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Original Article

Outcome of single manic episode in bipolar I disorder: a six-month follow-up after hospitalization

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Abstract

BACKGROUND: Bipolar I Disorder (BID) considered as the sixth leading cause of disability worldwide. After remission of a manic episode, most of patients spend about 50% of the following time with mood or cognitive symptoms. The aim of this study was to investigate the 6-month outcome of BID patients following their single manic episode.

METHODS: Adult bipolar patients (n = 13) with single manic episode admitted to Noor Hospital, Isfahan, Iran, from December 6 2008 to June 5 2009 were evaluated using diagnostic, symptomatic, and functional assessments. Patients were also evaluated monthly for six months to assess syndromic, symptomatic, and functional outcomes, self reported treatment adherence, and serum levels of major mood stabilizers. The Kaplan-Meier method and log-rank test at a significance level of < 0.05 were used.

RESULTS: Kaplan-Meier estimates of the cumulative probabilities of syndromal, symptomatic, and functional recovery during the first 6 months after admission for single manic episode were 0.89, 0.75, and 0.64, respectively. At the 3rd month 54% of BID patients reported full medication adherence while it decreased to 38% at the 6th month. Patients with full adherence revealed shortened time to functional recovery based on LIFE-RIFT compared with non-adherent patients (log rank: $\chi^2 = 4.5$, df = 1, p = 0.03). Substance abuse also associated with longer time to functional recovery based on LIFE-RIFT (log rank: $\chi^2 = 4.36$, p = 0.037).

CONCLUSIONS: Despite high rates of experienced syndromic and symptomatic recoveries for BID patients in single manic episode, functional recovery was much lower following hospitalization.

KEYWORDS: Bipolar Disorder, Outcome Assessment, Medication Adherence.

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Although there are many options for effective treatment of mania and depressive episodes of Bipolar I Disorder (BID), persistence of some symptoms, increased incidence of serious medical diseases, elevated risk of suicide, and significant decrease in psychosocial functioning has been reported during periods of remission in BID patients.[1] After remission of a depressive or manic episode, most of patients spend about 50% of the following time with mood symptoms. Further to residual mood symptoms, they frequently experience persistence of cognitive problems. This phenomenon results in more decrease in quality of life despite remission of acute episodes.[2,3] Multiple studies showed that "one-year relapse rates have ranged from 28 to 44% and enduring psychosocial impairment despite symptomatic recovery has been described in a substantial number of patients.[4] Because of this high level of psychosocial impairment, BID is considered as the sixth leading cause of disability worldwide".[5]

Since the clinical description of manic-depressive insanity by Kraepelin in 1921, large numbers of studies were designed to find outcome of BID. Some clinical characteristics indicated as potential risk factors of un-

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favorable outcome like male sex, older age at onset, poor occupational status, race, number of previous episodes, number of previous hospitalizations, low socioeconomic status, duration of illness, mixed episodes, presence of inter-episode symptoms, symptoms of depression during manic episodes, mood-incongruent symptoms, psychotic features, and substance abuse.[6-12]

However, limitations of methods of these outcome studies may explain diversity in results but restrict their interpretation. First, previous studies rarely attempted to assess treatment adherence systematically, thus the role of poor compliance on outcome has been left unexplained.[10] Second, until recently, relatively few studies on Iranian patients used structured diagnostic interviews.[13-16] Meanwhile, Iranian studies usually evaluated outcome qualitatively. In other words, they reported course of the disorder with descriptive adjectives (in partial remission; when symptoms reduced more than 50% or in full remission; when symptoms reduced more than 70% based on a standard assessment scale) and did not assess syndromic, symptomatic, and functional outcome quantitatively.[13-16] Third, most of studies followed patients after an indexed episode, not exactly after their first episodes. Earlier studying BID patients in the course of illness identifies more factors associated with recovery. In other words, multiple affective episodes may cause difficulties in detecting recovery predictors, where illness chronicity may become the most important factor for poor outcome.[10,17,18]

Given these considerations in mind, the aim of this study was to investigate the 6-month outcome of BID patients following their first manic episode. Rates of syndromic, symptomatic, and functional recoveries were examined as well as treatment adherence and substance abuse co-morbidities.

Methods

Subjects

All consecutive inpatients admitted for their first manic episode of BID were recruited from December 6, 2008 to June 5, 2009 (according to the Persian calendar). Potential subjects were identified by research staff who reviewed the medical records of all new admissions to the psychiatry unit of Noor University Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. Patients were included in this study if they met DSM-IV criteria for a current manic episode.[19] All patients were adult with age range from 18 to 65 years.

