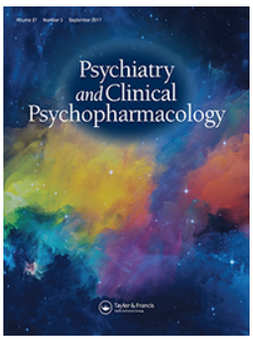

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The relationship between remission, non-specific structural cerebral pathologies, and atypical antipsychotic combination treatment in patients hospitalized with depression: a cross-sectional study

Mustafa Ugurlu[a], Gorkem Karakas Ugurlu[b] and Ali Caykoylu[b]

[a]Department of Psychiatry, Ankara Ataturk Training and Research Hospital, Ankara, Turkey; [b]Department of Psychiatry, Yildirim Beyazit University School of Medicine, Ankara, Turkey

ABSTRACT

OBJECTIVE: The aim of this study was to determine the relationship between clinical variables related to patients hospitalized with depression.

METHODS: The files of patients hospitalized with depression were examined. Sociodemographic characteristics, clinical features and imaging reports were considered. Data for statistical analysis was obtained only from files that provided clear information.

RESULTS: The appropriate treatment for anxiety and psychotic symptoms had a significant effect on response in depression. The presence of non-specific structural cerebral pathologies had an important relationship with the length of hospitalization and suicidal ideation.

CONCLUSIONS: Depression is a disorder of which cause, course and outcome has been determined by several different factors. Therefore, addressing depression in a holistic manner is extremely important.

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KEYWORDS
Anxiety; depression; mood disorders; suicide; treatment

Introduction

Depression is a common mental health problem that leads to significant disability and impaired quality of life [1–3]. The diagnosis is often complex, and there are issues in clinical practice that need to be clarified, including treatment, response and prognosis. However, research into depression has produced conflicting results. Therefore, there is a need for further research on the topic.

One cause of conflicting results is that the emergence, prognosis and treatment of depression are affected by many factors [4,5]. Other reasons include small sample sizes, sampling bias, measurement errors, incorrect interpretation of results and work on "sterile samples" (overly restricted samples that are unlike real life) [6].

The excessive focus is another research challenge. Excessive focus can be defined as considering only one aspect of the data set that was collected for the study. To benefit from all the data, the researcher should examine all possible meaningful relationships between variables in the data set, which will provide a deeper understanding of the issue under examination.

A review of the various studies in depressed patients presents us with a broader perspective. However, these reviews consist of different studies and consequently the results of different samples. However, all the features expressed in a review should be shown in the same patient sample. Therefore, the information provided by the review can be supported, and the importance of the review would be increased. For this purpose, we tried to understand what the data collected from patients hospitalized with depression could tell us. The main objective of this study was to obtain as much information as possible from the real-life data collected from patients hospitalized with depression and to examine the relationships between the information.

Methods

Study setting

This present study was conducted in the psychiatry clinic of a tertiary hospital. The hospital staff consisted of four nurses, four MD/psychiatry residents, one psychiatrist and three residents in training. The hospital maintained standard patent history files. A psychiatry resident made the initial assessment of the patient using the structured clinical interview for DSM-IV Axis I Disorders (SCID-I) [7,8]. The Hamilton Anxiety Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D) and Brief Psychiatric Rating Scale (BPRS) were administered on admission (a) and discharge (d). Medical tests including routine laboratory tests, cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) were performed during the hospital stay, and experts were consulted when necessary. This process continued as long as the

CONTACT Mustafa Ugurlu dr_ugurlu@yahoo.com

patients stayed in the hospital until the missing data was completed.

The programme was not set up as a study or research project, but as a treatment programme and, all data analysed were collected as part of routine diagnosis and treatment of the patients. Therefore, we did not seek/obtain ethical approval for the study but rather study approval from the hospital's administration. Also, depending on National Code on the Patient Rights (published on 1 August 1998), all patients must sign informed consents not only for specific trials but also for each medical application (diagnostic or therapeutic) in Turkey [9]. Therefore, a second consent has not been taken due to obtained initial informed consents. All researchers were trained on good clinical practice and declared that the presented study was in agreement with ethical standards outlined in the Declaration of Helsinki.

