ORIGINAL RESEARCH

Key Words: Bipolar disorder, anxiety disorder, substance use disorder, mood stabilizer, non-stabilization

Predictors of Non-Stabilization during the Combination Therapy of Lithium and Divalproex in Rapid Cycling Bipolar Disorder: A Post-hoc Analysis of Two Studies

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ABSTRACT ~ **Objective:** *To study predictors of non-stabilization (i.e., not bimodally stabilized for randomization or not randomized due to premature discontinuation) during open-label treatment with lithium and divalproex in patients with rapid-cycling bipolar disorder (RCBD) with or without comorbid recent substance use disorders (SUDs).* **Method:** *Data from the open-label phase of two maintenance studies were used. The reasons for non-stabilization were compared between patients with a recent SUD and those without. Predictors for non-stabilization were explored with logistic regression analyses.* **Results:** *Of 149 patients with recent SUD and 254 without recent SUD enrolled into the open-label acute stabilization phase, 21% and 24% were stabilized and randomized, respectively. Compared to those without recent SUD, patients with recent SUD were more likely to discontinue the study due to non-adherence to the protocol, 53% versus 37% (OR = 1.92) or refractory mania/hypomania, 15% versus 9% (OR = 1.87), but less likely due to refractory depression 16% versus 25% (OR = 0.58) or adverse events, 10% versus19% (OR = 0.44). A history of recent SUDs, early life verbal abuse, female gender, and late onset of first depressive episode were associated with increased risk for*

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non-stabilization with ORs of 1.85, 1.74, 1.10, and 1.04, respectively. ***Conclusions:*** *During open treatment with lithium and divalproex in patients with RCBD, a recent SUD, a lifetime history of verbal abuse, female gender, and late onset of first depression independently predicted non-stabilization. The non-stabilization for patients with SUD was related to non-adherence and refractory mania/hypomania.* Psychopharmacology Bulletin. *2010;43(1):23–38.*

INTRODUCTION

Lithium and divalproex are the two most commonly prescribed mood stabilizers.[1–4] There has been a long history of interest in the combination of these two mood stabilizers in the treatment of bipolar disorders.[5–14] One reason for the use of combination therapy is that patients with refractory bipolar disorder[5–7] or rapid cycling bipolar disorder (RCBD)[9,12,13] might respond better to combination therapy than lithium or divalproex monotherapy. Early studies revealed that rapid cycling[15] and substance abuse[16] were associated with lithium nonresponse. Open-label data also suggested that RCBD may respond better to divalproex than to lithium.[15,17] In addition, divalproex has shown efficacy in the acute treatment of bipolar mood episodes complicated by substance abuse.[16,18–20]

However, two prior studies conducted by our group involving patients with RCBD have shown that combination therapy with lithium and divalproex was much less effective than previously suggested.[21,22] Approximately only 20% of patients met the protocol-defined criteria for stabilization/randomization, i.e., a 17-item HAM-D score $\leq$ 20, YMRS score $\leq$ 12.5, GAS score $\geq$ 51 for a minimum of 4 weeks with lithium levels $\geq$ 0.8 meq/L and valproate levels $\geq$ 50 μg/ml. Of these two studies, one was conducted in patients with RCBD and a recent history of SUDs[22] and another was carried out in patients with RCBD, but no recent history of SUDs.[21] In addition, a previous analysis of a different group of our patients with RCBD showed that level of education, ethnicity, and legal history, but not SUDs, were associated with increased risk for non-adherence.[23]

Although the clinical data are less impressive than expected, preclinical studies have shown both lithium and divalproex to have neuroprotective effects through different intracellular mechanisms.[24] More importantly, the two agents have additive neuroprotective effects.[25] Likely, the combination therapy of these two agents will continue to play a major role in the treatment of patients with bipolar disorder. In this report, the reasons for non-stabilization in the two studies[21,22] were compared and independent predictors of non-stabilization as a group

were explored. Such information has the potential to guide the use of the combination treatment of lithium and divalproex in patients with bipolar disorder.

