Descriptive prospective study of therapeutic response trajectories in a cohort of patients with major depressive disorder

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ABSTRACT

Introduction: *Major depressive disorder (MDD) is a public health problem due to its high prevalence and biopsychosocial consequences. It is a clinically heterogeneous and complex disorder with a fluctuating course. In Chile, there are no studies on clinical trajectories in MDD.* ***Objective:*** *To describe the clinical response trajectories in patients with MDD under treatment in primary care centers (PCC) in Chile.* ***Method:*** *We conducted a prospective cohort study with a five-month follow-up, including patients treated in the Explicit Guarantees in Healthcare program for depression at seven PCC in the Valparaíso Region, Chile. We carried out four evaluations (weeks 0, 4, 12 and 20) to describe various clinical and sociodemographic variables related to the therapeutic evolution. We elaborated response trajectories in relation to the course of depressive symptoms.* ***Results:*** *159 participants were included (93% women), with an average age of 43 years old. The most frequently reported risk conditions for MDD were social isolation or poor support network and having witnessed domestic violence during childhood. Twelve response trajectories were obtained from a total of 16 possible patterns. Differences were observed when analyzing the therapeutic responses between weeks 0 and 12 and 0 and 20. The most frequent trajectories were the maintenance or worsening of depressive symptoms (37.7%).* ***Conclusions:*** *The results show a symptomatic variability during the course of MDD. In this five-month follow-up, more than a third of the participants did not improve their depressive symptoms.*

Keywords: *depression, mental health, primary health care.*

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INTRODUCTION

Major depressive disorder (MDD) is a highly relevant public health issue in Chile and the world. The World Health Organization estimates that 322 million people around the world live with MDD. In Chile there are currently about 840,000 cases[1], and it is the second specific cause of disability-adjusted life years and healthy life years lost in our country[2], reaching a lifetime prevalence of 9%[3]. MDD is a disorder with multiple causes, clinically heterogeneous and complex, which has a great sociocultural influence[4]. Its treatment can have several outcomes, for which possible categorizations arise, including reduction and remission of symptoms of depression or, on the other hand, it is possible that the treatment does not achieve the desired results. This means patients might not respond, might relapse or could even experience an increase in symptoms[5,6]. However, not all patients can be described by these established classifications.

The study of therapeutic response trajectories can be carried out from a descriptive and/or statistical approach, through latent class analysis or cluster analysis, among others[7,8]. This allows us to establish the ratio of people who experience an early, late or poor response and how certain factors may affect the course of treatment[9-11]. Uher et al[12] evaluated individual response trajectories in subjects who received escitalopram or nortriptyline for twelve weeks, obtaining nine latent response types, which allowed them to draw a distinction between patients with different timing towards responses. Likewise, one study reported gradual remissions[8] and another a rapid response[13].

Efforts have also been made to establish predictive models based on therapeutic response trajectories. Along this line, Henkel et al[14] pointed out that the decrease in the severity of MDD can be a predictor of early improvement during the first two weeks, since more than a third of all patients who did not show improvement in this period had no response in the subsequent course of treatment. Other factors studied the relation to the course of depression have been the use of drugs, psychotherapy[15], duration of treatment, age range, gender and social support network[16], thus being able to qualify the evolution of the therapeutic response and identify patients who need other alternatives in their treatment.

Although in Chile there are factors linked to the clinical course of MDD[17], no response trajectories have been described in these patients. Therefore, the objective of this study is to describe the response trajectories in patients with MDD undergoing treatment in primary care centers in Chile.

METHODOLOGY

Design

A prospective study with a five months follow-up was carried out, it analyzed various clinical and sociodemographic variables related to the therapeutic evolution of a cohort of patients admitted to treatment for MDD in primary health care, between April and October 2012.

Sample

All patients who were admitted to the Explicit Health Guarantees (GES) program of seven Family Health Care Centers of Viña del Mar-Quillota, Chile, aged 18 or over, who had not received antidepressants in the previous three months, and who wanted to participate in the study, were included.

