Journal of Affective Disorders 129 (2011) 183–190

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Improvement within 2 weeks and later treatment outcomes in patients with depressive disorders: The CRESCEND study

Jae-Min Kim *, Seon-Young Kim, Robert Stewart, Joon-An Yoo, Kyung-Yeol Bae, Sung-Won Jung, Min-Soo Lee, Hyeon-Woo Yim, Tae-Youn Jun

Department of Psychiatry, Chonnam National University Medical School, Gwangju, Republic of Korea
Section of Epidemiology, Institute of Psychiatry, London, United Kingdom
Department of Psychiatry, Keimyung University, School of Medicine, Daegu, Republic of Korea
Department of Psychiatry, College of Medicine, Korea University, Seoul, Republic of Korea
Department of Preventive Medicine, The Catholic University of Korea, College of Medicine, Seoul, Republic of Korea
Department of Psychiatry, The Catholic University of Korea, College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 1 July 2010
Received in revised form 6 September 2010
Accepted 6 September 2010
Available online 28 September 2010

Keywords:
Depression
Early improvement
Response
Remission
Predictor
Korea

ABSTRACT

Background: Although antidepressants are conventionally given for 4–6 weeks before deciding on response, several reports suggest that early improvement predicts later outcomes. In a naturalistic national cohort study, we sought to investigate the predictive value of early improvement on Hamilton Depression Rating Scale (HAMD) score for later outcomes (depression (HAMD), anxiety (HAMA), global severity (CGI-s) and functioning (SOFAS)), as well as socio-demographic and clinical correlates of early improvement.
Methods: Participants were recruited from 18 hospitals across South Korea. All met DSM-IV criteria for depressive disorders, scored ≥14 on the HAMD and received antidepressant treatment for up to 12 weeks. Treatment was naturalistic in that each clinician freely decided the types, doses, and regimes of antidepressant and concomitant medications. Early improvement was defined as a reduction in HAMD score of ≥20% compared with baseline within 2 weeks of treatment. Later treatment outcomes were measured at 4, 8, and 12 weeks.
Results: In a recruited sample of 568 patients, early improvement predicted 12 week treatment outcomes with high sensitivity and high negative predictive values. The predictive values for HAMD and HAMA 12-week responses were higher compared to CGI-s and SOFAS responses. Early improvement was associated with higher monthly income, baseline lower anxiety and higher functioning levels. The patients with early improvement more frequently received antidepressant monotherapy.
Limitations: The study was observational, and the treatment modality was naturalistic.
Conclusions: Early antidepressant improvement strongly predicted later outcomes, and was associated with higher income, lower anxiety, and higher function.

1. Introduction

Depression is associated with significant suffering, high morbidity and mortality rates, and psychosocial impairment (Cassano and Fava, 2002). Despite considerable development in the pharmacological treatment of depressive disorders, short term antidepressant trials have shown that less than one third of patients achieve remission (Keller et al., 2000; Trivedi et al., 2006). Most treatment guidelines suggest that antidepressant response becomes evident with a delay of 2 or 3 weeks, and that the treatment regimen should be changed if a partial response has not occurred after 4 to 6 weeks (American Psychiatric

* Corresponding author. Department of Psychiatry, Chonnam National University Medical School, Gwangju 501-757, Republic of Korea. Tel.: +82 62 220 6143; fax: +82 62 225 2351.
E-mail address: jmkim@chonnam.ac.kr (J.-M. Kim).

0165-0327/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2010.09.007

Association, 2000; Bauer et al., 2007; National Institute for Health and Clinical Excellence, 2009). However for people with depression, sustaining 4 to 6 weeks of distress with no response before review of treatment requires substantial patience, with ongoing risk of suicide attempt. If it were possible to predict likely treatment effect at an earlier stage, this might shorten the time to response, reduce unnecessary drug exposure, and maximize cost-effectiveness. One approach has therefore been to investigate associations between early and later treatment responses. It has been reported that improvement within 2 weeks [usually defined as a ≥20% score reduction on the Hamilton Rating Scale for Depression (HAMD, Hamilton, 1960)] in antidepressant trials can substantially predict later more prominent response (defined as a ≥50% score reduction on the HAMD) (Nierenberg et al., 1995; Stassen et al., 1993, 1997; Szegedi et al., 2003). A recent meta-analysis of 6562 patients from 41 clinical trials comparing mirtazapine with an active comparator or placebo concluded that early improvement can predict subsequent treatment outcome with high sensitivity (Szegedi et al., 2009). This was further replicated in a naturalistic study of inpatients suffering from a more severe degree of depression (Henkel et al., 2009). However, only HAMD changes were considered as a treatment outcome, despite the fact that a multifaceted evaluation has been recommended, moving beyond a simple HAMD response to encompass psychological well-being and functioning (Fava et al., 2007). A further limitation is that almost all previous research of this nature has been carried out in Western settings with potentially limited applicability in other ethnic groups and cultures.

