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Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: A multicentre, open label study

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Abstract

Major depressive disorder and alcohol dependence are common and serious mental illnesses. There is a great interest in discovering useful treatments for both mood symptoms and alcohol abuse in those patients with depressive disorders and comorbid alcohol dependence. The primary purpose of this study was to evaluate the effectiveness and tolerability of mirtazapine for the treatment of patients with alcohol dependence comorbid with a depressive disorder in an open label, naturalistic multicentre treatment setting. The 17-item Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impression-Severity (CGI-S) scale were measured at baseline and at weeks 4 and 8 for the assessment of treatment effectiveness. Alcohol craving was measured using the Obsessive Compulsive Drinking Scale (OCDS) and the Visual Analog Scale for Craving (VAS). This study showed a statistically significant reduction of the scores on the HDRS (13.9 ± 7.3, $p < 0.0001$), HARS (10.8 ± 7.2, $p < 0.0001$) and the CGI-S (1.7 ± 1.0, $p < 0.0001$) from baseline to the endpoint (week 8). The OCDS and VAS scores were also decreased significantly by 42.3% and 53.2% (9.0 ± 10.0, $p < 0.0001$; 2.5 ± 2.4, $p < 0.0001$, respectively). The number of patients with a 50% reduction or more in the HDRS and HARS scores was 103 (72.0%) and 106 (74.1%) at the endpoint, respectively. Adverse events related to mirtazapine were observed in 10% or more of the patients in this study. In conclusion, the results from this naturalistic study suggest that the use of mirtazapine for the patients with alcohol dependence comorbid with depressive disorder is accompanied by clinical improvement in their mood and alcohol craving.

Keywords: Alcohol dependence; Craving; Depressive disorder; Mirtazapine

1. Introduction

Major depressive disorder and alcohol dependence are common and serious mental illnesses; they have a lifetime prevalence of 4.25% and 10.20% in Koreans, respectively (Cho

Abbreviations: CGI-S, Clinical Global Impression-Severity; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; ITT, Intent-to-treat population; LOCF, Last observation carried forward; OCDS, Obsessive Compulsive Drinking Scale; VAS, Visual Analog Scale for Craving.

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et al., 2004). Anxiety and depressive symptoms of various severities frequently coexist with alcoholism. In the majority of cases, a collateral depressive-dysthymic-anxiety symptomatology subsides after 3–4 weeks of abstinence (Brown and Schuckit, 1988; Brown et al., 1991, 1995; Schuckit, 1996). However, the persistence of symptoms after a period of abstinence suggests there is the presence of a comorbid depressive disorder that requires specific treatment (Kranzler et al., 1998). Alcohol dependence comorbidity in depressed patients presents a particular challenge as the patient's depressive symptoms may be difficult to detect and they are often treatment-resistant, frequently prolonged and comlicated by the fluctuating treatment motivation of the patient (Bagby et al., 2002). In addition, reductions in depressive symptoms have been associated with an improved drinking recovery outcome (McGrath et al., 1996), and this suggests the treatment of depression can help to promote recovery from alcohol dependence. Therefore, finding useful treatments for both the mood symptoms and the alcohol abuse in patients with depressive disorders and comorbid alcohol dependence are of great interest. However, only minimal data is available on the treatment of this population.

Several antidepressants, including the selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors, have been investigated for use in patients with alcohol dependence and the results have been mixed (Moak et al., 2003; Cornelius et al., 1999; Torrens et al., 2005). These studies have focused on the drugs' effects on alcohol consumption patterns, and only a few studies have focused on the antidepressant activity itself.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant, and it has recently been used when patients are undergoing alcohol detoxification. Mirtazapine had shown efficacy on patient compliance in alcohol detoxification programs and its addition to a standard alcohol detoxification program might minimize psychological discomfort including anxiety and depression (Crockford and White, 2005; Liappas et al., 2004, 2005). The authors hypothesized that mirtazapine may present several advantages over other categories of antidepressants in the treatment of the postwithdrawal phase of alcoholism, because of its specific actions on the noradrenergic and serotonergic systems. However, these clinical trials excluded patients who had alcohol dependence comorbid with depressive disorder and were in acute withdrawal stage.

In this context, the primary purpose of this study was to evaluate the effectiveness and tolerability of mirtazapine treatment in patients suffering from alcohol dependence comorbid with depressive disorder in an open label and in a multicentre treatment setting.

2. Methods

2.1. Subjects

Patients diagnosed as suffering of alcohol dependence with a current depressive episode, according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV, American Psychiatric Association, 1994) criteria were enrolled in this study. All the patients were recruited between April 2004 and December 2004 from 19 nationwide sites, including university-based hospitals or chronic mental institutes in Korea. All subjects agreed to participate to this study after a complete explanation on the nature and procedure of the study.

Investigators' meetings for the study were held before and during the study, in which all investigators had to demonstrate their expertise in using the rating scales that were to be used in the study. All the study investigators were also given the study protocol and the methodology at these meetings.

The patients' inclusion criteria were as follows: (i) patients experiencing a depressive episode with a score ≥ 8 on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), meeting the criteria for a current DSM-IV diagnosis of alcohol dependence.; (ii) having no life-threatening medical condition; (iii) for the female patients of childbearing age, the subjects must guarantee they were using contraception. The exclusion criteria were as follows: (i) a history of psychiatric problem other than depressive disorder (ii) those patients who had another form of drug abuse, excluding nicotine and caffeine; (iii) the presence of confirmed organic brain diseases, including a history of cerebrovascular accidents, brain tumor or mental retardation; (iv) a past history of hypersensitivity to mirtazapine; (v) those patients who participated in clinical trials within 1 month before entering the study entry and those patients who were pregnant or breast feeding.

2.2. Study design

The patients received mirtazapine open label as monotherapy. Administration of other antidepressants other than mirtazapine and anticraving agents was not permitted during the study. Psychotropic medications such as mood stabilizers, antipsychotics and anxiolytics, if they had been taken by the patient at stable doses before entry into the trial for a minimum of 4 weeks, then these medications could be continued at the discretion of the investigator. The use of benzodiazepines was permitted during the study for protracted alcohol withdrawal symptoms or behavior control. Mirtazapine was prescribed with a flexible dosing schedule, and the dose was based on the investigators' experience and the patients' response from the baseline to week 8 (endpoint), although a dosing recommendation was provided. The recommended starting dose of mirtazapine was 15 mg/day, and could be increased up to 45 mg/day based on the clinician's judgment. All subjects received supportive psychotherapy at each study visit and 7-day alcohol detoxification including the oral benzodiazepine with gradual taper off based on clinician's judgment when appropriate.

2.3. Assessment

The patients' histories of alcohol use and diagnoses were determined by the modified form of a semi-structured interview that was used in our previous study (Kim et al., 2005). The