Procedures

The study was approved by the Human Beings Research Ethics Committee of the School of Medicine, (e-mail: varinialeiva@udec.cl) of Universidad de Chile. All participants signed an informed consent at their corresponding health centers. Four clinical evaluation telephone interviews were conducted, the first one at the beginning of the study, and the rest for follow-ups.

● **Evaluation 1 (admission to the study – week 0):** the MINI International Neuropsychiatric Interview 5.0[18] was applied to assess the presence of MDD and the existence of psychiatric comorbidity. The Beck Depression Inventory I (BDI-I)[19] was

applied to define the severity of symptoms of depression.

- **Evaluation 2 (week 4):** the sociodemographic and clinical data survey was applied.
- **Evaluation 3 (week 12):** the BDI-I was applied to evaluate the clinical response to the treatment received. The therapeutic follow-up survey was applied.
- **Evaluation 4 (week 20):** the instruments the same instruments of week 12 were applied.

Instruments

(MINI International Neuropsychiatric Interview, MINI)[18]. It is a brief structured interview based on the DSM criteria, which allows the standardization of psychiatric diagnoses. It is divided into modules that are identified by letters that correspond to a diagnostic category. At the beginning of each module there are screening questions corresponding to the main symptoms for the diagnosis of a specific pathology. All questions must be answered with "Yes" or "No". In this study, the following modules were assessed: (A) Major depressive episode (with melancholic symptoms), (C) Suicide risk, (D) Manic/hypomanic episode, (E) panic disorder, (F) Agoraphobia, (J) Alcohol abuse and dependence, (K) Substance (non-alcohol) dependence and abuse, (O) Generalized anxiety disorders, and (S) Social anxiety disorder.

(Beck Depression Inventory-I, BDI-I)[19]. It is an instrument of 21 self-administered questions, each one has four phrases that establish the level of symptoms of depression, thus classifying the level of depression as mild, moderate or severe. Each answer is scored between 0 and 3 points. Scores: 0-9 "absent depression", 10-16 "mild depression", 17-29 "moderate depression" and 30-63 "severe depression". The Spanish validated version[20] was used.

Sociodemographic and clinical data survey

Questionnaire prepared by the authors of this research to assess the presence of possible clinical and social risk factors for the disease, which includes variables such as age, gender, presence of significant other, children, roommates, place of

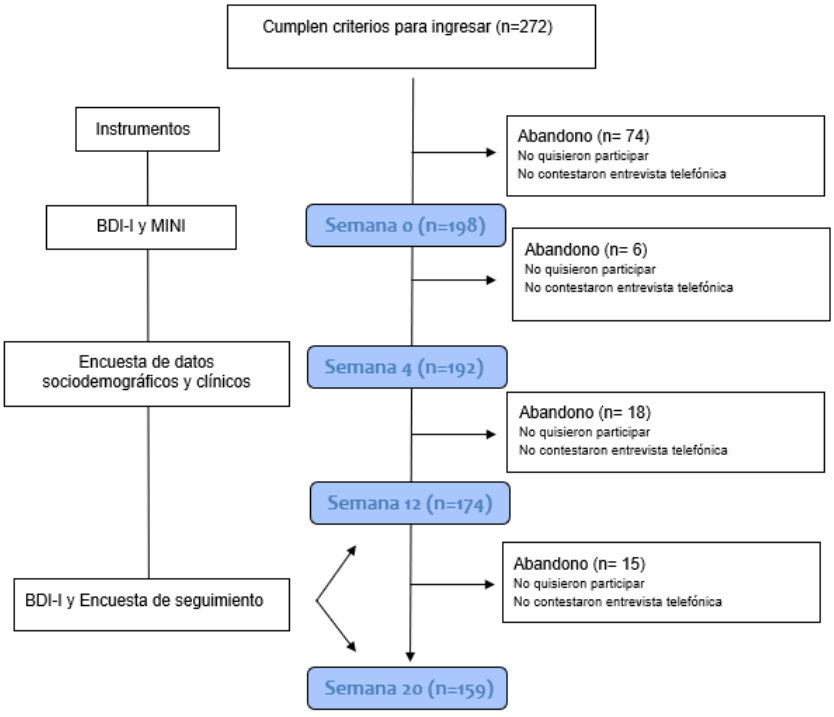

Figure 1. Participant Inclusion Flowchart

residence, schooling, current job, participation in social groups, membership in a church, geographic and economical accessibility to primary care health center, support networks, history related to depressive episodes and suicide, history of parental abandonment, death of primary caregivers, intrafamily violence, physical and/or emotional abuse, child sexual abuse, separation of parents, death of significant relatives, and labor conflicts.