They had no prior treatment with anticonvulsants, antidepressants, or antipsychotics. Potential subjects were excluded by diagnosis of any affective episode resulting from unstable medical or neurological disorder or acute substance intoxication or withdrawal, as determined by symptom resolution within 72 hours. Both patients and their legal guardians provided written informed consent after study procedures were fully explained.

This study was approved by the Behavioral Sciences Research Center and review board of Isfahan University of Medical Sciences, Isfahan, Iran.

Baseline Assessments

Demographic information was obtained by interviewing the patients and their legal guardian. BID diagnoses were confirmed using the Mini-International Neuropsychiatric Interview (M.I.N.I.).[20] Using the M.I.N.I., any psychiatric comorbidity except substance related disorders were ruled out. Young Mania Rating Scale (YMRS),[21,22] the 17-item Hamilton Depression Rating Scale (HAM-D),[23,24] and the Scale for the Assessment of Positive Symptoms (SAPS) [25] were performed. Socioeconomic status was ascertained using a 4-rank scale. The highest level of psychosocial functioning during the year prior to manic episode was assessed using Global Assessment of functioning (GAF) [19] and Longitudinal Interval Follow-Up Evaluation-Range Impaired Functioning Tool (LIFE-RIFT).[26] Family history of mood disorders in first degree relatives were questioned from patients and their legal guardian. A trained rater, second author, evaluated all assessments to prevent reliability problems.

Follow Up Assessments

Patients were re-evaluated using YMRS, HAM-D, SAPS, GAF, and LIFE-RIFT monthly from the 1st to the 6th month following discharge from the hospital. Based on DelBello et al work: "For each evaluation an overall rating of symptom severity was made based on the scores of the rating and diagnostic instruments using a 1- to 6-point scale (kappa = 0.92): 6 = full syndrome, severe, meets several DSM-IV criteria more than the minimum required for an affective episode (manic, hypomanic, mixed or major depressive episode); 5 = full syndrome, mild to moderate, meets minimal DSM-IV criteria required for an affective episode; 4 = marked symptoms, does not meet full affective syndrome criteria, but has several DSM-IV affective syndrome criteria scored greater than mild on the HAM-D or YMRS; 3 = partial remission, no DSM-IV affective syndrome criteria are rated greater than mild on the HAM-D or YMRS, but total HAM-D score > 10, YMRS score > 5, or any SAPS global item score > 2; 2 = residual symptoms, one or more mild symptoms, but YMRS score ≤ 5 and HAM-D score ≤ 10, and SAPS global item scores are all ≤ 2; 1 = usual self, no significant symptoms".[27]

Based on ratings, syndromic and symptomatic recovery and syndromic recurrence were picked out, and the percent of months without symptoms (1 or 2), with subsyndromal symptoms (3 or 4), and with a full syndrome (5 or 6) were estimated. Syndromic and symptomatic recoveries were defined a priori by 2 months with a LIFE overall score of ≤ 4 and by 2 months with a LIFE overall score of ≤ 2, respectively. Syndromic recurrence was determined by 1 week (2 weeks for depression) with a LIFE overall score of ≥ 5 any time after syndromic recovery.[10] Functional recovery was elucidated by obtaining a rating resemble or better than premorbid psychosocial functioning in all four of the areas of functioning on the LIFE for at least 2 months.[26] To evaluate functional recovery, the four functional domains (role performance, interpersonal relationships, recreational enjoyment, and sexual activity) were assessed for each during one month period.

Treatment Assessments

As a naturalistic study, the researchers would not change treatment decisions. Therefore, researchers reviewed medications prescribed during each follow-up period with the patients and their primary caregivers. Treatment compliance of medications for every interval period was firmed by reviewing monthly use of drugs with the patients and their primary caregiver separately. Adherence of each drug was described as full adherence (taking drug > 75% of the time as prescribed), non-adherence (taking drug < 25% of the time as prescribed), or partial adherence (taking drug between 25 and 75 percent of the time as prescribed). As an objective ascertainment, serum concentrations of one major mood stabilizers (valproate or lithium) were assessed to validate medication adherence at baseline, the 3rd, and the 6th month of the study.

Substance Abuse

Substance abuse for opioids, methamphetamines, cannabis, and alcohol was assigned by urine sample tests at monthly assessment time.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 15. The cumulative probabilities of syndromic, symptomatic, and functional recovery, as well as syndromic recurrence throughout the 6-month following first manic episode were estimated using the Kaplan-Meier method. The cumulative probabilities of outcomes between adherence/non-adherence, substance abuse/no substance abuse compared using log-rank test at a significance level of $p < 0.05$.

