



Short Communication

## Mirtazapine In Comorbid Major Depression And Alcohol Use Disorder: A Long-Term Follow-Up Study

Jack R Cornelius<sup>1\*</sup>, Antoine B Douaihy<sup>1</sup>, Duncan B Clark<sup>1</sup>, Dennis C Daley<sup>1</sup>, Tammy A Chung<sup>1</sup>, Maribeth A Wesesky<sup>2</sup>, D Scott Wood<sup>2</sup> and Ihsan Salloum<sup>3</sup>

### 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.

**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

### Abbreviations

MDD: Major Depressive Disorder; AD: Alcohol Dependence; AUD: Alcohol Use Disorder

\*Corresponding author: Jack R. Cornelius, 3811 O'Hara Street, PAARC Suite, Pittsburgh PA 15213, USA, Tel: 412-246-5186; Fax: 412-246-6550; E-mail: [corneliusjr@upmc.edu](mailto:corneliusjr@upmc.edu)

Received: July 27, 2013 Accepted: November 08, 2013 Published: November 12, 2013

### 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. [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.

### Methods

#### 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.

### 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].

The long-term follow-up evaluation that is the primary focus of the current manuscript was conducted in a single assessment that was collected two years after each of the study participants had entered the acute phase study. The long-term follow-up evaluation utilized the same study instruments that had been used in the acute phase study. Participant-rated depressive symptoms were assessed with the Beck Depression Inventory (BDI) [9]. Observer-rated depressive symptoms were assessed with the Hamilton Depression Rating Scale (HDRS) [10]. Drinking behavior was evaluated using the Timeline Follow-Back Method (TLFB) [11]. To ensure a high level of participation for these evaluations, a \$20.00 payment was made to patients completing each assessment [12].

### 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 [13].

### 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. Participants in the long-term follow-up evaluation included 3 women and 7 men, and 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 (Table 1).

During the 8-week acute phase study which had preceded the long-term follow-up study, statistically significant improvements (decreases) had been noted for both the depressive symptoms and the level of alcohol use of the study population [5]. In the long-term follow-up study that is now being presented, those improvements in depressive symptoms and in level of alcohol use were noted to have persisted, as shown in Figure 1. Specifically, at the long-term follow-up evaluation, the large magnitude improvements in depressive symptoms (BDI) and drinking (TLFB) persisted, as compared to baseline levels ( $p < .01$ ). 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 ( $t=5.4$ ;  $p < .001$ , comparing baseline level to follow-up level). Six of the 10 used antidepressants during the follow-up period, including three who used mirtazapine and three who used various SSRI medications. At baseline, only three of the ten participants were employed, while at the follow-up assessment seven were employed. At Baseline, 4 of the 10 subjects were diagnosed with Dysthymia, while at the Follow-Up visit, only one was diagnosed with Dysthymia. At baseline, the mean number of DSM-IV criteria for dysthymic disorder (as noted on the MINI) was 3.1, while at the follow-up assessment the mean number of DSM-IV criteria for dysthymic disorder had fallen to 0.4, which was a significant decrease ( $p=0.040$ ).

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. ( $t=3.13$ ;  $p=0.012$ ).

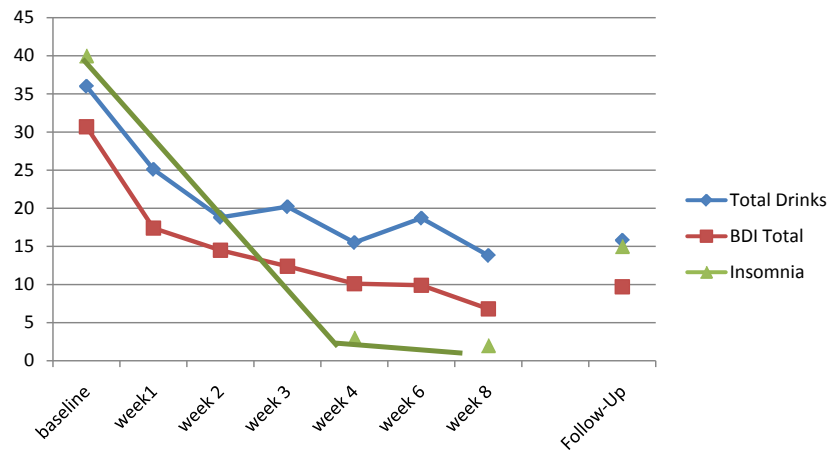
### Discussion

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

**Table 1:** Demographic Characteristics and Clinical Symptoms of Subjects

Sex (% female)	30.0%										
Ethnic (% Caucasian)	80.0%										
	Baseline		End of Acute Phase (Visit 8)				Follow-Up Visit				
	Mean	St. Dev.	Mean	St. Dev.	t	p	Mean	St. Dev.	t	p	
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).



