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Psycho- pharmacological therapy in diabetic foot: evidence supporting early institution.

KEYWORDS: Depression; Anxiety; Quality of Life; Diabetic foot; Psycho- pharmacotherapy

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ABSTRACT

Background: Benefits of counseling and psycho- pharmacotherapy on depression and anxiety in patients of diabetic foot were studied.

Methods: Hospital anxiety and depression (HAD) scores and quality of life enjoyment and satisfaction (QoL-ES) scores were calculated in 50 hospitalized patients of diabetic foot at baseline and after 6 weeks of psycho- pharmacotherapy. Time to glycaemic control, dietary and medication compliance were assessed.

Results: At baseline, 24(48%) patients had severe and 20(40%) patients had moderate depression. Mean depression and anxiety scores decreased [14.26±2.38 (95%CI 13.58-14.93) v/s 8.86±2.52 (95%CI 8.14-9.57);p<0.0000001, 12.64±3.37 (95%CI 11.67-13.6) v/s 7.68±2.64 (95%CI 6.92 - 8.43);p<0.0000001] and QoL-ES scores increased significantly over 6 weeks [38.92±5.52 (95% CI37.34-40.49) v/s 47.76±6.75 (95%CI 45.84-49.67);p<0.0000001]. Decrease in depression correlated with increase in QoL (p=0.0417). 94% were compliant to medications and 78% to diet.

Conclusion: Depression and anxiety are common in diabetic foot patients, and their treatment improves quality of life and glycemic control.

1. Introduction

Diabetes is one of the largest global health care concerns, in terms of prevalence, cost, and subsequent morbidity and mortality for patients living with the illness. India has the largest numbers [1, 2] with Maharashtra showing the highest prevalence [3]. Indians are also more prone to develop complications of diabetes at an earlier age [4]. Diabetic foot ulcers (DFU) have an estimated prevalence of 25% [5], with a high morbidity due to their poor healing rates, high recurrence and amputation rates [6- 8]. Diabetes is a significant risk factor for the development of psychiatric problems in all age groups with major depression seen in up to 28% of diabetics [9, 10], which interferes with adequate self-treatment and glycaemic control [11-13]. Treatment with psycho and /or pharmacotherapy has shown to improve both depression and glycaemic control [14- 16], however, the symptoms of depression are missed in a majority of diabetics, thus remaining untreated. Studies also repeatedly have found that the course of depression is more severe in those with diabetes, with high relapse rates following initial episodes and a protracted period of recovery, further justifying its early and sustained treatment [17, 18]. We studied the prevalence of depression and anxiety among in-patients of diabetic foot and the benefit that psycho-pharmacotherapy produces in them, and its subsequent effect on the compliance to medication, glycaemic control and overall quality of life of patients

2. Material and methods

This was a pre- post quasi- experimental study done on 50 consecutive patients of diabetic foot admitted in our hospital, a tertiary level government health care centre. This study was done in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards, after approval from the Institutional Ethics Committee and with informed consent of all the patients involved.

2.1 Sample size

50 consecutive patients admitted with a diabetic foot were included in the study. A purposive method of sampling was used.

2.2 Inclusion criteria

1. Patients with a diabetic foot
2. Patient hospitalized for the treatment of diabetic foot
3. Patients having uncontrolled blood glucose levels, defined by a random blood glucose level (RBG) of >200mg/dL and confirmed by a fasting blood glucose (FBG) level of >126mg/dL [19].

2.3 Exclusion criteria

Patients with any known psychiatric illnesses.