Procedure

The authors reviewed the files of patients admitted with depression diagnosis during the years 2012–2015. The data from patient files that were examined in the study were extracted as follows:

(1) Files coded as F32–33 (depressive disorders) according to the World Health Organization's International Classification of Disease (ICD-10) [10] system were screened from the hospital archive.
(2) Each file was assessed by one psychiatrist and one resident in training. A semi-structured form was used during the assessment. Sociodemographic data (age, gender and education level) and clinical characteristics from the SCID-I diagnosis (comorbidity, the age of onset, the number of previous episodes, the number of hospitalizations, the length of hospitalization, suicidal ideation, treatment characteristics, psychiatric or medical comorbidity, cranial MRI and EEG reports) were recorded on the form.
(3) Non-specific structural cerebral pathology was determined in patients using the crainal MRI. Later, reports and consultation notes for these patients were examined. Patients who were assessed by a radiologist and neurologist as having non-specific structural change (atrophy, ischemic gliotic focus, lacunar infarct, and hyperintense areas) were grouped.
(4) Treatment response to anxiety (Resp-A = HAMAa – HAMAd), treatment response to depression (Resp-D = HAMDa – HAMDd), treatment response to psychotic symptoms (Resp-P = BPRSa – BPRSd) and the remission variables (HAMDd $\leq$ 6 [11]) were calculated. The study protocol is summarized in Figure 1.

Assessment tools

Hamilton Anxiety Scale (HAM-A): HAM-A was one of the first rating scales to measure the severity of anxiety symptoms. It is still one of the most widely used rating scales and has been translated into Turkish [12–14]. It consists of 14 items that are assessed by the interviewer.

Hamilton Rating Scale for Depression (HAM-D): HAM-D is the standard measure of the severity of

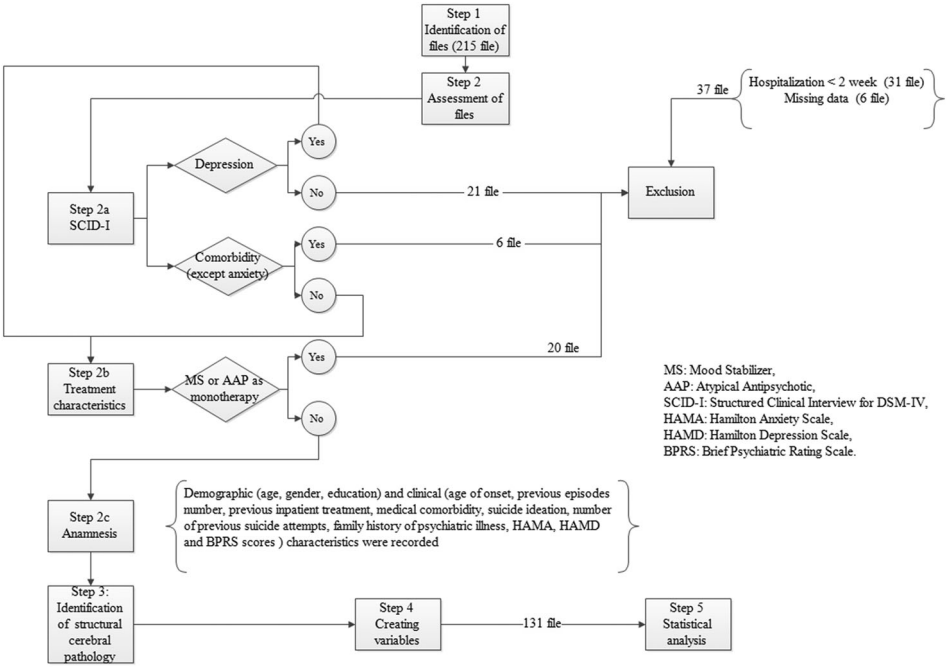


Figure 1. Schematic representation of the study method.

depression, and is used to assess the effectiveness of the patient's treatment. The scale has been translated into Turkish [15–17]. It consists of 17 items that are assessed by the interviewer.

Brief Psychiatric Rating Scale (BPRS): The BPRS is a useful instrument for measuring the severity of symptoms and change in symptoms for patients with depression [18]. It is also used for the measurement of psychotic symptoms in depressed patients [19].

Inclusion and exclusion criteria

The inclusion criteria were:

(a) at least two weeks of inpatient care,
(b) diagnosis of a major depressive disorder.