Using data from the Clinical Research Center for Depression (CRESCEND) programme, a large prospective observational clinical study with a nationwide sample of people with depressive disorders in Korea, we aimed to carry out the following:

1. To describe early (2 weeks) improvement as a predictor for later (12 weeks) outcomes applying standard screening statistics (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristics (ROC)), defining the outcome not only by response based on HAMD score changes but also applying assessment scales measuring anxiety, global severity and functioning.
2. To estimate pretreatment predictors of early improvement in terms of socio-demographic and clinical characteristics.
3. To describe differences in treatment-related characteristics between those with and without early improvement in terms of type and regimen of antidepressant used, concomitant medications, medication side effects, and number of attendances in the 12-week treatment period.

2. Methods

2.1. Study outline

The CRESCEND study is a major nine-year prospective clinical research programme begun in 2005 with a large nationwide sample supported by the Korean government. It aims to provide naturalistic data from clinical settings to facilitate investigations of the characteristics, course, and outcomes associated with depressive disorders. In total, 18 hospitals (16 university and 2 general hospitals) have collaborated in the ongoing CRESCEND study. The central coordinating center is located in the Psychiatric Department of the Catholic University Medical Center in Seoul, which provides educational support and coordination for the enrollment and follow-up of study participants. The data management center is in the Preventative Medicine Department of the Catholic University College of Medicine, which provides support for obtaining data and quality control. Other regional centers are located across South Korea, and have a role in recruitment and follow-up. With respect to the selection of regional centers, a nationwide distribution was sought. In this respect, at least two hospitals were recruited for each province, and these were chosen as the ones which were anticipated to be assessing and treating the largest numbers of people with depressive disorders (rather than hospitals primarily providing inpatient care for people with chronic psychotic disorders). Availability of personnel and study facilities were also considerations. Enrolment took place in a naturalistic clinical environment from both outpatient and inpatient settings, regardless of depression subtypes, and regardless of physical comorbidity. Treatment interventions were also conducted in a naturalistic fashion with full autonomy for each clinician in determining the type, dose, and regimen of antidepressant and other medications. Assessments were scheduled at baseline, 1, 2, 4, 8, 12, 24, and 52 weeks later, and thereafter every 1 year. At each visit, clinical review took place to decide treatment modalities. All other data on socio-demographic, clinical, and treatment-related characteristics were obtained by clinical research coordinators, who were trained and certified in clinical report form (CRF) implementation and data collection methods by the central coordinating center, and supervised by the clinicians of the regional centers. Participants' data were recorded on a predetermined CRF at each visit, recorded in the website homepage of the CRESCEND study (www.smileagain.or.kr) within 2 days, and monitored by personnel from the data management center.

2.2. Study sample

All people with depressive disorder reviewed at the study hospitals were approached regarding participation. All inclusion instances represented new treatment episodes whether depressive symptoms were first-onset or recurrent. The clinicians assessing and diagnosing the patients applied Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (DSM-IV) (American Psychiatric Association, 1994). The study itself was specifically designed to fit into clinical care settings as closely as possible. There was no advertisement for recruitment of participants, and no economic compensation for study participation. The time frame for baseline recruitment was from January 2006 to August 2008.

Broad inclusion criteria and minimal exclusion criteria were applied. Inclusion criteria were: i) outpatients and inpatients aged over 7 years and ii) a DSM-IV diagnosis of depressive disorder (major depressive disorder with or without psychotic features, dysthymic disorder, depressive disorder not otherwise specified). Exclusion criteria were: i) a current or lifetime comorbid DSM-IV diagnosis of schizophrenia, other psychotic disorders, bipolar disorders, organic psychosis, or dementia, ii) a medical and neurological illnesses of sufficient severity to interfere with the evaluations and interviews for the study, and