Journal of Affective Disorders 129 (2011) 64–67

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Long-term naturalistic follow-up of lithium augmentation: Relevance to bipolarity

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ARTICLE INFO

Article history:
Received 26 January 2010
Received in revised form 5 June 2010
Accepted 26 August 2010
Available online 16 September 2010

Keywords:
Antidepressant-refractory depression
Treatment-resistant depression
Bipolar disorder
Augmentation therapy
Lithium augmentation
Bipolarity

ABSTRACT

Background: Whether bipolarity (unrecognized bipolar disorder) is related to the treatment response to lithium augmentation in antidepressant-refractory depression remains unclear. This study of responders and non-responders to lithium augmentation of 29 antidepressant-refractory patients with major depression, whom we had studied during 1995–1997, compared the bipolar diagnosis at the follow-up based on diagnostic confirmation after long-term follow-up.

Methods: Before being classified as stage 2 treatment-resistant depression, these patients had been treated adequately with at least two tricyclic or heterocyclic antidepressants from different pharmacological classes (a minimum of the equivalent of 150 mg of imipramine for 4 weeks). During 1995–1997, 29 patients received lithium augmentation. Their treatment responses were recorded. Mean follow-up was 8.0 years (range, 1–13 years). Bipolar conversion and full remission were evaluated.

Results: After the long-term follow-up, diagnoses were changed to bipolar depression in 3 of 4 lithium responders and 3 of 25 lithium non-responders; lithium augmentation was more effective for unrecognized bipolar patients. Only the family history of bipolar disorder predicted subsequent bipolar conversion.

Limitations: Treatment was not controlled in this naturalistic study, which had a small sample size.

Conclusions: Results of this long-term follow-up study suggest that bipolarity is related to a positive response to lithium augmentation in stage 2 treatment-resistant major depression. The family history of bipolar disorder suggests false unipolar depression, and therefore indicates lithium responders.

1. Introduction

The most important issue in the treatment of major depression is treatment-resistant depression, which is generally defined as the persistence of significant or moderate depressive symptoms despite at least two treatment trials with antidepressants from different pharmacological classes (Bauer et al., 2002; Lam et al., 2009; Thase and Rush, 1995). It is classified as stage 2 major depression according to the staging of depression based on prior treatment response proposed by Thase and Rush (1995). It is estimated to occur in 5–10% of major depression cases (Inoue et al., 2002). Lithium, thyroid hormones, and atypical antipsychotic drugs are recommended in various treatment guidelines as augmentation for antidepressant therapies (Bauer et al., 2002; Lam et al., 2009). Nevertheless, little evidence has been reported for stage 2 major depression except for that related to atypical antipsychotic drugs (DeBattista and Hawkins, 2009; Stimpson et al., 2002). Lithium augmentation, a representative

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doi:10.1016/j.jad.2010.08.022

augmentation therapy for treatment-resistant depression, has been studied in stage 1 major depression (nonresponse to an adequate trial of one medication) (Thase and Rush, 1995), but it was demonstrated as ineffective in stage 2 major depression in a study with a notably small sample size (Nierenberg et al., 2003).

Lithium augmentation is effective not only for unipolar depression, but also for bipolar depression (Goodwin and Jamison, 2007; Nelson and Mazure, 1986). Several clinical studies – including a meta-analysis – of lithium augmentation have included unipolar and bipolar patients (Bauer and Döpfmer, 1999); such subject selection has been criticized on methodological grounds (Stimpson et al., 2002). On the other hand, lithium alone is effective for bipolar depression and is recommended as a first-line treatment (Yatham et al., 2009). Consequently, although one might expect that depressed bipolar patients will respond to lithium augmentation better than unipolar patients will, this notion has not been investigated using randomized–controlled trials, although it has been suggested by results of a retrospective study (Goodwin and Jamison, 2007; Nelson and Mazure, 1986). Furthermore, a favorable response to lithium augmentation in bipolar depressed patients might simply represent a response to lithium rather than a response to the combination of agents.