The exclusion criteria were:

(a) patients with any psychiatric diagnosis except anxiety disorder or major depressive disorder, for example, patients with bipolar or psychotic disorders,
(b) patients using a mood stabilizer,
(c) patients using an antipsychotic as monotherapy,
(d) patients with depressive disorder due to a general medical condition,
(e) patients with comorbid dementia,
(f) patients whose files contained incomplete data.

Statistical analysis

The distribution of variables was assessed with the Shapiro–Wilk test, and the statistical significance threshold was set as $p < .05$. To examine the relationship among all clinical variables, we used comprehensive statistical techniques, such as comparative statistics, correlation analysis, linear and logistic regression and path analysis. Variables that have significant differences in the comparative analysis or have a significant correlation were used in the regression and path analysis. In the path analysis, we examined how the clinical characteristics of major depression are associated with one another. Path analysis can be used to describe the effects of exogenous variables (treatment category or non-specific structural cerebral pathology) on endogenous (Resp-D or length of hospitalization) variables directly, indirectly, and by the sum of these variables. Path analysis enables an easy understanding of these effects by visualization in a path diagram. Exogenous variables in the model are those that are not explained by any variable. Endogenous variables in the model are those that are explained by exogenous variables or other endogenous variables (age of onset and Resp-P were both endogenous and exogenous variable in our study) [20,21]. Path analysis can predict that the equations system determines all causal links in a variables system, solves complex relationships between variables, and clearly reveals the strength of the relationship [22]. Suhr stated that if a path coefficient value is smaller than 0.10, there is the presence of a weak effect; if a path coefficient value is between 0.10 and 0.50, there is the presence of a moderate effect; if a path coefficient value is greater than 0.50, there is the presence of a strong effect [23].

Results

Of the 215 patient files that were examined in this study, 78 files were excluded, due to:

(1) diagnosis of bipolar disorder (9 files),
(2) psychotic disorder diagnosis (12 files),
(3) other comorbid psychiatric disorder (6 files),
(4) hospitalization of fewer than two weeks (31 files),
(5) mood stabilizer or antipsychotic as monotherapy (20 files),
(6) missing data (6 files).

The final data set contained 131 patient files.

The sociodemographic and clinical characteristics of the patients enrolled in the study were presented in Table 1. All modelling and path analysis was performed considering the correlations between variables, as presented in Table 2.

Atypical antipsychotic combination and treatment response

The number of patients in the antidepressant monotherapy group (A-M) was 41 (31.3%), and the number of patients receiving atypical antipsychotic combination therapy (AA-C) was 90 (68.7%). Table 3 shows the variables that were significantly different in comparison between the treatment groups. There were no significant differences between other variables (for all pairwise comparisons, $p < .05$). When performing logistic regression analysis, the only variable that determined inclusion in the combination therapy group was the BPRS score ($R^2 = 0.144$; Wald (1) = 7.692; $\beta = 1.07$; $p = .006$). A one-unit increase in BPRS scores increased the possibility of receiving combination treatment by approximately 7%.

In path analyses, the treatment category did not appear to have a direct effect on the treatment response. However, it was found to have an indirect effect on treatment response in association with a reduction in BPRS score (Figure 2). Compared to the antidepressant monotherapy group, the patients receiving atypical antipsychotic combination therapy had a 27% increase in the Resp-P score. A one-unit increase in the Resp-P score was associated with a 62% increase in Resp-D score.

Table 1. Clinic and demographic characteristics of patients with major depression.

		Nn	%
Sex	Woman	86	65.6
	Man	45	34.4
Education	Primary school	92	70.2
	High school and college	39	29.8
Suicide ideation	No	54	41.2
	Yes	77	58.8
Family history of psychiatric illness	No	65	49.6
	Yes	66	50.4
Medical comorbidity	No	57	43.5
	Yes	74	56.5
Non-specific structural cerebral pathology	No	47	35.9
	Yes	46	35.1
Treatment category	AA-C	90	68.7
	A-M	41	31.3
Remission	Remission	33	25.2
	Non-remission	98	74.8
	n	Mean	SD
Age	131	48.3	15.4
Number of hospitalization	131	1.7	1.2
Length of hospitalization (day)	131	31.4	14.4
Age of onset	131	39.3	16.6
Number of previous suicide attempts	131	0.7	1.2
Number of previous episodes	131	2.9	1.6
HAMAa	131	23.0	6.3
HAMAd	131	10.2	5.3
HAMDa	131	24.1	6.6
HAMDd	131	10.5	5.3
BPRSa	131	25.9	9.5
BPRSd	131	12.2	6.4
Resp_A	131	12.7	6.0
Resp_D	131	13.6	6.2
Resp_P	131	13.6	7.8

