = 23)
Age, mean (SD), y	37.7 (11.3)	40.7 (12.5)
Sex, N (%)		
Female	12 (57)	12 (52.2)
Male	9 (43)	11 (47.8)
Duration of current MDE, mean (SD), wks	119.8 (160.8)	126.4 (170.4)
Age at onset of first MDE, mean (SD), y	24.4 (13.6)	26.3 (13.5)
Number of prior MDEs, mean (SD)	2.3 (1.4)	2.1 (1.5)
Diagnosis of comorbidity, N (%)	4 (19)	8 (35)
Medication, N (%)		
Paroxetine	6 (28.6)	10 (43.5)
Sertraline	7 (33.3)	6 (26.1)
Venlafaxine	5 (23.8)	5 (21.7)
Moclobemide	3 (14.3)	2 (8.7)

[a]There were no significant differences between groups.
Abbreviations: CT = cognitive therapy, LA = lithium augmentation, MDE = major depressive episode.

and behavioral skills. As well, it presented a rationale for the combination of medication and CT in the treatment of depression. Subjects were expected to consolidate their skills through out-of-session homework assignments. During the 8 weeks of CT, patients had a medication check up every 4 weeks.

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) was conducted to evaluate the effect of CT and LA on depression scores, as measured by the HAM-D-17, over the study period. Independent t tests and chi-square tests were used to compare the treatment groups at baseline and to evaluate changes between the groups at the end of sequential treatment and 4 weeks later. The chi-square analyses were used to examine outcome based on a categorical variable (i.e., response/nonresponse). Analysis of covariance (ANCOVA) was conducted on depression scores at the end of combination treatment and the endpoint visit. The independent variable was treatment group. The covariates were age, age at onset of current MDE, duration of MDE, number of prior MDEs, and randomization HAM-D-17 score. Effect sizes (Cohen d) were also calculated for the independent t tests that examined between-group differences in treatment outcome. Both observed case (OC) and intention-to-treat (ITT) analyses were performed. The OC analysis involved patients who completed the full 8-week sequential combination protocol, in which only observed data were used, to evaluate "completers" of treatment. The ITT analysis included any patient who began augmentation and had at least 1 evaluable follow-up visit. This approach used a last-observation-carried-forward (LOCF) technique, where missing values were replaced with the last observation for that patient. The significance level was set at $p < .05$ (2-tailed).

Table 2. Mean HAM-D-17 and BDI Scores During LA and CT

Measurement	LA Mean (SD)	CT Mean (SD)
HAM-D-17 scores		
Baseline	23.1 (3.9)	24.4 (5.2)
Randomization	11.6 (1.9)	12.1 (2.2)
End of randomization	12.8 (7.2)	15.8 (7.1)
Endpoint	9.2 (6.7)	14.8 (9.9)
BDI scores		
Baseline	30.0 (10.1)	28.5 (9.3)
Randomization	22.4 (10.3)	22.7 (8.6)
End of randomization	15.9 (11.2)	19.6 (9.0)
Endpoint	15.1 (11.4)	19.9 (10.3)

Abbreviations: BDI = Beck Depression Inventory, CT = cognitive therapy, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LA = lithium augmentation.

RESULTS

Forty-four outpatients (20 men, 24 women) with a mean ± SD age of 39.3 ± 11.9 years were enrolled; 21 received LA and 23 received CT. There were no significant differences between treatment groups on baseline clinical or demographic variables (Table 1). An independent samples t test revealed no significant differences between the treatment groups at randomization based on HAM-D-17 scores ($t = 0.84$, $df = 42$, $p = .40$) (Table 2).

Efficacy

The primary objective was to compare final outcomes. Based on OC analysis, a repeated-measures ANOVA over the entire study period as well as the 8-week sequential treatment period showed no significant decreases over time in HAM-D-17 scores for either treatment group. A 2-factor repeated-measures ANOVA over the entire study period as well as the 8-week sequential period found nonsignificant main effects for time and treatment, as well as a nonsignificant interaction effect. Using ITT analysis, similar results were found. Although the groups did not differ at the end of the combination treatment period based on OC analysis ($t = 1.29$, $df = 36$, $p = .20$), there was a significant between-group difference in HAM-D-17 scores 4 weeks after discontinuation of CT or LA at the endpoint visit (Table 2). The LA group had significantly lower HAM-D-17 scores than the CT group ($d = 0.34$, $t = 2.04$, $df = 37$, $p = .04$). Based on ITT analysis, there was also not a significant between-group difference at the end of the combination treatment period but there was a significant between-group difference at the endpoint visit ($d = 0.32$, $t = 2.02$, $df = 42$, $p = .04$). At both time points, the LA group had lower HAM-D-17 scores than the CT group. No significant differences in BDI scores emerged between the 2 treatment groups at the end of sequential combination treatment or 4 weeks later (Table 2). A paired samples t test, based on OC analysis, found a significant decrease in HAM-D-17 scores at the endpoint visit compared with the end of the combination treatment period