METHOD

Patient Population

The data for this study were derived from two studies previously conducted by our center among patients with RCBD.[21,22] These studies were conducted to assess the efficacy of lithium and divalproex for managing the acute and maintenance treatment of RCBD with[22] or without[21] a "recent" history of SUD. A "recent" SUD was defined as having a diagnosis of substance dependence and continuing to meet abuse or dependence criteria for a substance(s) in the last 6 months at the initial assessment or having a diagnosis of substance abuse and continuing to abuse a substance(s) in the last 6 months. The study designs, inclusion, and exclusion criteria of these two studies have been summarized elsewhere.[26]

In addition to meeting psychiatric inclusion criteria, patients who had acute medical conditions were excluded. Patients were also excluded from study participation if they had previous intolerance to documented lithium levels of 0.8 meq/L or divalproex levels of 50 μg/ml, had been completely non-responsive to past lithium treatment, had alcohol-related liver disease as reflected by diffuse elevations in liver function tests exceeding the upper limits of the normal range by 50%, were pregnant or planning to become pregnant, were taking exogenous steroids, required anticoagulant drug therapy, or were actively suicidal as evidenced by a score $\geq$ 3 on item 3 of the 17-item Hamilton Depression Rating Scale (HAM-D).[27]

Initial Assessments

Written informed consent was obtained from each subject before any study-related procedures were performed. During the screening visit, psychiatric and medical histories were obtained. Physical examinations were performed which included the collection of clinical laboratory tests. The procedures for the psychiatric diagnostic assessments have also been described in detail previously.[26,28] Briefly, the diagnoses of RCBD, anxiety disorders including generalized anxiety disorder (GAD), panic disorder, and obsessive-compulsive disorder (OCD), SUDs, and other DSM-IV Axis I disorders were ascertained by extensive clinical interview (ECI) alone[21] and with the Mini-International Neuropsychiatric Interview (MINI)[29] by research psychiatrists and research assistants. For the diagnosis of SUDs, the

SCID-P (the Structured Clinical Interview for the DSM-IV, Patient Edition)[30] was used instead of MINI. The ECI consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, which is similar to the SCID-P, but also contains items to assess mental status, demographics, and other variables of interest. During the MINI administration, if any inconsistency occurred with the evaluations of ECI, a psychiatrist would re-evaluate the patient until a consensus was reached between research staff. Collateral information from the mandatory presence of a patient's significant other(s) was required in all cases during the initial assessment.

Pretreatment psychiatric assessments included Hamilton Depression Rating Scale-17 item (HAMD-17),[17] Young Mania Rating Scale (YMRS)[31] and Global Assessment Scale (GAS)[32] for both studies,[21,22] and Addiction Severity Index[33] and Timeline Follow-Back for Recent Drinking[34] for patients with recent SUDs.[22]

Open-Label Acute Stabilization Phase

Eligible patients were enrolled into the open-label acute stabilization phase and were seen by a research psychiatrist every 2 weeks. For patients who had been receiving no medication, lithium monotherapy was initiated at 300 mg twice daily and titrated over 3–6 weeks to minimum blood levels of 0.8 meq/L. Divalproex was then initiated at 250 mg twice daily and increased over 3–6 weeks to minimum blood levels of 50 μg/ml. The order of initiating these two medications could be reversed depending on the preference of patients. If patients were already taking psychotropic medications other than lithium and divalproex, these medications were gradually weaned over 3 months as lithium and divalproex were concurrently initiated and titrated upwards. If patients were already taking lithium, but not divalproex, divalproex was initiated as described. If patients were already taking divalproex, but not lithium, lithium was initiated and titrated as described. All psychotropic medications other than lithium and divalproex were discontinued a minimum of 4 weeks before random assignment to either double-blind lithium or the combination of lithium and divalproex.

At each visit, the same severity measures administered at the screening visit were once again administered, and patients were assessed for adverse events. Patients who met stabilization criteria for a minimum of 4 consecutive weeks were eligible to be randomized to the double-blind maintenance phase. The stabilization criteria for entering the maintenance phase were a 17-item HAM-D score $\leq$ 20, YMRS score $\leq$ 12.5, GAS score $\geq$ 51, lithium levels $\geq$ 0.8 meq/L, and valproate levels $\geq$ 50 μg/ml.