Note: AA-C, atypical antipsychotic + antidepressant combination; A-M, antidepressant monotherapy; BPRSa, Brief Psychiatric Rating Scale at admission; BPRSd, Brief Psychiatric Rating Scale at discharge; HAMAa, Hamilton Anxiety Scale Score at admission; HAMAd, Hamilton Anxiety Scale Score at discharge; HAMDa, Hamilton Depression Scale Score at admission; HAMDd, Hamilton Depression Scale Score at discharge; Resp-A: Treatment response for Anxiety (HAMAa – HAMAd); Resp-D, Treatment response for Depression (HAMDa – HAMDd); Resp-P, Treatment response for Psychotic Symptoms (BPRSa-BPRSd).

Suicidal ideation, length of hospitalization and non-specific structural cerebral pathologies

The variables affecting the length of hospitalization were tested by path analysis, and the age of onset, number of previous hospitalizations and HAM-A scores were found to be significantly important variables. The presence of non-specific structural cerebral pathology was found to be a significantly relevant variable that affected the age of onset (Figure 3).

Binary comparisons between the non-specific structural cerebral pathology group and the suicidal thought group (χ^2 (1) = 7.953; p = .005) and non-specific structural cerebral pathology group and medical comorbidity group (χ^2 (1) = 7.301; p = .007) showed a statistically significant difference. The presence of non-specific structural cerebral pathology reduced the risk of suicide by 48%. When grouping was performed according to the presence of suicidal ideation, the presence of non-specific structural cerebral pathology (R^2 = 0.295; Wald (1) = 5.613; β = 0.324; p = .018) and the number of previous

Table 2. Correlation between clinical characteristics.

		LoH	NoH	AoO	NoS	MC	NoE	HAMAh	HAMAd	HAMDh	HAMDd	BPRSh	BPRSd	Resp-A	Resp-D
NoH	*r*	.185*													
AoO	*r*	.247**	.086												
NoS	*r*	−0.002	.006	−0.107											
MC	*r*	.180*	.100	.208*	.039										
NoE	*r*	.111	.346**	−0.291**	−0.048	.114									
HAMAh	*r*	.221*	.060	.023	.033	.053	.119								
HAMAd	*r*	.119	.056	.157	−0.050	.044	.060	.500**							
HAMDh	*r*	.190*	.082	.237**	.040	.100	−0.030	.656**	.363**						
HAMDd	*r*	.148	.113	.227**	−0.116	.092	.029	.385**	.824**	.507**					
BPRSh	*r*	.103	.094	.163	.084	−.029	.008	.530**	.137	.389**	.118				
BPRSd	*r*	.204*	.084	.210*	−.018	.020	.035	.468**	.657**	.285**	.564**	.563**			
Resp_A	*r*	.084	.004	−.153	.104	.007	.077	.583**	−.326**	.334**	−.351**	.426**	−.085		
Resp_D	*r*	.077	−.016	.064	.135	.023	−.044	.400**	−.311**	.636**	−.295**	.376**	−.169	.732**	
Rssp_P	*R*	.007	.075	.041	.109	−.004	−.046	.293**	−.365**	.296**	−.287**	.707**	−.086	.655**	.638**

Note: AoO, age of onset; BPRSa, Brief Psychiatric Rating Scale at admission; BPRSd, Brief Psychiatric Rating Scale at discharge; LoH, length of hospitalization; HAMAa, Hamilton Anxiety Scale Score at admission; HAMAd, Hamilton Anxiety Scale Score at discharge; HAMDa, Hamilton Depression Scale Score at admission; HAMDd, Hamilton Depression Scale Score at discharge; MC, total number of medical comorbidity; NoE, number of total depressive episodes; NoH, number of total hospitalization; NoS, number of total suicide; Resp-A, treatment response for anxiety (HAMAa – HAMAd); Resp-D, treatment response for depression (HAMDa – HAMDd); Resp-P, treatment response for psychotic symptoms (BPRSa – BPRSd).
*p < .05.
**p < .01.