in patients in the LA-treated group ($t = 2.29$, $df = 15$, $p = .03$). However, using ITT analysis, no difference was found between HAM-D-17 scores at these 2 visits in the LA group. In the CT group, there was no significant difference in HAM-D-17 scores between the end of the sequential combination treatment visit and the endpoint visit, using both OC and ITT analyses.

The 2 groups did not differ in the proportion of patients who converted from partial to full response. Based on OC analysis, 8 of 19 subjects (42%) in the LA group and 6 of 20 subjects (30%) in the CT group achieved remission (HAM-D-17 score ≤ 7) at the completion of the study, or endpoint ($\chi^2 = 0.62$, $df = 1$, $p = .43$). Using ITT analysis, similar results were obtained with 8 of 21 LA subjects (38%) and 6 of 23 CT subjects (26%) achieving remission ($\chi^2 = 0.73$, $df = 1$, $p = .39$). When the BDI criteria (BDI score ≤ 8) were used, 3 of 22 in the CT group (14%) and 5 of 20 LA subjects (25%) achieved remission ($\chi^2 = 0.88$, $df = 1$, $p = .34$).

A series of 1-way analyses of covariance (ANCOVA) were conducted using HAM-D-17 scores at the end of the combination treatment visit and at the endpoint visit as the dependent variables and the randomization HAM-D-17 score, age, age at onset of current MDE, duration of MDE, and number of prior MDEs as covariates. Using both OC (N = 29) and ITT (N = 33) analysis, the HAM-D-17 randomization scores accounted for 26.4% ($F = 7.90$, $df = 1,22$; $p = .01$) and 28.6% ($F = 10.39$, $df = 1,26$; $p = .003$) of the variation in HAM-D-17 scores, respectively, at the end of combination treatment. None of the covariates using both OC and ITT methods of analysis were significantly related to HAM-D-17 scores at the endpoint visit. Based on OC analysis, even after controlling for the combined effect of the covariates, there was a trend toward statistical significance ($F = 3.83$, $df = 1,22$; $p = .06$), accounting for 14.8% of the variance in HAM-D-17 scores at the end of combination treatment. Based on ITT analysis, there was a significant between-group difference ($F = 4.90$, $df = 1,26$; $p = .036$), accounting for 15.9% of the variance in HAM-D-17 scores at the end of combination treatment. The adjusted mean HAM-D-17 scores for the CT group were 15.87 compared with 10.89 for the LA group. None of the other covariates were significant.

Tolerability

Rates of discontinuation were similar in the 2 groups, with 26% (6) of 23 subjects in the CT group and 29% (6) of 21 subjects in the LA group not completing the protocol ($\chi^2 = 0.034$, $df = 1$, $p > .05$). The most common reason for discontinuation in the CT group was "failure to improve" (N = 4); the remaining 2 subjects were lost to follow-up. In the LA group, 2 subjects discontinued due to failure to improve, 2 withdrew consent, 1 experienced medical complications, and 1 was lost to follow-up. There were no significant between-group differences in reported side effects.

Baseline Predictors of Response Status

There were no significant differences between response status and age ($t = 0.09$, $df = 41$, $p = .92$), sex ($\chi^2 = 0.67$, $df = 1$, $p = .67$), number of prior MDEs ($t = 0.44$, $df = 34$, $p = .66$), age at onset of first MDE ($t = 1.14$, $df = 38$, $p = .25$), or duration of current episode ($t = 0.18$, $df = 41$, $p = .85$). There were also no significant baseline predictors of response within the 2 treatment groups.

Serum Levels and Outcome

All subjects had serum lithium levels in the range of 0.4 to 1.0 mEq/L. During the final 4 weeks of LA, 15 subjects remained on LA treatment: 4 (27%) had serum lithium levels 0.8 mEq/L or greater, 6 (40%) had serum lithium levels in the 0.6 to 0.79 mEq/L range, and 5 (33%) had serum lithium levels in the 0.4 to 0.59 mEq/L range. Using criteria similar to that used by Katona and colleagues,[25] subjects in the LA group (N = 21) were divided into 2 groups based on serum lithium levels: those who obtained at least 2 serum lithium levels of 0.4 mEq/L or greater (N = 13) and those who failed to attain such levels (N = 8). The chi-square test revealed that response to LA was not significantly related to attained levels of serum lithium ($\chi^2 = 0.05$, $df = 1$, $p = .81$).