2.4 Study design

All hospitalized patients of diabetic foot were screened at admission by excluding the presence of a known psychiatric illness and by performing a RBG level on a venous blood sample, after taking informed consent. Those patients with an RBG of >200mg/dL were subjected to a FBG test the next morning. Those patients with a FBG >126mg/dL were included into the study. Details of the disease course were recorded. All patients received standard treatment for DFU and glycaemic control. All patients were interviewed by a qualified psychiatrist, wherein they were administered the Hospital anxiety and Depression (HAD) questionnaire [20] and the Quality of Life Enjoyment and Satisfaction Questionnaire (QoL-ES) [21] within 24 hours of admission. The baseline HAD and Quality of Life scores for all the patients were calculated from these questionnaires. All patients received counseling from a trained counselor, once a week, in addition to standard care for diabetic foot. Pharmacotherapy was prescribed for patients with either severe anxiety or depression, who were identified from their HAD scores (0-7 Normal; 8-10 Mild; 11-14 Moderate; 15-21 Severe) [20]. Escitalopram 10mg once a day, was started orally as a starting dose, which was then increased to 20mg once a day if necessary, after one week of treatment. All psycho-pharmacological drug therapy were initiated and modified by a qualified psychiatrist. FBGs of patients were reassessed daily till target FBG levels between 70- 130mg/dL were reached, beyond which they were reassessed weekly for glycemic control and medication compliance. Counseling and medication was continued for 6 weeks. At 6 weeks, the HAD and QoL-ES questionnaires were re-administered, and a venous blood sample was sent for HbA1c levels.

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2.5 Primary end- points

1. Baseline hospital anxiety (HAD_{A-0}) scores of patients admitted with a diabetic foot.
2. Baseline hospital depression (HAD_{D-0}) scores of patients admitted with a diabetic foot.
3. Baseline quality of life ($QoL\text{-}ES_0$) scores of patients admitted with a diabetic foot.
4. Anxiety scores at 6 weeks (HAD_{A-6}).
5. Depression scores at 6 weeks (HAD_{D-6}).
6. Quality of life scores at 6 weeks ($QoL\text{-}ES_6$).
7. Percentage decrease in HAD_D scores over 6 weeks (HAD_{Dd}).
8. Percentage decrease in HAD_A scores over 6 weeks (HAD_{Ad}).
9. Percentage increase in QoL-ES scores over 6 weeks ($QoL\text{-}ES_I$).
10. Correlation between HAD_{Dd}, HAD_{Ad} and $QoL\text{-}ES_I$.

2.6 Secondary end- points

1. To identify the demographic, social and treatment variables that affect magnitude of decrease in depression (HAD_{Dd}).

2. To identify the demographic, social and treatment variables that affect magnitude of decrease in anxiety (HAD_{Ad}).

3. To identify the demographic, social and treatment variables that affect magnitude of increase in quality of life ($QoL\text{-}ES_I$).

Factors that were analyzed are:
i. Age
ii. Sex
iii. Amputation status
iv. Adequacy of pain control
v. Duration of complaints
vi. Previous hospital admissions for similar complaints
vii. Employment status
viii. Duration of unemployment
ix. Level of education
x. Addictions
xi. Sleep disturbances.

4. Time taken to achieve glycemic control. Glycemic control was said to be achieved when the patients had an FBG between 70 and 130mg/dL and HbA1c level below 7%, 6 weeks after initiation of therapy. In patients who achieved glycemic control, time to glycemic control was taken as the number of days from the initiation of therapy to the first time target FBG between 70- 130mg/dL was achieved.

5. Medication compliance. Patients were considered to be compliant to their medications if they took more than 80% of their medications over the course of 6 weeks [22].

6. Dietary compliance. Patients were considered to be compliant to their diet if they adhered to their dietary regimen for more than 80% of the time over a period of 6 weeks [22].

2.7 Statistical analysis

All statistical analysis was done on the NCSS-11 data analysis software. Normality of the data was assessed by applying a Kolmogorov- Smirnov test. HAD and QOL scores at 6 weeks were compared to their corresponding baseline scores by a Mann-Whitney U/ Wilcoxon rank sum test. A multiple linear regression was performed to assess the correlation between decrease in HAD scores and increase in QoL-ES scores and to identify the variables affecting HAD_{Dd}, HAD_{Ad} and $QoL\text{-}ES_I$. The Mann Whitney U/ Wilcoxon rank sum test was also used to compare time taken to achieve glycemic control between patients receiving insulin and those receiving only OHAs.

2.8 Ethical approval and consent

This study was conducted at Seth G.S. Medical College and K.E.M. Hospital, Mumbai. It was approved by the Institutional Ethics Committee of the same institute. Written consent was obtained from all the participants in the study in a language of their comprehension.