Treatment category: Antidepressant monotherapy (0) vs Atypical antipsychotic combination (1)
Resp-D : Hamilton Depression Scale Score at admission - Hamilton Depression Scale Score at discharge
Resp-P : Brief Psychiatric Rating Scale Score at admission - Brief Psychiatric Rating Scale Score at discharge
* Standardized regression coefficient, p < 0,05.

p	CMIN/DF	GFI	CFI	RMSEA
0,755	0,098	0,990	1,0	0

Explanation: Receiving combined treatment causes a recovery in BPRS scores (possibly in psychotic symptoms). A decrease in BPRS scores also mediates a reduction in depression scores.

Figure 2. The relationship between the treatment responses with treatment category.

suicide attempts (Wald (1) = 7.737; $\beta = 3.167$; $p = .005$) were found to be significantly important.

Remission

Binary logistic regression analysis was performed for the analysis of predictive factors for remission, and it was found that the increase in Resp-A score ($R^2 = 0.72$; Wald (1) = 16.026; $\beta = 2.529$; $p < .001$) and presence of suicidal ideation (Wald (1) = 4.850, $\beta = 0.103$, $p = .028$) were significantly important. While the presence of suicidal ideation reduced the likelihood of remission by about 90%, a one-unit increase in the Resp-A score increased the likelihood of remission by 2.5 times.

Discussion

In this study, the majority of patients had received a combination treatment. Adding an atypical antipsychotic to antidepressant treatment is common in the treatment of depression [24,25]. In treatment-resistant or severe cases of depression, the antipsychotic combination is the preferred method [26,27]. Psychotic and anxiety symptoms improved more in patients treated with atypical antipsychotics than in patients treated with antidepressant monotherapy, and this was consistent with other studies [28,29]. However, combination treatment did not have a significant direct effect on treatment response in depressive symptoms (Res-D). Figure 2 shows that the combination treatment had an indirect effect on depressive symptoms that was associated with a reduction in psychotic symptoms (Res-P). Other studies of patients with schizophrenia showed that atypical antipsychotics had antidepressant effects that indirectly reduced positive and negative symptoms, as well as a direct effect [30].

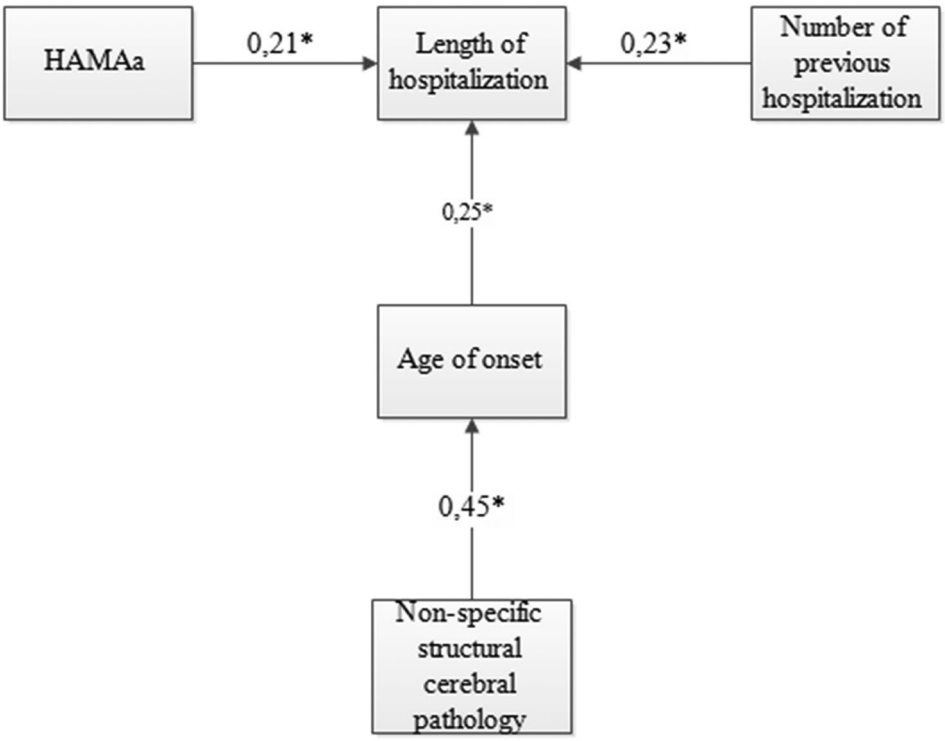
The current researchers believe that the length of hospitalization has been an indirect indicator of treatment resistance and severity of depression [31]. In this present study, pairwise comparison of atypical antipsychotic combination treatment *vs.* antidepressant monotherapy showed that the length of hospitalization was significantly longer for patients who received an atypical antipsychotic combination treatment (i.e. there was higher treatment resistance or disorder severity in this group). However, further analysis indicated that BPRS scores were a more specific factor.