Bipolar disorder is a common reason for stage 2 treatment-resistant major depression (Inoue et al., 2006; Parker et al., 2005; Sharma et al., 2005). Unrecognized bipolarity or misdiagnosis of major depression among patients with bipolar disorder might account for a considerable share of all treatment-resistant major depression because antidepressant monotherapy is inappropriate for treatment of bipolar depression (Goodwin and Jamison, 2007). False unipolar depression (Goodwin and Jamison, 2007), which is depression classified as unipolar that subsequently experiences a manic or hypomanic episode, must respond to lithium treatment. Our previous study examined the efficacy of lithium augmentation in stage 2 major depression, i.e., treatment-resistant major depression (Abekawa et al., 1998; Inoue et al., 1996). We have since treated and followed up them for a long period (1–13 years). To elucidate the relation between lithium augmentation for stage 2 major depression and bipolarity, the final follow-up diagnosis was compared in responders and non-responders to results of lithium augmentation published to date (Abekawa et al., 1998; Inoue et al., 1996).

2. Methods

2.1. Subjects

This study was a naturalistic follow-up study of 29 adult patients with antidepressant-refractory major depressive disorder (DSM-III-R) who received lithium augmentation. During 1995–1997, we investigated their demographic characteristics, symptoms, and treatment responses to a lithium augmentation therapy (Abekawa et al., 1998; Inoue et al., 1996). Inclusion criteria were moderate depressed symptoms after adequate treatment with two or more tricyclic and tetracyclic antidepressants from different pharmacological classes (a minimum of the equivalent of 150 mg of imipramine for 4 weeks); they were stage 2 major depression. Depressed patients with brain MRI or EEG evidence of organic brain disease were excluded from this study. Patients with concurrent severe medical problems were also excluded from this study.

2.2. Assessment

According to the Clinical Global Impressions (CGI) scale (National Institute of Mental Health, 1985), treatment efficacies of lithium augmentation were evaluated as worse, no change, minimally improved, much improved, or very much improved. Patients rated very much improved or much improved were regarded as responders. Following the completion of this study, these patients continued to attend our department and receive treatment. Treatment, symptoms, and social functioning were recorded prospectively for 13 years during 1995–2008. The authors investigated the final diagnosis, severity of symptoms, social functioning (employment, etc.), scores of Global Assessment of Functioning (GAF) scale, whether the patients had experienced full remission during the 13 years, and the prevalence of bipolar spectrum disorder at the start of lithium augmentation (Ghaemi et al., 2001). A score of 80 or higher on the GAF scale is a good and straightforward indicator of full remission (Inoue et al., 2006).

2.3. Data analyses

Continuous data are presented as means with standard deviations (SD). For dichotomous variables, Fisher's exact test was used to calculate the p values. For all other continuous variables, a t-test with or without Welch's correction was used. Differences were considered significant at $p<0.05$.

3. Results

3.1. Initial treatment effect of lithium augmentation and clinical and demographic data

Of 29 patients with treatment-resistant (stage 2) major depressive disorder, only 4 patients were responders (response rate = 13.8%). Clinical and demographic parameters at the start of lithium augmentation (gender, age, age at onset, number of previous depressive episodes, duration of index episode, comorbidity, prevalence of bipolar spectrum disorder, marital status, employment status, education and family history of bipolar disorder) were not statistically different between responders ($n=4$) and non-responders ($n=25$) (Table 1).

3.2. Final diagnosis at follow-up and outcome

After the mean follow-up period of 8.0 years (range, 1–13 years), among the 29 patients with major depression, 6 patients were diagnosed with bipolar disorder (1 bipolar I and 5 bipolar II). At follow-up, 3 of 4 responders and 3 of 25 non-responders were bipolar patients (Table 1). Bipolar conversion, i.e. prevalence of unrecognized bipolar disorder or false unipolar depression, was significantly higher in lithium responders than in non-responders ($p=0.02$, Fisher's