3. Results

3.1 Depression scores [*Fig 1*]

Mean baseline hospital depression scores (HAD_{D-0}) in the study patients were 14.26 ± 2.38 (95% CI 13.58 - 14.93) which decreased to 8.86 ± 2.52 (95% CI 8.14 - 9.57) (HAD_{D-6}) after 6 weeks; $p < 0.0000001$.

All 50 (100%) patients suffered from some degree of depression at baseline, of which 24 (48%) had severe and 20 (40%) had moderate depression. After 6 weeks, 35 (70%) patients suffered from some degree of depression, of which 1 (2%) had severe and 12 (24%) had moderate depression.

3.2 Anxiety scores

Mean baseline hospital anxiety scores (HAD_{A-0}) in the study patients were 12.64 ± 3.37 (95% CI 11.67 - 13.6) which decreased to 7.68 ± 2.64 (95% CI 6.92 - 8.43) (HAD_{A-6}) after 6 weeks; $p < 0.0000001$.

44 (88%) patients suffered from some degree of anxiety at baseline, of which 19 (38%) suffered from severe and 18 (36%) from moderate anxiety. After 6 weeks, 28 (56%) patients suffered from some degree of anxiety, of which 1 (2%) suffered from severe and 3 (6%) from moderate anxiety.

3.3 Quality of life scores [*Fig 2*]

The QoL-ES questionnaire had a possible highest score of 80. At baseline, the mean $QoL\text{-}ES_0$ score of the patients was 38.92 ± 5.52 (95% CI 37.34 - 40.49). After 6 weeks, the mean score improved to 47.76 ± 6.75 (95% CI 45.84 - 49.67) ($QoL\text{-}ES_6$). This increase in the QOL score was statistically significant ($p < 0.0000001$).

3.4 Correlation between HAD reduction and QoL increase [*Fig 3*]

The mean percentage decrease in the HAD_D scores over 6 weeks was 36.85 ± 18.09% (95% CI 31.84 - 41.87%) (HAD_{Dd}).

The mean percentage decrease in the anxiety scores over 6 weeks was 37.76 ± 20.126% (95% CI 32.18 - 43.34%) (HAD_{Ad}).

The mean percentage increase in QoL-ES scores over 6 weeks was 24.5 ± 21.75 % (95% CI 18.47 - 30.53%) ($QoL\text{-}ES_I$).

A multiple regression analysis comparing HAD_{Ad} and HAD_{Dd} against $QoL\text{-}ES_I$ showed a linear correlation between HAD_{Dd} and $QoL\text{-}ES_I$ (regression coefficient = 0.374; p=0.0417).

3.5 Factors affecting decrease in depression levels [*Table 1*]

A multiple regression was done for all demographic, social and treatment variables that could possibly affect the increase in quality of life. Independent variables mentioned in section 2.6 were analyzed for their effect on HAD_{Dd} by performing a multiple regression analysis. Regression analysis had an R^2 of 18.56% and an average absolute percentage error of 51.16%. Only the presence of sleep disturbances at baseline correlated independently with the magnitude of HAD_{Dd}. Patients with irregular sleep at baseline (regression coefficient = 18.35; p = 0.0182) correlated with a greater decrease in depression levels.

An analysis for co- variance showed no correlation between any of the independent variables.

3.6 Factors affecting decrease in anxiety levels [*Table 2*]

A multiple regression was done for all demographic, social and treatment variables that could possibly affect the increase in quality of life. Independent variables mentioned above were analyzed for their effect on HAD_{Ad} by performing a multiple regression analysis. The regression performed had an R^2 of 29.18% and an average absolute percentage error of 41.678%. Employment status and sleep disturbances at baseline correlated independently with the

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magnitude of HAD_{Ad}. Patients who were unemployed at baseline (regression coefficient =-25.27; p = 0.0049) and those who had sleep disturbances at baseline (regression coefficient = 19.43; p = 0.0160) showed a greater decrease in anxiety levels.

3.7 Factors affecting increase in quality of life

A multiple regression was done for all demographic, social and treatment variables that could possibly affect the increase in quality of life. Independent variables mentioned in section 2.6 were analyzed for their effect on $QoL\text{-}ES_I$ by performing a multiple regression analysis. The regression performed had an R^2 of 18.82% and an average absolute percentage error of 139.73%. None of the above mentioned variables correlated independently with the magnitude of $QoL\text{-}ES_I$.

