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Mirtazapine in Comorbid Major Depression and Alcohol Use Disorder: A Long-Term Follow-Up Study

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Abstract

Background/Objective—To date, pharmacotherapy trials of depressed alcoholics (MDD/AUD) have focused on SSRI medications, with disappointing results, so effective treatments for that comorbid population are lacking. Mirtazapine is an FDA-approved medication for treating MDD with a unique pharmacological profile whose efficacy may exceed that of SSRIs. Results from our recent open label study suggest robust acute phase efficacy for mirtazapine for decreasing both the depression and the drinking of that population. However, to date, no studies have evaluated the longer-term efficacy of mirtazapine in that population. We now report findings from a first long-term (two-year) naturalistic follow-up evaluation involving subjects from the acute phase trial. We hypothesized that the improvements would persist at follow-up.

Methods—An eight-week open label study of mirtazapine and motivation therapy was conducted involving persons 18 to 55 years of age with DSM-IV diagnoses of comorbid MDD/AD. Two years after entry into the acute phase study, a long-term evaluation was conducted using the same instruments that had been used at baseline to assess whether the improvements seen during the acute phase trial had persisted.

Results—Ten of the twelve patients who entered the acute phase study participated in the follow-up study. The large magnitude improvements ($p < .01$) in depressive symptoms (BDI), drinking (TLFB), and sleep disturbance (HDRS) persisted at the follow-up evaluation. Two of the subjects demonstrated MDD on structured interview at follow-up, while all ten had demonstrated MDD at baseline. Six of the ten used antidepressants during the follow-up period. At baseline, three were employed, while at follow-up seven were employed.

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Conclusions—These findings suggest long-term efficacy for mirtazapine for decreasing the drinking and depression of depressed alcoholics. Double-blind, placebo-controlled studies are warranted to clarify the efficacy of mirtazapine in depressed alcoholics.

Keywords

mirtazapine; comorbid; major depression; alcohol dependence; long-term follow-up

1.0 Introduction

Previous studies of antidepressant medications among persons with comorbid major depressive disorder in combination with alcohol dependence have focused on selective serotonin reuptake inhibitors or tricyclic medications, and the results of those trials have been disappointing [1–3]. Lovieno et al., 2011 [4] also noted the complete lack of study data on a number of newer antidepressants such as mirtazapine for treating comorbid populations. Thus, to date, no medications have consistently demonstrated efficacy for treating the large population of persons with comorbid major depressive disorder and alcohol dependence. Therefore, comorbid major depression and alcohol dependence currently represent a considerable unmet treatment need.

The authors recently conducted a first open label study evaluating the acute phase efficacy of mirtazapine for treating both the depressive symptoms and the drinking of persons with comorbid AD/MDD. Previous studies involving mirtazapine had not assessed level of drinking as an outcome variable. Results from our recent open label study [5] suggest robust acute phase efficacy for mirtazapine for decreasing both the depression and the drinking of that population. However, to date, no studies have evaluated the longer-term efficacy of mirtazapine in that population. We now report findings from a first long-term (two-year) naturalistic follow-up evaluation involving subjects from the acute phase trial. We hypothesized that mirtazapine would demonstrate long-term within-group efficacy for decreasing both the depressive symptoms and level of alcohol use of our subjects.

2.0 Methods

2.1 Subjects

Before entry into the acute phase treatment protocol, the study was explained, and written informed consent was obtained from all subjects after all procedures had been fully explained. The study was approved by the University of Pittsburgh Institutional Review Board. This study was conducted at the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center. Subjects were recruited for participation in the treatment study through posters and by responding to newspaper or radio advertisements.

Participants were required to be outpatients between 18 and 55 years of age at baseline to be included in the study. At the baseline assessment, participants were evaluated for the DSM-IV diagnoses of alcohol dependence and major depressive disorder, using an instrument called the MINI International Neuropsychiatric Interview [6]. The MINI has demonstrated good reliability, validity, and clinical utility [7]. The comorbid presence of both current

alcohol dependence and current major depressive disorder was required for inclusion in the treatment study. The MINI provides guidelines for identifying substance-induced mood disorders. Persons with substance-induced mood disorders were excluded from participation in the current study. Other exclusion criteria included a DSM-IV diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia. Persons with any substance abuse or dependence other than nicotine dependence or cannabis abuse or dependence were excluded from the study.

2.2 Treatment and assessment

Following completion of the baseline assessment, participants were treated using an open-label study design. The study medication was taken once per day at bedtime. Subjects were given 15 mg of mirtazapine for the first two weeks of the trial and 30 mg for the last six weeks of the medication trial. Protocol assessments were conducted weekly in the first month and biweekly in the second month. Brief (about 10 to 15 minutes) Motivation Enhancement Therapy was also provided at each assessment, which focused on medication compliance and compliance with study procedures [8].

Two years after entry into the acute phase study, a long-term evaluation was conducted using the same instruments that had been used at baseline to assess whether the improvements seen during the acute phase trial had persisted. To ensure a high level of participation for these evaluations, a \$20.00 payment was made to patients completing each assessment [9]. Participant-rated depressive symptoms were assessed with the Beck Depression Inventory (BDI) [10]. Drinking behavior was evaluated using the timeline follow-back method (TLFB) [11].

2.3 Statistical Analysis

Descriptive statistics were calculated for all variables. Continuous baseline measures were compared by paired, 2-tailed *t* tests for continuous variables. Categorical baseline measures were compared by chi-square analysis, corrected for continuity. Statistical analyses were completed on an intent-to-treat study group. All tests of significance were 2-tailed. An alpha level of less than or equal to 0.05 was used in the study to indicate statistical significance. All analyses were conducted using the Statistical Package for the Social Sciences, version 15.0 [12].