Patients not meeting these criteria after 24 weeks were discontinued from the study. Patients who did not achieve a score of ≤ 20 on the HAM-D over 4 consecutive weeks during weeks 12–24 were classified as having refractory depression. Patients who did not achieve a score of ≤ 12.5 on the YMRS over 4 consecutive weeks during weeks 12–24 were classified as being in a refractory manic/hypomanic/mixed state.

Concomitant Treatments

During the open treatment with lithium and divalproex, patients were gradually weaned from all other psychiatric medications at least 4 weeks before randomization. Initiation of psychotherapy was not permitted during the maintenance phase, but patients were permitted to continue any ongoing psychotherapy that had begun before study entry. Patients could receive lorazepam in doses up to 2–4 mg/d for anxiety, agitation, and insomnia. For severe, insomnia, zolpidem up to 10 mg/d could be prescribed.

Safety Monitoring and Discontinuation from the Study

Safety was evaluated during the scheduled visits with the investigator by monitoring adverse experience reported, physical examination and clinical laboratory assessments. The severity, frequency, and outcomes of adverse events were recorded. Physical exam and laboratory tests were repeated at study endpoint or at the time of premature discontinuation. Patients could discontinue the study due to refractory to treatment, adverse events, lack of adherence, or other reasons. The lack of adherence was defined as a total of two missed scheduled visits during the open-label phase.

Data Analysis

The demographics, baseline characteristics, and dispositions of these two studies were compared with univariate analyses. T-tests were used to evaluate continuous variables, with standard deviation to reflect the magnitude of variance. Chi-square tests were used to evaluate categorical data, with odds ratio (OR) for risk estimate and 95% confidence interval (CI) to reflect the magnitude of variance. Statistical significance was set at $\alpha = 0.05$, two-tailed, in order to detect potentially clinically meaningful associations. Given the exploratory nature of the study, no adjustment for multiple comparisons was made.

Logistic regression was performed in a combined sample to evaluate the following predictors of non-stabilization: age at study entry, age onset of the first mania/hypomania, age onset of the first depression, gender (male vs. female), bipolar subtype (type I vs. II), a lifetime history of any SUD, alcohol use disorder, and drug use disorder, a recent history of any SUD, a lifetime history of any comorbid anxiety disorder, generalized anxiety disorder (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD), a lifetime history of physical, sexual, and verbal abuse, the number of episodes in the last 12 months (overall, depressive, manic/hypomanic), a lifetime history of psychosis, and the time from the onset of first manic/hypomanic episode to first mood stabilizer treatment.

RESULTS

Demographics and Baseline Characteristics

As shown in Table 1, patients enrolled into the study without a recent history of SUDs[21] were more likely to be female with an OR of 3.10 (95% CI 2.03 to 4.72) and less likely to have bipolar I disorder with an OR of 0.20 (95% CI 0.13 to 0.32) compared to those enrolled in the study with a recent SUDs.[22] At the screening visit, patients without recent SUDs were more likely depressed with an OR of 1.43 (95% CI 0.95 to 2.15) compared to those with a recent SUD, but they were less likely to be manic/hypomanic/mixed with an OR of 0.65 (95% CI 0.43 to 0.98). Those without recent SUDs were also less likely to have anxiety disorders or psychotic episodes with an OR of 0.39 (95% CI 0.25 to 0.60) and 0.49 (95% 0.32 to 0.73), respectively.

In terms of previous treatment, patients without recent SUD were less likely to have received lifetime medications for bipolar disorder including lithium with an OR of 0.43 (95% CI 0.28 to 0.66), divalproex with an OR of 0.52 (95% 0.34 to 0.79), and antipsychotics with an OR of 0.42 (95% CI 0.24 to 0.69). However, there was no significant difference in receiving antidepressant treatment. Patients without a history of recent SUD had fewer mood episodes in the last 12 months and fewer previous hospitalizations compared to those with a recent history of SUD (Table 1).