3.8 Measures of glycaemic control

All 50 patients achieved glycemic control by the end of 6 weeks. The mean duration taken to achieve glycemic control was 10.58 ± 5.29 days (95% CI 9.11 – 12.04 days).

47 (94%) patients were compliant with their medications whereas 39 (78%) patients were compliant with their dietary regimens.

42 (84%) patients received subcutaneous insulin injections with or without oral hypoglycemics (OHA), whereas 8 (16%) patients were on OHAs only.

The mean time to achieve glucose control in patients receiving insulin was significantly shorter than patients receiving only OHAs [9.87 ± 5.33 days (95% CI 8.24 – 11.47 days) v/s 14.37 ± 6.29 days (95% CI 10.01 – 18.73) days; p = 0.0249 as calculated by the non-inferiority test using the Mann-Whitney U or Wilcoxon Rank-Sum Test]. 32 (76.19%) of the 42 patients were compliant with their medications as opposed to 8 (100%) of 8 patients only on OHAs, however, this difference was not statistically significant (two- tailed p value = 0.1432, calculated using Mid- P exact test).

4. Discussion

Diabetes is one of the largest global health care concerns ,in terms of prevalence, cost, and subsequent morbidity and mortality for patients living with the illness .India has about 41 million individuals who are currently diagnosed with diabetes [1, 2] compared to 30.3 million in the United States [23, 24]. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, [23, 24] with the highest prevalence in the state of Maharashtra (9.2 million) [3].

Indians are also more prone to develop complications of diabetes at an earlier age (20-40 years) compared with Caucasians (>50 years) [4]. Diabetic foot ulcers (DFU) have an estimated prevalence of 25% among diabetics [5], with a high morbidity due to their poor healing rates, high recurrence and amputation rates [6- 8]. Therefore, keeping blood glucose (BG) levels as close to normal with medication, diet and exercise is essential [4]. Poor glycaemic control has been documented across the Indian diabetic population [25] accounting for micro- and macrovascular changes that predispose diabetic patients to complications such as diabetic myonecrosis [26] and muscle infarction [27]. Even in the Diabetes Control and Complications Trial (DCCT), where a multidisciplinary team provided consistent supervision and support, only 5% of patients were able to maintain normal BG levels [28]. Diabetics need to have a high and sustained degree of motivation and diligence to control their diabetes through life which places a stressful demand from a psychobehavioral perspective [28]. The added complications and financial burden further affect the quality of life QOL and mental well- being of patients [29- 37/39]. Diabetes is a significant risk factor for the development or aggravation of psychiatric problems in all age groups with major depression seen in upto 28% of diabetics [9, 10], which interferes with adequate self-treatment and glycemic control [11- 13]. In fact a strong association between hyperglycemia and depression was confirmed in a recent meta-analysis [40], and there already exists a documented higher prevalence rate of depression in people with diabetes compared with the general population [17, 40]. The prevalence of depression is even higher in patients with complications of diabetes [41].

All 50 (100%) of our in- patients suffered from some degree of depression at admission. Studies repeatedly have found that the course of depression is also more severe in diabetes, with high relapse rates following initial episodes and a protracted period of recovery, further justifying its early and sustained treatment [17, 18]. In our patients, 24 (48%) had severe and 20 (40%) had moderate depression. Anxiety disorders have also found to be more prevalent in Diabetics and are also associated with poor metabolic control [13]. In fact, one study found equal rates of symptoms of anxiety and depression in adult diabetics [13]. In our study, 44 (88%) patients suffered from some degree of anxiety at baseline, of which 19 (38%) suffered from severe and 18 (36%) from moderate anxiety.

As many as 2 out of 3 cases of depression in diabetics remain undetected, primarily because many symptoms of depression (e.g., fatigue) often overlap with those of diabetes [18] leading to a vicious cycle of poor medication compliance, disease progression and disease complications [11- 13, 17] further impeding adequate treatment of the disease. Symptoms like reduced energy and motivation have a definite negative impact on self-treatment and the presence of chronic hyperglycemia and the threat of its complications easily lead to feelings of helplessness, self-blame, and hopelessness thus creating a loop effect [42, 43]. Our findings suggest that almost all patients of diabetic foot suffer from either depression, or anxiety, hence we advocate mental health evaluation and psychopharmacotherapy as part of the management protocol for Dfs.