Therapeutic follow-up survey
Questionnaire prepared by the authors of this research that considers the characterization of therapy, pharmacological adherence, and user satisfaction.

Analysis
For the sociodemographic descriptive analysis, means (standard deviation) and proportions were used. Fisher's exact test or Pearson's chi-square test was applied to compare qualitative variables. The student's t-test was used for quantitative variables. A statistical significance level of 5% was used. Data were analyzed using Stata 16 statistical software (Texas, Stata Corp).

Definition of response trajectories
To describe the trajectories, the following severity categories of the BDI-I were used: "absent symptoms of depression", "mild", "moderate" and "severe", which correspond to levels "0", "I", "II" and "III", accordingly. Then, in order to evaluate the patterns of change in therapeutic response, the levels of each patient between weeks 0 and 12 and between weeks 12 and 20 were compared. The combination of the four levels of response and the two follow-ups (weeks 12 and 20) enabled 16 possible response trajectories. These are grouped into four possible categories of the response trajectory **(Table 1)**.

It should be noted that the 0-0 trajectory, which shows participants without symptoms of depression at both week 12 (patients showing remission) and week 20, is seen only through the second measurement (weeks 12-20).

RESULTS

The sample included 159 participants, with an average age of 43.3 ± 13.5 (range 19 to 78 years old). 93% (n=148) of the participants were women. Regarding employment, 47.8% of the sample had a job (n=76), including occasional, stable jobs (more than 6 months) and housework. 13.2% (n=21) reported participating in meetings or activities in neighborhood council, mothers' centers, a church, sports, recreational, and/or cultural groups. The

Table 1. Definition of the possible trajectories between two evaluations.

Possible Trajectories (weeks 0-12 – weeks 12-20)	Interpretation	Response Trajectory Category
0-I; 0-II; 0-III; I-II; I-III; II-III	symptoms worsen	1
I-I; II-II; III-III	Symptoms remain the same	2
I-I; II-II; III-III	Symptoms improve	3
III-0; II-0; I-0	Symptoms remission	4

initial BDI-I average was 29.2 ± 9.4 points. To assess potential biases, the group that completed follow-up was compared with those that dropped out, without finding significant differences in age (p=0.202), employment (p=0.345), social participation (p=0.420) or baseline score. of BDI-I (p=0.093).

Regarding the risk factors for depression, the average was 2.6 ± 1.7 risk factors; the ratio for each factor can be seen in **Table 2**. The mean years of studies was 11.2 ± 3.4 years. The sociodemographic variables are detailed in **Table 2**.

Therapeutic response between weeks 0 and 12

According to the symptomatic variation between week 0 and week 12, 48.4% (n=77) maintained symptomatic severity, 33.3% (n=53) presented improvement, 9.4% (n=15) showed signs of remission (ie, presented a BDI-I ≤ 9) and 8.8% (n=14) worsened. The patients who did not have a clinical response to treatment, that is, those

Table 2. Participants Sociodemographic characteristics.

Variables		n	Average or ratio
Presence of a significant other		141	(88,7%)
*Nº of Children		2 (2)	
Place of residence	Urban	148	(93,1%)
	Rural	11	(6,9%)
	Social isolation or lack of support network	105	(66%)
	Having witnessed domestic violence in childhood	80	(50.3%)
	Death or illness of a significant family member in the last year	61	(38.4%)
	Physical abuse, sexual abuse, or both, during childhood	59	(37.1%)
	Job loss or severe conflict in the last year	47	(29.6%)
	Separation from parents before 11 years old	44	(27.8%)
	Death of the father or being abandoned by him before the age of 11	40	(25.2%)
	Parents separating in the year prior to MDD diagnosis	32	(20.1%)
	Death of the mother or being abandoned by her before the age of 11	27	(17%)
	Being separated from parents before 11 years old	22	(13.8%)

*Value expressed as median (interquartile range).