Reasons for Non-Stabilization

There was no significant difference in randomization rates between those with and without a recent history of SUDs. Among those who were not stabilized, the patients with recent SUD were more likely to

TABLE 1

COMPARISONS OF BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF PATIENTS WITH RAPID CYCLING BIPOLAR DISORDER WITH OR WITHOUT A RECENT HISTORY OF SUBSTANCE USE DISORDER WHO WERE ENROLLED INTO TWO STUDIES

	WITHOUT RECENT SUD N = 254*		WITH RECENT SUD N = 149**			WITHOUT VS. WITH RECENT SUD	
	N	%	N	%	OR	WALD 95% CL	PEARSON'S P
Gender							
– Female	162	63.8	54	36.2	3.10	2.03 to 4.72	<0.0001
– Male	92	36.2	95	63.8			
Bipolar subtypes							
– Bipolar I	96	37.8	112	75.2	0.20	0.13 to 0.32	<0.0001
– Bipolar II	158	62.2	37	24.8			
Mood state at screening							
– depressed	142	55.9	70	47.0	1.43	0.95 to 2.15	0.0832
– hypomanic/ manic/mixed	95	37.4	74	49.7	0.65	0.43 to 0.98	0.0371
– euthymic	17	6.7	5	3.4	2.07	0.75 to 5.72	0.1545
Lifetime History							
– substance use disorder	142	55.9	149	100.0	n/a	n/a	n/a
– anxiety disorder	61	24.0	67	45.0	0.39	0.25 to 0.60	<0.0001
– psychotic episode	90	35.4	79	53.0	0.49	0.32 to 0.73	0.0005
– suicide attempt	97	38.2	69	46.3	0.72	0.48 to 1.08	0.1098
– sexual abuse	63	24.8	33	22.1	1.16	0.72 to 1.87	0.5457
– physical abuse	73	28.7	50	33.6	0.80	0.52 to 1.23	0.3107

(*continued*)

TABLE 1 (*CONTINUED*)

	WITHOUT RECENT SUD N = 254*		WITH RECENT SUD N = 149**			WITHOUT VS. WITH RECENT SUD	
	N	%	N	%	OR	WALD 95% CL	PEARSON'S P
Lifetime medication received							
Bipolar medications	117	46.1	99	66.4	0.43	0.28 to 0.65	<0.0001
Lithium	73	28.7	72	48.3	0.43	0.28 to 0.66	<0.0001
Divalproex	92	36.2	78	52.3	0.52	0.34 to 0.78	0.0015
Antipsychotics	30	11.8	37	24.8	0.41	0.24 to 0.69	0.0007
Antidepressants	188	74.0	104	69.8	1.23	0.79 to 1.93	0.3603
	Mean	SD	Mean	SD			Pearson's P
Age							
– at study entry	36.7	10.0	36.2	10.1	–	–	0.6303
– at first bipolar diagnosis	35.1	9.7	33.4	10.3	–	–	0.1029
– at first depression	14.7	6.7	13.6	6.9	–	–	0.2022
– at mania/hypomania	16.9	7	15.5	7.2	–	–	0.0579
No. of Episodes in last 12 months							
– total	10.3	6.6	12.2	7.7	–	–	0.0123
– depression	5.2	3.3	6	3.9	–	–	0.0367
– mania/hypomania/ mixed	5.2	3.3	6.1	3.9	–	–	0.0189
No. of Previous hospitalization	1.3	3	2.1	3.7	–	–	0.0256

Abbreviations: Cl = confidence interval; OR = odds ratio; SD = standard deviation; SUD = substance use disorder.
*Calabrese et al., 2005; **Kemp et al., 2008.

TABLE 2

COMPARISONS OF DISPOSITIONS OF PATIENTS WITH RAPID CYCLING BIPOLAR DISORDER WITH OR WITHOUT A RECENT HISTORY OF SUBSTANCE USE DISORDER WHO ENROLLED INTO THE TWO STUDIES

	WITHOUT RECENT SUD*		WITH RECENT SUD**		WITH VS. WITHOUT RECENT SUD		
	N	%	N	%	OR	WALD 95% CL	PEARSON'S P
Total number of patients entered the study	254		149				
Number of patients stabilized and randomized	60	23.6	31	20.8	0.85	0.52 to 1.39	0.5138
Number of patients prematurely discontinued							
Total	194		118				
– Lack of adherence	71	36.6	62	52.5	1.92	1.21 to 3.05	0.0057
– Non-response to treatment	65	33.5	37	31.4	0.91	0.56 to 1.48	0.6947
– depression	48	24.7	19	16.1	0.58	0.32 to 1.05	0.0714
– mania/hypomania/mixed	17	8.8	18	15.3	1.87	0.92 to 3.80	0.078
– Adverse events	48	24.7	15	12.7	0.44	0.24 to 0.83	0.0102
– Unable to discontinue concomitant medications	3	1.5	1	0.8	0.54	0.06 to 5.29	0.5946
– Relapse substance use disorder	5	2.6	n/a	n/a			
– Other reasons	2	1.0	3	2.5	2.50	0.41 to 15.21	0.3025