In addition to its association with poorer self-management and metabolic control, depression also strongly correlates with other negative outcomes, including complications and decreased QoL [40, 44]. Psychopathology and psychological distress are individual characteristics that seem to play a critical role in diabetes management control and psycho- behavioral interventions such as coping skills, behavioral therapies (BT) and cognitive BT offer an effective treatment modality for depression in adults with diabetes [42, 43, 45-47]. Regardless of causal link, treatment with either psycho and/or pharmacotherapy has shown to improve symptoms of both, depression and anxiety, and diabetes control [14- 16].

In our study, a total of 33 (66%) patients had either severe anxiety, depression, or both, and hence received pharmacotherapy along with counseling. The remaining 17 (34%) patients received only counseling. After 6 weeks of therapy, there was a significant reduction in the levels of anxiety and depression in all 50 patients. The percentage reduction in levels of depression had a linear correlation with an increase in QoL, however, the decrease in anxiety levels did not correlate with the increase in QoL. The highest reduction in depression levels was seen in patients who had irregular sleep at baseline, whereas the reduction in anxiety levels was more in patients who were unemployed and had sleep disturbances at baseline. These findings probably reflect on the subset of patients who benefitted most from the psycho- therapeutic intervention and indicate that inadequate or irregular sleep may be an important cause- effect phenomena for depression and anxiety.

The results of the Diabetes Control and Complications Trial showed that only 5% of patients were compliant with their medications in spite of regular supervision [28]. In an analysis of 11 retrospective studies between 1966 and 2003, adherence to treatment ranged from 36% to 93% in patients taking OHAs as compared to approximately 62% in those taking insulin [48]. Lowest compliance was seen in patients taking insulin plus an OHA (39%) [49]. Our results show that 47 (94%) patients were compliant with their medications whereas 39 (78%) patients were compliant with their dietary regimens, which

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resulted in a majority of patients achieving glycaemic control within 9 to 12 days of starting their medications. This could be attributed to the counseling and psycho- pharmacotherapy that the patients received during their 6 weeks in the study, which have not found mention in the other studies [48, 49], however long term follow up is necessary. We also observed that patients who received insulin achieved glycaemic control significantly faster as compared to those who did not, however, the medication compliance of patients receiving insulin was lower than those only on OHAs, though not significant.

Conclusion

A majority of patients with diabetic foot have moderate to severe depression and anxiety. The intertwined association of depression and diabetes leads to a concatenation of events leading to escalation of both entities, where care of either in isolation from the other would be self defeating. Early detection and intervention for depression leads to improved quality of life, glycaemic control and treatment compliance amongst patients.

Table 1: Multiple regression to assess factors affecting decrease in depression.

Independent Variable	Regression coefficient b(i)	Standard Error Sb(i)	Standardized Coefficient	T-Statistic to test H0: β(i)=0	Probability level	Reject H0 at 5% ?	Power of test at 5%
Intercept	33.38367	18.0519	0.0000	1.849	0.0722	No	0.4375
Age	0.0010	0.3211654	0.0414	0.251	0.8030	No	0.0569
Sex	3.921795	3.80181	0.1966	1.032	0.3088	No	0.1715
Education	-1.827718	3.140704	-0.1013	-0.582	0.5640	No	0.0876
Employment status	-0.751387	4.07266	-0.0419	-0.184	0.8546	No	0.0537
Duration of unemployment	0.007165541	0.0518911	0.0296	0.138	0.8909	No	0.0521
Duration of complaints	0.06405681	0.1104588	0.1002	0.580	0.5654	No	0.0874
Amputation	-1.675029	2.939529	-0.0929	-0.570	0.5721	No	0.0860
Adequacy of pain control	0.7868708	3.782713	0.0351	0.208	0.8363	No	0.0547
Previous hospital admissions	2.753316	2.8338	0.1532	0.972	0.3374	No	0.1574
Addictions	-1.299115	3.038818	-0.0723	-0.428	0.6714	No	0.0701
Sleep disturbances	9.176946	3.716605	0.4099	2.469	0.0182[+]	Yes	0.6724

[+] Statistically significant value: The above regression co- efficients t-tests shows the decrease in depression levels to correlate with only presence of sleep disturbances, with patients having irregular sleep at baseline correlating with a greater decrease in depression levels.