**The total number of risk factors exceeds 100%, since each participant could have been exposed to more than one.

who maintained or worsened their symptoms, corresponded to 57.2% (n=91).

Therapeutic response between weeks 12 and 20
46.5% (n=74) maintained symptomatic severity, 20.1% (n=32) presented improvement, 6.9% (n=11) showed signs of remission and 19.5% (n=31) worsened. In addition, 6.9% (n=11) of the participants did not present symptoms of depression at both week 12 and week 20 . Patients who did not have a clinical response to treatment, that is, those who maintained or worsened their symptoms, corresponded to 66% (n=105).

Therapeutic response between weeks 0 and 20
If week 0 and week 20 are compared, 43.4% (n=69) of the sample continued with severe symptoms, 33.3% (n=53) showed improvement, 9.4% (n=15) worsened and 13.8% (n=22) showed signs of remission. The total number of individuals who did not respond to treatment corresponded to 52.8% (n=84).

Response trajectories
12 out of 16 possible trajectory patterns were obtained **(Figure 2)**. Graph 4 shows the most frequent ones, with 29.6% (n=47) of the participants, who did not show variations in symptomatic severity during the weeks reviewed.

Participants who still had or worsened their symptoms of depression; meaning, those who did not have a clinical response to treatment, corresponded to 37.7% (n=60) of the total (graphs 1, 2 and 4).

Participants who improved their symptoms and/or showed signs of remission displayed greater variability regarding symptomatic evolution. Graph 9 shows a symptomatic decrease in both week 12 and week 20, unlike what can be seen with participants shown in graphs 7 and 8. On the other hand, graph 6 shows a pattern of four participants, who in the first evaluation presented severe symptoms of depression, in week 12 had a

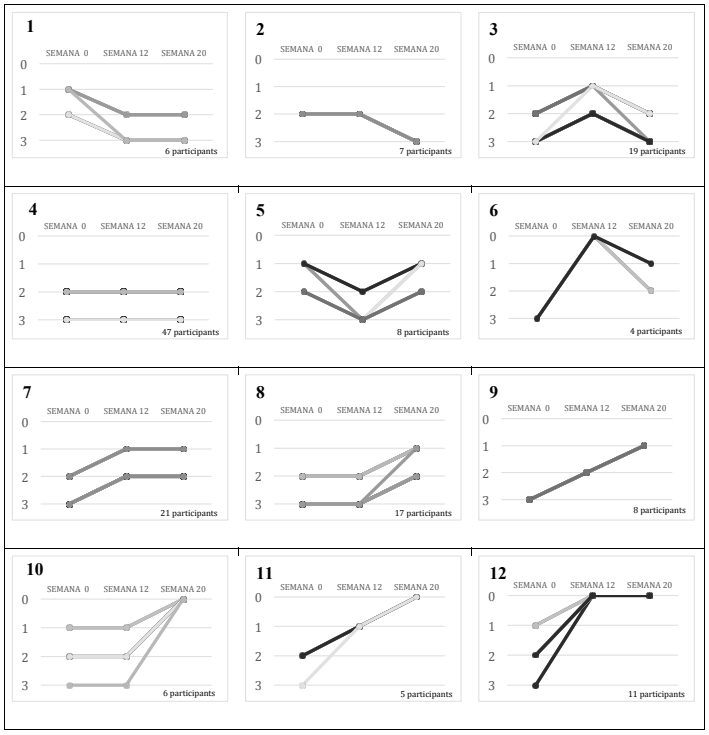

Figure 2. Participants Response trajectories Axis X represents time (weeks).
Axis Y represents the response categories according to BDI-I. The gray color of the trajectories symbolize the variations of the responses of the participants in each graph.

remission of symptoms, but in week 20 showed mild or moderate symptoms again.

DISCUSSION

This investigation analyzed a cohort of female participants mainly (93%), with an average age of 43, whose most frequent psychosocial risk factors for MDD were social isolation and/or poor support network, having witnessed domestic violence in childhood and the death of someone important in the last year. All of them were being treated for MDD in the Explicit Health Guarantees plan in primary care centers.

