Original article

Diagnostic conversion to bipolar disorder in unipolar depressed patients participating in trials on antidepressants

J. Holmskov [a,b,*], R.W. Licht [b,c], K. Andersen [a], T. Bjerregaard Stage [d], F. Mørkeberg Nilsson [e], K. Bjerregaard Stage [a], J.B. Valentin [b], P. Bech [f], R. Ernst Nielsen [b,c]

[a] Institute of Clinical Health, University of Southern Denmark, Department of Psychiatry, Odense, Region of Southern Denmark, Denmark
[b] Unit for Psychiatric Research, Aalborg University Hospital, Psychiatry, Aalborg, Denmark
[c] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[d] Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark
[e] Psychiatric Department, Geriatric Psychiatric Unit, Psychiatric Centre Ballerup, Capital Region, Denmark
[f] Psychiatric Research Unit, Psychiatric Centre North Zealand, Copenhagen University Hospital, Copenhagen, Denmark

A R T I C L E   I N F O

A B S T R A C T

Objective: In unipolar depressed patients participating in trials on antidepressants, we investigated if illness characteristics at baseline could predict conversion to bipolar disorder.
Method: A long-term register-based follow-up study of 290 unipolar depressed patients with a mean age of 50.8 years (SD = 11.9) participating in three randomized trials on antidepressants conducted in the period 1985–1994. The independent effects of explanatory variables were examined by applying Cox regression analyses.
Results: The overall risk of conversion was 20.7%, with a mean follow-up time of 15.2 years per patient. The risk of conversion was associated with an increasing number of previous depressive episodes at baseline, [HR 1.18, 95% CI (1.10–1.26)]. No association with gender, age, age at first depressive episode, duration of baseline episode, subtype of depression or any of the investigated HAM-D subscales included was found.
Limitations: The patients were followed-up through the Danish Psychiatric Central Research Register, which resulted in inherent limitations such as possible misclassification of outcome.
Conclusion: In a sample of middle-aged hospitalized unipolar depressed patients participating in trials on antidepressants, the risk of conversion was associated with the number of previous depressive episodes. Therefore, this study emphasizes that unipolar depressed patients experiencing a relatively high number of recurrences should be followed more closely, or at least be informed about the possible increased risk of conversion.

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1. Introduction

Mental illnesses are generally understood as spectrums differentiated into disorders according to presence or absence of specific symptoms [1]. The *International Classification of Mental and Behavioral Disorders 10th version* (ICD-10) [2] and the *Diagnostic and Statistical Manual of Mental Disorders 5th edition* (DSM-5) [3] have divided the affective spectrum into depressive disorders (or unipolar depressive disorders) and bipolar disorders. Besides symptomatic differences and differences in the course of illness, the pharmacological treatment strategies differ to some degree

between unipolar depressive disorder and bipolar disorder [4]. However, a substantial number of patients originally diagnosed as suffering from unipolar depressive disorder subsequently develop mania or hypomania thereby "converting" into bipolar disorder. The risk of conversion is observed to be between 0.5 and 1.0% per year [5,6].

The search for predictors of conversion from unipolar depressive disorder to bipolar disorder is of clinical relevance, since patients at high risk should be followed more closely or at least be informed about the possible risk of conversion. Hypomanic symptoms below diagnostic threshold have been suggested as clinical risk factors for diagnostic conversion [7] alongside rapid onset of depression [8,9], pharmacological-associated hypomania and mood-congruent psychotic features [9]. A relatively high risk of conversion has also been shown in adolescents suffering from

* Corresponding author at: Unit for Psychiatric Research, Aalborg University Hospital, Psychiatry, Mølleparkvej 10, 9000 Aalborg, Denmark. Tel.: +45 976 436 09.
   E-mail address: jho@rn.dk (J. Holmskov).

unipolar depressive disorder [10]. Certain characteristics of patients with an episode of bipolar depression as opposed to patients with an episode of unipolar depression may also predict conversion from unipolar depressive disorder to bipolar disorder, since a unipolar depression in a patient who later on develops hypomania or mania may essentially have been a bipolar depression even though this diagnosis cannot be given at this time. Thus, hypersomnia or leaden paralysis [11–14], psychotic symptoms [8,15–18], and psychomotor retardation [13,16,17] appearing to occur more often in patients diagnosed with bipolar disorder than in patients diagnosed with unipolar depression could potentially predictive factors in conversion. Furthermore, it has also been found that patients suffering from bipolar disorder or a unipolar depression that later develops into bipolar disorder are characterized by a higher number of previous depressive episodes [5,11,14,15,19–24], shorter episodes of depression [17,25], higher frequency of comorbid substance abuse [24,26,27], higher frequency of family history of mood disorders [14,23–25], and earlier age of onset [14,19,23,24,28–30]. Cyclothymic or hyperthymic temperament is also associated with later development of bipolar disorder [4,23,24] as well as suicidal acts and male sex [24]. Finally, in patients diagnosed with unipolar depression, somatic complaints [12,13,19], anxiety [17,28], sleep loss [12–14, 17,19,25,31], and appetite loss [12,13,25,26] appear more frequently than in patients with bipolar disorder. Finally, it has been reported that stressful precipitations at onset, being unmarried, presence of attention deficits disorder, and pathological mood-elevation during treatment with an antidepressant or other mood-elevation agent such as stimulants and corticosteroids may increase the likelihood of developing a bipolar disorder [4].