Abbreviations: CI = confidence interval; OR = odds ratio; SUD = substance use disorder.
*Calabrese et al., 2005; **Kemp et al., 2008.

discontinue the study due to non-adherence to the protocol with an OR of OR = 1.92 (95% CI 1.21 to 3.05) or refractory mania/hypomania/mixed with an OR of 1.87 (95% CI 0.92 to 3.08) compared to those without recent SUD. In contrast, patients with recent SUD were less likely to discontinue the study due to refractory depression with an OR of 0.58 (95% CI 0.32 to 1.05). However, those without recent SUD were more likely to discontinue the study due to adverse events compared to those with a recent SUD with an OR of 2.08 (95% CI 1.12 to 3.87) (Table 2).

Predictors for Non-Stabilization

Among the 21 variables considered for logistic regression analysis, 6 including a history of recent SUD, early life verbal abuse, and psychosis, female gender, age onset of first depression, and age at the study entry, remained in the model after a stepwise model building process. After controlling for these 6 variables in the model, a history of recent SUD, female gender, and a later onset of first depression were still significantly associated with increased risk for non-stabilization with an of OR of 1.85 (95% CI 1.09 to 3.15), 1.74 (95% CI 1.04 to 2.90), and 1.04 (96% CI 1.01 to 1.08), respectively. A history of early life verbal abuse was associated with a trended increase in the risk for non-stabilization with an OR of 1.10 (95% CI 1.00 to 1.21). On the other hand, older age at study entry and a history of psychosis were associated with a trended decrease in the risk for non-randomization with an OR of 0.98 (95% CI 0.95 to 1.00) and 0.61 (95% CI 0.37 to 1.00), respectively (Table 3).

TABLE 3

PREDICTORS OF THE PROBABILITY FOR NON-RANDOMIZATION DURING OPEN-LABEL TREATMENT OF LITHIUM AND DIVALPROEX IN PATIENTS WITH RAPID CYCLING BIPOLAR DISORDER

PREDICTORS	OR	95% CL	P VALUE
History of recent substance use disorder	1.85	1.09 to 3.15	0.023
Being female	1.74	1.04 to 2.90	0.036
Age of onset of first depression	1.04	1.01 to 1.08	0.039
History of verbal abuse	1.10	1.00 to 1.21	0.056
Age at the study entry	0.98	0.95 to 1.00	0.062
History of psychosis	0.61	0.37 to 1.00	0.052

Abbreviation: Cl = confidence interval; OR = odds ratio.

DISCUSSION

This post-hoc analysis highlights the limitation of the effectiveness of the combination treatment of lithium and divalproex in RCBD. Only about 20% of patients met the protocol-defined stabilization criteria for bimodal response over 4 consecutive weeks. In other words, about 1 of 5 patients was adherent with treatment, tolerated the side effects, and achieved stabilization (a 17-item HAM-D score $\leq$ 20 and YMRS score $\leq$ 12.5) over a 4-week period.[21,22]

Among those who were not stabilized, non-adherence to treatment was the most common reason in both studies. Patients with a recent history of SUD had a significantly higher rate of non-adherence compared to those without a recent history of SUD (Table 2). This is consistent with most previous studies, in which a history of SUDs was associated with increased risk for non-adherence in patients with schizophrenia or bipolar disorders.[35–41]

The second most common reason for non-stabilization was non-response to treatment (Table 2). Although the overall non-response rates in both studies were similar, the causes were different. Patient without a recent history of SUD had a numerical increase in refractory depression, but the patients with a recent history of SUD had a significantly higher rate of refractory mania/hypomania. These results suggest that the combination of lithium and divalproex were less effective for treating manic/hypomanic symptoms in those with a recent history of SUD. Therefore, other pharmacological treatments such as atypical antipsychotics should be considered in this subgroup of patients.[42–44]

In the logistic regression analyses, a history of recent SUD was independently associated with increased risk for non-stabilization. This finding and the results from univariate analyses (Table 2) suggest that patients with a recent history of SUD were less likely to be stabilized because either they were non-adherent to the protocol or they had refractory mania/hypomania.