As proven by a research carried out in Chile[3,21] and abroad[22], MDD is two times more frequent in women. For this group, it ranks first as the cause of healthy years of life lost due to living with a disability between the ages of 20 and 44[2].

Regarding the general characteristics of the participants, the distribution by gender and age is consistent with other samples of patients with MDD[1,23]. Most of them lived in urban areas (93%), were in a relationship (89%), and had little participation in social organizations (13%). This information is related to the condition of social isolation or low support network, which is consistent with what was mentioned by Zeeck et al[16], who in a naturalistic multicenter study followed-up patients treated for MDD for up to three months after discharge. They confirmed that having a social support network was a good predictor of the symptomatic course after therapeutic discharge. Also, from a qualitative perspective, Smith et al emphasized that social support has a core role in the course of depression, being able to establish a real change in the therapeutic outcome.

The second most reported risk factor for MDD was having witnessed intrafamily violence in childhood. This fact is emphasized in a study that assessed environmental and genetic risk factors in a 30-year follow-up cohort. Patients who had witnessed abuse from a partner towards their mother, was a risk factor for MDD in adolescents[25].

12 response trajectories were obtained according to the evolution of depression symptoms

Hartman et al[7], point out that definitions of patterns of change in response to treatment depend on the number of measurements over time. In this study there were three measurement points (weeks 0, 12 and 20). If the measurement of weeks 0 and 20 is solely evaluated, four possible patterns can be obtained and be interpreted as: improvement (symptomatic decrease), worsening (symptomatic increase), maintenance, and remission **(Figure 2)**.

In addition, the patient may or may not respond to treatment, grouping the four response categories into only two of them: responsive patients (improvement and/or remission) and non-responsive (persistent or worsening symptoms).

Therefore, if they were classified according to the start and end of the follow-up, certain information that could be relevant to assess their evolution could be lost, and along with it, the choice and modification of therapy. In our investigation, the most frequent clinical situation showed persistent or worsening symptoms (38%).

In a prospective study conducted by Bogner et al[26] the group of participants who initially displayed more severe symptoms which persisted in 12 months, proved to have 16 times more chances of being diagnosed with MDD at 24 months, compared to subjects who at 12 months presented declining symptoms. However, the authors only included older patients, so their results should be compared considering the age difference with our sample.

Regarding the weaknesses of the study, the first one corresponds to 113 participants leaving the study. Although it reduced the statistical power of the sample size, we did not exhibit possible biases in the group that did complete the follow-up. Two other conditions that reduce external validity is the fact that most participants were middle - aged females, thus our results should be limited to this group.

It is possible that the therapeutic trajectories are different in men with MDD and in seniors, which are grounds for future investigations. To our knowledge, depression response trajectories have not been studied in the national literature. Therefore, this study reveals symptomatic variability during the course of depression, which makes it possible to design more precise therapeutic strategies in particular cases. We emphasize the need to carry out prospective studies that have an inferential analysis of the data, setting prediction models of the clinical trajectory, identifying higher risk groups that can be part of an intervention with a highly preventive in nature compared to a non-responsive trajectory.