Results

According to inclusion and exclusion crirteria, 16 patients diagnosed with first episode of mania in this study. Among them, 13 patients due for the six-month follow up period, 10 fi-

nalized all visits. Table 1 summarizes the baseline characteristics of recruited patients.

Male/female ratio was 9/4 (69.2% vs. 30.8%). According to the records, 5 patients (38.5%) were employed at the time of admission while 10 (76.9%) of them had been employed during one year before admission time. Of these patients, 5 (38.5%) had positive family history for BID. Three of them (23%) had comorbid opioid dependency. The age of the patients ranged between 18-53 years with the mean age of 26.7 ± 9.9. The mean of education in years was 11.4 ± 3.2 (range: 5 to 16 years). The means of YMRS, HAM-D, SAPS, LIFE-RIFT, and GAF were 32.3 ± 7.2, 10.5 ± 3.4, 11.8 ± 5.1, 14.7 ± 3.7, and 24.2 ± 7.6, respectively.

Adherence to Pharmacological Treatment

During hospitalization, 9 patients (69%) were treated with valproate (range: 600-1400 mg/day) as a sole mood stabilizer, while 2 patients took valproate plus lithium (range: 600-1200 mg/day) and 1 patient took valproate plus oxcarbazepine (300 mg/day). One patient took lithium (900 mg/day), carbamazepine (600 mg/day), and topiramate (150 mg/day) as mood stabilizers. Of total patients 7 (54%) were treated with a typical antipsychotic (perphenazine) and 7 (54%) with an atypical antipsychotic (5 on olanzapine and 2 on risperidone). Three patients (23%) finally received ECT (range: 5-8 sessions) despite pharmacotherapy.

All of the patients had full adherence based on self reports and reports of caregivers at the baseline of the study. Table 2 shows the cross tabulation between the treatment adherence and therapeutic serum levels of valproate or lithium -as main mood stabilizers- at 3 months intervals.

Syndromic Recovery and Recurrence

Eleven (84%) patients had syndromic recovery during the six-month period following initial hospitalization. The Kaplan-Meier estimate of cumulative probability of syndromic recovery was 0.89 (95 %CI: 0.69 to 0.99), with a mean time to syndromic recovery of 2.07 ± 0.43 months, following initial hospitalization. Kaplan-Meier analyses revealed that opioid abuser versus non-opioid abusers had longer time to syndromic recovery (log rank: $\chi^2 = 5.526$, df = 1, p = 0.019). Any patient did not have syndromic recurrence within 6 months following initial hospitalization.

Table 1. Baseline characteristics of the recruited patients

Case No. / Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
Age	21	18	18	20	32	27	28	24	18	23	38	27	53
Gender	M	M	M	F	F	F	M	M	M	M	F	M	M
SES	2	1	3	3	2	3	3	2	2	1	3	1	1
Opioid	+	-	-	-	-	-	+	+	+	-	-	+	-
Cannabis	-	-	-	-	-	-	+	-	-	-	-	+	-
Methamphetamine	-	-	-	-	-	-	+	-	-	-	-	-	-
Alcohol	-	-	-	-	-	-	-	-	-	-	-	+	-
YMRS	33	37	39	44	30	20	35	33	27	22	31	27	42
HAM-D	19	10	10	9	7	6	14	13	11	8	11	11	8
SAPS	10	14	15	13	11	5	17	16	11	0	12	11	19
GAF	25	5	25	15	25	35	25	25	25	35	25	25	25
LIFE-RIFT	18	8	18	20	10	12	19	11	13	15	16	16	15

M: Male; F: Female; SES: Socioeconomic Status; YMRS: Young Mania Rating Scale (range: 0-60); HAM-DL: Hamilton Depression Rating Scale (range: 0-50); SAPS: Scale for the Assessment of Positive Symptoms (range: 0-150); GAF: Global Assessment of Functioning (range: 0-100); LIFE-RIFT: Longitudinal Interval Follow-Up Evaluation-Range Impaired Functioning Tool (0-50).