DISCUSSION

Although between-group differences in remission rates were not statistically significant, it is clinically meaningful that one third or more of patients in both groups achieved remission status (42% in the LA group and 30% in the CT group), which is comparable to reports comparing venlafaxine with SSRI therapy.[12] The LA group also had significantly lower final mean ± SD HAM-D-17 scores (score = 9.2 ± 6.7) compared with the CT group (score = 14.8 ± 9.9) 4 weeks after completing combination treatment ($p = .043$). This advantage in favor of lithium appears contrary to previous reports that CT, more than pharmacotherapy, is associated with a beneficial "carry-over" effect.[26] In this study, it is likely that the 8 weeks of either sequential CT or LA was too short a duration of treatment and a follow-up assessment after 4 weeks was too soon. It also appeared that clinical improvement in some patients (evidenced by conversion to remission) was cancelled out by no change or a deterioration in others.

How do our results compare with other reports of these respective interventions? When Katona and colleagues[25] examined LA under placebo-controlled conditions, a response criterion of HAM-D-17 scores less than 10 failed to confirm a superior effect in the LA group. However, in

contrast to our results, LA showed superiority when only subjects with 2 or more serum lithium levels of 0.4 mEq/L or greater were included. Similarly, in bipolar patients, those who achieved higher serum lithium levels (0.8–1.0 mEq/L) had significantly less risk of developing subsyndromal symptoms and having a major affective relapse compared with subjects with low therapeutic-range serum lithium levels (0.4–0.6 mEq/L).[27] In general, starting LA at a dose of 600 mg daily and increasing to 900 mg daily has been the recommended regimen for augmentation therapy.[14] In retrospect, our dosing regimen for lithium may have been subtherapeutic in some individuals; a requirement that dosing be increased to achieve serum levels of lithium between 0.5 and 1.0 mEq/L may have resulted in superior rates of remission.[28] However, this previous literature[27,28] evaluated LA of tricyclic antidepressants, while our study involved LA of SSRI treatment, where relatively fewer investigations have been reported.

Most investigations of combined psychotherapy and pharmacotherapy have examined concurrent as opposed to sequential approaches.[29] Favorable results for the combination of Cognitive Behavioral Analysis System Psychotherapy (CBASP) with nefazodone compared with either treatment alone[30] are not directly comparable to our results since the depressed population in that trial met criteria for "chronic depression" and did not go through a sequential protocol. However, in one evaluation of sequential CT, Paykel et al.[15] reported a significant reduction in relapse rates in patients who continued antidepressant medication while receiving 16 sessions of CT (29%), compared with those who maintained antidepressant therapy with clinical management (47%). CT was also shown to significantly reduce rates of relapse in patients who discontinued antidepressant therapy prior to randomization to CT or standard clinical management at 4-year follow-up.[21] Also, as the HAM-D-17 may not have been sensitive enough to detect small changes or subclinical symptoms of affective disorders, the Paykel Clinical Interview for Depression may have been a better measure to use as it has been shown in previous studies to detect small increments of change that are near the normal end of the spectrum.[31,32]

Although the form of CT delivered in this trial was modified slightly from Beck et al.,[24] other successful combination CT-pharmacotherapy trials have introduced greater modification. For example, Fava and colleagues[33,34] supplemented CT with lifestyle modification and "well-being therapy." Recommended individualized targets for psychotherapy in treatment-refractory depression have also been proposed.[35] Finally, the meta-analysis by Thase et al.[36] provides support for combination psychotherapy-pharmacotherapy in severe recurrent depression, although the combination of CT and antidepressant medication was not included in that analysis.

We recognize that the optimal research protocol would have included placebo controls for both medication and psychological treatment. This would have controlled for nonspecific treatment effects and would permit conclusions about efficacy to be drawn about each of the specific interventions. Also, we recognize the limitations of a single-blind design, brief duration of concomitant therapy, and small sample size with limited power to detect differences in changes over time between 2 active treatment interventions. We believe that an adequately powered trial is required not only to compare different forms of combination strategies similar to those reported here but also to compare these treatments with optimized monotherapies.

Drug names: paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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