Correlation analysis suggested that when anxiety and depression symptoms were increased, the length of hospitalization was also prolonged. Patch analysis showed that increasing age of onset, HAMAa [32] and the number of previous hospitalizations [33] were associated with an increased length of hospitalization. Other studies suggested that comorbid anxiety negatively affected prognosis and treatment response

Table 3. Comparison of treatment categories.

	Treatment categories	*n*	Mean	SD	Med	Min	Max	*z*	*p*
BPRSa	AA-C	90	27.7	9.5	28	6	60	−3.572	<.001
	A-M	41	22.1	8.3	22	6	53		
Resp-A	AA-C	90	13.4	6.2	13	−1	31	−2.102	.036
	A-M	41	11.3	5.4	9	2	26		
Resp-P	AA-C	90	15.1	8.0	15	−1	44	−3.074	.002
	A-M	41	10.5	6.4	9	0	26		
LoH (day)	AA-C	90	33.2	15.6	29.5	14	83	−1.962	.050
	A-M	41	27,3	10,7	25	14	66		

Note: AA-C, atypical antipsychotic + antidepressant combination; A-M, antidepressant monotherapy; BPRSa, Brief Psychiatric Rating Scale at admission; LoH, length of hospitalization; Resp-A, treatment response for anxiety (HAMAa – HAMAd); Resp-P, treatment response for psychotic symptoms (BPRSa – BPRSd).



HAMAa: Hamilton Anxiety Scale Score at admission
* Standardized regression coefficient, p < 0,05.

p	CMIN/DF	CFI	RMSEA
0,755	0,570	1,0	0,0

Explanation: Factors affecting the length of hospital stay in depressed patients are high levels of anxiety, high number of previous hospitalizations, and late onset of depression (due to structural pathologies).

Figure 3. Factors affecting the length of hospitalization in patients with depression.

in depression [32,34]. Also, comorbid anxiety was also associated with initial depressive episodes and their recurrence [35]. The greater the number of depressive episodes, the worse becomes the prognosis of depression [36]. Poor prognosis and severe depression may prolong the length of hospitalization [37].

The advanced age of onset has been associated with recurrence [38], more severe depression, more anxiety, somatic symptoms [39] and treatment response [40]. Although the relationship between non-specific structural cerebral pathologies and the age of onset of depression have been shown before [41], and the relationship between structural cerebral pathologies and depression is still controversial. A large body of published neuroimaging research into major depressive disorder has now identified several neuroanatomical changes in affected patients [42–44]. At first glance, it does not seem to be a major factor in the length of hospitalization, but there is an indirect relationship between the presence of non-specific structural cerebral pathology and the length of hospitalization.

A one-unit increase in the number of previous suicide attempts increased the risk of suicide ideation by 3.2 times. The number of previous suicide attempts is associated with an increased risk of suicide ideation [45]. Although white matter lesions [46], particularly structural abnormalities in the frontal area [47] and neurodegenerative changes [48] have been shown in patients who attempted suicide. Our study has shown that the presence of non-specific structural cerebral pathology was associated with a 32% decrease in the risk of suicidal ideation. Although it is hard to explain this with the biological effect of the non-specific structural cerebral pathology, can be attributed to the fact that the patients with the non-specific structural cerebral pathology have more social support because of their poor general health status. Also, these patients were less exposed to the destructive effects of the depression because depression was later in the onset of age. In this way, they can develop good social networks until the onset of the disease. Finally, due to poor health conditions, regular clinical follow-up can also be protective against suicide [49–51].