In a well-defined sample of hospitalized unipolar depressed patients participating in trials on antidepressants, we aimed at investigating potential associations between illness characteristics at baseline and the risk of later diagnostic conversion from unipolar depressive disorder to bipolar disorder.

2. Materials and methods

2.1. Design and study subjects

The study was performed as a long-term follow-up study of patients who participated in three clinical trials conducted by the Danish University Antidepressant Group (DUAG) 1985–1994 [32–34]. DUAG was established in 1983 as an organization to conduct high quality, investigator-driven randomized clinical trials in the setting of a permanent multicenter group. The first DUAG trial investigating effects and adverse effects of citalopram and clomipramine was not included in our study due to a substantial amount of missing data making us unable to identify patients and thereby following them in registers [35]. The second DUAG trial investigated antidepressant effects and adverse effects of paroxetine versus clomipramine [32]. The third DUAG trial investigated antidepressant effects and adverse effects of moclobemide versus clomipramine [33]. The fourth DUAG trial investigated dose-effect and plasma concentration-effects of antidepressant therapy with clomipramine [34]. The inclusion criteria of the three studied trials were a diagnosis of major depression, and a HAM-D score > 18 whether as part of unipolar depressive disorder or bipolar disorder. However, due to our study aim, patients with a diagnosis of bipolar disorder at baseline, defined as an ICD-8: 29619, 296.39, or ICD-10: F30.x, F31.x diagnosis in the Danish Psychiatric Central Research Register or based on patient reported data from the trial case report forms (CRF), were excluded from the current study.

Data derived from CRFs from the three DUAG trials outlined above were linked to the nationwide Danish healthcare registers via a unique personal identifier number [36]. During the recruitment period from April 1985 until 1995, the registers contained complete information about all psychiatric admissions including diagnoses, and from 1995 onwards, the registers also contained complete information about all outpatient hospital-based treatments [37]. The follow-up period ended in 2011. The study investigated associations between baseline characteristics in all patients included, as explanatory variables, and diagnostic conversion as dependent outcome.

2.2. Explanatory variables

The Newcastle Scale was used to define the depressions as endogenous or non-endogenous [38,39]. Melancholia was based on the Bech-Rafaelsen Melancholia Scale (MES) [40].

All patients underwent ratings with the Hamilton Depression Scale (HAM-D) [41] from which we extracted subscale scores according to the HAM-D ABC model proposed by Bech [42], comprising the HAM-D$_6$ (items 1, 2, 7, 8, 10 and 13), stress-related arousal (items 4, 5, 6, 9, 11, 12, 14, 15 and 17), and suicide risk behavior (items 3 and 16), the Maier-Philipp Severity subscale (HAM-D items 1, 2, 7, 8, 9 and 10) [43], and the Gibbons Global Depression Severity (HAM-D items 1, 2, 3, 7, 9, 10, 11 and 14) [44].

Age, gender, age at first episode, number of previous depressive episodes, and duration of index episode were defined as additional explanatory variables.

2.3. Statistical analysis

Initially, crude risks of conversion were computed.

Secondly, we conducted Cox regression analyses with diagnostic conversion (hypomania or mania defined as an ICD-10 diagnosis within F30.x–F31.x or an ICD-8 diagnosis of 296.1, 296.2, 296.3, 296.8, 296) as outcome and the explanatory variables as co-variates.

Due to high correlation between the five HAM-D subscales, the initial regression was conducted without any of the subscales entered as explanatory variables. Subsequently, the subscales were entered separately, utilizing a total of six regressions analyses. The results reported on baseline characteristics were retrieved from the initial regression. The analysis was conducted with entry defined as entry into the respective original trial, and patients were followed until diagnostic conversion, death or end of follow-up period December 31, 2011, whichever came first.

In case of missing data, we imputed these using the multiple imputation technique with linear, logistic or negative binomial regression models depending on the nature of the covariate. The input variables for the imputation were gender and age at inclusion. Data were imputed for 26 participants, with 70 of 3480 (2%) observations being imputed.

Hazard ratios (HR) were computed, and a P-value < 0.05 was considered statistically significant. All analyses were carried out in Stata 13.

2.4. Ethics

The Danish Data Protection Agency and Statistics Denmark approved identification of the patients utilizing data from the CRFs and data from the Danish registers. In accordance with rules of data protection the original data had been anonymized.

The Regional Scientific Ethical Committees for Southern Denmark approved the study.

3. Results

A total of 360 patients were included in DUAG trials 2, 3 and 4. In the current study, we were able to identify and include