**Figure 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).

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, with decreases in symptoms of dysthymia (chronic depression), and with an increase in employment among persons with comorbid major depression and an alcohol use disorder (AUD). The magnitude of the improvements in depressive symptoms, in level of drinking, and in level of sleep problems noted in the current study utilizing mirtazapine were consistently greater than the improvement in those symptoms noted in our previous studies using the SSRI antidepressant fluoxetine in comorbid populations [2,14,15]. 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, and an open label study design was utilized, so we cannot rule out the possibility that some (or all) of the therapeutic effect that was noted in this study may have resulted from placebo effect, from the brief motivation enhancement therapy used in the acute phase study, or from the extra attention and monitoring afforded by the study. Also, six of the subjects used antidepressant medications during the follow-up period, which may have contributed to maintaining the antidepressant effect through the follow-up period. 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.

#### Acknowledgement

This research was supported in part by grants from the National Institute on Alcohol Abuse and Alcoholism (R21AA022123-01A1, R01 AA013370, R01 AA015173, K24 AA15320, K02 AA018195, and K02 AA00291); and from the National Institute on Drug Abuse (R01 DA019142, P50 DA05605, K02 DA017822, and the NIDA Clinical Trials Network (CTN)) and from the Department of Veterans Affairs, Veterans Health Administration, the VAPHS Office of Research and Development and the VISN 4 Mental Illness Research, Education, and Clinical Center (MIRECC, Director: D. Oslin; Pittsburgh Site Director: G. Haas), VA Pittsburgh Healthcare System. NIH (NIAAA/NIDA) had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Presented in part at the 22nd Annual Meeting of the American Academy of Addiction Psychiatry (AAP), Scottsdale, Arizona, December 10, 2011; at the 165th Annual Meeting of the American Psychiatric Association (APA), Philadelphia, Pennsylvania, May 5-9, 2012; and at the 35th Annual Scientific Meeting of the Research Society on Alcoholism (RSA), San Francisco, California, June 23-27, 2012.

The contents of this manuscript do not represent the views of the Department of Veterans Affairs or the United States Government.

#### References

- Salloum IM, Jones YO (2008) Efficacy of pharmacotherapy for comorbid major depression and substance use disorders: A review. *Curr Psychiatry Rev* 4:14-27.
- Cornelius JR, Bukstein OG, Wood DS, Kirisci L, Douaihy A, et al. (2009) Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid major depression and an alcohol use disorder. *Addict Behav* 34: 905-909.
- Cornelius JR, Douaihy A, Bukstein OG, Daley DC, Wood SD, et al (2011) Evaluation of cognitive behavioral therapy/motivation enhancement therapy (CBT/MET) in a treatment trial of comorbid alcohol use disorder/ major depressive disorder adolescents. *Addict Behav* 36:843-848.
- Lovieno N, Tedeschini E, Bentley KH, Evins AE, Papakostas GI (2011) Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: A meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 72:1144-1151.
- Cornelius JR, Douaihy AB, Clark DB, Chung T, Wood DS, et al. (2012) Mirtazapine in Comorbid Major Depression and Alcohol Dependence: An Open-Label Trial. *J Dual Diagn* 8: 200-204.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20: 22-33.
- Sheehan, DV, Lecrubier Y, Sheehan H, Amorim P, Janavs J, Weiller E, Hergueta MS, Baker R, Dunbar GC (2008) MINI International Neuropsychiatric Interview. In A. John Rush, Jr., Michael B. First, and Deborah Blacker. *Diagnostic Measures for Adults, Handbook of Psychiatric Measures*, (Chapter 5, 2nd edtn) 48-51. American Psychiatric Publishing, Inc. Washington, DC.
- Miller WR, Zweben A, DiClemente CC, Rychtarik RG (1992) *Motivational Enhancement Therapy Manual. Project MATCH Monograph Series, Vol 2.* National Institute on Alcohol Abuse and Alcoholism, Washington, DC.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. *Arch Gen Psychiatry* 4: 561-571.
- Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23: 56-62.


11. Sobell LC, Sobell MB, Leo GI, Cancilla A (1988) Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict* 83: 393-402.
12. Festinger DS, Marlowe DB, Dugosh KL, Croft JR, Arabia PL (2008) Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. *Drug Alcohol Depend* 96: 128-135.
13. Norusis MJ (1992) *Statistical Package for the Social Sciences*. McGraw-Hill, New York, NY.
14. Cornelius JR, Salloum IM, Ehler JG, Jarrett PJ, Cornelius MD, et al. (1997) Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 54: 700-705.
15. Cornelius JR, Bukstein OG, Douaihy AB, Clark DB, Chung TA, et al. (2010) Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend* 112: 39-45.

### Author Affiliations

[Top](#)

<sup>1</sup>Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA  
<sup>2</sup>University of Pittsburgh Medical Center, Pittsburgh, PA, USA  
<sup>3</sup>University of Miami, Miami, FL, USA

#### Submit your next manuscript and get advantages of SciTechnol submissions

- ❖ 50 Journals
- ❖ 21 Day rapid review process
- ❖ 1000 Editorial team
- ❖ 2 Million readers
- ❖ More than 5000 
- ❖ Publication immediately after acceptance
- ❖ Quality and quick editorial, review processing

Submit your next manuscript at • [www.scitechnol.com/submission](http://www.scitechnol.com/submission)