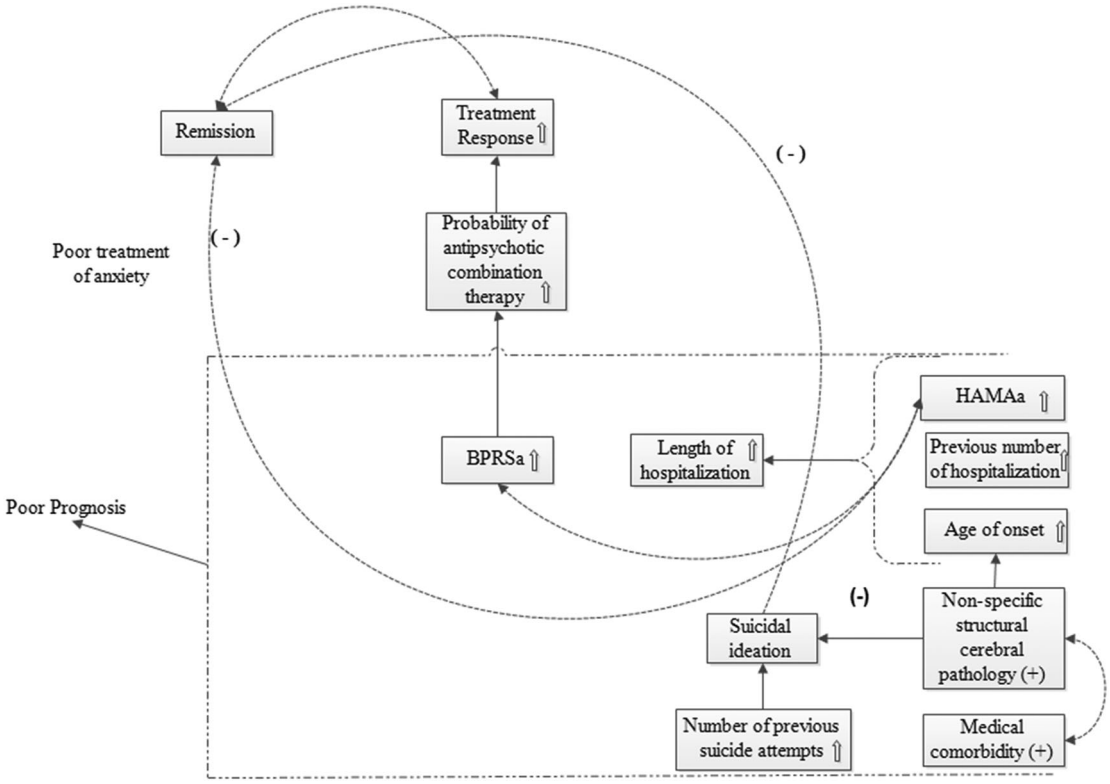


Figure 4. An overview representation of the relationship between clinical variables in patients with depression.

Finally, suicidal ideation and appropriate treatment of comorbid anxiety emerged as significant factors in remission. The relationship between suicidal ideation, multiple hospitalizations and the severity and recurrence of depression has been shown previously [52]. Independently of depression, anxiety increases the risk of suicidal ideation [53]. Furthermore, patients with greater pre-treatment anxiety took longer to respond to treatment, and had higher rates of recurrence [54,55], increased risk of withdrawal from treatment [56] and decreased response to acute antidepressant treatment [57].

The main limitation of our study is that it has a retrospective design, but to overcome this limitation, we used rigorous research criteria and robust information. Another limitation is that it does not include more details of the treatment because the patients were treated with medications in various dosages and different class. Therefore, we classified the treatment as antidepressant monotherapy and atypical antipsychotic combination.

As a result, successful treatment for anxiety and severity of anxiety symptoms appeared to be critical variables in patients with depression. Furthermore, the importance of atypical antipsychotics in combination with treatment response was again demonstrated, and it was shown that non-specific structural cerebral pathologies are important indirect variables in the prognosis and remission of depression. Depression is a disorder of which its cause, course and outcome are determined by many different factors. Therefore, addressing depression in a holistic manner is extremely important. Figure 4, which shows the relationship between clinical variables in hospitalized patients with depression, provides a comprehensive understanding of depression and provides an example of this approach.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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