REFERENCES

1. World Health Organization. Depression and other common mental disorders: global health estimates [Internet]. Ginebra; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;jsessionid=480A4092B461D5E45E14DC765057E603?sequence=1
2. Ministerio de Salud de Chile. Informe Final Estudio de Carga de Enfermedad y Carga Atribuible. Santiago; 2008.
3. Vicente B, Kohn R, Rioseco P, Saldivia S, Levav I, Torres S. Lifetime and 12-month prevalence of DSM-III-R disorders in the Chile psychiatric prevalence study. Am J Psychiatry. 2006;163(8):1362–70.
4. Malhi GS, Mann JJ. Depression. Lancet. 2018;392(10161):2299–312.
5. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991;48(9):851–5.
6. Nierenberg A, DeCecco L. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. J Clin Psychiatry. 2001;62:5–9.
7. Hartmann A, von Wietersheim J, Weiss H, Zeeck A. Patterns of symptom change in major depression: Classification and clustering of long term courses. Psychiatry Res. 2018;267:480–9.
8. Kelley ME, Dunlop BW, Nemeroff CB, Lori A, Carrillo-Roa T, Binder EB, et al. Response rate profiles for major depressive disorder: Characterizing early response and longitudinal nonresponse. Depress Anxiety. 2018;35(10):992–1000.
9. Smagula SF, Butters MA, Anderson SJ, Lenze EJ, Dew MA, Mulsant BH, et al. Antidepressant response trajectories and associated clinical prognostic factors among older adults. JAMA Psychiatry. 2015;72(10):1021–8.
10. Paul R, Andlauer TFM, Czamara D, Hoehn D, Lucae S, Pütz B, et al. Treatment response classes in major depressive disorder identified by model-based clustering and validated by clinical prediction models. Transl Psychiatry. 2019;9(1).
11. Frässle S, Marquand AF, Schmaal L, Dinga R, Veltman DJ, van der Wee NJA, et al. Predicting individual clinical trajectories of depression with generative embedding. NeuroImage Clin. 2020;26.
12. Uher R, Muthén B, Souery D, Mors O, Jaracz J, Placentino A, et al. Trajectories of change in depression severity during treatment with antidepressants. Psychol Med. 2010;40(8):1367–77.
13. Thibodeau MA, Quilty LC, De Fruyt F, De Bolle M, Rouillon F, Bagby RM. Latent classes of nonresponders, rapid responders, and gradual responders in depressed outpatients receiving antidepressant medication and psychotherapy. Depress Anxiety. 2015;32(3):213–20.
14. Henkel V, Seemüller F, Obermeier M, Adli M, Bauer M, Mundt C, et al. Does early improvement triggered by antidepressants predict response/remission? - Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord. 2009;115(3):439–49.

15. Lutz W, Stulz N, Köck K. Patterns of early change and their relationship to outcome and follow-up among patients with major depressive disorders. J Affect Disord. 2009;118(1–3):60–8.
16. Zeeck A, Von Wietersheim J, Weiss H, Scheidt CE, Völker A, Helesic A, et al. Prognostic and prescriptive predictors of improvement in a naturalistic study on inpatient and day hospital treatment of depression. J Affect Disord. 2016;197:205–14.
17. Salvo L, Saldivia S, Parra C, Rodríguez R, Cifuentes M, Acevedo P, et al. Características clínicas del trastorno depresivo mayor en tratamiento en el nivel secundario de atención. Rev Med Chil. 2017;145(3):335–43.
18. Ferrando L, Bobes J, Gibert J, Franco-Alonzo L, Soto O, Franco L. MINI International Neuropsychiatric Interview. Versión en español 5.0.0. DSM-IV. Madrid; 1998.
19. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4(6):561–71.
20. Sanz J, Vázquez C. Fiabilidad, validez y datos normativos del inventario para la depresión de Beck. Psicothema. 1998;10(2):303–18.
21. Araya R, Rojas G, Fritsch R, Acuña J, Lewis G. Common mental disorders in Santiago, Chile: Prevalence and socio-demographic correlates. Br J Psychiatry. 2001;178:228–33.
22. Accortt EE, Freeman MP, Allen JJB. Women and major depressive disorder: Clinical perspectives on causal pathways. J Women's Heal. 2008;17(10):1583–90.
23. Departamento de Epidemiología División de Planificación Sanitaria (Chile). Encuesta Nacional de Salud 2016-2017. Santiago; 2017.
24. Smith L, Hill N, Kokanovic R. Experiences of depression, the role of social support and its impact on health outcomes. J Ment Heal. 2015;24(6):342–6.
25. Kwong ASF, López-López JA, Hammerton G, Manley D, Timpson NJ, Leckie G, et al. Genetic and environmental risk factors associated with trajectories of depression symptoms from adolescence to young adulthood. JAMA Netw Open. 2019;2(6).
26. Bogner HR, Morales KH, Reynolds CF, Cary MS, Bruce ML. Prognostic factors, course, and outcome of depression among older primary care patients: The PROSPECT study. Aging Ment Heal. 2012;16(4):452–61.

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