The third most common reason for non-stabilization was due to adverse events. A higher rate of discontinuation due to adverse events in those without a recent history of SUDs was unexpected. This suggests that the combination of lithium and divalproex was relatively safe and well tolerated in those with a recent SUD. In a double-blind, placebo-controlled study of valproate in the treatment of patients with bipolar I disorder and alcohol dependence, Salloum and colleagues reported that only 1 of 15 patients who prematurely discontinued the study was due to adverse events.[19] These findings should help clinicians to assuage the safety and tolerability concerns in this subgroup of

patients. However, in a smaller retrospective study, Manwani and colleagues found that patients with a lifetime SUD were more likely to have lifetime reason for non-adherence due to side effects than those without a lifetime SUD, 19% versus 10%.[37]

The result of female gender as an independent predictor for non-stabilization is also unexpected. In a treatment of nicotine dependence with transdermal nicotine patches, female patients were also less likely to adhere to the treatment compared to male patients.[45] Since the majority of non-stabilization in our study was due to non-adherence, it is quite possible that female gender was associated with increased risk for non-adherence to the study protocol. However, other studies suggests that male patient were more likely to non-adhere to treatment than female patients.[35,36,46,47]

The result of a history of early life verbal abuse associated with non-stabilization in our study is somewhat consistent with previous studies in which have shown that childhood abuse was associated with non-adherence to treatments,[36,48] less response to antidepressant treatment,[49] or more severe manic symptoms.[50] However, in our study only verbal abuse, not physical abuse or sexual abuse was associated with increased the risk for non-stabilization. Similarly, in a Stanley Foundation Bipolar Network study, only physical abuse was associated with increased risk for more manic symptoms.[50] Clearly, it is worthy of further investigation to determine if there is a differential effect of early childhood abuse on the outcome of lithium and divalproex combination treatment.

Psychosis during a mood episode is an indicator of the severity of the illness. Our data suggests that patients with psychosis were more likely to be stabilized with the combination with lithium and divalproex than those without a history of psychosis. A higher rate of responder in patients with bipolar disorder and psychotic features was observed in patients treated with divalproex.[51] Similarly, McElory et al. found that divalproex oral loading was as effective as haloperidol in reducing manic and psychotic symptoms.[52] Moreover, Swann and colleagues found both lithium and divalproex were effective in the treatment of bipolar mania with psychosis.[53]

The late onset of first depression associated with an increased risk for non-stabilization was unexpected. However, an older age at the study entry associated with a decreased risk for non-stabilization is consistent with a previous study that older patients were more likely to adhere to their treatments than younger patients.[54] Previous studies have also shown that patients with early onset bipolar disorder were more likely to have a chronic course, more severe symptoms, more comorbidities, and were less likely to respond to treatments.[55,56] According to these

data, patients with late onset of depression should be more likely to be stabilized than those with early onset of depression. However, some studies have shown that patients with earlier onset of bipolar disorder responded better to lithium or mood stabilizer treatment than those with late onset bipolar disorder.[51,57] Apparently, our results are consistent with these findings.

Limitations

These findings must be considered in view of several methodological limitations. First, the original studies were not designed to compare the factors for non-stabilization. Therefore, there might not be enough power to detect true differences between those with and without a recent SUD. Second, for the regression analyses, although we tried to control for confounding factors, variables not considered in the model could still affect the outcome. In addition, although the sample size in our study was relatively large, it was still not large enough to study independent predictors for each individual cause of patient disposition. Third, our study only included patients with RCBD, therefore, our results might not be generalizable to other bipolar populations. Four, not adjusting for multiple comparisons may increase the chance of Type I error. Therefore, the results from univariate analyses should be viewed as preliminary.

Conclusions

During open treatment with lithium and divalproex in patients with RCBD, patients with a history of recent SUD who were not stabilized were likely due to non-adherence to the protocol or refractory mania/hypomania. As a group, a recent SUD, a lifetime of verbal abuse, female gender, and late onset of first depression were independently associated with increased risk for non-stabilization. ✤

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