Table 2. Cross tabulation between the treatment adherence and therapeutic serum levels of valproate or lithium at 3 months intervals

Serum level	Adherence		
	Full	Partial	Missing
First measure:			
Therapeutic	0	0	0
Non-therapeutic	13	0	
Second measure:			
Therapeutic	2	2	2
Non-therapeutic	5	0	
Third measure:			
Therapeutic	2	1	7
Non-therapeutic	3	0	

Therapeutic serum level: valproate ≥ 50 µg/ml or lithium ≥ 1 mEq/L

Symptomatic Recovery

Ten patients (77%) achieved symptomatic recovery. The cumulative probability of symptomatic recovery was 0.75 (95% CI: 0.51 to 0.91), with a mean time of 1.83 ± 0.39 months following initial hospitalization. Patients with therapeutic serum levels of valproate or lithium had greater probability and short time to symptomatic recovery compared with patients with non-therapeutic serum levels (log rank: χ^2 = 11.0, df = 1, p = 0.001). Full adherence (log rank: χ^2 = 1.06, df = 1, p = 0.30), substance abuse (log rank: χ^2 = 1.51, df = 1, p = 0.21), and gender (log rank: χ^2 = 0.03, df = 1, p = 0.86) had no statistically significance probability on symptomatic recovery.

Functional Recovery

Four patients (30%) achieved functional recovery based on GAF while 5 (38%) had functional recovery based on LIFE-RIFT. The cumulative probability of functional recovery was 0.64 (95% CI: 0.36 to 0.92), with mean time of 5.36 ± 0.37 months following initial hospitalization based on GAF. The cumulative probability of functional recovery was 0.55 (95% CI: 0.26 to 0.84), with mean time of 4.9 ± 0.37 months based on LIFE-RIFT. The Kaplan-Meier estimates analysis revealed no statistically significant predictors of functional recovery based on GAF. Patients with full adherence revealed shortened time to functional recovery based on LIFE-RIFT compared with non-adherent patients (log rank: χ^2 = 4.5, df = 1, p = 0.03). Substance abuse also associated with longer time to functional recovery based on LIFE-RIFT (log rank: χ^2 = 4.36, p = 0.037).

Discussion

To our knowledge, this is the first study to assess symptomatic, syndromic, and functional outcomes and evaluate the effect of medication adherence on outcome of bipolar one disorder patients, single manic episode, following initial hospitalization for mania in Iran. In addition to rate adherence based on patient reports, measurement of serum concentrations of valproate and lithium was used as objective method for assessing medication adherence. The other strength of this study was selection of patients in early days of their single manic episodes. Selection of patients after an index episode, not exclusively in their first episode, may result in missing the effects of prior episodes.[13-16]

While most of the current patients experienced syndromic (84%) and symptomatic recovery (77%), only 30% of them got functional recovery. This emphasize on the role of residual mood or cognitive symptoms to delay functional recovery despite symptomatic recovery.[11,28]

Treatment adherence has been considered as one of the most important factors that have strong effects on outcome of BID. Considering functional recovery as the main objective of any treatment interventions, patients with full adherence revealed shortened time to functional recovery compared with non-adherent patients. All of the patients in the present study had full adherence and therapeutic se-

rum levels of valproate or lithium at the first assessment. Regarding 4 patients with therapeutic serum levels at the third month of the follow up, 2 patients reported full adherence while the other 2 had partial adherence. However, 5 patients with self-reported full adherence had non-therapeutic serum levels. At the sixth month, 2 patients with full adherence and 1 with partial adherence had therapeutic serum levels. On the other hand 3 patients with full adherence did not have therapeutic serum levels. Consistent with finding of other studies, it was concluded that rate of non-adherence continuously rise up after first hospitalization which is accompanied by lowered therapeutic serum levels.[29] In addition, the more far from hospitalization, the more mismatch between subjective self-reported adherence rate and subjective therapeutic serum levels. This indicates insufficiency of treatment adherence self reports and importance of serum measures as a valid indicator for adherence.[27]

Conclusions

The present results revealed that substance abuse was associated with longer time to syndromic and functional recovery but not symptomatic recovery. This finding is consistent with other similar studies.[30,31] Given the importance of functional recovery, discussing BID patients about defeating effects of substance abuse on illness outcome would be considered as a major part of treatment plan.[32]

This study had serious limitations. Further studies with larger samples and longer follow-up duration are needed for strengthening these results. Assessing family history based on patients and guardian reports might have low validity. As a naturalistic study, competence of serum levels could not be correlated with desirable outcome. Because different responses may be the result of different types of treatment regimen not difference in serum levels. We also had great missing rates which may be related to the nature of BID with poor insight and anosognosia of the patients. Also the effect of non-pharmacological interventions on the output was not evaluated.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MB developed and wrote the protocol. He also supervised the data gathering, data analysis, and interpretation of results. RK was responsible for patients follow up, assessments, data gathering, and documentation. MRM was responsible for the data analysis and interpretation. He also prepared the manuscript. All authors have read and approved the content of the manuscript.

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