3.0 Results

A total of 12 subjects entered the acute phase study and 10 of those subjects completed the long-term follow-up evaluation. All subjects participated in protocol ratings and provided data at all data collection times throughout the study, and none dropped out of the study. Subjects were 3 women and 7 men, who included 8 Caucasians, 1 Native American, and 1 Asian American. The subjects ranged in age from 21 to 50 years of age. The mean age of study subjects was 36.1 years ($SD=13.4$). At baseline, subjects demonstrated prominent depressive symptoms and drinking behavior, with a mean BDI of 31.8 ($SD=8.3$), and TLFB of 33.9 ($SD=14.9$) drinks per week.

During the 8-week course of the acute phase study, statistically significant improvements (decreases) were noted for both the depressive symptoms and the level of alcohol use of the study population, as noted in Figure 1. Those improvements (compared to baseline levels) persisted at the one-year follow-up assessment, as noted in Figure 1.

The large magnitude improvements in depressive symptoms (BDI) and drinking (TLFB) persisted at the follow-up evaluation ($p < .01$). Two of the subjects demonstrated MDD on structured interview at follow-up, while all ten had demonstrated MDD at baseline. BDI scores went from 30.7 (± 8.59) at Baseline, to 6.8 (± 5.71) at the end of the acute phase, to 9.7 (± 6.65) at the Follow Up visit ($t = 5.4$; $p = < .001$). Six of the 10 used antidepressants during the follow-up period. At baseline, three were employed, while at follow-up seven were employed. At Baseline, 4 of the 10 subjects were diagnosed with Dysthymia and at the Follow Up visit, only one was diagnosed with Dysthymia.

At baseline, all 10 subjects were diagnosed with alcohol dependence (AD) while at the Follow Up visit, only 5 were diagnosed with AD. Drinks per week went from 37.9 (± 16.73) at Baseline, to 16.96 (± 12.93) at the end of the acute phase, to 16.1 (± 10.59) at the Follow Up Visit. ($t = 3.13$; $p = 0.012$).

4.0 Discussion

This report describes findings from the first long-term naturalistic follow-up study involving comorbid AD/MDD subjects who had participated in an acute phase trial involving mirtazapine. At the follow-up assessment, the subjects continued to demonstrate significantly fewer depressive symptoms and a lower level of drinking than they had exhibited at baseline of the acute phase study. The findings of the follow-up study suggest long-term efficacy for mirtazapine for treating the depressive symptoms and the drinking of persons with comorbid AD/MDD. The results of this study also suggest that treatment with mirtazapine is associated with improved sleep and with an increase in employment among persons with comorbid major depression and an alcohol use disorder (AUD). Double-blind placebo-controlled studies involving mirtazapine are warranted to assess the efficacy of mirtazapine versus placebo for treating patients with comorbid AUD/MDD.

The results of this study should be interpreted in light of some limitations. First, the sample size in this pilot study was limited, as was the number of assessment instruments. Also, no placebo control group was used, so we cannot rule out the possibility that some (or all) of the therapeutic effect that was noted in this clinical trial may have resulted from the brief motivation enhancement therapy used in study, or from the extra attention and monitoring afforded by the study. In addition, it is unclear to what extent the results of this study generalize to inpatient populations or populations using cocaine, opiates, etc., in addition to their depression and their alcohol use disorder.

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Abbreviations

MDD	Major Depressive Disorder
AD	Alcohol Dependence
AUD	Alcohol Use Disorder

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Fig. 1.

Follow-up level of drinking (number of drinks/week on the Timeline Follow-Back) and self-reported level of depressive symptoms (Beck Depression Inventory, BDI)

Table 1

Demographic Characteristics and Clinical Symptoms of Subjects

	Sex (% female)		Ethnic (% Caucasian)		Baseline				End of Acute Phase (Visit 8)				Follow-Up Visit			
	30.0%	80.0%			Mean	St. Dev.	Mean	St. Dev.	t	p	Mean	St. Dev.	t	p	Mean	St. Dev.
BDI Total	30.7	8.59	6.8	5.74	5.538	0.000	9.7	6.65	-1.456	0.179						
HAM-D 27	21.4	3.17	2.0	2.40	5.779	0.000	6.9	6.77	-2.333	0.045						
Drinks per Week	37.9	16.73	16.9	12.93	3.125	0.012	16.1	10.59	0.255	0.804						
Average Drinks per Occasion	7.9	2.85	4.4	2.60	1.704	0.123	6.0	3.64	-1.450	0.181						
DSM MDD Symptom Count	7.6	0.97					1.3	2.83	7.138	0.000						
DSM Dysthymia Symptom Count	3.1	2.88					0.4	1.26	2.398	0.040						
DSM Alcohol Dependence Symptom Count	4.9	1.45					2.3	1.77	2.751	0.022						
DSM Cannabis Dependence Symptom Count	0.7	1.34					0.2	.63	1.103	0.299						
Insomnia Symptom Count	3.33	1.30	3.17	1.34	8.2	0.000	1.7	2.95	1.82	0.101						

Key: BDI, Beck Depression Inventory; HAM-D 27, Hamilton Depression Rating Scale, 27-item version; DSM, Diagnostic and Statistical Manual.

t values result from comparisons with baseline values. Insomnia score = difficulty falling asleep score (HDRS question #4) plus sleep continuity score (HDRS question #5) plus early morning waking score (HDRS question #6).