Table 2: Multiple regression to assess factors affecting decrease in anxiety.

Independent Variable	Regression coefficient b(i)	Standard Error Sb(i)	Standardized Coefficient	T-Statistic to test H0:β(i)=0	Probability level	Reject H0 at 5% ?	Power of test at 5%
Intercept	8.034348	20.69895	0.0000	0.388	0.7001	No	0.0666
Age	0.5410572	0.333165	0.2495	1.624	0.1126	No	0.3533
Sex	11.9493	7.887712	0.2693	1.515	0.1381	No	0.3148
Education	0.08834971	6.516098	0.0022	0.014	0.9893	No	0.0500
Employment status	-25.27484	8.449653	-0.6338	-2.991	0.0049[+]	Yes	0.8302
Duration of unemployment	-0.06858224	0.0538299	-0.2543	-1.274	0.2104	No	0.2371
Duration of complaints	0.01492277	0.1145859	0.0210	0.130	0.8971	No	0.0518
Amputation	7.626925	6.098715	0.1900	1.251	0.2187	No	0.2301
Adequacy of pain control	2.24799	2.24799	0.0451	0.286	0.7761	No	0.0590
Previous hospital admissions	-3.479732	5.879358	-0.0870	-0.592	0.5575	No	0.0889
Addictions	-5.645281	6.304713	-0.1412	-0.895	0.3762	No	0.1408
Sleep disturbances	19.43625	7.710936	0.3902	2.521	0.0160[#]	Yes	0.6902

[+] Statistically significant value: The above regression co- efficients t-tests shows the decrease in anxiety levels to correlate with employment status, with patients who were unemployed at baseline correlating with a greater decrease in anxiety levels.

[#] Statistically significant value: Patients having irregular sleep at baseline correlate with a greater decrease in anxiety levels.

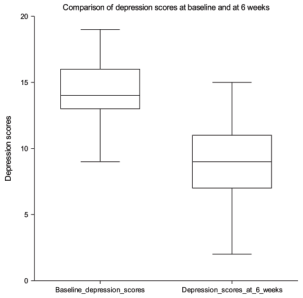

Fig 1: Comparison of depression scores at baseline and at 6 weeks.

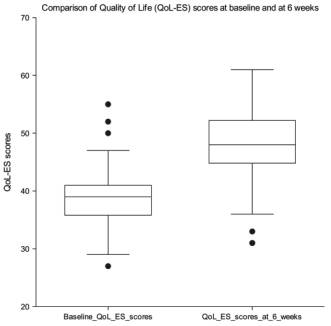

Fig 2: Comparison of quality of life scores at baseline and at 6 weeks.

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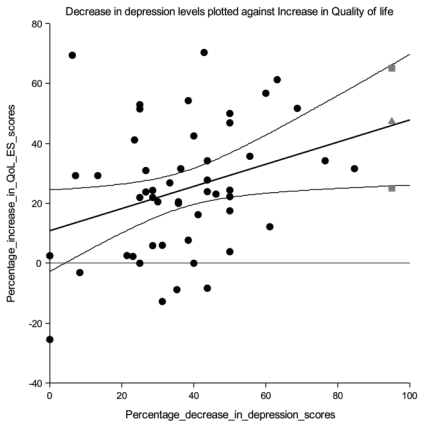

Fig 3: Decrease in depression levels plotted against increase in quality of life.

- ● - Data points of scatter plot
- ▲ - Regression line
- ■ - Confidence limits

Ave Abs Pct Error- Average Absolute Percentage Error

Regression summary

R^2	9.5%
Adjusted R^2	5.65%
Mean Square Error	446.5785
Square Root of MSE	21.1324
Ave Abs Pct Error	128.312

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